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Air pollution exposure during pregnancy and lung function in childhood: The LUIS study

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Abstract

Background: The adverse effects of high air pollution levels on childhood lung function are well-known. Limited evidence exists on the effects of moderate exposure levels during early life on childhood lung function. We investigated the association of exposure to moderate air pollution during pregnancy, infancy, and preschool time with lung function at school age in a Swiss population-based study.

Methods: Fine-scale spatiotemporal model estimates of particulate matter with a diameter <2.5 µm ($PM_{2.5}$) and nitrogen dioxide (NO_2) were linked with residential address histories. We compared air pollution exposures within different time windows (whole pregnancy, first, second, and third trimester of pregnancy, first year of life, preschool age) with forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) measured cross-sectionally using linear regression models adjusted for potential confounders.

Results: We included 2182 children, ages 6–17 years. Prenatal air pollution exposure was associated with reduced lung function at school age. In children aged 12 years, per 10 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ during pregnancy, FEV_1 was 55 mL lower (95% CI −84 to −25 mL) and FVC 62 mL lower (95% CI −96 to −28 mL). Associations were age-dependent since they were stronger in younger and weaker in older children. $PM_{2.5}$ exposure after birth was not associated with reduced lung function. There was no association between NO_2 exposure and lung function.

Conclusion: In utero lung development is most sensitive to air pollution exposure, since even modest $PM_{2.5}$ exposure during the prenatal time was associated with reduced lung function, most prominent in younger children.

KEYWORDS

air pollution, fetus, lung, nitrogen dioxide, particulate matter

Jakob Usemann, Rebeca Mozun, Alexander Moeller, and Philipp Latzin shared authorship.

1 | BACKGROUND

Traffic-related air pollutants are known to have detrimental effects on respiratory morbidity and lung functional development.[1–5] There is growing awareness that exposure to air pollution especially in early-life, has an impact on a child's respiratory health, with potential long-term effects on lung function trajectories throughout life.[6,7]

The association between air pollution exposure after birth and later lung function is reported consistently.[2,3,8,9] Several studies have investigated the impact of air pollution during the sensitive period of fetal lung development and its association with lung function during childhood (summarized in Table 1).[4,5,10,11,13,14,16,18] These studies show that fetal lung development is especially sensitive to air pollution exposure,[4,5,11,16,18] but it is still debated if susceptibility to air pollution differs between pregnancy trimesters and if there is sex-specific susceptibility.

Different traffic-related air pollutants have been studied, mainly nitrogen dioxide (NO_2), nitrogen oxide (NO_x),[4,5,10,12,18] and particulate matter (PM) with an aerodynamic diameter less than 10 μm (PM_{10}) [5,11,12,18] or 2.5 μm ($PM_{2.5}$).[13,14,16] Particles with a smaller size (i.e., $PM_{2.5}$) are considered more harmful to the respiratory system than larger ones due to their transplacental passing in the fetus[19] and deeper penetration into the periphery of the small airways in the breathing child.[20] However, previous studies mainly assessed PM_{10}, and only five studies (with ~175–500 participants) have assessed the adverse effects of prenatal $PM_{2.5}$ exposure.[13–17] New exposure assessment models using a combination of satellite data, land use, and meteorological data allow individual prediction of NO_2[21] and $PM_{2.5}$,[22] opening up the possibility to more precisely study the effect of air pollution in larger populations.[23]

The WHO updated guidelines[24] emphasize a need to further reduce air pollution emissions and now indicate much lower annual cut-offs for NO_2 (<10 $\mu g \cdot m^{-3}$) and $PM_{2.5}$ (<5 $\mu g \cdot m^{-3}$). In most previous studies,[4,5,10,12,18,25,26] subjects were exposed to rather higher pollution levels, and the impact of moderate levels of NO_2 and $PM_{2.5}$ (<30 $\mu g \cdot m^{-3}$) during the sensitive period of early lung development has scarcely been investigated.

To address these knowledge gaps, we analyzed within a large population-based study[27] the association of moderate exposure to fine scale modeled $PM_{2.5}$ and NO_2[21,22] for different vulnerability time windows, including whole pregnancy, each trimester of pregnancy, early infancy, and preschool time with lung function in school-aged children. We hypothesize that prenatal air pollution exposure is associated with stronger deficits in forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) than postnatal exposure.

