ERJ Express. Published on November 14, 2008 as doi: 10.1183/09031936.00084008

Air pollution during pregnancy and lung function in newborns: a birth cohort study

Philipp Latzin[1,2], Martin Röösli[2], Anke Huss[2], Claudia E Kuehni[2], Urs Frey[1]

[1] Division of Respiratory Medicine, Department of Paediatrics, Inselspital and University of Bern, Switzerland

[2] Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland

Corresponding Author: Philipp Latzin, MD, Division of Pediatric Respiratory Medicine, University Children's Hospital of Bern, Inselspital, 3010 Bern, Switzerland, Tel. +41-31-632-95-81, Fax. +41-31-632-48-07, Email: philipp.latzin@insel.ch

Short title: Air pollution and newborns' lung function

Manuscript word count: 2823 / 3000

Abstract

Postnatal exposure to air pollution is associated with diminished lung growth during school age. We aimed to determine whether prenatal exposure to air pollution is associated with lung function changes in the newborn.

In a prospective birth cohort of 241 healthy term-born neonates we measured tidal breathing, lung volume, ventilation inhomogeneity and exhaled nitric oxide (eNO) during unsedated sleep at age 5 weeks. We estimated maternal exposure to particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}), nitrogen dioxide (NO_2), ozone (O_3), and distance to major roads during pregnancy. The association between these exposures and lung function was assessed using linear regression.

Minute ventilation was higher in infants with higher prenatal PM_{10} exposure (24.9 mL/min per μg/m^3 PM_{10}; p=0.002). Exhaled NO was increased in infants with higher prenatal NO_2 exposure (0.98 ppb per μg/m^3 NO_2; p<0.001). Postnatal exposure to air pollution did not modify these findings. No association was found for prenatal exposure to ozone and lung function parameters.

Our results suggest that prenatal exposure to air pollution might be associated with higher respiratory need and airway inflammation in newborns. Such alterations during early lung development may be important regarding long-term respiratory morbidity.

Abstract word count: 196 / 200

Keywords: air pollution, exhaled nitric oxide, infant, lung growth, lung function

Introduction

There is growing evidence that air pollution has adverse effects on lung function and development (1). Both cross-sectional as well as longitudinal studies have clearly shown diminished lung function in children exposed to higher levels of air pollution (1-4). A causative association has been suggested in the observation of decreased age-related lung function decline in adults after reduced exposure to air pollution (5). Moreover, short- and long-term exposure to pollutants has been associated with airway inflammation (6;7).

Growth and development of the respiratory system take place mainly during the prenatal and early postnatal period (8;9) and adverse effects of prenatal exposures, such as tobacco smoking of the mother, on lung development are well documented (10). Although air pollution might possibly lead to comparable developmental changes, no epidemiological studies have examined potential associations between prenatal air pollution and lung functional development and inflammation or oxidative stress in the newborn (8;11). This early developmental phase is thought to be very important in determining long-term lung growth (9). So-called “tracking” of lung function was found in retrospective (12) and prospective cohort studies (13). Therefore, early changes in lung function may have a considerable impact upon long-term respiratory morbidity and even mortality.

The aim of our study was thus to assess in a prospective birth cohort, whether increased maternal exposure to air pollution during pregnancy is associated with changes in tidal breathing, lung volume or airway inflammation, measured during natural sleep in five weeks old infants.

Methods

Study design

This prospective birth cohort study comprised a group of unselected, healthy neonates recruited antenatally since 1999 in the region of Berne, Switzerland (14). Exclusion criteria for the study were preterm delivery (< 37 weeks), significant perinatal disease including respiratory distress and later diagnosis of chronic respiratory disease. Potential risk factors (sociodemographic status, smoke exposure and parental atopic disease) were assessed by interviews using standardized questionnaires. The Ethics Committee of the Region of Berne approved the study and written consent was obtained at enrolment.

Lung function

Lung function measurements were performed in unsedated neonates during quiet natural sleep in the supine position with the head midline, via an infant mask (Size 1; Homedica AG), according to the ERS/ATS standards of infant lung function testing (15). Flow was measured using an ultrasonic flowmeter (Spiroson®, EcoMedics AG, Duernten, Switzerland).

Tidal breathing

For analysis, we used the first 100 regular breaths of tidal breathing during non-REM sleep from the total 10-min recording, and excluded sighs and ten breaths before and after a sigh. From these, mean tidal breathing parameters of flow, volume and flow-volume loop were calculated as per the ERS/ATS standards for infant lung function testing (15). Main outcome parameters were minute ventilation (tidal volume multiplied with respiratory rate) and mean tidal inspiratory and expiratory flow (15).

Multiple-breath washout

Lung volume and ventilation inhomogeneity were determined using multiple-breath washout (MBW) technique by ultrasonic flowmeter as previously described (16). Main outcomes were functional residual capacity (FRC) at airway opening, FRC per body weight, and lung clearance index (LCI).

Nitric oxide

Exhaled nitric oxide (eNO) was measured online with a rapid-response chemiluminescence analyser (CLD 77 AM; EcoMedics AG) in the range of 0–100 ppb. Contamination of exhaled NO by ambient NO was avoided by using NO-free air for inspiration. We measured eNO breath-by-breath and calculated mean eNO over 100 breaths (14). As eNO is flow dependent, we adjusted eNO for minute ventilation in the multivariable analysis and present results for both eNO concentration and NO output (eNO concentration multiplied with corresponding expiratory flow) (14).

Exposure assessment

Air pollution data included daily mean levels of particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}) and nitrogen dioxide (NO_2) as well as the daily maximum of mean hourly levels of ozone (O_3) for the period from January 1999 to July 2007. Air pollution was measured at the monitoring station of Payerne (part of the Swiss National Air Pollution Monitoring Network NABEL), which lies within the study area and reflects temporal variability of air pollutants during the study period.

We used these regional data to calculate the mean exposure to each pollutant for each subject during pregnancy: between date of conception and birth date as well as separately for each trimester. In addition, we calculated postnatal exposure to air pollution between birth and date of

lung function test. As a proxy for traffic-related air pollution exposure, we computed distance from the mothers' home coordinates to the closest major road of at least 6 m (1st class road) and at least 4 m (2nd class road) in width, respectively. This was done analogous to another Swiss cohort study (for street categories of the VECTOR25 see Appendix Table of (17)). Calculations were performed with a geographic information system (GIS, ArcGIS, version 9, Environmental Systems Research Institute, Redlands, USA). Addresses were geo-coded using the building registry of the Swiss Federal Statistical Office, and street information was obtained from the VECTOR25 map of the Swiss Federal Office of Topography (www.swisstopo.ch).

Statistical analysis

The association between mean exposure levels of each pollutant during pregnancy and during the postnatal period as well as distance to 4 and 6 m roads and pulmonary function data was assessed by linear regression analysis. We first performed univariable regression analysis for each exposure variable and second used a multivariable model, in which we adjusted also for gender, postnatal age, season of birth, outdoor temperature on the measurement day and maternal smoking during pregnancy. Season of birth was parameterised using a cosine function which assumed a value of 0 at first of July and 1 at first of January. We performed sensitivity analyses that included length and weight at study date, year and month of birth, infectious season, exposure to air pollution during the last two days before lung function, paternal educational status and maternal asthmatic disease. Data analyses were performed using STATA version 10 for Windows (STATA Corporation, College Station, USA).

