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List of abbreviations

CVD	Cardiovascular disease
BP	Blood pressure
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
CNS	Central nervous system
PM	Particulate matter
NO_2	Nitrogen dioxide
BMI	Body mass index
GIS	Geographic information system
GC-MS	Gas chromatography – mass spectrometry

Abstract

Background: Air pollution has been associated with cardiovascular diseases (CVD) in adults, while less is known about the effects in children. Blood pressure (BP) in childhood has been suggested to be an important risk factor of high BP development in later life. Therefore, the effects of indoor air pollutants: nitrogen dioxide (NO_2), benzene, toluene and distance to major road on BP at birth were determined.

Methods: Within a subset of 119 mothers and their newborns in the ENVIR*ON*AGE birth cohort, BP was measured with automated oscillometric measurement devices. Representative indoor samples were collected during a two week period in the first weeks of life. UV spectroscopy and GC-MS analyses of these samples were performed by ISSEP (L'Institut Scientifique de Service Public, Liège, Belgium). Using geographic information system (GIS), distances to major roads were determined. Evaluation of the associations between exposure levels and BP was performed using multiple linear regression models in SAS 9.4.

Results: For newborn's BP at birth, an increase was observed in systolic BP for each IQR increment in NO_2 levels (0.99 mmHg ; 95% CI: -0.01 , 2.01 ; p = 0.05), while a positive trend was observed for diastolic BP (0.69 mmHg ; 95% CI: -0.19 , 1.57 ; p = 0.12). A negative trend was observed in systolic and diastolic BP for each IQR increment in distance to nearest major road (-0.51 mmHg ; 95% CI: -1.13 , 0.13 ; p = 0.11 and -0.49 mmHg ; 95% CI: -1.04 , 0.05 ; p = 0.08, respectively). No associations were found with benzene or toluene levels. For maternal BP, no associations were found with exposure levels or distant to nearest major road.

Conclusion: Newborn blood pressure is associated with indoor air quality, NO_2 levels and distance to major road could be contributors. Because of a small study population, this pilot study will be further extended in the future to elucidate these associations.

Samenvatting

Achtergrond: Luchtvervuiling is geassocieerd met cardiovasculaire ziekten in volwassenen. In kinderen is hier echter weinig over bestudeerd. Bloeddruk van kinderen is een belangrijke factor in hoge bloeddrukvorming later in het leven. Om deze reden, werd in deze studie het effect van luchtvervuilende partikels binnenshuis (stikstof dioxide (NO_2), benzeen, tolueen) alsook de afstand tot grote wegen bestudeerd op bloeddrukken van moeder en pasgeborenen.

Methoden: Bloeddrukken van moeder en pasgeborenen werden gemeten in een subset van 119 moeder-kind paren van het ENVIR*ON*AGE geboortecohort. Representatieve stalen voor het opmeten van luchtvervuiling binnenshuis werden in de eerste weken na de bevalling verzameld. UV spectroscopie en GC-MS analyses werden uitgevoerd door een extern laboratorium (ISSEP; L'Institut Scientifique de Service Public, Liège, Belgium). Afstanden tot grote wegen werden berekend aan de hand van een geografisch informatie systeem (GIS) en de evaluatie van de associaties werd uitgevoerd door het gebruik van meervoudige lineaire regressie modellen in SAS 9.4.

Resultaten: Voor bloeddrukken van pasgeborenen, werd een stijging in systolische bloeddruk waargenomen voor elke IQR stijging in NO_2 levels (0.99 mmHg ; 95% BI: -0.01 , 2.01 ; $p = 0.05$), terwijl een positieve trend werd waargenomen in diastolische druk (0.69 mmHg ; 95% BI: -0.19 , 1.57 ; $p = 0.12$). Een negatieve trend werd waargenomen in systolische en diastolische bloeddruk voor elke IQR stijging in afstand tot grote wegen (-0.51 mmHg ; 95% BI: -1.13 , 0.13 ; $p = 0.11$ en -0.49 mmHg ; 95% BI: -1.04 , 0.05 ; $p = 0.08$, respectievelijk). Voor benzeen en tolueen levels werden er geen associaties ondervonden alsook voor bloeddrukken van moeder met blootstellingen aan de partikels of afstand tot grote wegen.

Conclusie: Bloeddruk van pasgeborenen is geassocieerd met de luchtkwaliteit binnenshuis. Stikstof dioxide en afstand tot grote wegen zijn mogelijk beïnvloedende factoren hierop. Door een klein aantal deelnemers, zal dit aantal verhoogd worden in de toekomst om deze associaties beter te kunnen bestuderen.

1 Introduction

Cardiovascular disease (CVD) is a great public health concern and is the leading cause of mortality globally, according to the World Health Organization (WHO). A major risk factor of CVD is an increased blood pressure (BP), or hypertension (1). According to the Barker hypothesis, intrauterine events have an important effect on the development of diseases in adult life (fetal origin of adult disease). Preterm birth and low birth weight have already been associated with hypertension and CVD in adulthood. At this way, early BP measurements and follow-up could be of importance (2).

1.1 Blood pressure

BP is the pressure by which the blood stream is exerted against the walls of the arteries, in which oxygenated blood is carried away from the heart to the peripheral tissues. This pressure is regulated by hemodynamic factors (heart, kidney, blood vessels and hormones) and the central nervous system (CNS). A normal BP is maintained by a balance between total peripheral resistance in arterioles, which connect the arteries with the capillaries and contain smooth muscle cells, and cardiac output (3). The latter is determined by the heart rate, contractility, filling (preload) and ejection (afterload) pressure (4). The kidney is one of the key regulators of BP because of its important role in sodium excretion to maintain body fluid homeostasis. Pressure natriuresis is a process in which an increased BP level will lead to a higher sodium excretion and urine volume in order to maintain normal BP levels (5). Endocrinal regulation of BP is possible by excess of mineralocorticoids or glucocorticoids produced by the adrenal cortex and dysregulated levels of thyroid hormones. Mineralocorticoids, such as aldosterone, act mainly on the colon and kidney where they stimulate sodium reabsorption in the circulation and hence increase BP by changing the body fluid composition (6). Glucocorticoids, like cortisol, can also activate mineralocorticoid receptors when present at excessive levels (7). Abnormalities in thyroid hormone levels are also believed to contribute to hypertension since this condition is frequently seen in hyper- and hypothyroidism (8). On the other hand, BP is also regulated by feedback mechanisms in the walls of the carotid sinuses and aortic arch. These mechanisms, called baroreceptors, monitor and buffer changes in BP by sensing stretches of the arteries. In case of stimulation, impulses are transmitted to the CNS and feedback signals return the BP to baseline levels by alteration of cardiac output or vascular resistance (9).

1.1.1 Measurement

Since BP is a significant marker of cardiovascular health, correct measurement is essential. BP is typically expressed as the ratio systolic blood pressure (SBP)/diastolic blood pressure (DBP). Systolic BP is the maximal pressure measured during contraction of the heart, while diastolic BP is a minimal pressure measured during relaxation and refilling of the heart. Different measurement methods are classified in invasive and non-invasive methods (10).

Non-invasive

Non-invasive methods include auscultation, palpation, oscillometric and ultrasound techniques. By making use of a manual sphygmomanometer (a cuff wrapped around the upper arm, inflated by an associated bag), the underlying brachial artery will be occluded and blood flow will be paused when this cuff is inflated to a pressure above the estimated systolic pressure. After reaching this point, the pressure is slowly allowed to decline and by making use of auscultation of the brachial artery downstream of the cuff and based on the sounds heard, systolic and diastolic BP can be determined. These Korotkoff sounds are classified in five phases (11, 12):

I: First tapping sounds after deflating the cuff represent the systolic BP.
II: Murmur sounds.
III: Sounds become louder.
IV: Hereafter, sounds become softer.
V: No sounds detectable, this pressure represent the diastolic BP.

Another way is the palpatory method, by which systolic BP can be determined by palpation of the radial artery right after the start of the cuff deflation (12).

The automated oscillometric measurement method is comparable with the auscultatory method with the difference that oscillations of arteries are recorded and evaluated instead of the Korotkoff sounds. By making use of algorithms, systolic and diastolic BP are calculated and presented on the display (13).

