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# Air pollution exposure impairs lung function in infants

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## Abstract

**Aim:** To assess associations between air pollution exposure and infant lung function.

**Methods:** Healthy infants from Stockholm were recruited to two cohorts ($n = 99$ and $n = 78$). Infant spirometry included plethysmography and raised volume forced expiratory flows. In pooled analyses, lung function at ~6 months of age was related to time-weighted average air pollution levels at residential addresses from birth until the lung function test. The pollutants included particulate matter with an aerodynamic diameter < 10 μm ($PM_{10}$) or <2.5 μm and nitrogen dioxide.

**Results:** There were significant inverse relations between air pollution exposure during infancy and forced expiratory volume at 0.5 s ($FEV_{0.5}$) as well as forced vital capacity (FVC) for all pollutants. For example, the decline was 10.1 ml (95% confidence interval 1.3–18.8) and 10.3 ml (0.5–20.1) in $FEV_{0.5}$ and FVC, respectively, for an interquartile increment of 5.3 μg/m$^3$ in $PM_{10}$. Corresponding associations for minute ventilation and functional residual capacity were 43.3 ml/min (−9.75–96.3) and 0.84 ml (−4.14–5.82).

**Conclusions:** Air pollution exposure was associated with impaired infant lung function measures related to airway calibre and lung volume, suggesting that comparatively low levels of air pollution negatively affect lung function in early life.

**KEYWORDS**
air pollution, infancy, lung function, spirometry

## 1 | INTRODUCTION

There is growing consensus that impaired lung function early in life predicts later respiratory morbidity.[1-3] Lung development begins in utero and is particularly intense during the first years of age, which makes infancy a potentially critical time period for lung injury and influence by adverse factors.[4] For example, preterm birth and maternal smoking during pregnancy are well known risk factors for early

life lung morbidity.[2] Air pollution can contribute to airway disease and dominating parts of the population in urban areas across the world are exposed to levels exceeding the health based guidelines proposed by the World Health Organisation.[5] Several epidemiological studies have shown inverse associations between air pollution exposure and lung function in children.[6-15] In particular, there is evidence that early life exposure affects lung function measured later in childhood,[6,11,12,14] as well as in adulthood.[16] However, effects by

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these risk factors on lung function in infancy have only been investigated to a limited extent.

Very few studies have explored effects of air pollution exposure on lung function in infancy.[8,9,15] In general, adverse effects were indicated, but the outcome assessment was primarily restricted to tidal volume analyses. Consequently, these studies did not utilise the full potential of infant spirometry. Such studies are urgently needed to shed light on the observed inverse associations between air pollution exposure in infancy and lung function later in life.

The aim of this study was to investigate infant lung function in relation to air pollution exposure in an area with comparatively low levels, using infant spirometry including plethysmography and raised volume forced expiratory flows.

## 2 | PATIENTS AND METHODS

### 2.1 | Study population

The Etiologic Mechanisms for air pollution effects in the Infant Lung cohort (EMIL) was recruited among children born in Stockholm city between 2014 and 2017, identified through the Swedish birth register. Healthy full-term newborn infants were selected to obtain an equal number living on streets with high air pollution levels, corresponding to a level of particulate matter with an aerodynamic diameter of $<10\,\mu m$ ($PM_{10}$) over $50\,\mu g/m^3$ as 90-percentile of daily averages, or a level below $35\,\mu g/m^3$. The parents of the selected children were contacted by mail and 104 (3.8%) accepted to participate. Information on exposures, lifestyle and health was obtained via questionnaires.

A second cohort was included by adding air pollution data to an earlier recruited birth cohort, using the same methodology as for EMIL: The Lungfunktion och virusinfektioner för tidigt födda barn cohort (LUFT), Swedish acronym for lung function and viral infections in preterm infants. LUFT aimed at investigating lung function in relation to preterm birth and viral respiratory tract infections,[17] and recruited a control group of term healthy infants in Stockholm County born between 2009 and 2011 at Karolinska Danderyd University Hospital. Caregivers of 236 healthy term infants were asked to participate in the study, and 109 (46%) accepted. We included 78 of these infants who underwent infant spirometry at $6\pm3$ months of age. Around half of them (53%) lived in the highly urbanised municipalities Stockholm, Solna and Sundbyberg. Information on respiratory health and background factors was collected using a questionnaire.

Ethical approval was granted by the regional ethical review board in Stockholm for both cohorts as well as for the combined analysis. Written informed consent was collected from the child's caregiver before the start of data collection.