Results

Between 1999 and 2007, the study enrolled 241 infants, with data from 221 (87%) used for tidal breathing analysis, 205 (81%) for eNO analysis and 181 (72%) for MBW analysis. Reasons for exclusion were insufficient duration of quiet sleep during lung function testing (n=16), lower respiratory tract infection before the measurement (n=3), technical problems (n=1 for tidal breathing, n=17 for eNO) and strict quality control criteria of MBW (n=41). Anthropometric and lung function data as well as air pollution exposure and distribution of possible risk factors are given in Table 1. Daily mean values of PM_{10} and smoothed temporal trends are shown in Figure 1.

The association between prenatal exposure to air pollution and lung function at 5 weeks of age is given in Table 2 for both the univariable and the adjusted model. Mean PM_{10} exposure during pregnancy was associated with changes in tidal breathing parameters. Each increase of 1 $\mu g/m^3$ PM_{10} was associated with an increase in minute ventilation of 24.9 (95%-CI, 9.3 to 40.5) mL/min (p=0.002). Similar associations were found between PM_{10} and respiratory rate (Figure 2) and tidal breathing flows, especially the inspiratory flow (Table 2). No association was found between air pollution and lung volume or ventilation inhomogeneity assessed by MBW (Table 2). Exhaled NO was associated with mean NO_2 exposure (Figure 3); increasing by 0.98 (95%-CI, 0.45 to 1.51) ppb per $\mu g/m^3$ higher mean prenatal NO_2 exposure ($p<0.001$; table 2).

The association between postnatal exposure to air pollution and lung function is given in Table 3. There was no consistent association in both the univariable and adjusted model for any of the examined pollutants. Both the associations between PM_{10} and minute ventilation as well as

between NO_2 and eNO were strongest for exposure during the 3rd trimester of the pregnancy (Figure 4).

No association was found for distance to 4 or 6 m roads and lung function parameters (Table 4). However, a trend was found towards a stronger association of prenatal PM_{10} exposure with minute ventilation for newborns of mothers living close to major roads. For example, in infants of mothers who lived within 150 m of a 6 m road minute ventilation was 39.2 (17.2 – 61.1) mL/min higher per $\mu g/m^3$ higher prenatal PM_{10} exposure compared to 12.6 (-10.0 – 35.3) mL/min higher minute ventilation in infants of mothers who lived further than 150 m away (p for interaction 0.06). A comparably weak trend towards a stronger association was found in infants of smoking mothers.

The observed associations remained stable in the sensitivity analyses as shown in Table 5, including assessing the relationships without adjustment for outdoor temperature or season and with adjustment for paternal education, month or year of birth and exposure to air pollution on the two days before the lung function measurement.

Discussion

Summary

To our knowledge, this is the first study examining air pollution during pregnancy and subsequent lung growth and development in early life. In our study, exposure to PM_{10} during pregnancy was associated with higher respiratory need in newborns as reflected by higher minute ventilation and tidal flows. Higher levels of NO_2 during pregnancy were found to be related to elevated eNO, indicative of the induction of inflammatory processes.

Methodological aspects

In light of the cost- and time-consuming nature of infant lung function testing, which has to date hampered such research in healthy infants, our study has several methodological strengths. We measured lung function in a standardised way based on ERS/ATS standards and used latest recommendations for analysis (15;16). We used the same equipment, the same masks and the same measurement order throughout the whole study period to ensure comparability. We analysed 100 tidal breaths, giving more robust estimates than 30 breaths as recommended by the standards (15). Since all infants were healthy, breast-fed, of a narrow age range and measured during natural sleep, the contributions of these other possible influencing factors are comparable within the cohort. Causes of lung function changes in older children, such as physical activity, obesity or hypoxia were negligible in our study (18). Selection bias is not an issue, as participants were recruited prenatally without knowledge of exposure to air pollution or lung function after birth. Furthermore both exposure and outcome variables are objective measures and were independently assessed and analysed. We were able to adjust for known biological and time-variant confounders, such as smoking during pregnancy, season or outdoor temperature. Further possible confounding factors, such as socio-economic status, number of siblings, postnatal

exposure to air pollution and seasonal fluctuations (e.g. month and year of birth, infectious season) were considered in sensitivity analyses and did not affect our results.

A limitation of our study was that we did not sample individual exposure to air pollution, which while possible after recruitment is expensive and difficult to do. This is a limit of most studies assessing long-term exposure to air pollution. Therefore, in addition to using mean air pollutant levels during pregnancy as a proxy for temporal variability, we also used distance of homes to major roads as a proxy for spatial variability in exposure to traffic-related air pollutants (17). One limitation of our study in this regard is the fact that we only used road proximity without having information about traffic density.

In contrast to studies in cooperative subjects, measurements of forced expiratory volumes and flows need sedation in infants and are thus not well accepted by parents of healthy subjects.

Although clear associations robust towards a range of sensitivity analyses may indicate a true association, we cannot prove causality. Furthermore, multiple comparisons were performed due to the nature of the study design with different exposures and several outcome parameters. We cannot totally exclude that positive associations may have occurred due to chance and thus recommend replication of our results, preferably in a different cohort with varying pollution levels.

Comparison with other studies

Studies in cooperative school children showed a reduction of lung growth upon exposure to particulate matter (1;3). We found no association between PM_{10} and lung volume in unsedated sleep, possibly because FRC in infants is dynamically regulated to maintain end-expiratory lung

volume above airway closure (19). Thus, the increased minute ventilation in infants with higher prenatal PM_{10} exposure may be a compensatory mechanism for lower lung volumes. In line with these observations, no study has so far demonstrated an effect of prenatal smoke exposure on lung volume in infants (10).

We found a clear association between NO_2 exposure during pregnancy and postnatal eNO levels. Such a causal association seems plausible as NO_2 is known to induce inflammatory processes (20). Nevertheless we cannot exclude that NO_2 acts as a proxy for a complex mixture of combustion pollutants that originates primarily from vehicular traffic (21). The role of up-regulated inducible nitric oxide synthase (iNOS) in this process is unknown, but may provide a link between environmental air pollution and the evolution of asthma.

No association between ozone and lung function was found. Results from other studies are contradictory, with an association between ozone and lung volume and inflammation shown by some groups (1;6), but not by others, e.g. one study from Switzerland with summer daytime ozone exposure levels comparable to ours (22).

Several studies showed that living closer to major roads has adverse effects on lung function and respiratory symptoms (2;17). However, there is still an ongoing debate about a possible threshold regarding traffic-related pollution as well as the boundary between traffic-related exposure and background pollution levels (23). In our study, in contrast to temporal variation (mean pollutant levels), spatial variation during pregnancy alone (distance to roads) was not associated with lung function changes. In this regard, important factors special to our study have to be mentioned. First, we calculated exposure during a time period of 9 months (pregnancy) for each subject

individually, whereas most other studies dealt with mean annual exposure levels. Second, women maintain a mobile lifestyle during pregnancy. As such, exposure at home – usually during times with lower pollution levels – does not necessarily contribute to overall exposure as much as e.g. in the less mobile elderly population. Third, the particular environmental situation in urban Switzerland with high population and road network density leads to homogenous distribution of $PM_{2.5}$ and PM_{10} (24). Taken together, these points may explain why for exposure assessment over a limited time period (such as pregnancy) in mobile subjects living in areas with homogenously distributed PM_{10} levels, temporal variation of regional pollution levels may be more important than small-scale spatial variations of air pollutants. Still, the relative contribution of background exposure and road proximity to health effects remains controversial (23).