To determine systolic BP, also ultrasound techniques relying on the Doppler effect can be used. This is based on the recording of frequencies reflected by the moving red blood cells in vessels and is considered as a sensitive method (14).

Invasive

In case of rapid BP changes (for instance, as a result of cardiovascular instability) or when other non-invasive methods are not possible due to arrhythmias, obesity or side effects of long-term measurements of these methods, an invasive measurement can be chosen. Hereby, the intravascular BP is measured by inserting a catheter into an artery linked to a transducer (14).

1.1.2 Parameters

Three BP values are generally recorded: a diastolic, systolic and mean arterial pressure (MAP). These pressures are expressed in millimeters of mercury or mmHg. A SBP/DBP ratio around 120/80 mmHg is believed to be optimal for an adult, while this is for a MAP (the average pressure during a cardiac cycle divided by the period) around 95 mmHg (12). In oscillometric devices, the latter is based on the fact that at MAP, the oscillometric amplitude reaches a maximum.

Another important indicator of cardiac capacity is the pulse pressure (PP), this shows the BP variation as a difference between systolic and diastolic pressure (10, 12, 15).

Systolic and diastolic BP both have been positively associated with CVD. A high systolic BP (>160 mmHg) may be an indicator of arterial stiffening, atherosclerosis development and vascular structure changes while a decreased diastolic BP (<70 mmHg) may reflect a poor reserve and perfusion of the heart muscles. Pulse pressure has been only shown useful as a predictive factor in elderly persons with risk factors (16). It has been indicated that combining these BP components gives a better reflection of CVD risk assessment (17).

1.1.3 Hypertension

In Table 1, BP categories are listed according to the guidelines of the European Society of Hypertension in 2013 (18). In case of a frequent diastolic BP of 90 mmHg (or higher) or a systolic BP of 140 mmHg (or higher), the diagnosis of hypertension is established. Prehypertension (high – normal BP) is a condition in which a person has a higher risk to develop hypertension and should initiate lifestyle changes in order to prevent definite hypertension (19).

Table 1 *BP categories as defined by the European Society of Hypertension in 2015.*

BP category	SBP (mmHg)		DBP (mmHg)
High - normal BP	130 – 139	or	85 – 89
Grade 1 hypertension	140 – 159	or	90 – 99
Grade 2 hypertension	160 – 179	or	100 - 109
Grade 3 hypertension	≥ 180	or	≥ 110

Health effects of hypertension include an increased risk for CVD. Due to an increased afterload, the ventricle wall tension will also be increased and consequently, this can result in hypertrophy of the heart. Also, atherosclerosis formation in the coronary arteries will be accelerated and this is an important risk factor for myocardial infarction (20). Another target organ is the kidney, which is an important regulator of BP and at this way, when damaged, can contribute to further chronic hypertension. Kidney diseases resulting from vasculature damage, can cause hypertrophy and in severe cases even necrosis which could lead to necessary dialysis (21). Hypertension is also a major risk factor for strokes. Studies have shown a decrease in the incidence and mortality of strokes when hypertension was controlled well. An important association with systolic BP was indicated (22). High BP can cause abnormalities in the microvasculature of the retina, which is called hypertensive retinopathy. Because of the similarities of microvasculature in retina, brain and kidney, visualizing the retinal vasculature offers an important non-invasive view on the health of the human microvasculature. Severe and uncontrolled high BP can lead to blurred vision and an increase in cardiovascular and renal disease risk (23).

1.1.4 Hypotension

A BP of 90/60 mmHg or lower, is called hypotensive. Low BP is widely spread among the population and typical symptoms include, dizziness, nausea, headache, fatigue, cold limbs,… Hypotension was regarded as not alarming for a long time, but recent studies have shown that low BP has also effects on cognition, depression and even possibly on dementia. Concentration problems and reduced performances in hypotension are indicated (24). Chronic hypotension has also been associated with depression and anxiety, independent of age and gender (25). Another finding independent of age and gender was that lower BP values were associated with an increased risk of dementia. There are indications that the degenerative process is enhanced by a low BP (26).

1.1.5 Influencing factors

Some factors that can influence BP are age, race, diet, stress, diabetes, exercise, smoking and alcohol consumption. Abnormalities in BP can be treated with pharmaceutical agents, but most of all a healthy lifestyle is recommended in order to prevent adverse health effects (27).

1.1.6 Newborns

Previous studies have shown a significant correlation on the third day after birth between systolic and diastolic BP of mothers and their newborn. Determining factors that can influence the newborn BP are divided in maternal and neonatal factors (28).

Increasing maternal age has been associated with a higher systolic BP in newborns, but also hypertension and preeclampsia were shown to have an impact. Antenatal corticosteroids, used to reduce preterm delivery risk, are proven to have an increasing effect on neonatal BP during the first hours of life (29). Neonatal factors include birth weight and gestational age, due to important intrauterine developments. A direct relation with systolic BP is shown and preterm newborns seems to have an increased risk on hypertension and CVD later on in life (29, 30). Some studies have reported that the mode of delivery has also an impact, in particular newborns born by caesarean section would have a lower systolic BP. Due to important developments during the intrauterine period, gestational age is an important factor in determining of newborn BP (30).

Of all the possible BP measurement methods described in 1.1.1, oscillometric measurement is generally used in newborns because variability is excluded and this method is painless, non-invasive and easy to use (10).

Because of the immature BP regulation by the autonomic nervous system in newborns and several influencing factors, it is difficult to estimate a normal BP range. This range is required in the management of abnormalities in newborn BP, which are a frequent problem but difficult to define. A mean systolic pressure of 70 mmHg and a mean diastolic pressure of 40 mmHg are however assumed to be normal. During the first days of life, significant elevations in BP were recorded in previous studies. This could be due to an increase in weight (31, 32).

1.1.7 Hypertension

Newborn hypertension has a lower incidence than hypotension and is mostly linked with renovascular problems. Also conditions such as umbilical catheterization, endocrine, cardiovascular and pulmonary causes should be considered. Hypertensive newborns can be symptomatic (marks of congestive heart failure, retinopathy,…) or asymptomatic (irritability, difficulties in feeding,…) (33). Most of the time, a high BP will resolve over time although extended treatment might be required. Treatment options include restriction of fluid in order to avoid an overload, pain relief and antihypertensive medication. An important aspect is not to lower the BP too fast, because this could have adverse effects on the cerebral perfusion pressure (33, 34).

1.1.8 Hypotension

On the other hand, hypotension in newborns has a high incidence, especially in extremely low birth weight newborns (birth weight < 1000g). Symptoms include, cold limbs, arrhythmias (bradycardia, tachycardia), hypouresis,… Some possible causes for a low BP are a pneumothorax, myocardial dysfunction and hypovolemia. Based on the actual cause, therapy should be directed and often involves a combination of low BP medication, volume replacement and corticosteroid administration (33, 35).

1.2 Indoor air pollution

Adverse health effects of air pollution are well established and it is suggested that also BP can be affected. As shown in Figure 1, indoor air pollution can consist of penetrated outdoor pollutants (pesticides, radon,…) and indoor pollutants from sources such as tobacco smoke, cooking, domestic energy sources (heating systems, fireplaces…), building materials, carpets, furniture and household products (air fresheners, detergents,…) (36, 37). High indoor concentrations of particulate matter (PM; $PM_{2.5}$, particle diameter smaller than 2.5 µm) were positively associated with increased systolic and diastolic BP (38). This positive association is demonstrated in many studies and a high concentration of air pollution is also linked with an increased cardiovascular event risk such as myocardial infarctions. Long-term exposure is shown to enhance atherosclerosis development (39). In a study with schoolchildren in Pakistan, which were exposed to a high traffic-related air, higher BP were reported compared to less exposed children (40). In addition, adverse pregnancy outcomes such as preterm delivery and low birth weight were also linked to air pollution exposure. These pollutants could be absorbed into the bloodstream of the mother and at this way, cross the placental barrier. Consequently, also the fetus would then be exposed to the pollution (41).