### 2.2 | Air pollution exposure assessment

Exposure to air pollution was estimated based on further development of a validated methodology utilised in several epidemiological studies from our group.[18,19] It entails use of an emission inventory together with a high-resolution Gaussian dispersion model to estimate annual outdoor levels of different air pollutants over time at geographical locations within Stockholm County. The emission inventory is updated yearly and contains detailed information on local emissions from road and ferry traffic, industrial areas and households. Meteorological data are also included. Further, a street canyon contribution was added for addresses in the most polluted street segments of the inner city of Stockholm with multistorey houses on both sides. Annual average long-range contributions were added to the locally modelled concentrations based on continuous measurements at regional background stations.

In this study, we selected nitrogen dioxide ($NO_2$), $PM_{10}$ and particulate matter with an aerodynamic diameter of $<2.5\,\mu m$ ($PM_{2.5}$) to characterise air pollution exposure from partly different sources. Long-term exposure was estimated as time-weighted average levels of these pollutants at the residential addresses from birth to the date of lung function measurements, or for the mother during pregnancy, based on residential history. Estimated annual levels were adjusted for variations during shorter time periods using urban background monitor measurements with a 15 min resolution. In addition, three-day average air pollution levels prior to the lung function measurements were estimated for sensitivity analyses focusing on the role of short-term exposure.

### 2.3 | Pulmonary function testing

Infant spirometry was performed at approximately 6 months ($\pm3$ months) using the MasterScreen BabyBody Plethysmograph (Erich Jaeger AG, Würzburg, Germany). Before testing, the infant was examined by a physician, and weight and length were measured. History of respiratory symptoms prior to examination or any abnormal physical signs at examination contraindicated the examination. Respiratory symptoms were assessed during 2 weeks before the examination in the EMIL study and during 3 weeks in the LUFT study. The infants were sedated using oral or rectal chloral hydrate (50–75 mg/kg body weight). Pulse and oxygen saturation were monitored throughout the examination. We used

a standardised protocol based on international guidelines,[20-23] including tidal breathing analysis, plethysmography and raised volume forced expiratory flows. Minute ventilation was chosen to represent respiratory need, functional residual capacity (FRC) as a proxy for lung volume, and forced expiratory volume at 0.5 s ($FEV_{0.5}$) and forced vital capacity (FVC) corresponding to a full dynamic spirometry. All measurements were made during behaviourally determined quiet sleep. All examination reports were visually reviewed and quality checked according to guidelines[20-23] by the first author (BL) before inclusion. Mean FRC and the highest $FEV_{0.5}$ and FVC values were used for analysis.

Applying a strict quality control protocol for each spirometry measure we obtained minute ventilation data in 173 infants, FRC data in 163, FVC data in 127 and $FEV_{0.5}$ data in 125 infants. The most common reason for missing spirometry data was that the infant woke up during the examination of forced expiratory flows, which involves gentle squeezing of the chest, and primarily affected the $FEV_{0.5}$ and FVC data.

## 2.4 | Statistical analysis

Normally distributed continuous variables were presented as means and standard deviations (SD), and non-normal continuous variables as medians and interquartile range (IQR). Differences in proportions were tested using the Pearson chi-square test. Differences in non-normally distributed continuous variables were tested using Wilcoxon´s rank sum test and in normally distributed continuous variables using Student's $t$-test. Spearman correlation coefficients were provided, with levels of 0.6 and higher interpreted as strong and from 0.4 to 0.59 as moderate correlations.

In pooled analyses of the two cohorts, lung function measures were related to time-weighted average IQR of air pollution levels at residential addresses using linear regression with Stata 14.2 software pack (StataCorp, College Station,). A similar methodology was used in an earlier study from our group.[11] Standard assumptions for linear regression were met and no variables were transformed. Associations were expressed as regression coefficients and 95% confidence intervals (95% CI) per IQR increase in $PM_{2.5}$, $PM_{10}$ and $NO_2$, respectively. Potential confounding covariates for adjusted analyses were selected a priori based on previous literature. Outside temperature at day of lung function test, window towards a busy road, gas stove in the residence, education level of caregivers, current smoking in the household, other children in the household and gestational age at birth were all evaluated as confounders, but not included in the final model as they did not consistently influence the associations.