Mechanisms

The changes in lung function seen in our infants with increased prenatal exposure to particulate matter are similar to those observed in premature infants with bronchopulmonary dysplasia (25), in infants of smoking mothers (26) and in animal models of prenatal nicotine exposure (27). Thus, our findings indicate considerable impact of air pollution on lung development already present at an early developmental stage, and are suggestive of either increased respiratory need due to increased resistance (smaller airways), decreased compliance (smaller or stiffer airways) and/or factors influencing control of breathing (e.g. hypoxia).

The exact mechanisms for these changes are unknown. Some hypotheses have been proposed in the literature (28). Oxidative stress and inflammation of the airways in the mother after exposure to air pollution may affect the blood-air barrier (29), potentially leading to reduced fetal breathing movements and decreased alveolarization (30). The effect could be also mediated via systemic inflammation in the mother upon air pollution leading to decreased placental blood flow with

reduced transfer of nutrients to the fetus (30). Although entirely unknown, the increasing role thought to be played by nanoparticles could also be involved in either process (31). Furthermore, evidence for decreased birth weight upon higher exposure to air pollution suggests that growth factors may be involved (32), possibly also applicable to lung growth. In our cohort, all associations were unaltered by birth weight, suggesting that the effect is even independent of birth weight.

Relevance

Due to the need for an outcome parameter assessable early after birth, we measured well-defined physiological surrogates for lung growth and development in this age group. Early changes in lung function track into later life (13) and are believed to have a huge impact upon long-term respiratory morbidity, e.g. asthma occurrence (33).

The higher respiratory need as reflected by increased minute ventilation upon higher prenatal exposure to particulate matter might be clinically important, especially for premorbid infants with an already reduced breathing capacity or infants that are acutely sick.

From a public health point of view, our results are particularly crucial in areas with higher outdoor pollution, or considerable indoor pollution from biomass fuels where it is practically impossible for an individual to avoid exposure. Especially in these areas, altered lung function may be one mechanism responsible for the association between PM_{10} and infant mortality, particularly since a stronger association for respiratory rather than non-respiratory mortality has been observed after PM_{10} exposure (34). It thus seems worthwhile to investigate a possible effect of activities during pregnancy associated with exposure to pollution (e.g. cooking at open fireplace) on infant morbidity, because exposure to indoor pollution could be substantially reduced by using cleaner fuels and improved stove constructions for cooking (35).

Conclusion

This is the first prospective birth cohort study suggesting a relationship between prenatal PM_{10} and NO_2 exposure with lung function and inflammation after birth. Our findings involving airway mechanics provide additional evidence to epidemiological studies since they suggest potential mechanisms behind adverse outcomes of pollution. Influences during the vulnerable phase of pregnancy are known to affect lung development and growth (9;13) and the evolution of asthma and allergy. If the hypothesis of Barker is correct, these early influences on the respiratory system result in a higher burden of respiratory disease in older people and shortened life expectancy (12). Our results thus provide further rationale for more stringent measures to reduce air pollution.

Acknowledgements

The authors thank the study nurses Christine Becher, Monika Graf and Barbara Hofer for help with the lung function measurements. They also thank Laure Sauteur for her help in the analysis of the measurements and Cindy Thamrin and Matthias Egger for critical appraisal of the manuscript. Furthermore they thank the Amt für Geoinformation Bern for providing the geo-data VECTOR25 and Rudolf Weber from the Federal Office for the Environment for providing air pollution data of the monitoring station in Payerne.

This study was supported by Swiss National Foundation grant 3200-B0-112099 to U.F. and P.L., Swiss Federal Office of Public Health Tobacco Prevention Fund 07.005776 to U.F. and Swiss National Foundation PROSPER grant 3200-069349 to C.K.

Reference List

(1) Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K et al. The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 2004; 351(11):1057-1067.

(2) Gauderman WJ, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D et al. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. Lancet 2007; 369(9561):571-577.

(3) Horak F, Studnicka M, Gartner C, Spengler JD, Tauber E, Urbanek R et al. Particulate matter and lung function growth in children: a 3-yr follow-up study in Austrian schoolchildren. Eur Respir J 2002; 19(5):838-845.

(4) Moshammer H, Hutter HP, Hauck H, Neuberger M. Low levels of air pollution induce changes of lung function in a panel of schoolchildren. Eur Respir J 2006; 27(6):1138-1143.

(5) Downs SH, Schindler C, Liu L-JS, Keidel D, Bayer-Oglesby L, Brutsche MH et al. Reduced Exposure to PM10 and Attenuated Age-Related Decline in Lung Function. N Engl J Med 2007; 357(23):2338-2347.

(6) Nickmilder M, Carbonnelle S, de Burbure C, Bernard A. Relationship between ambient ozone and exhaled nitric oxide in children. JAMA 2003; 290(19):2546-2547.

(7) Delfino RJ, Staimer N, Gillen D, Tjoa T, Sioutas C, Fung K et al. Personal and ambient air pollution is associated with increased exhaled nitric oxide in children with asthma. Environ Health Perspect 2006; 114(11):1736-1743.

(8) Dockery D, Skerrett P, Walters D, Gilliland F. Development of lung function. In: Effects of air pollution on children's health and development; A review of the evidence. WHO, 2005: 108-133 (http://www.euro.who.int/air/activities/20060421_1).

(9) Stick S. Paediatric origins of adult lung disease bullet 1: The contribution of airway development to paediatric and adult lung disease. Thorax 2000; 55(7):587-594.

(10) Stocks J, Dezateux C. The effect of parental smoking on lung function and development during infancy. Respirology 2003; 8(3):266-285.

(11) Pinkerton KE, Joad JP. Influence of air pollution on respiratory health during perinatal development. Clin Exp Pharmacol Physiol 2006; 33(3):269-272.

(12) Barker DJP, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of Birth-Weight and Childhood Respiratory-Infection to Adult Lung-Function and Death from Chronic Obstructive Airways Disease. BMJ 1991; 303(6804):671-675.

(13) Stern D, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. Lancet 2007; 370(9589):758-764.

(14) Latzin P, Kuehni CE, Baldwin DN, Roiha HL, Casaulta C, Frey U. Elevated exhaled nitric oxide in newborns of atopic mothers precedes respiratory symptoms. Am J Respir Crit Care Med 2006; 174(12):1292-1298.

(15) Bates JHT, Schmalisch G, Filbrun D, Stocks J. Tidal breath analysis for infant pulmonary function testing. Eur Respir J 2000; 16(6):1180-1192.