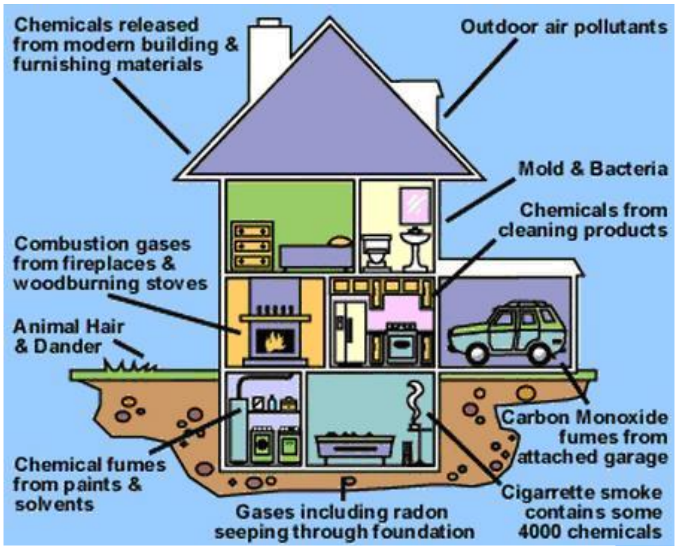

__Figure 1__ An overview of potential sources of indoor air pollution.

This mechanism is best understood for carbon monoxide, which will reduce the oxygen capacity of blood by binding to hemoglobin. Binding affinity of fetal blood is higher than compared to adults, which will make the elimination difficult and enhance further oxygen deprivation and consequent growth retardation and other adverse outcomes (42).

1.2.1 Nitrogen dioxide

An important component of PM is nitrogen dioxide (NO_2). While traffic is the most important outdoor source, coal burning energy facilities like ovens, stoves and fireplaces are the most important indoor sources. Outdoor levels can influence indoor levels, for example especially in case of underground parking garages. NO_2 will most likely enter the human body through inhalation (36). There is a growing body of evidence that exposure is positively associated with a higher systolic and diastolic BP, this association was stronger in CVD patients. Recent studies suggest that chronic inhalation of this kind of pollution could lead to a state of oxidative stress and inflammation, which could cause an increased BP (43). Increased preeclampsia risks in NO_2 exposed pregnant women were also reported (44). NO_2 may be directly toxic on the fetus because experimental studies suggested that exposure to NO_2 during pregnancy could lead to complications due to decreases in antioxidant reserves and increased placental lipid peroxidation (45).

1.2.2 Benzene

Indoor benzene levels are associated with use of household products (detergents, air fresheners,…), paint, photocopiers, printers and tobacco smoke. Indoor concentrations are usually higher than outdoor concentrations, which are mainly associated with traffic-related air pollution (36). Health effects of benzene exposure are mainly on the respiratory (asthma, pulmonary infections,…) and immune (allergies, eczema, decreased level of DNA repair markers,…) system. Furthermore, benzene is a known human carcinogen (46). Some animal studies have shown that acute exposure to high concentrations resulted in ventricle arrhythmias (47). Also a significant increase in prevalence of hypertension in exposed workers was reported. This could be due to impairment of the nitric oxide process (48, 49). Maternal exposure has been associated with preterm birth and low birth weight. Animal studies have shown that benzene crosses the placental barrier and could expose the fetus to the adverse effects. Benzene levels have also been found in cord blood (49).

1.2.3 Toluene

Indoor sources of toluene are comparable to those of benzene (household products, tobacco smoke,…) and are often higher as outdoor concentrations due to combustion of fuels or traffic. Furthermore, toluene is also associated with gasoline and is used in the production of benzene (46). Adverse health effects on the CNS of acute and chronic exposures to toluene are well established. While nausea and sleepiness are some of the acute symptoms, studies have shown that chronic exposure can have destructive effects on myelin level, most likely through oxidative stress (50). Little is known about the cardiovascular effects of toluene exposure, although a study has shown an correlation with increased prevalence of CVD (46). Also, a significant increase in systolic BP was reported in workers exposed to toluene levels (51).

Maternal exposure has been, as it is for benzene, associated with preterm birth and low birth weight. Toluene can easily cross the placental barrier and is also been traced in cord blood (46).

1.2.4 Distance to major road

Residential distance to a major road is an important indicator of exposure to traffic-related air pollution, since there is a greater exposure with closer proximity to multiple toxic components released by motor vehicle exhaust. It has been suggested that this proximity is associated with respiratory and cardiovascular diseases, recent studies suggest also an association with BP (52). Risks of preterm birth and low birth weight have been shown to be increased for women living in highly polluted or impoverished areas (53).

1.3 Hypothesis

Considering the Barker hypothesis (fetal origin of adult disease), the research question of this study was whether indoor air pollution (NO_2, benzene and toluene) and distance to nearest major road, to which newborn and mother were exposed, was associated with blood pressure. The hypothesis that these have an adverse effect on blood pressure of mother and newborn was studied in the ENVIR*ON*AGE birth cohort.

2 Methods

2.1 Study characteristics and population

Participants were recruited for the ENVIR*ON*AGE birth cohort, a prospective cohort studying the ENVIRonmental influence *ON* AGEing in early life, in the East-Limburg Hospital (ZOL) in Genk, Belgium. 119 mother-newborn pairs were enrolled between October 2013 and March 2015. Ethical approval was obtained from the Ethical Committees of Hasselt University and East-Limburg Hospital. Mothers were recruited at time of delivery and provided written informed consent. A detailed questionnaire was handed about health, education, socioeconomic status, place of residence, diet, smoking, alcohol consumption and use of medication during pregnancy. Besides à term babies, preterm newborns from 28 weeks of gestational age, with no serious health issues or complications during delivery were included. Participants were seen by researchers at maternity ward three days after delivery in order to complete the measurements and to provide all necessary information and informed consent for enrollment in this study. Mothers were re-contacted by phone to proceed with the study, appointments were made for placing indoor air pollution tubes.

2.2 Blood pressure measurements

BP of mother and newborn were measured three days after birth. These measurements were done at the maternity ward at the East-Limburg Hospital in Genk.

2.2.1 Mother

Blood pressures (systolic, diastolic BP and pulse) of participating mothers were measured with an automated oscillometric measurement device (Omron 705IT, Omron Corporation, Japan). The measurements were preferably done in the morning while the participants were sitting in a rest position and according to the guidelines of the European Society of Hypertension on the right upper arm (54). Five consecutive measurements were taken with 1 minute apart and the mean value of the last 3 measurements were calculated to estimate the mother's final BP.

2.2.2 Newborn

BP of newborns were measured with an advanced oscillometric measurement device like generally used in newborn intensive care units (Welch Allyn Vital Signs Monitor 6000 Series, Welch Allyn, USA). To ensure an accurate measurement, appropriate cuffs were used according to the limb circumference of the newborn that was compared to the given ranges, as shown in Figure 2 (10). In order to avoid negative influences on the measurements, these were taken preferably in the morning, in between feedings and while the newborn was laying in a supine rest position. Newborn BP were taken 5 times with an 2 minute interval according to the guidelines of the European Society of Hypertension on the right upper arm (54). State of newborn was registered during measurement (quit/active sleep, quit/active state or crying).

Figure 2 *BP measurement in newborn with an advanced measurement device (Welch Allyn Vital Signs Monitor 6000 series) and appropriate cuff based on the limb circumference.*

2.3 Indoor air pollution measurements

To investigate a possible association between BP of mothers and their newborns and indoor air pollution, the latter was evaluated in the first weeks of life. A hanging air exposure system was applied in each participants home to evaluate concentrations of NO_2, benzene and toluene. Benzene and toluene were measured within the same tube, as shown in Figure 3.

Figure 3 *Hanging air exposure system for measurement of indoor concentrations of 1 : NO_2 and 2 : benzene and toluene (within the same tube).*

This hanging system was most often placed in the living room or bedroom (where most of the time was spent) for 2 weeks. Windows, doors and furniture were avoided and a height of at least a meter and a half high was preferred. In addition, a questionnaire was handed to the participants which included questions about the home temperature, domestic energy sources, neighborhood traffic, ventilation systems and other potential variables for an adjustment of the measured particle concentrations by the analyzing laboratory.