The final model included age, sex, length, weight, season of birth, study cohort and maternal smoking during pregnancy. Season of birth was defined as winter (December to February), spring (March to May), summer (June to August) and autumn (September to November). Current smoking was defined as current smoking indoors by at least one caregiver in the home environment of the infant and parental asthma as doctor diagnosed asthma in the EMIL cohort and as using asthma medication on a regular basis in the LUFT cohort. In the interpretation we focus on the adjusted results because the crude results are affected by confounding by the variables included in the model. Interactions between air pollution exposure and covariates were evaluated using interaction terms.

Sensitivity analyses were performed by introducing two of the air pollutants to the regression model, sequentially for each of the three pollutants, as well as by adding short-term air pollution exposures to the model. A $p$-value below 0.05 was considered statistically significant, except in interaction analyses, where a $p$-value below 0.1 was used.

## 3 | RESULTS

### 3.1 | Study subjects with lung function tests

A total of 177 infants were studied, who had acceptable data for at least one of the lung function measures: 99 from EMIL and 78 from LUFT. In EMIL, two children failed all lung function tests because they did not fall asleep and two because of technical problems with the spirometer. One child was excluded from EMIL due to viral croup at the examination and one from LUFT because of asthma diagnosed during follow-up.

### 3.2 | Characteristics of study subjects

There were no major differences between the two cohorts regarding birthweight, gestational age, parental asthma, season of birth or median $PM_{2.5}$ and $PM_{10}$ exposure (Table 1). However, the median $NO_2$ exposure was higher in the EMIL cohort, while maternal smoking during pregnancy was more common in the LUFT cohort.

### 3.3 | Correlations between air pollution exposures

There were moderate or strong correlations between $PM_{2.5}$, $PM_{10}$ and $NO_2$ exposures calculated as time-weighted averages from birth to examination (Table S1). Correlations between average air pollution levels three days prior to examination and the long-term measure were moderate for $PM_{10}$ and strong for $NO_2$. There were strong correlations between time-weighted average pre- and postnatal exposure for all three air pollutants.

### 3.4 | Lung function in relation to age, length and height

The mean age, length and weight at time of examination were higher in the infants from the EMIL cohort than in those from the LUFT cohort (Table 2). These differences were also reflected in the lung

TABLE 1 Descriptive data in infants of two birth cohorts from Stockholm

| | Combined cohorts [n = 177] | EMIL cohort [n = 99] | LUFT cohort [n = 78] |
|---|---|---|---|
| **Anthropometry data:** | | | |
| Male, n (%) | 96 (54.2) | 60 (60.6) | 36 (46.2) |
| Birthweight (g), mean (SD) | 3545 (436.0) | 3565 (408.9) | 3521 (469.6) |
| Gestational age at birth (weeks), mean (SD) | 39.7 (0.10) | 39.9 (0.14) | 39.4 (0.14) |
| **Smoking exposure:** | | | |
| Maternal smoking during pregnancy, n (%) | 5 (2.8) | 0 (0) | 5 (6.4) |
| Current smoking in the household, n (%) | 2 (1.1) | 0 (0) | 2 (2.6) |
| **Parental asthma:** | | | |
| No, n (%) | 134 (77.5) | 78 (80.4) | 56 (73.7) |
| One parent, n (%) | 34 (19.7) | 18 (18.6) | 16 (21.1) |
| Both parents, n (%) | 5 (2.9) | 1 (1.0) | 4 (5.3) |
| **Season of birth:** | | | |
| Winter (Dec-Feb), n (%) | 36 (20.3) | 19 (19.2) | 17 (21.8) |
| Spring (Mar-May), n (%) | 42 (23.7) | 27 (27.3) | 15 (19.2) |
| Summer (Jun-Aug), n (%) | 36 (20.3) | 22 (22.2) | 14 (17.9) |
| Autumn (Sep-Nov), n (%) | 63 (35.6) | 31 (31.3) | 32 (41) |
| **Air pollution exposure[#]** | | | |
| $PM_{2.5}$ µg/m$^3$, median (IQR) | 5.84 (1.65) | 5.59 (1.24) | 6.53 (1.79) |
| $PM_{10}$ µg/m$^3$, median (IQR) | 13.4 (5.26) | 13.9 (5.29) | 11.5 (5.41) |
| $NO_2$ µg/m$^3$, median (IQR) | 14.4 (11.4) | 17.6 (13.6) | 10.6 (8.39) |

*Note*: Data on heredity missing for two children each in the EMIL and LUFT cohorts, respectively.

Abbreviations: IQR, Interquartile range; $NO_2$, Nitrogen dioxide; $PM_{10}$, particulate matter with an aerodynamic diameter less than 10 µm; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 µm; SD, Standard deviation.