2 | STUDY DESIGN AND METHODS

The LUIS was a cross-sectional-population based study that was conducted from 2013 to 2016 among schoolchildren aged 6–17 years living in the canton of Zurich, Switzerland (ClinicalTrials.gov: NCT03659838).[27] Briefly, LUIS was embedded in a non-profit respiratory health promotion activity.[28] The campaign offered all schools in the canton of Zurich to participate. Lung function technicians visited the schools who agreed to participate with a study bus which contained the same lung function equipment throughout the study, according to recommendations.[29] One field worker measured the children's height and weight and performed the lung function tests, while the other interviewed the children using a short digital questionnaire. Parental questionnaires were collected at the same time. Parents signed the informed consent and completed a detailed questionnaire. Children assented orally, and those aged 15 years or older also signed their consent.

2.1 | Air pollution exposure

MeteoSwiss data and statistical models[21,22] were used to calculate the residential mean exposure by pollutant for different exposure windows: whole pregnancy, first, second, third trimester, the first year of life, and preschool time (birth until 6.5 years).

Residential NO_2 and $PM_{2.5}$ concentrations were estimated from fine-scale prediction models with NO_2 data from 2005 to 2016 and $PM_{2.5}$ data from 2003 to 2013.[21,22] For children born before fine scale prediction models were available, individual exposure were back extrapolated using data from the pollumap dispersion model.[30] Air pollution was assigned to each participant using the extrapolated surfaces. Therefore, for each participant in the final data set, daily air pollution exposures were available throughout the required time period.

The parental questionnaire inquired about the current residential address and changes in the residential address before the lung function assessment. For each participant, addresses were then geocoded. Finally, environmental exposures for NO_2 and $PM_{2.5}$ were linked to each child's home address. Address changes were considered, and exposures were weighted by the time (resolution in days) spent at each address. For details, see Supporting Information.

2.2 | Lung function outcome

Spirometry was performed according to recommendation[29] with the outcomes FVC, FEV_1, FEV_1/FVC ratio, and maximum expiratory flow between 25% and 75% of FVC ($FEF_{25\%-75\%}$). Spirometry parameters were expressed in milliliters (mL) and as *z*-scores according to Global Lung Initiative reference values.[31] Quality control was done as described previously[27] according to standards.[32]

2.3 | Risk factors

We assessed the child's age, sex, weight, height, ethnicity, and body mass index using WHO growth references,[33] asthma (wheezing or

TABLE 1 Overview of studies assessing particulate matter or nitrogen dioxide during pregnancy and lung function at school-age.

References	Country	Study size	Age at lung function in years	Pollutant	Mean/median pollutant level during pregnancy
Bougas et al.[10]	France	788	8.5	NO_2	71.7 $\mu g \cdot m^{-3}$
Cai et al.[11]	England	5276	8 and 15	PM_{10_road}	0.9 $\mu g \cdot m^{-3}$
				PM_{10_other}	5.2 $\mu g \cdot m^{-3}$
				PM_{10_total}	32.6 $\mu g \cdot m^{-3}$
He et al.[12]	China	2942	17.5	PM_{10}	61.3 $\mu g \cdot m^{-3}$
				NO_2	62.3 $\mu g \cdot m^{-3}$
				NO	46.1 $\mu g \cdot m^{-3}$
				SO_2	16.3 $\mu g \cdot m^{-3}$
Jedrychowski et al.[13]	Poland	176	5	$PM_{2.5}$	32.4 $\mu g \cdot m^{-3}$
Lee et al.[14]	USA	171	6.9	$PM_{2.5}$	10.9 $\mu g \cdot m^{-3}$
Majewska et al.[15]	Poland	294	4,5,6,7,8,9	$PM_{2.5}$	34.5 $\mu g \cdot m^{-3}$
				PAH	18.8 $ng \cdot m^{-3}$
Morales et al.[4]	USA	620	4.5	NO_2	25.6 $\mu g \cdot m^{-3}$
				Benzene	0.8 $\mu g \cdot m^{-3}$
Mortimer et al.[5]	USA	232	8.6	PM_{10}	47.0 $\mu g \cdot m^{-3}$
				NO_2	21.0 $\mu g \cdot m^{-3}$
Neophytou et al.[16a]	USA	222	6–9	$PM_{2.5}$	16.7 $\mu g \cdot m^{-3}$
				O_3	47.1 ppb
Stapleton et al.[17]	Spain	487	4,7,9, 11	PM_{10}	32.9 $\mu g \cdot m^{-3}$
				$PM_{2.5}$	15.2 $\mu g \cdot m^{-3}$
				$PM_{2.5}$ Absorbance	2.4 $1^{-5} \cdot m^{-1}$
				PM_{coarse}	19.3 $\mu g \cdot m^{-3}$
				NO_2	38.6 $\mu g \cdot m^{-3}$
				NO_x	71.5 $\mu g \cdot m^{-3}$
Usemann et al.[18]	Switzerland	232	6.1	PM_{10}	21.8 $\mu g \cdot m^{-3}$
				NO_2	18.5 $\mu g \cdot m^{-3}$
This study	Switzerland	2182	12 (6–17)	$PM_{2.5}$	24.1 $\mu g \cdot m^{-3}$
				NO_2	26.6 $\mu g \cdot m^{-3}$