2.3.1 Sampling

Before and after sampling, all tubes were kept at 4°C in the dark. Time of begin and end of measurement was noted. A diffusion cap was placed on the 2 lined side of the metallic tube for benzene and toluene, while for NO_2 the white cap was removed to start the measurement. Also control tubes were included. After 2 weeks of sampling, the tubes were collected, closed carefully and immediately stored in a cool box. Preservation was maximum 2 weeks in a fridge at 4°C and the tubes were sent as soon as possible to the ISSEP (L'Institut Scientifique de Service Publique, Liège, Belgium) laboratory for analysis of the present particles.

NO_2 concentrations were analyzed using UV spectroscopy, while benzene and toluene concentrations were analyzed by gas chromatography-mass spectrometry (GC-MS).

2.4 Distance to major road

Distances between residential addresses of the participants at birth and the nearest major road (N – road ; > 10,000 motor vehicles passing by/24 hours) were determined by using a geographic information system (GIS).

2.5 Statistical analysis

Measurement of the indicators of exposure (NO_2, benzene, toluene and distance to nearest major road) were $\log_{10}$ - transformed to improve normality. Pearson correlation coefficients were calculated to assess the correlations between exposures and BP. Multiple linear regression analyses were performed using SAS 9.4 to assess the associations and models were adjusted for gestational age, birth weight, gender, maternal age, education, smoking status and season of delivery. The Shapiro-Wilk test and Q-Q plots of the residuals were used to test the assumptions of all linear models.

3 Results

3.1 Characteristics

3.1.1 Study population

Sociodemographic and clinical characteristics are shown in Table 2. 119 mother - newborn pairs were enrolled in this study.

Maternal age averaged (± SD) 29.5 (± 4.7) years and pre-pregnancy body mass index (BMI) 24 (± 5) kg/m^2. The majority of the mothers (87% ; n = 100) did not smoke during pregnancy, had a high education (51.8% ; n = 59) and was nulliparous (61.3% ; n = 73). Average BP (SBP/DBP) at birth was 121/75 mmHg. Approximately half of the newborns were female (51.3% ; n = 61), they had an average gestational age of 38.7 (± 2.1) weeks and weight of 3251 (± 624) g. 104 (90.4%) newborns had an European ethnicity (at least two European grandparents). Average BP at birth was 70/43 mmHg.

Table 2 Characteristics of included mother-newborn pairs (n = 119).

	Mean ± SD or number (%)
Maternal variables	
Age (years)	29,47 ± 4,67
Pre-pregnancy BMI (kg/m²) [a]	24,03 ± 5,04
Parity	
▪ 1	73 (61,34)
▪ 2	34 (28,57)
▪ ≥ 3	12 (10,08)
Smoking status	
▪ Non smokers	66 (57,39)
▪ Past smokers	34 (29,57)
▪ Smokers	15 (13,04)
Education	
▪ Low	13 (11,4)
▪ Middle	42 (36,84)
▪ High	59 (51,75)
Diastolic blood pressure, at birth (mmHg) [b]	75 ± 9
Systolic blood pressure, at birth (mmHg) [b]	121 ± 12
Newborn variables	
Gender	
▪ Female	61 (51,26)
Gestational age (weeks)	38,70 ± 2,13
Birth weight (g)	3251 ± 624
Ethnicity	
▪ European	104 (90,43)
Season at delivery	
▪ Winter	31 (26,05)
▪ Spring	12 (10,08)
▪ Summer	31 (26,05)
▪ Autumn	45 (37,82)
Diastolic blood pressure, at birth (mmHg) [c]	43 ± 9
Systolic blood pressure, at birth (mmHg) [c]	70 ± 11

Data available for [a] n = 111, [b] n = 90 and [c] n = 82. Maternal education: low (no diploma), middle (high school diploma) or high (college or university diploma).

3.1.2 Exposure levels

The two week indoor exposure levels of NO2, benzene and toluene are presented in Table 3. Average geometrical (± SD) NO_2 levels were 12.02 (± 1.74) µg/m^3, benzene levels 1.51 (± 2.04) µg/m^3 and toluene levels 7.08 (± 3.33) µg/m^3. Average distance to the nearest major road was 258.95 (± 3.75) m.

***Table 3** Geometrical exposure characteristics for NO_2, benzene and toluene levels during the two week measurement and distance to the nearest major road (n = 119).*

Exposure	**Mean ± SD**	**25th percentile**	**75th percentile**	**IQR**
Two week indoor air pollution (µg/m^3)				
NO_2	12.02 ± 1.74	9.12	15.49	6.37
Benzene	1.51 ± 2.04	1.05	2.88	1.83
Toluene	7.08 ± 3.33	3.85	19.24	15.39
Distance to the nearest major road (m)	258.95 ± 3.75	98.65	875.99	777.34

3.2 Associations between exposure levels and newborn BP

Unadjusted data analysis

The correlation between unadjusted exposure levels of NO_2, benzene, toluene and distance to nearest major road and BP of newborn at birth (n = 82) is shown in Figure 4. We observed a significant positive association between NO_2 levels and systolic BP (p = 0.03 ; r = 0.24) and a borderline significant positive association with diastolic BP (p = 0.07 ; r = 0.20). While benzene levels showed a positive trend with systolic and diastolic BP (p = 0.09 ; r = 0.19 and p = 0.14 ; r = 0.17, respectively), distance to the nearest major road showed a negative trend (p = 0.14 ; r = 0.17 and p = 0.12 ; r = 0.17, respectively). Toluene levels were not associated with systolic or diastolic BP (p = 0.59 ; r = 0.06 and p = 0.47 ; r = 0.08, respectively).