(16) Latzin P, Sauter L, Thamrin C, Schibler A, Baldwin DN, Hutten GJ et al. Optimized temperature and deadspace correction improve analysis of multiple breath washout measurements by ultrasonic flowmeter in infants. Pediatr Pulmonol 2007; 42(10):888-897.

(17) Bayer-Oglesby L, Schindler C, Hazenkamp-von Arx ME, Braun-Fahrlander C, Keidel D, Rapp R et al. Living near Main Streets and Respiratory Symptoms in Adults: The Swiss Cohort Study on Air Pollution and Lung Diseases in Adults. Am J Epidemiol 2006; 164(12):1190-1198.

(18) Lockwood AH, Merkus PJFM, Tetrault GA, Gauderman WJ, Avol E, Gilliland F. Air Pollution and Lung Function. Correspondence. N Engl J Med 2004; 351(25):2652-2653.

(19) Kerem E. Why do infants and small children breathe faster? Pediatr Pulmonol 1996; 21(1):65-68.

(20) Persinger RL, Poynter ME, Ckless K, Janssen-Heininger YMW. Molecular mechanisms of nitrogen dioxide induced epithelial injury in the lung. Mol Cell Biochem 2002; 234(1):71-80.

(21) Brunekreef B. Health effects of air pollution observed in cohort studies in Europe. J Expo Sci Environ Epidemiol 2007; 17 Suppl 2:S61-S65.

(22) Ackermann-Liebrich U, Leuenberger P, Schwartz J, Schindler C, Monn C, Bolognini C et al. Lung function and long term exposure to air pollutants in Switzerland. Am J Respir Crit Care Med 1997; 155(1):122-129.

(23) Holguin F. Traffic related exposures and lung function in adults. Thorax 2007; 62(10):837-838.

(24) Roosli M, Braun-Fahrlander C, Kunzli N, Oglesby L, Theis G, Camenzind M et al. Spatial variability of different fractions of particulate matter within an urban environment and between urban and rural sites. J Air Waste Manag Assoc 2000; 50(7):1115-1124.

(25) Schmalisch G, Wilitzki S, Wauer RR. Differences in tidal breathing between infants with chronic lung diseases and healthy controls. BMC Pediatrics 2005; 5(1):36.

(26) Sovik S, Lossius K, Eriksen M, Grogaard J, Walloe L. Development of oxygen sensitivity in infants of smoking and non-smoking mothers. Early Hum Dev 1999; 56(2-3):217-232.

(27) Hafstrom O, Milerad J, Sundell HW. Altered breathing pattern after prenatal nicotine exposure in the young lamb. Am J Respir Crit Care Med 2002; 166(1):92-97.

(28) Holgate S. Mechanisms by which air pollution injures the child's respiratory system. In: Effects of air pollution on children's health and development; A review of the evidence. WHO, 2005: 29-43 (http://www.euro.who.int/air/activities/20060421_1).

(29) Nel A. Atmosphere. Air pollution-related illness: effects of particles. Science 2005; 308(5723):804-806.

(30) Kajekar R. Environmental factors and developmental outcomes in the lung. Pharmacol Ther 2007; 114(2):129-145.

(31) Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. Science 2006; 311(5761):622-627.

(32) Slama R, Morgenstern V, Cyrys J, Zutavern A, Herbarth O, Wichmann H et al. Traffic-Related Atmospheric Pollutants Levels during Pregnancy and Offspring's Term Birth Weight: A Study Relying on a Land-Use Regression Exposure Model. Environ Health Perspect 2007; 115(9):1283-1292.

(33) von Mutius E. Paediatric origins of adult lung disease. Thorax 2001; 56(2):153-157.

(34) Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. Does particulate air pollution contribute to infant death? A systematic review. Environ Health Perspect 2004; 112(14):1365-1370.

(35) Boy E, Bruce N, Delgado H. Birth weight and exposure to kitchen wood smoke during pregnancy in rural Guatemala. Environ Health Perspect 2002; 110(1):109-114.

Legends to the Figures

Figure 1)

Daily mean levels of PM_{10} concentration (single dots) at the fixed monitoring station in Payerne. The trend line was computed by a *LOWESS* smoother using locally-weighted polynomial regression with a smoother span of 0.05. Note the logarithmic scale of the y-axis.

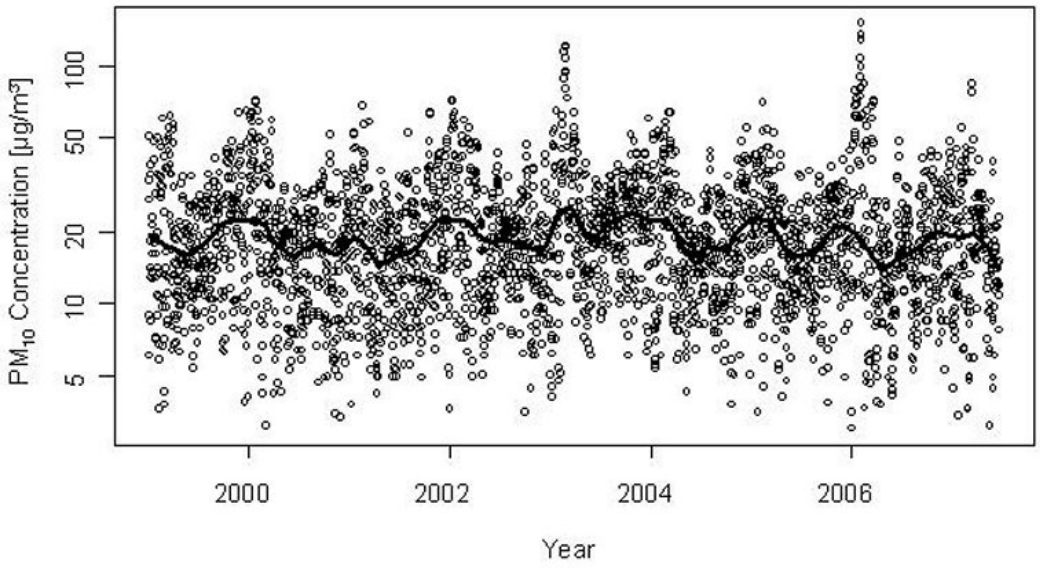


Figure 2)

Individual respiratory rate at 5 weeks of age plotted against mean concentration of PM_{10} levels during pregnancy. An increase from the lowest to the highest quartile of prenatal PM_{10} exposure was associated with a change in respiratory rate from 42/minute to 48/minute.