Note: Age at lung function is given in years mean (range).

Abbreviations: NO, nitric oxide; NO_2, nitrogen dioxide; PAH, polycyclic aromatic hydrocarbons; PM, particulate matter; SO_2, sulfur dioxide.

[a]Pollutant means are given for pregnancy until 3 years of life.

use of inhaled corticosteroid use in the past 12 months), active smoking, current respiratory infection (cough or cold at the day of lung function test), the month of lung function test, maternal and paternal smoking, maternal smoking during pregnancy, maternal and paternal asthma, socioeconomic status (Swiss socioeconomic position index, range from 0 to 100),[34] and pets in the household. Average NO_2 and $PM_{2.5}$ concentrations were individually calculated for the 7 days preceding the lung function test.

2.4 | Statistics

Average daily $PM_{2.5}$ and NO_2 exposures for different time periods (whole pregnancy, each trimester, first year of life, and preschool time) were analyzed as continuous measures. Linear regression models were fitted to assess the associations of lung function measurements with $PM_{2.5}$ and NO_2 (per 10 $\mu g \cdot m^{-3}$ increment). The basic model included known factors to be associated with lung

function measures and was adjusted for the child's sex, ethnicity, age, and height at lung function.[31] In a more extended model, we also included socioeconomic status, maternal smoking during pregnancy, indoor parental smoking, and 7-day short-term air pollution preceding the lung function measurement.[18,35] $p < .05$ are labeled as statistically significant.

We investigated whether the effect of $PM_{2.5}$ and NO_2 exposure on lung function measurements is different for children with asthma, with respiratory infection at the time of lung function, for boys and girls, and for different ages of the child. Therefore, we added interaction terms between air pollution ($PM_{2.5}$ and NO_2) with each of the following items (asthma of the child, respiratory infection at lung function, and the child's sex and age at lung function) into the regression models. We found a significant interaction for the association between air pollution exposure and age at lung function, indicating that the effects of air pollution on lung function are different for different ages. Therefore, we present the estimated association between air pollution exposure for different ages (8, 12, and 16 years). There was no significant interaction between air pollution exposure with the child's sex and asthma, or respiratory infection at lung function (data not shown).

Spearman's correlations between different time periods for $PM_{2.5}$ and NO_2 measures were calculated. There was a high correlation between the different exposure time periods (Supporting Information S1: Tables 1 and 2). Therefore, we analyzed the association between air pollution during each exposure time period with the child's lung function in separate models.

2.5 | Sensitivity analysis

For sensitivity analyses, we ran a model that only included covariates associated with the outcome with a $p < .1$ and a model including all measured covariates. These models included for example, weight at lung function, the month of lung function (a proxy for the season to account for, e.g., pollen exposure), and smoking of the child; for details, see Supporting Information S1: Figure 1. We also conducted an analysis using lung function measured in *z*-scores.

3 | RESULTS

From 3870 participants, 718 were excluded due to insufficient lung function quality, resulting in 2674 with good quality FEV_1 and FVC measures. Of those, 494 had missing air pollution data, resulting in a final study sample of 2180 with lung function and air pollution exposures (Supporting Information S1: Figure 2). Study population characteristics are given in Table 2. The mean age (standard deviation) at lung function was 12 (2.6) years, and 1113 (51%) were male (Table 2). The analyzed sample was similar to the original cohort (Supporting Information S1: Table 3). The distribution of individual pregnancy mean $PM_{2.5}$ levels decreased over time (Supporting Information S1: Figure 3). Thereby, average air pollution estimates during pregnancy were higher than during the preschool period (Table 3). While exposures did not differ between sexes, subjects who were born earlier and thus older at lung function were exposed to higher air pollution levels than younger ones (Supporting Information S1: Table 4).