[#]Air pollution exposure expressed as time-weighted average exposure at home addresses from birth to lung function test.

function variables, with generally higher mean volumes and flows in the infants from the EMIL cohort.

## 3.5 | Lung function in relation to air pollution exposure

Minute ventilation was increased in relation to air pollution exposure (Figure 1 and Table S2); however, only the association with $NO_2$ was statistically significant. $FEV_{0.5}$ and FVC were significantly decreased for all air pollutants. The decline was 10.1 ml (95% CI 1.3–18.8) and 10.3 ml (0.5–20.1) in $FEV_{0.5}$ and FVC, respectively, for an IQR increment of 5.3 µg/m$^3$ in $PM_{10}$. Corresponding declines were 9.2 ml (0.4–18.2) and 10.0 ml (0.03–19.9) in $FEV_{0.5}$ and FVC, respectively, for an IQR increment of 1.7 µg/m$^3$ in $PM_{2.5}$, as well as 8.7 ml (0.6–16.8) and 10.7 ml (1.6–19.7) for an increment of 11.4 µg/m$^3$ in $NO_2$. In view of the strong correlations between pre- and postnatal exposure for the three pollutants, showing correlation coefficients of 0.6 and higher (Table S1), separate analyses for prenatal exposure were not meaningful.

## 3.6 | Stratified analyses

In stratified analyses focusing on time-weighted average $PM_{10}$ exposure during infancy and $FEV_{0.5}$, as well as FVC, associations were observed only in males; however, the sex interaction was not statistically significant (Figure 2 and Table S3). Results were consistent between the two cohorts. Similar findings appeared in relation to $PM_{2.5}$ and $NO_2$ (data not shown).

## 3.7 | Sensitivity analyses

Sensitivity analyses based on two-pollutant models and focusing on postnatal exposure generally showed some weakening of the associations with $FEV_{0.5}$ and FVC, compared to the one-pollutant models, but the inverse relationships prevailed, albeit no longer statistically significant (Table S4). Coefficients and significant p-values were generally robust when short-term exposure was included in the models. However, the association between $NO_2$ exposure and minute ventilation became non-significant when including short-term

TABLE 2 Lung function data and anthropometry at examination of infants in two birth cohorts from Stockholm

| | Combined cohorts [n = 177] | | | EMIL cohort [n = 99] | | | LUFT cohort [n = 78] | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | N | Mean | SD | N | Mean | SD |
| At time of spirometry: | | | | | | | | | |
| Age, months | 177 | 5.51 | 1.61 | 99 | 6.51 | 1.24 | 78 | 4.25 | 1.04 |
| Height, cm | 177 | 66.9 | 3.85 | 99 | 69.0 | 2.97 | 78 | 64.1 | 2.94 |
| Weight, kg | 177 | 7.68 | 1.27 | 99 | 8.39 | 1.04 | 78 | 6.78 | 0.93 |
| Minute ventilation, ml/min | 173 | 2220 | 320 | 99 | 2340 | 310 | 74 | 2070 | 260 |
| FRC mean, ml | 163 | 143.0 | 32.1 | 98 | 156.4 | 28.0 | 65 | 122.7 | 27.1 |
| FEV$_{0.5}$ max, ml | 125 | 223.9 | 45.7 | 82 | 245.5 | 33.7 | 43 | 182.7 | 36.6 |
| FVC max, ml | 127 | 277.2 | 58.9 | 84 | 308.0 | 40.5 | 43 | 217.2 | 40.1 |