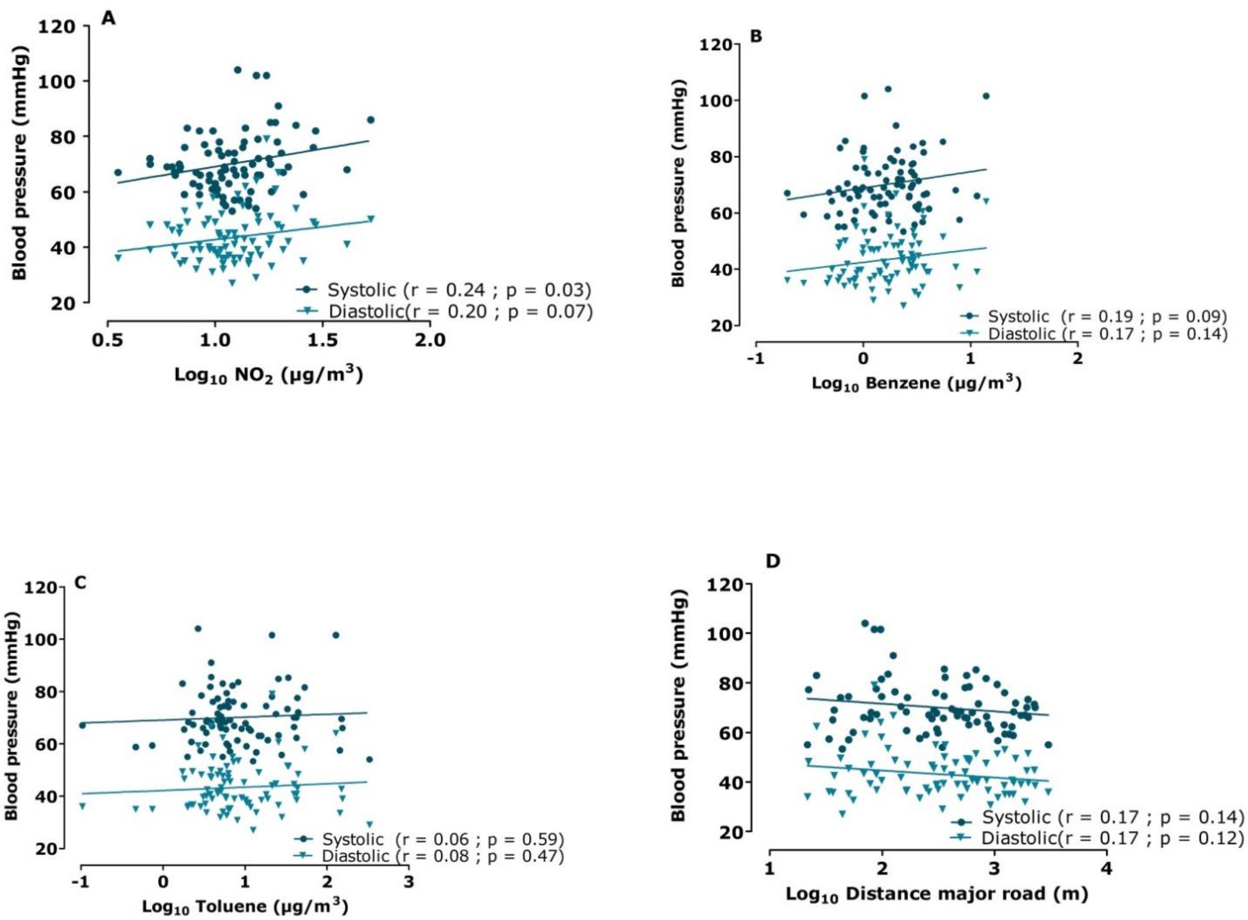

Figure 4 *Correlations between BP of newborn at birth (mmHg, n = 82) and log_{10}- transformed exposure levels of NO_2, benzene, toluene (μg/m^3) and distance to nearest major road(m).* ***A****. NO_2 levels were significantly correlated with an increase in systolic BP and borderline significantly correlated with an increase in diastolic BP.* ***B****. Benzene levels showed a positive trend with increases in BP.* ***C****. Toluene levels did not show a significant correlation with BP and* ***D****. Distance to nearest major road showed a decreasing trend in BP.*

Adjusted data analysis

Models were adjusted for gestational age, birth weight, gender, maternal age, education, smoking status and season of delivery. Adjusted estimates (95% CI) expressing the effect on BP of newborn, are shown in Table 4. We observed an increase in systolic BP for each IQR increment in NO_2 levels (0.99 mmHg ; 95% CI: -0.01 , 2.01 ; p = 0.05), while a positive trend was observed for diastolic BP (0.69 mmHg ; 95% CI: -0.19 , 1.57 ; p = 0.12). A negative trend was observed in systolic and diastolic BP for each IQR increment in distance to nearest major road (-0.51 mmHg ; 95% CI: -1.13 , 0.12 ; p = 0.11 and -0.49 mmHg ; 95% CI: -1.04 , 0.05 ; p = 0.08, respectively). No significant associations were found between benzene (p = 0.64 and p = 0.83, respectively) or toluene (p = 0.89 and p = 0.91, respectively) levels and systolic or diastolic BP of newborn at birth.

3.3 Associations between exposure levels and maternal BP

Unadjusted data analysis

Unadjusted estimates (95% CI) expressing the effect of exposure levels on BP of mother (n = 90), are shown in Table 5. No significant effect of exposure to indoor NO_2 levels on systolic or diastolic BP was observed (p = 0.88 and p = 0.38, respectively), neither for benzene levels (p = 0.48 and p = 0.74, respectively), toluene levels (p = 0.49 and p = 0.15) or distance to nearest major road (p = 0.82 and p = 0.96).

Adjusted data analysis

Models were adjusted for gestational age, birth weight, gender, maternal age, education, smoking status and season of delivery. Adjusted estimates (95% CI) expressing the effect on BP of mother, are shown in Table 6. No significant associations were found between maternal systolic and diastolic BP and indoor exposure to NO_2 levels (p = 0.70 and p = 0.20, respectively), benzene (p = 0.35 and p = 0.64, respectively), toluene (p = 0.62 and p = 0.16, respectively) or distance to nearest major road (p = 0.62 and p = 0.86, respectively).

Table 4 *Adjusted estimates (95% CI) express the change in mmHg BP of newborn for an IQR increment in NO_2,benzene, toluene levels (μg/m^3) and distance to nearest major road (m).*

Exposure variables	Log_{10} NO_2	Log_{10} Benzene	Log_{10} Toluene	Log_{10} Distance major road
Systolic BP	0.99 mmHg (-0.01 , 2.01) **p = 0.05**	0.51 mmHg (-1.64 , 2.66) p = 0.64	0.09 mmHg (-1.25 , 1.44) p = 0.89	-0.51 mmHg (-1.13 , 0.12) p = 0.11
Diastolic BP	0.69 mmHg (-0.19 , 1.57) p = 0.12	0.20 mmHg (-1.65 , 2.05) p = 0.83	0.07 mmHg (-1.09 , 1.22) p = 0.91	-0.49 mmHg (-1.04 , 0.05) p = 0.08

Table 5 *Unadjusted estimates (95% CI) express the change in mmHg BP of mother for an IQR increment in NO_2,benzene, toluene levels (μg/m^3) and distance to nearest major road (m).*

Exposure variables	Log_{10} NO_2	Log_{10} Benzene	Log_{10} Toluene	Log_{10} Distance major road
Systolic BP	0.07 mmHg (-0.90 , 1.04) p = 0.88	-0.88 mmHg (-3.35 , 1.59) p = 0.48	-0.56 mmHg (-2.16 , 1.04) p = 0.49	0.08 mmHg (-0.61 , 0.77) p = 0.82
Diastolic BP	0.33 mmHg (-0.42 , 1.08) p = 0.38	-0.32 mmHg (-2.25 , 1.60) p = 0.74	-0.91 mmHg (-2.14 , 0.32) p = 0.15	0.01 mmHg (-0.53 , 0.56) p = 0.96

Table 6 *Adjusted estimates (95% CI) express the change in mmHg BP of mother for an IQR increment in NO_2,benzene, toluene levels (μg/m^3) and distance to nearest major road (m).*

Exposure variables	Log_{10} NO_2	Log_{10} Benzene	Log_{10} Toluene	Log_{10} Distance major road
Systolic BP	0.19 mmHg (-0.79 , 1.17) p = 0.70	-1.22 mmHg (-3.81 , 1.37) p = 0.35	-0.41 mmHg (-2.04 , 1.22) p = 0.62	0.18 mmHg (-0.54 , 0.89) p = 0.62
Diastolic BP	0.51 mmHg (-0.28 , 1.31) p = 0.20	-0.50 mmHg (-2.64 , 1.63) p = 0.64	-0.93 mmHg (-2.26 , 0.39) p = 0.16	0.05 mmHg (-0.54 , 0.64) p = 0.86

4 Discussion

In this study, we evaluated the association of indoor air pollutants NO_2, benzene, toluene and distance to nearest major road with BP of mother and newborn at birth. The key finding was an association of indoor NO_2 levels with newborn BP, also a trend for distance to nearest major road was observed. In contrast, no associations were observed for maternal BP.

Air pollution and BP

Epidemiological studies suggest a positive association between air pollution and BP (systolic and diastolic) (38). Little is known about the cardiovascular effects of indoor air pollutants, but there is a growing body of evidence indicating these are also linked with an increase in BP. Lin et al. reported an association with indoor air concentrations (48h measurement) of PM_{10}, $PM_{2.5}$ and NO_2 in a panel of 40 healthy adolescents (55). This effect of indoor $PM_{2.5}$ (24h measurement) was also reported by Baumgartner et al., they found a positive association in 280 women with systolic and diastolic BP (38). However, little is known about the cardiovascular effects in children. A study with schoolchildren in Pakistan, showed an association between traffic-related air pollution (4 month measurement) and increases in diastolic and systolic BP (40).

NO_2

In adults, previous studies have shown different associations between long-term exposures to NO_2 and BP. Foraster et al. reported a positive association with systolic BP in a study with 3,700 participants over a period of 2 years. These associations were shown to be stronger in subjects with CVD (43). However, inverse associations between NO_2 exposure and BP are also reported. In a study population of a Danish cohort of almost 57,000 participants and over a follow-up period of 5 years, an inverse association with systolic BP was reported (56). There is also some inconsistency in studies about the short-term effects of NO_2 on BP, while a study of Brook et al. have suggested a positive association with BP levels, another study with young adults did not observed this (39, 55).

Less is known about the effects of air pollution on BP in children. However, some studies have been performed. A study with 700 children from 9 to 10 years-old in schools around an airport in the United Kingdom did not show an association between NO_2 exposure and BP of these children (57). These findings were consistent with a study in Germany, based on almost 2,000 children in two cities. For both studies, annual concentrations were used (58). In contrast to previous studies, the PIAMA birth cohort in the Netherlands reported an association of annual NO_2 concentrations with diastolic BP in 1,500 healthy children of an age of 12 years old (59).