3.1 | Association of different air pollution exposure windows with lung function at school-age

Prenatal $PM_{2.5}$ exposure was associated with reduced lung function, most prominent in younger children (Figure 1, Table 4). We found a significant interaction for the association between $PM_{2.5}$ exposure during pregnancy and age at lung function (8, 12, and 16 years; *p*-values for interaction all <.001).

For children aged 8 years, a 10 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ during pregnancy was associated with lower FEV_1 (−103.1 mL, 95% confidence interval [CI] −157.5 to −48.8 mL), lower FVC (−88.7 mL, 95% CI −151.3 to −26.2 mL), lower $FEF_{25\%-75\%}$ (−185.8 mL/s, 95% CI −300.3 to −71.4 mL/s), and lower FEV_1/FVC (−0.015, 95% CI −0.026 to −0.005) in the adjusted models. Associations were similar for $PM_{2.5}$ during the first year of life and more pronounced for exposure during preschool age (Figure 1A). For children aged 12 years, associations were weaker. For example, a 10 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ during pregnancy was associated with lower FEV_1 (−54.9 mL, 95% CI −84.7 to −25.2 mL) in the adjusted models, similarly for all pregnancy trimester (Figure 1B). For age 16 years, the association of air pollution exposure during pregnancy was not significant, while exposure during the first year and during preschool age was associated with higher FEV_1 and FVC (Figure 1C). There was no association between NO_2 exposure and lung function during any time window (Table 5, Figure 1A–C). Nonsignificant associations with similar effect sizes were also seen for the first, second, and third trimesters, the first year of life, and preschool time for the different ages.

3.2 | Sensitivity analyses

The associations remained stable in the sensitivity analysis when the basic model was additionally adjusted separately for all assessed covariates (Supporting Information S1: Table 5). Results were also similar when we adjusted only for covariates which were significantly associated with the outcome, and when we adjusted for all measured covariates (Supporting Information S1: Table 6). We also performed an analysis using lung function *z*-scores as outcomes, indicating a consistent negative association between higher $PM_{2.5}$ exposures during pregnancy with lung function at school age (Supporting Information S1: Table 7, Figure 4). To assess the robustness of the effect of $PM_{2.5}$ exposure from different trimesters, we mutually adjusted the extended model to air pollution levels of the least correlated from the other two trimesters. The estimated associations

TABLE 2 Characteristics of the study population ($n = 2180$).

Subjects *n*	Total *n* = 2180	Boys *n* = 1112	Girls *n* = 1068
Characteristic at lung function			
Age (years)	11.99 ± 2.63	12.1 ± 2.63	11.95 ± 2.64
Body mass index (*z*-score)	0.08 ± 1.16	0.11 ± 1.21	0.03 ± 1.12
Height (cm)	152 ± 15.9	154 ± 16.8	151 ± 14.7
Weight (kg)	45 ± 16.1	45.9 ± 16.7	44 ± 15.2
Asthma of the child	303 (13.9)	160 (14.4)	143 (13.4)
Child smoking	69 (3.2)	43 (3.9)	26 (2.4)
Current respiratory infection	799 (36.6)	397 (35.6)	402 (37.5)
Living characteristics			
Socioeconomic status (0–100)[a]	69 (10.8)	70.1 ± 10.8	69.8 ± 10.9
Smoking during pregnancy	149 (6.8)	73 (6.5)	76 (7.1)
Maternal smoking	362 (16.6)	172 (15.5)	190 (17.8)
Paternal smoking	747 (34.3)	386 (34.7)	361 (33.8)
Maternal asthma	193 (8.9)	85 (7.7)	108 (10.9)
Paternal asthma	146 (6.7)	68 (6.1)	78 (7.2)
Pets in the household	936 (42.9)	487 (45.5)	487 (45.5)
Living on a farm	50 (2.3)	23 (2.1)	27 (2.5)
Lung function			
FEV_1 (L)	2.48 ± 0.78 (0.85–5.58)	2.59 ± 0.87 (0.85–5.58)	2.36 ± 0.67 (0.91–4.52)
FEV_1 (*z*-scores)	−0.55 ± 0.98 (−4.18 to 3.59)	−0.54 ± 0.99 (−3.37 to 3.59)	−0.57 ± 0.97 (−4.18 to 2.78)
FVC (L)	2.91 ± 0.94 (0.84–6.48)	3.07 ± 1.05 (0.84–6.48)	2.71 ± 0.77 (0.92–5.01)
FVC (*z*-scores)	−0.43 ± 1.03 (−4.13 to 3.88)	−0.43 ± 1.08 (−3.46 to 3.88)	−0.43 ± 0.97 (−4.13 to 2.77)
FEV_1/FVC	0.86 ± 0.06 (0.56–1)	0.84 ± 0.06 (0.56–1)	0.87 ± 0.06 (0.61–1)
FEV_1/FVC (*z*-scores)	−0.21 ± 1.07 (−3.38 to 2.91)	−0.18 ± 1.07 (−3.38 to 2.91)	−0.24 ± 1.07 (−3.12 to 2.41)
$FEF_{25\%-75\%}$ (L/s)	2.75 ± 1.1 (0.77–7.66)	2.78 ± 1.1 (0.77–7.23)	2.72 ± 0.93 (0.83–7.66)
$FEF_{25\%-75\%}$ (*z*-scores)	−0.61 ± 1.1 (−3.91 to 3.78)	−0.63 ± 1.01 (−3.91 to 2.73)	−0.63 ± 0.99 (−3.49 to 3.78)