Abbreviations: FEV$_{0.5}$, forced expiratory volume in 0.5 s; FRC, functional residual capacity; FVC, forced vital capacity; SD, Standard deviation.
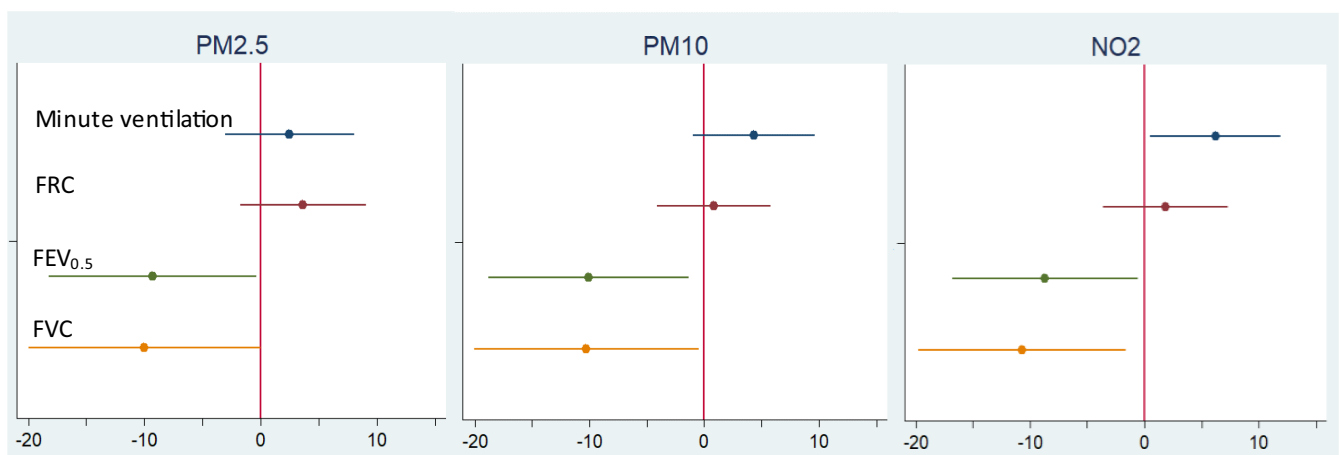


FIGURE 1 Lung function measures in infants in relation to air pollution exposures from birth to examination in combined analyses of two cohorts from Stockholm. Lung function measures expressed in ml except for minute ventilation (cl/min). Air pollution exposures expressed as interquartile range of time-weighted average exposure. Data are presented as beta-coefficient and 95% CI from linear regression models adjusted for age, sex, length, weight, season of birth, study cohort and maternal smoking during pregnancy. Abbreviations: Particulate matter with an aerodynamic diameter less than 2.5 μm (PM$_{2.5}$), interquartile range (IQR), nitrogen dioxide (NO$_2$), particulate matter with an aerodynamic diameter less than 10 μm (PM$_{10}$), functional residual capacity (FRC), forced expiratory volume in 0.5 second (FEV$_{0.5}$) and forced vital capacity (FVC)
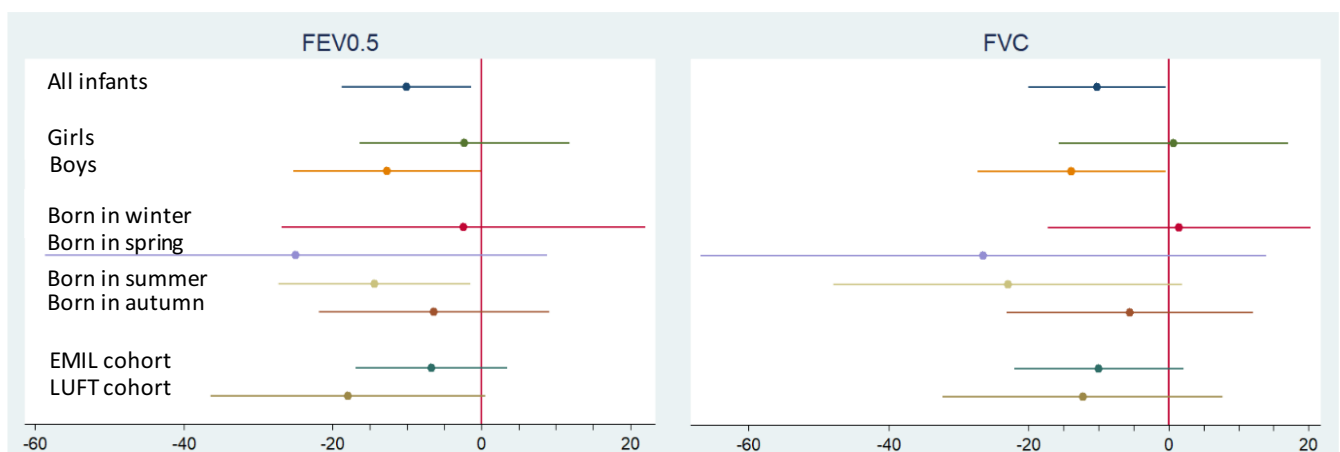


FIGURE 2 Time-weighted average PM$_{10}$ exposure from birth to examination and FEV$_{0.5}$ as well as FVC in infants of two cohorts from Stockholm, stratifying for covariates. Data are presented as beta-coefficient and 95% CI from linear regression models adjusted for age, sex, length, weight, season of birth pæd study. Lung function measures expressed in ml. Air pollution exposures expressed as interquartile range of time weighted average exposure. Maternal smoking during pregnancy not included due to few individuals in the smoking group. Abbreviations: Forced expiratory volume in 0.5 second (FEV$_{0.5}$) and forced vital capacity (FVC)

exposure in the regression model (Table S5). This is explained by the particularly strong correlation between short- and long-term exposure for $NO_2$ (cf Table S1).