In newborns, only one study has explored the effects of prenatal air pollution exposure on BP. Van Rossem et al. studied the link between calculated prenatal exposure levels (outdoor, trimester-specific) and BP in newborns in a birth cohort with over 1,000 mother-newborn pairs. They showed an inverse association between second trimester exposure to NO_2 and a lower newborn BP, while prenatal PM levels were associated with a higher BP. This could be due to different reaction mechanisms (60).

The majority of these studies has been performed with outdoor air pollution concentrations while in this study, indoor concentrations were measured. For NO_2, it is known that outdoor and indoor concentrations are highly correlated and that in comparison with $PM_{2.5}$, outdoor particles can penetrate more easily into indoor settings. In this way, this could also affect the cardiovascular health of humans (61). Given the inconsistent data for both short- and long-term exposure and lack of data for newborns, comparisons are rather difficult. We measured the concentrations of indoor NO_2 during a 2 week period, but by making use of the questionnaires (about residential addresses) and the assumption that there were no drastic differences in levels, we assumed that this exposure reflected a more long-term exposure to NO_2. For newborn BP at birth, NO_2 levels showed a borderline significant positive association with systolic BP, while for diastolic BP a positive trend was observed. Since the fetus undergoes important developmental changes during the prenatal period, these could be more susceptible for the adverse effects of prenatal exposure levels. Stronger associations of air pollution exposure and BP has also been shown in other susceptible groups such as cardiovascular and diabetes patients (60).

Benzene

Only a few studies have explored the effect of benzene levels on BP. A study of Kotseva et al. in 345 industrial workers (which were exposed to high benzene concentrations) and the same number of controls, has shown a significant increase in BP and prevalence of hypertension in exposed subjects (48). This increase in BP in exposed workers, was also shown by Wiwanitkit et al. By making use of a biomarker of benzene exposure, urine phenol, associations were explored. Groups exposed to higher levels showed a significantly higher rate in hypertension compared to groups exposed to less concentrations (49).

In children, no previous studies were found about an assessment of effects of benzene exposure on BP which makes comparison difficult. Maternal benzene exposure has been associated with preterm birth, low birth weight and the occurrence of spina bifida and given the fact that fetuses are in a susceptible window of their life, one could hypothesize that prenatal exposure levels could affect also newborn's BP (46). In our results however, no such associations were found neither with systolic or diastolic BP. The few studies which have shown an association with BP have been performed in industrial workers exposed to high concentrations of benzene during a long time, which makes comparison difficult.

Toluene

A linear association between toluene exposure levels and prevalence of CVD has been suggested, although further studies are recommended (62). For BP, Mohammadi et al. explored the effects of exposure on 433 women in a Iranian pharmaceutical company. A significant difference was observed in systolic BP (not diastolic BP) and hypertension prevalence with a control group (51). Significant associations with systolic BP were also found in 262 industrial workers in 2 Danish companies. A decrease in systolic BP after a 6 week period without exposure was reported (63). As paintings and ink are an important source of toluene exposure, a study of Gericke et al. in workers in a printing business which have been exposed for over 20 years has shown an association with systolic BP, however they did not adjusted for probable confounders. Similar trends were reported for diastolic BP (64).

As it was for benzene, no studies were found about associations between toluene exposure and BP in children. However, many adverse effects of maternal exposure are well established such as low birth weight and preterm birth. Furthermore, it is known that toluene can easily cross the placental barrier (46). However, in our results we were not able to find any significant association with newborn BP. The associations found in the literature were mainly about industrial workers which were exposed to high concentrations during a period of several years, which makes it difficult to compare.

Distance to major roads

Distance to a major road is an important indicator of exposure to air pollution and has been associated with CVD. In a German cohort study with almost 4,500 participants, a higher risk for coronary artery calcification with a closer distance to a major road has been reported. This condition represents a long-term exposure and a possible mechanism could be an increased BP (65). Association with early markers of atherosclerosis have also been shown in healthy children (66). In a Dutch cohort study of 5,000 participants, over a period of 8 years, cardiovascular mortality has been associated with residential addresses near to a major road (52). A recent study of Kirwa et al. in 68,000 postmenopausal women over a period of 5 years, has shown a positive association between distance to major roads (associated with levels of multiple air pollutants) and prevalence of hypertension (67). As expected, a trend was observed for newborn BP, although not significant.

Results in the* ENVIRONAGE *birth cohort

Newborn BP

As expected for newborn's BP at birth, NO_2 levels were positively associated with systolic BP and a positive trend was observed for diastolic BP. A negative trend was observed for distance to nearest major road. However, no significant associations were found with benzene or toluene levels.

Maternal BP

For the exposure levels of NO_2, benzene, toluene and distance to nearest major road, no significant associations were found for maternal BP. The fact that there was an association of NO_2 with newborn BP and a trend with distance and not in mothers, might be due to some variation in maternal BP that could be caused by external factors shortly after birth. Emotional stress is well known to be a regulator of BP. On the other hand, also hypotension is common in postpartum period, due to possible hemorrhages during and after birth (68). These variations in maternal BP shortly after birth could make it difficult to see a clear association with air pollution exposure. Another possible explanation could be that stronger associations of air pollution exposure and BP are shown in susceptible groups such as cardiovascular and diabetes patients and therefore, these associations could be more clear for newborns (60). Because of this, a bigger sample size and future follow-ups could be suggested for maternal BP in association with air pollution.

Reference concentrations

In this study, the mean indoor NO_2 concentration level was 12.02 μg/m^3, while the WHO guidelines have set up a threshold at 40 μg/ m^3 (36). This means that for even concentrations below the advised concentrations, biological effects can be observed and further studies are needed to clarify whether lower acceptable thresholds should be implemented.

Mean indoor exposure levels of benzene and toluene were 1.51 μg/m^3 and 7.08 μg/m^3, respectively. Reference concentrations for both were much higher, 0.03 mg/m^3 and 5 mg/ m^3, respectively (46). These in comparison relatively low exposure levels were measured in the homes of study participants, which are advised not to do any painting while pregnant. Therefore we expect these levels to be much lower than those in industry.

Biological mechanisms

Possible mechanisms in changes of BP by air pollution particles have been described by Brook et al., although there is still some uncertainty. Mechanisms are divided for acute and chronic exposure and in Figure 5, an overview is given.

Elevations in BP due to acute exposure have been suggested to be mediated by autonomic nervous system changes which result in activation of the sympathetic nervous system and subsequent increase in BP. Little is known about the precise pathways, but receptors lining the respiratory system might trace stimulations due to air pollution inhalation. An autonomic imbalance might also induce oxidative stress in the cardiovascular system and at this way, reduce nitric oxide (NO) availability which results in vasoconstriction and an increase in BP.

Elevations in BP due to long-term exposure have been suggested to be mediated through oxidative stress and subsequent vascular inflammation. Also, as described for acute exposures, an autonomic imbalance can still contribute to oxidative stress formation. All these changes can result in vascular remodeling and endothelial dysfunction, which is an important event in atherosclerosis formation (39, 69).

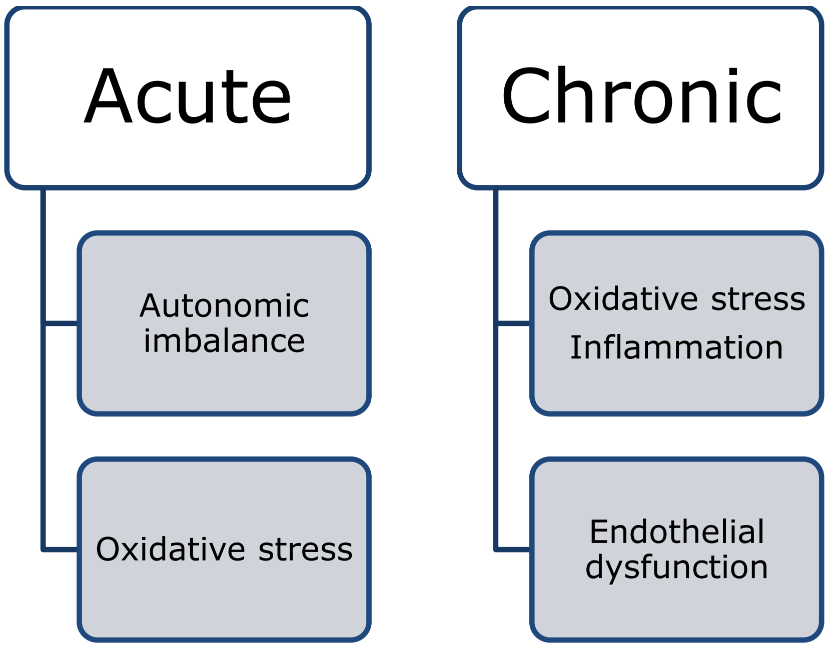

Figure 5 *Overview of possible pathways in BP elevation after acute and chronic exposure to air pollution particles.*

Clinical relevance

BP in childhood is shown to be an important predictor of CVD and high BP in adulthood. Since there is a trend in maintaining a BP range, it is very important to elicit the possible adverse effects of air pollutants on BP (59). Even small differences can be important. Lewington et al. have shown that in middle aged persons, a decrease of 2 mmHg in systolic BP would lower cardiovascular mortality with 7% and stroke mortality with 10%. This would mean that even small decreases in BP due to life style changes could have an positive impact on prevention of CVD (70).