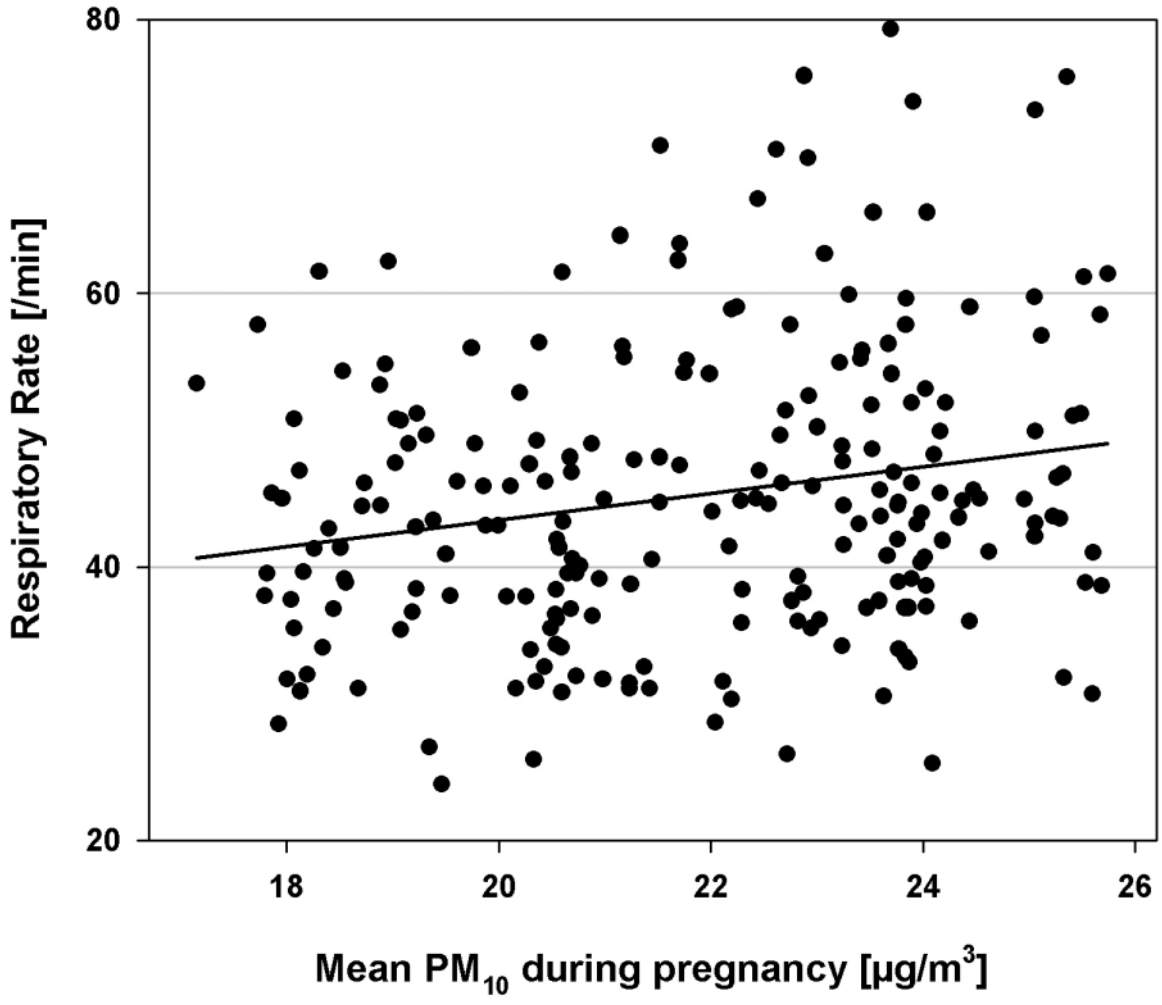


Figure 3)

Individual concentration of exhaled NO at 5 weeks of age plotted against mean concentration of NO_2 levels during pregnancy. An increase from the lowest to the highest quartile of prenatal NO_2 exposure was associated with a change in exhaled NO levels from 12.1 to 15.2 ppb.

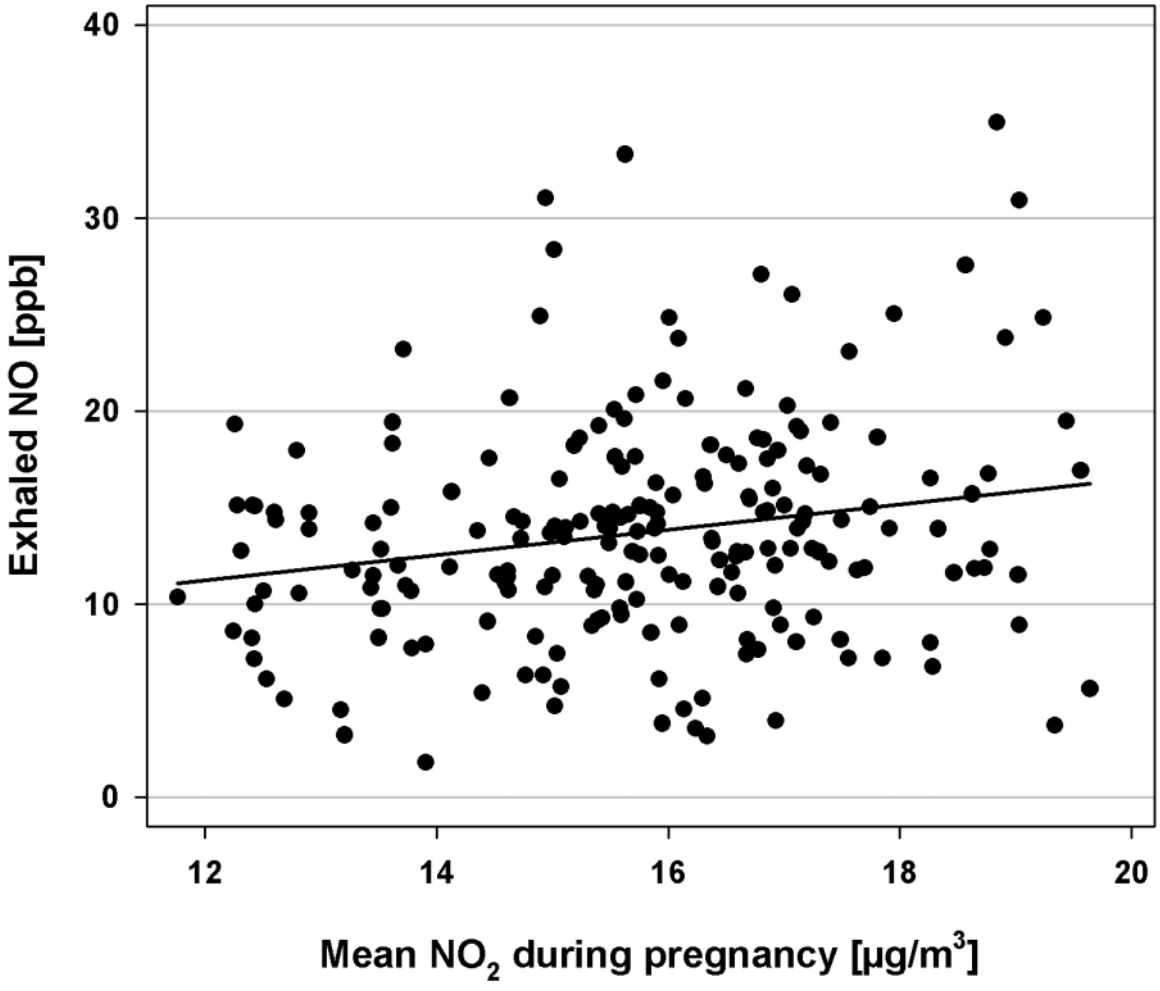
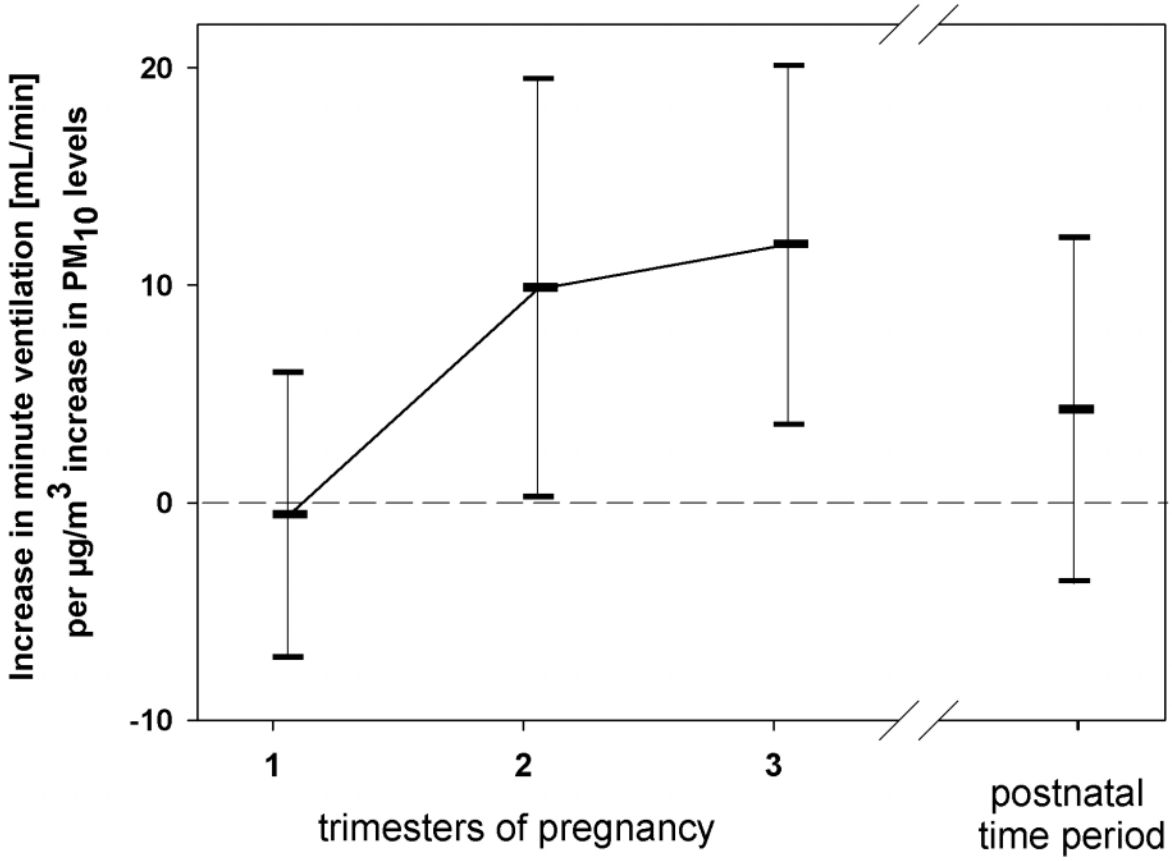