## 4 | DISCUSSION

In this study, we found that exposure to ambient air pollution from birth and onwards was associated with adverse effects on lung function in 6-month-old infants, including decreased $FEV_{0.5}$ and FVC, and increased minute ventilation.

Our findings of an increased minute ventilation are in accordance with earlier research on infant lung function[8,9,15] which were limited to tidal volume analysis and did not include forced expiratory flows. The observed decrease in $FEV_{0.5}$ in relation to air pollution exposure in our study is indicative of a reduced airway calibre and the decrease in FVC points to reduced lung volumes. While an isolated decrease in $FEV_{0.5}$ may be a sign of airway obstruction, the concomitant decrease in FVC could indicate a generally smaller lung volume. Both narrower airways and smaller lung volumes provide explanations for the increase in minute ventilation and respiratory need observed in our, as well as in earlier studies in infancy.[8,9,15] The mechanisms behind the inverse association between air pollution and infant lung function are likely to be multifactorial, but growth factors affecting lung size may be of interest.[4,24] Specific mechanisms behind restricted lung growth are unclear, but a decrease in alveolar cell proliferation in relation to PM exposure has been shown in animal models.[25]

Our findings are of particular interest in view of earlier studies showing inverse associations between air pollution exposure in infancy and lung function measured later in childhood, adolescence and early adulthood.[6,7,10,11,12,13,14,16] Effects of postnatal and prenatal exposure could not be separated in our study because of correlated exposure between the two periods. Studies investigating prenatal air pollution exposure and lung function later in childhood have found inverse associations on both $FEV_1$ and FVC.[6,26] Because of high correlations between prenatal and early postnatal air pollution exposures and limited study sizes, it has not been possible to conclusively separate the effects of the two time periods. However, our results suggest that long-term exposure is more important for adverse lung functions effects than short-term exposure.

An important aspect of our study is the comparatively low air pollution levels in the Stockholm area, particularly for $PM_{2.5}$.[18,19] However, the air pollution levels in the busiest streets may be close to, or exceed, EU standards for $PM_{10}$ and $NO_2$. Our findings of inverse associations between air pollution exposure and lung function measures in infants are particularly alarming given that air pollution levels in most urban areas of the world are considerably higher than in Stockholm.

A major strength of our study was the detailed infant lung function measurements, including plethysmography and raised volume forced expiratory manoeuvres. Where earlier studies have shown an increase in respiratory need, our methodology can also provide physiological explanations to the observations. All measurements for our two cohorts were performed by the same teams of experienced test operators in accordance with international guidelines, minimising misclassification of the outcome. Another strength was the validated air pollution exposure assessment methodology, enabling high geographical resolution.[19] Still, some misclassification of exposure is expected, but to the extent that it is non-differential it would tend to weaken associations between exposure and outcome. One limitation of our study was the high nonresponse to the invitation to participate, which may have affected the generalisability. For example, the study sample included fewer smokers than the general population and the results may be particularly relevant for non-smoking households. On the other hand, the low number smoking parents resulted in a low risk of confounding from this exposure. Furthermore, several children did not provide valid results for some lung function measures, particularly regarding $FEV_{0.5}$ and FVC.

Our findings are also of relevance in clinical practice. Air pollution is a common exposure worldwide, primarily in urban areas. The inverse associations in our study amount to around 5 percent decrease of the mean $FEV_{0.5}$ and FVC per pollutant interquartile range among infants from an area with relatively low exposure levels. Although this may not be clinically noticeable in healthy infants, it could have a substantial impact in children with already compromised airways such as those born preterm.[15] Furthermore, given the mounting evidence of lung function impairment in children and adolescents related to air pollution exposure early in life, our results indicate that already the infant lung is adversely affected by air pollution exposure. Our findings provide further incentive for reductions of ambient air pollution levels, even in areas with comparatively low levels.

## 5 | CONCLUSION

Air pollution exposure early in life was associated with impaired infant lung function measures related to both airway calibre and lung volume. The role of pre- vs postnatal exposure could not be disentangled because of high correlations in exposure between the two periods. Our results suggest that comparatively low levels of air pollution may negatively affect lung function in infants, which could contribute to explaining the adverse effects observed later in life.

### CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

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