Strengths and limitations

This study has strengths and limitations. Strengths include the association of distance to nearest major road with BP in newborns and mothers, because this distance is an indirect marker of exposure to traffic-related air and at this way, a second confirmation tool for the adverse health effects. Another strength is that there are almost no published studies about the effects on BP of prenatal exposure.

However, since mother-newborn pairs are recruited at the moment of delivery in the hospital, we could only measure the indoor concentrations of NO_2, benzene and toluene after BP measurement. Nevertheless, by making use of detailed questionnaires about residential addresses and life style habits, we assumed that there were no important differences between these periods.

Perspectives

In order to follow up the associations between indoor air pollutants and BP of mother and child, BP measurements can be repeated in the future. Also intima-media thickness of the carotid artery wall and pulse wave velocity, which are early markers of atherosclerosis, could be measured by making use of ultrasound techniques (66).

5 Conclusion

Newborn blood pressure was positively associated with indoor NO_2 levels. The mean indoor concentrations in this study however, were lower as reference concentrations set up by health organizations (12.02 µg/m^3 and 40 µg/m^3, respectively). Consequently, especially for susceptible subgroups like newborns, adverse health effects could occur even below these reference guidelines. Further studies are needed to clarify whether these guidelines should be lowered. A trend was observed with distance to nearest major road, which supports the suggested impact on blood pressure of proximity to traffic. For maternal blood pressure, no significant associations were found. Because of a small study population, this pilot study will be further extended in the future in order to elicit these associations and to follow up the possible adverse health effects that could persist in later life.

References

1. Yang L, Li L, Lewington S, Guo Y, Sherliker P, Bian Z, et al. Outdoor temperature, blood pressure, and cardiovascular disease mortality among 23 000 individuals with diagnosed cardiovascular diseases from China2015 2015-05-14 00:00:00. 1178-85 p.
2. Barker DJ. The fetal and infant origins of adult disease. Bmj. 1990;301(6761):1111.
3. Beevers G, Lip GY, O'Brien E. ABC of hypertension: The pathophysiology of hypertension. Bmj. 2001;322(7291):912-6.
4. Fukuta H, Little WC. The Cardiac Cycle and the Physiologic Basis of Left Ventricular Contraction, Ejection, Relaxation, and Filling. Heart Failure Clinics. 2008;4(1):1-11.
5. Crowley SD, Gurley SB, Oliverio MI, Pazmino AK, Griffiths R, Flannery PJ, et al. Distinct roles for the kidney and systemic tissues in blood pressure regulation by the renin-angiotensin system. The Journal of Clinical Investigation. 2005;115(4):1092-9.
6. Zennaro M-C, Rickard AJ, Boulkroun S. Genetics in endocrinology: Genetics of mineralocorticoid excess: an update for clinicians. European Journal of Endocrinology. 2013;169(1):R15-R25.
7. Whitworth JA, Mangos GJ, Kelly JJ. Cushing, cortisol, and cardiovascular disease. Hypertension. 2000;36(5):912-6.
8. Fommei E, Iervasi G. The Role of Thyroid Hormone in Blood Pressure Homeostasis: Evidence from Short-Term Hypothyroidism in Humans. The Journal of Clinical Endocrinology & Metabolism. 2002;87(5):1996-2000.
9. Victor RG. Carotid baroreflex activation therapy for resistant hypertension. Nat Rev Cardiol. 2015;advance online publication.
10. Stebor AD. Basic principles of noninvasive blood pressure measurement in infants. Adv Neonatal Care. 2005;5(5):252-61; quiz 62-4.
11. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005;45(1):142-61.
12. Boron W, Boulpaep E. Medical Physiology. Second ed. Philadelphia: Saunders Elsevier; 2009. 437-42 p.
13. Ramsey M, III. Blood pressure monitoring: Automated oscillometric devices. Journal of Clinical Monitoring. 1991;7(1):56-67.
14. Ward ML, Jeremy A. Blood pressure measurement. Continuing Education in Anaesthesia Critical Care & Pain. 2007;7(4):122-6.
15. Sesso HD, Stampfer MJ, Rosner B, Hennekens CH, Gaziano JM, Manson JE, et al. Systolic and Diastolic Blood Pressure, Pulse Pressure, and Mean Arterial Pressure as Predictors of Cardiovascular Disease Risk in Men. Hypertension. 2000;36(5):801-7.
16. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension2007 2007-06-01 00:00:00. 1462-536 p.
17. Franklin SS, Lopez VA, Wong ND, Mitchell GF, Larson MG, Vasan RS, et al. Single Versus Combined Blood Pressure Components and Risk for Cardiovascular Disease: The Framingham Heart Study. Circulation. 2009;119(2):243-50.
18. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2013.
19. Falkner B. Hypertension in children and adolescents: epidemiology and natural history. Pediatric Nephrology (Berlin, Germany). 2010;25(7):1219-24.
20. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, et al. Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease. New England Journal of Medicine. 2001;345(18):1291-7.
21. Middleton JP, Pun PH. Hypertension, chronic kidney disease, and the development of cardiovascular risk: a joint primacy. Kidney Int. 2010;77(9):753-5.
22. Dubow J, Fink M. Impact of Hypertension on Stroke. Current Atherosclerosis Reports. 2011;13(4):298-305.