Figure 4)

Association between lung function and pollution levels during the 3 trimesters of pregnancy and the time between birth and lung function, respectively. The increase in minute ventilation (with 95%-CI) in mL/min per PM_{10} concentration of the respective trimester of pregnancy or the postnatal time period, respectively is indicated. Respective values (95%-CI) for the association between increase in eNO per $\mu g/m^3$ increase in nitrogen dioxide concentration are 0.09 (-0.08 to

0.25) ppb for the first trimester, 0.18 (-0.09 to 0.45) ppb for the second trimester, 0.20 (-0.01 to 0.41) ppb for the third trimester and 0.06 (-0.23 to 0.34) ppb for the postnatal time period.



Tables

Table 1) Demographics, lung function data, exposure to air pollution and possible risk factors of the study infants.

	Median	Interquartile Range (IQR)	Range
Anthropometric data (n=222)			
Age at study date, days	34	32 – 37	25 – 55
Weight at study date, kg	4.3	4.0 – 4.8	2.9 – 6.3
Length at study date, cm	55.0	53.3 – 56.8	48.0 – 61.5
Gestational age at birth, wks	40.0	39.0 – 40.9	37.0 – 42.3
Birth weight, kg	3.4	3.1 – 3.7	2.2 – 4.9
Lung function data at 5 weeks of age			
Tidal breathing parameter (n=221)[1]			
Minute ventilation, mL/min	1401	1239 – 1566	733 – 2334
Respiratory rate, per min	44.4	37.8 – 51.2	24.1 – 79.3
Tidal volume, mL	32.3	28.1 – 36.6	21.0 – 51.1
Tidal expiratory flow, mL/sec	41.5	35.6 – 49.1	20.0 – 79.6
Tidal inspiratory flow, mL/sec	53.9	47.9 – 59.0	30.0 – 82.0
Multiple-breath washout (n=181)[3]			
FRC, mL	97.2	85.1 – 108.0	56.3 – 145.4
FRC per weight, mL/kg	22.2	19.7 – 25.2	12.3 – 35.8
LCI	6.9	6.4 – 7.4	5.5 – 10.1
Inflammatory markers (n=205)[1]			

eNO, ppb[4]	13.4	10.2 – 16.6	1.8 – 34.9
NO output, nL/s[4]	0.582	0.458 – 0.721	0.068 – 1.422
Outdoor temperature, °C	10	3 – 15	-6 – 27
Distance to measurement station, km[6]	42.1	39.6 – 47.4	15.9 – 136.4
Distance to 4 m road, m[6]	79	38 – 155	3 – 747
Distance to 6 m road, m[6]	190	83 – 401	3 – 3794
Mean daily prenatal exposure to air pollution			
PM_{10}, µg/m^3	22.1	20.2 – 23.8	17.1 – 25.7
Nitrogen dioxide, µg/m^3	15.8	14.7 – 17.0	11.8 – 19.6
Ozone, µg/m^3[3, 5]	86.7	79.6 – 94.9	74.1 – 111.7
Mean daily postnatal exposure to air pollution			
PM_{10}, µg/m^3	20.0	16.6 – 23.4	10.6 – 49.6
Nitrogen dioxide, µg/m^3	15.1	10.9 – 19.7	7.0 – 31.2
Ozone, µg/m^3[3, 5]	87.5	56.3 – 109.9	25.0 – 156.2
Potential risk factors			Number (%)
Male sex, no. (%)			122 (55)
One older sibling, no. (%)			71 (32)
Two or more older siblings, no. (%)			44 (20)
Maternal asthma, no. (%)[7]			22 (10)
Maternal atopy, no. (%)[8]			85 (38)
Maternal smoking in pregnancy, no. (%)			26 (12)
Low maternal education, no. (%)[9]			74 (34)

High maternal education, no. (%)[9]	68 (31)
Low paternal education, no. (%)[9]	42 (20)
High paternal education, no. (%)[9]	113 (53)
Living closer than 150 m to a 4 m road, no. (%)	162 (72)
Living closer than 150 m to a 6 m road, no. (%)	98 (44)
Living closer than 75 m to a 4 m road, no. (%)	108 (48)
Living closer than 75 m to a 6 m road, no. (%)	50 (22)

[1] calculated as the mean value of 100 breaths without sighs.

[2] defined as the ratio of time to peak tidal expiratory flow (T_{PTEF}) over expiratory time (T_E) .

[3] calculated as the mean value of all technically acceptable washout measurement traces.

[4] measured in the third quartile of the expiratory cycle. NO output is calculated as eNO*expiratory flow.

[5] based on maximum hourly value of each day.

[6] for one subject, this could not be determined, as no GIS data were available.

[7] defined as self-reported, doctor-diagnosed asthma.

[8] defined as self-reported, doctor-diagnosed asthma, hay fever or eczema.

[9] parental education was categorized into low (less than four year of apprenticeship), middle (at least four years of apprenticeship) and high (tertiary education).

Table 2) Associations between prenatal pollutant levels and lung function at age 5 weeks. Data is given as unit change in lung function value per μg/m^3 increase in the mean prenatal exposure of the respective pollutant.

	Univariable model			Adjusted model[1]		
	coefficient	CI 95%	p-value	coefficient	CI 95%	p-value
Tidal breathing						
Minute ventilation, mL/min[2]						
PM_{10}	19.8	4.9 – 34.7	0.010	24.9	9.3 – 40.5	0.002
NO_2	0.6	-18.3 – 19.5	0.948	12.5	-12.4 – 37.5	0.324
O_3	0.7	-2.8 – 4.2	0.696	-0.2	-5.0 – 4.6	0.929
Mean tidal expiratory flow, mL/sec						
PM_{10}	0.59	0.02 – 1.16	0.043	0.81	0.22 – 1.40	0.007
NO_2	-0.13	-0.84 – 0.59	0.730	0.61	-0.33 – 1.54	0.202
O_3	0.05	-0.08 – 0.19	0.448	-0.04	-0.22 – 0.14	0.666
Mean tidal inspiratory flow, mL/sec						
PM_{10}	0.71	0.18 – 1.23	0.009	0.81	0.26 – 1.36	0.004
NO_2	0.17	-0.49 – 0.84	0.610	0.07	-0.81 – 0.95	0.871
O_3	-0.007	-0.13 – 0.12	0.909	0.05	-0.12 – 0.22	0.560
Respiratory rate, per minute						
PM_{10}	0.97	0.36 – 1.58	0.002	1.15	0.52 – 1.77	<0.001
NO_2	0.32	-0.46 – 1.10	0.419	1.50	0.52 – 2.49	0.003
O_3	0.08	-0.07 – 0.22	0.297	-0.005	-0.20 – 0.19	0.961
Tidal volume, mL[2]						

PM_{10}	-0.23	-0.56 – 0.09	0.158	-0.23	-0.56 – 0.10	0.177
NO_2	-0.28	-0.69 – 0.12	0.173	-0.78	-1.30 – -0.27	0.003
O_3	-0.02	-0.09 – 0.06	0.629	0.01	-0.09 – 0.11	0.830
Multiple-breath washout						
FRC_{ao}, mL/kg						
PM_{10}	0.09	-0.19 – 0.37	0.525	0.09	-0.22 – 0.39	0.573
NO_2	0.06	-0.26 – 0.39	0.713	0.09	-0.38 – 0.56	0.706
O_3	0.01	-0.04 – 0.07	0.635	0.03	-0.06 – 0.11	0.537
LCI^4						
PM_{10}	-0.02	-0.07 – 0.03	0.425	-0.02	-0.07 – 0.04	0.565
NO_2	-0.04	-0.09 – 0.02	0.170	-0.05	-0.13 – 0.03	0.247
O_3	-0.001	-0.01 – 0.01	0.825	-0.006	-0.02 – 0.01	0.368
Inflammatory markers						
eNO, ppb						
PM_{10}	0.17	-0.20 – 0.53	0.369	0.44	-0.08 – 0.80	0.016
NO_2	0.66	0.22 – 1.10	0.004	0.98	0.45 – 1.51	<0.001
O_3	-0.02	-0.11 – 0.06	0.608	0.01	-0.09 – 0.11	0.856
NO output, pL/sec						
PM_{10}	16.5	1.5 – 31.5	0.031	15.6	-0.2 – 31.3	0.053
NO_2	23.6	5.2 – 42.1	0.012	41.0	17.8 – 64.2	0.001
O_3	-0.21	-3.7 – 3.3	0.905	-0.13	-4.7 – 4.5	0.956

[1] this model was adjusted for gender, postnatal age, season of birth, outdoor temperature at the measurement day and maternal smoking in pregnancy. eNO was further adjusted for minute ventilation.

[2] similar results were obtained with minute ventilation and tidal volume per body weight.

Table 3) Associations between postnatal pollutant levels and lung function at age 5 weeks. Data is given as unit change in lung function value per μg/m^3 increase in the mean postnatal exposure of the respective pollutant.

	Univariable model			Adjusted model[1]		
	coefficient	CI 95%	p-value	coefficient	CI 95%	p-value
Tidal breathing						
Minute ventilation, mL/min^2						
PM_{10}	5.5	-0.9 – 11.9	0.090	4.3	-3.6 – 12.2	0.280
NO_2	0.9	-5.2 – 7.0	0.770	-11.3	-24.2 – 1.6	0.087
O_3	0.2	-0.9 – 1.3	0.749	2.4	0.27 – 4.6	0.028
Mean tidal expiratory flow, mL/sec						
PM_{10}	0.27	0.02 – 0.50	0.031	0.14	-0.16 – 0.43	0.361
NO_2	0.13	-0.10 – 0.36	0.260	-0.41	-0.90 – 0.08	0.097
O_3	-0.01	-0.05 – 0.03	0.601	0.09	0.005 – 0.17	0.038
Mean tidal inspiratory flow, mL/sec						
PM_{10}	0.05	-0.18 – 0.27	0.678	0.12	-0.15 – 0.40	0.377
NO_2	-0.11	-0.33 – 0.10	0.312	-0.33	-0.78 – 0.13	0.161
O_3	0.03	-0.01 – 0.07	0.145	0.07	-0.004 – 0.15	0.063
Respiratory rate, per minute						
PM_{10}	0.30	0.04 – 0.56	0.026	0.08	-0.23 – 0.40	0.599
NO_2	0.18	-0.07 – 0.43	0.419	-0.31	-0.84 – 0.21	0.238
O_3	-0.01	-0.06 – 0.04	0.629	0.09	0.007 – 0.18	0.035
Tidal volume, mL^2						
PM_{10}	-0.08	-0.22 – 0.06	0.242	0.01	-0.15 – 0.18	0.886