23. Cheung CY-l, Ikram MK, Sabanayagam C, Wong TY. Retinal Microvasculature as a Model to Study the Manifestations of Hypertension. Hypertension. 2012;60(5):1094-103.
24. Duschek S, Schandry R. Cognitive performance and cerebral blood flow in essential hypotension. Psychophysiology. 2004;41(6):905-13.
25. Hildrum B, Mykletun A, Stordal E, Bjelland I, Dahl AA, Holmen J. Association of low blood pressure with anxiety and depression: the Nord-Trøndelag Health Study. Journal of Epidemiology and Community Health. 2007;61(1):53-8.
26. Moretti R, Torre P, Antonello RM, Manganaro D, Vilotti C, Pizzolato G. Risk factors for vascular dementia: Hypotension as a key point. Vascular Health and Risk Management. 2008;4(2):395-402.
27. Svetkey LP, Erlinger TP, Vollmer WM, Feldstein A, Cooper LS, Appel LJ, et al. Effect of lifestyle modifications on blood pressure by race, sex, hypertension status, and age. J Hum Hypertens. 2004;19(1):21-31.
28. Zinner SH, Rosner B, Oh W, Kass EH. Significance of blood pressure in infancy. Familial aggregation and predictive effect on later blood pressure. Hypertension. 1985;7(3 Pt 1):411-6.
29. Kent A, Chaudhari T. Determinants of Neonatal Blood Pressure. Current Hypertension Reports. 2013;15(5):426-32.
30. Morrison KM, Anand SS, Yusuf S, Atkinson SA, Schulze KM, Rao-Melacini P, et al. Maternal and pregnancy related predictors of cardiometabolic traits in newborns. PLoS One. 2013;8(2):e55815.
31. Kent AL, Kecskes Z, Shadbolt B, Falk MC. Normative blood pressure data in the early neonatal period. Pediatr Nephrol. 2007;22(9):1335-41.
32. Salihoglu O, Can E, Beskardes A, Koc BS, Tan I, Can G, et al. Delivery room blood pressure percentiles of healthy, singleton, liveborn neonates. Pediatr Int. 2012;54(2):182-9.
33. Fanaroff JM, Fanaroff AA. Blood pressure disorders in the neonate: Hypotension and hypertension. Seminars in Fetal and Neonatal Medicine.11(3):174-81.
34. Flynn JT. Hypertension in the neonatal period. Current Opinion in Pediatrics. 2012;24(2):197-204.
35. Seri I, Noori S. Diagnosis and treatment of neonatal hypotension outside the transitional period. Early Human Development. 2005;81(5):405-11.
36. Jarvis D, Adamkiewicz G, Heroux M, Rapp R, Kelly F. Nitrogen dioxide. In: WHO Guidelines for Indoor Air Quality: Selected Pollutants. Geneva: World Health Organization; 2010.
37. Valley SJ. Available from: http://www.valleyair.org/aqinfo/IndoorAirQuality.htm.
38. Baumgartner J, Schauer JJ, Ezzati M, Lu L, Cheng C, Patz JA, et al. Indoor Air Pollution and Blood Pressure in Adult Women Living in Rural China. Environmental Health Perspectives. 2011;119(10):1390-5.
39. Brook RD, Rajagopalan S. Particulate matter, air pollution, and blood pressure. Journal of the American Society of Hypertension. 2009;3(5):332-50.
40. Sughis M, Nawrot T, Ihsan-ul-Haque S, Amjad A, Nemery B. Blood pressure and particulate air pollution in schoolchildren of Lahore, Pakistan. BMC Public Health. 2012;12(1):1-8.
41. Pope DP, Mishra V, Thompson L, Siddiqui AR, Rehfuess EA, Weber M, et al. Risk of Low Birth Weight and Stillbirth Associated With Indoor Air Pollution From Solid Fuel Use in Developing Countries. Epidemiologic Reviews. 2010;32(1):70-81.
42. Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. Epidemiology. 2004;15(1):36-45.
43. Foraster M, Basagana X, Aguilera I, Rivera M, Agis D, Bouso L, et al. Association of long-term exposure to traffic-related air pollution with blood pressure and hypertension in an adult population–based cohort in Spain (the REGICOR study). Environ Health Perspect. 2014;122:404-11.
44. Wu J, Ren C, Delfino RJ, Chung J, Wilhelm M, Ritz B. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the south coast air basin of California. Environ Health Perspect. 2009;117(11):1773-9.
45. Maroziene L, Grazuleviciene R. Maternal exposure to low-level air pollution and pregnancy outcomes: a population-based study. Environmental Health. 2002;1:6-.
46. Bolden AL, Kwiatkowski CF, Colborn T. New Look at BTEX: Are Ambient Levels a Problem? Environmental Science & Technology. 2015;49(9):5261-76.
47. Wilbur S, Wohlers D, Paikoff S, Keith L, Faroon O. ATSDR evaluation of health effects of benzene and relevance to public health. Toxicology and Industrial Health. 2008;24(5-6):263-398.
48. Kotseva K, Popov T. Study of the cardiovascular effects of occupational exposure to organic solvents. Int Arch Occup Environ Health. 1998;71 Suppl:S87-91.
49. Wiwanitkit V. Benzene exposure and hypertension: an observation. Cardiovasc J Afr. 2007;18(4):264-5.

50. Coskun O, Oter S, Korkmaz A, Armutcu F, Kanter M. The oxidative and morphological effects of high concentration chronic toluene exposure on rat sciatic nerves. Neurochem Res. 2005;30(1):33-8.
51. Mohammadi S, Golabadi M, Labbafinejad Y, Pishgahhadian F, Attarchi M. Effects of exposure to mixed organic solvents on blood pressure in non-smoking women working in a pharmaceutical company. Arh Hig Rada Toksikol. 2012;63(2):161-9.
52. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. The Lancet. 2002;360(9341):1203-9.
53. Wilhelm M, Ritz B. Residential proximity to traffic and adverse birth outcomes in Los Angeles county, California, 1994-1996. Environmental Health Perspectives. 2003;111(2):207-16.
54. Parati G, Stergiou GS, Asmar R, Bilo G, de Leeuw P, Imai Y, et al. European Society of Hypertension guidelines for blood pressure monitoring at home: a summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. J Hypertens. 2008;26(8):1505-26.
55. Lin LY, Lin CY, Lin YC, Chuang KJ. The effects of indoor particles on blood pressure and heart rate among young adults in Taipei, Taiwan. Indoor Air. 2009;19(6):482-8.
56. Sorensen M, Hoffmann B, Hvidberg M, Ketzel M, Jensen SS, Andersen ZJ, et al. Long-term exposure to traffic-related air pollution associated with blood pressure and self-reported hypertension in a Danish cohort. Environmental health perspectives. 2012;120(3):418-24.
57. Clark C, Crombie R, Head J, van Kamp I, van Kempen E, Stansfeld SA. Does traffic-related air pollution explain associations of aircraft and road traffic noise exposure on children's health and cognition? A secondary analysis of the United Kingdom sample from the RANCH project. Am J Epidemiol. 2012;176(4):327-37.
58. Liu C, Fuertes E, Tiesler CM, Birk M, Babisch W, Bauer CP, et al. The associations between traffic-related air pollution and noise with blood pressure in children: results from the GINIplus and LISAplus studies. Int J Hyg Environ Health. 2014;217(4-5):499-505.
59. Bilenko N, Rossem Lv, Brunekreef B, Beelen R, Eeftens M, Hoek G, et al. Traffic-related air pollution and noise and children’s blood pressure: Results from the PIAMA birth cohort study. European Journal of Preventive Cardiology. 2015;22(1):4-12.
60. van Rossem L, Rifas-Shiman SL, Melly SJ, Kloog I, Luttmann-Gibson H, Zanobetti A, et al. Prenatal air pollution exposure and newborn blood pressure. Environ Health Perspect. 2015;123(4):353-9.
61. Sorensen M, Loft S, Andersen HV, Raaschou-Nielsen O, Skovgaard LT, Knudsen LE, et al. Personal exposure to PM2.5, black smoke and NO2 in Copenhagen: relationship to bedroom and outdoor concentrations covering seasonal variation. J Expo Anal Environ Epidemiol. 2005;15(5):413-22.
62. Xu X, Freeman NC, Dailey AB, Ilacqua VA, Kearney GD, Talbott EO. Association between exposure to alkylbenzenes and cardiovascular disease among National Health and Nutrition Examination Survey (NHANES) participants. Int J Occup Environ Health. 2009;15(4):385-91.
63. Morck HI, Winkel P, Gyntelberg F. Health effects of toluene exposure. Dan Med Bull. 1988;35(2):196-200.
64. Neubert D, Bochert G, Gericke C, Hanke B, Beckmann G. Multicenter field trial on possible health effects of toluene. I. Toluene body burdens in workers of the rotogravure industry. Toxicology. 2001;168(2):139-57.
65. Hoffmann B, Moebus S, Möhlenkamp S, Stang A, Lehmann N, Dragano N, et al. Residential Exposure to Traffic Is Associated With Coronary Atherosclerosis. Circulation. 2007;116(5):489-96.
66. Iannuzzi A, Verga MC, Renis M, Schiavo A, Salvatore V, Santoriello C, et al. Air pollution and carotid arterial stiffness in children. Cardiol Young. 2010;20(2):186-90.
67. Kirwa K, Eliot MN, Wang Y, Adams MA, Morgan CG, Kerr J, et al. Residential Proximity to Major Roadways and Prevalent Hypertension Among Postmenopausal Women: Results From the Women's Health Initiative San Diego Cohort. Journal of the American Heart Association. 2014;3(5).
68. Dennis A, Stenson A. The use of transthoracic echocardiography in postpartum hypotension. Anesth Analg. 2012;115(5):1033-7.
69. Brook RD, Bard RL, Burnett RT, Shin HH, Vette A, Croghan C, et al. Differences in blood pressure and vascular responses associated with ambient fine particulate matter exposures measured at the personal versus community level. Occupational and Environmental Medicine. 2010.
70. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.

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