NO_2	-0.08	-0.22 – 0.05	0.204	-0.07	-0.35 – 0.20	0.595
O_3	0.01	-0.02 – 0.03	0.611	-0.01	-0.06 – 0.03	0.573
Multiple-breath washout						
FRC_{ao}, mL/kg						
PM_{10}	-0.06	-0.16 – 0.05	0.290	-0.09	-0.22 – 0.04	0.174
NO_2	-0.05	-0.15 – 0.06	0.379	-0.23	-0.46 – -0.01	0.042
O_3	-0.002	-0.02 – 0.02	0.780	-0.008	-0.05 – 0.03	0.649
LCI^4						
PM_{10}	0.01	-0.008 – 0.03	0.265	0.007	-0.02 – 0.03	0.527
NO_2	0.01	-0.006 – 0.03	0.212	0.02	-0.02 – 0.06	0.407
O_3	-0.001	-0.01 – 0.002	0.555	0.001	-0.006 – 0.01	0.819
Inflammatory markers						
eNO, ppb						
PM_{10}	-0.04	-0.20 – 0.11	0.614	0.05	-0.14 – 0.23	0.614
NO_2	-0.003	-0.15 – 0.14	0.968	0.06	-0.22 – 0.35	0.666
O_3	0.01	-0.02 – 0.04	0.418	0.02	-0.02 – 0.07	0.302
NO output, pL/sec						
PM_{10}	3.9	-2.8 – 10.6	0.254	1.9	-6.1 – 10.0	0.635
NO_2	2.4	-3.6 – 8.4	0.438	0.04	-12.5 – 12.6	0.994
O_3	0.17	-0.93 – 1.28	0.758	0.97	-1.09 – 3.03	0.356

[1] this model was adjusted for gender, postnatal age, season of birth, outdoor temperature at the measurement day and maternal smoking in pregnancy. eNO was further adjusted for minute ventilation.

[2] similar results were obtained with minute ventilation and tidal volume per body weight.

Table 4) Associations between distance to roads and lung function at age 5 weeks. Data is given as unit change in lung function value per living 10 m further away from the next road.

	Univariable model			Adjusted model[1]		
	coefficient	CI 95%	p-value	coefficient	CI 95%	p-value
Tidal breathing						
Minute ventilation, mL/min[2]						
Distance 6 m road	0.06	-0.57 – 0.69	0.853	-0.02	-0.66 – 0.62	0.957
Distance 4 m road	1.12	-1.54 – 3.79	0.407	1.13	-1.54 – 3.79	0.407
Mean tidal expiratory flow, mL/sec						
Distance 6 m road	0.005	-0.02 – 0.03	0.679	0.003	-0.02 – 0.03	0.809
Distance 4 m road	0.05	-0.06 – 0.15	0.375	0.05	-0.05 – 0.15	0.349
Mean tidal inspiratory flow, mL/sec						
Distance 6 m road	-0.006	-0.03 – 0.02	0.618	-0.006	-0.03 – 0.02	0.585
Distance 4 m road	0.03	-0.06 – 0.13	0.535	0.03	-0.07 – 0.12	0.583
Respiratory rate, per minute						
Distance 6 m road	0.0007	-0.03 – 0.03	0.955	0.001	-0.03 – 0.02	0.931
Distance 4 m road	0.02	-0.09 – 0.13	0.717	0.02	-0.08 – 0.13	0.657
Tidal volume, mL[2]						
Distance 6 m road	-0.0007	-0.01 – 0.01	0.922	-0.0007	-0.01 – 0.01	0.921
Distance 4 m road	0.004	-0.05 – 0.06	0.886	0.003	-0.05 – 0.06	0.923
Multiple-breath washout						
FRC_{ao}, mL/kg						
Distance 6 m road	0.003	-0.01 – 0.01	0.575	0.005	-0.01 – 0.02	0.356

Distance 4 m road	0.02	-0.02 – 0.07	0.296	0.02	-0.02 – 0.07	0.303
LCI[4]						
Distance 6 m road	0.0015	-0.001–0.004	0.162	0.001	-0.001–0.003	0.325
Distance 4 m road	-0.003	-0.01 – 0.006	0.530	-0.002	-0.01 – 0.006	0.663
Inflammatory markers						
eNO, ppb						
Distance 6 m road	-0.002	-0.02 – 0.01	0.784	-0.004	-0.02 – 0.01	0.608
Distance 4 m road	-0.006	-0.07 – 0.05	0.845	-0.005	-0.07 – 0.05	0.860
NO output, pL/sec						
Distance 6 m road	0.0001	-0.001–0.001	0.778	0.0001	-0.001–0.001	0.857
Distance 4 m road	0.0001	-0.002–0.003	0.695	0.0001	-0.002–0.003	0.608

[1] this model was adjusted for gender, postnatal age, season of birth, outdoor temperature at the measurement day and maternal smoking in pregnancy. eNO was further adjusted for minute ventilation.

[2] similar results were obtained with minute ventilation and tidal volume per body weight.

Table 5) Sensitivity Analyses of the association between PM_{10} and minute ventilation, and between nitrogen dioxide and exhaled NO.

	PM_{10} and minute ventilation[1]		Nitrogen dioxide and eNO[2]	
	coefficient	CI 95%	coefficient	CI 95%
Main model[3]	24.9	9.3 – 40.5	0.98	0.45 – 1.51
Without adjustment for age	25.3	9.7 – 40.9	1.03	0.50 – 1.55
Without adjustment for gender	22.9	7.3 – 38.5	0.98	0.45 – 1.51
Without outdoor temperature	24.8	9.4 – 40.2	1.01	0.52 – 1.50
Without seasonal adjustment	25.0	9.4 – 40.7	0.93	0.40 – 1.46
Without smoking during pregnancy	24.7	9.0 – 40.4	0.98	0.46 – 1.51
With distance to 6m roads	24.7	8.9 – 40.5	0.96	0.44 – 1.48
With gestational age	24.7	9.0 – 40.4	0.99	0.47 – 1.52
With height and weight at study date	23.6	9.0 – 38.2	0.93	0.41 – 1.46
With paternal education	24.3	8.6 – 40.1	0.93	0.39 – 1.47
With maternal asthmatic disease	24.8	9.1 – 40.5	0.97	0.45 – 1.50
With year of birth	28.0	7.0 – 49.0	0.94	0.28 – 1.60
With month of birth	22.5	5.6 – 39.4	1.20	0.58 – 1.83
With infectious season[4]	23.8	7.2 – 40.4	0.85	0.20 – 1.51
With number of siblings[5]	24.5	9.0 – 40.0	1.02	0.49 – 1.56
With air pollution two days before lung function[6]	24.1	8.3 – 39.9	1.07	0.53 – 1.61

[1] Values refer to changes in minute ventilation in mL/min per $\mu g/m^3$ increase in mean prenatal PM_{10} exposure.

[2] Values refer to changes in eNO in ppb per $\mu g/m^3$ increase in mean prenatal nitrogen dioxide exposure.

[3] The main model is equivalent to the adjusted model in table 2. This model is adjusted for gender, postnatal age, season of birth, outdoor temperature at the study day and maternal smoking during pregnancy. eNO is additionally adjusted for minute ventilation.

[4] Infectious season was categorized into four categories, based on month of birth (November to April for winter season and Mai to October for summer season) and on a known two-year periodicity of respiratory virus epidemics.

[5] Number of siblings was categorized into no older siblings, one older sibling or two and more older siblings.

[6] We included mean exposure to PM_{10} at the two days before lung function into the model for minute ventilation and to nitrogen dioxide into the model for eNO.