Note: Values are mean ± standard deviation and (range) reported for lung function parameters, or number (percentage). Body mass index was calculated according to WHO reference equations.[33] Lung function measurements are presented in *z*-scores according to Quanjer et al.[31]

[a]The Swiss-socioeconomic scores range from 0 (lowest) to 100 (highest).[34]

were overall similar, although slightly attenuated (Supporting Information S1: Table 8).

4 | DISCUSSION

4.1 | Main findings

We modeled individual air pollution exposure during pregnancy, each pregnancy trimester, infancy, and early childhood to assess the association with lung function at school age. We found that $PM_{2.5}$ exposure during pregnancy was associated with airflow limitation and reduced lung volumes at school age. This effect was most prominent in children of early school-age and weaker in the older. We did not identify trimester-specific time windows of susceptibility, possibly because $PM_{2.5}$ exposure levels were highly correlated across these time windows. NO_2 exposure during any exposure time was not associated with childhood lung function.

4.2 | Comparison with literature: Prenatal PM exposure and lung function

We observed, per 10 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ during pregnancy, a reduction of approximately 100 mL FEV_1 and 90 mL FVC loss in 8-year-old children, and a reduction of approximately 5 mL FEV_1 and

TABLE 3 Distribution of estimated residential outdoor air pollutants for different time windows for the study population ($n = 2180$).

	Minimum	Maximum	Mean ± SD	Median
Pregnancy				
$PM_{2.5}$ $\mu g \cdot m^{-3}$	3.4	53.2	24.1 ± 5.5	23.5
NO_2 $\mu g \cdot m^{-3}$	7.1	66.5	26.6 ± 10.5	23.9
First trimester				
$PM_{2.5}$ $\mu g \cdot m^{-3}$	3.3	49.5	24.2 ± 6.3	23.5
NO_2 $\mu g \cdot m^{-3}$	2.8	66.9	26.5 ± 10.9	24.1
Second trimester				
$PM_{2.5}$ $\mu g \cdot m^{-3}$	2.6	54.9	24.1 ± 6.4	23.2
NO_2 $\mu g \cdot m^{-3}$	5.5	66.9	26.6 ± 11.1	24.1
Third trimester				
$PM_{2.5}$ $\mu g \cdot m^{-3}$	4.2	54.9	23.9 ± 6.3	23.3
NO_2 $\mu g \cdot m^{-3}$	5.6	65.8	26.7 ± 11.1	24.5
First year of life				
$PM_{2.5}$ $\mu g \cdot m^{-3}$	5.7	52.6	23.5 ± 5.3	22.9
NO_2 $\mu g \cdot m^{-3}$	6.8	62.6	26.5 ± 5.3	23.9
Preschool				
$PM_{2.5}$ $\mu g \cdot m^{-3}$	11.9	38.6	20.7 ± 3.8	20.4
NO_2 $\mu g \cdot m^{-3}$	9.2	56.9	25.8 ± 10.1	23.2
Short-term exposure before lung function test[a]				
$PM_{2.5}$ $\mu g \cdot m^{-3}$	4.8	27.3	13.1 ± 4.1	12.7
NO_2 $\mu g \cdot m^{-3}$	1.1	63.5	21.4 ± 10.9	19.9

Abbreviations: NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 µm.

[a]7 days mean preceding the lung function test.

6 mL FVC loss in 12-year-old children. Although this deficit is only moderate, it is important to consider that this finding was observed for only a 10 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$. We observed that higher $PM_{2.5}$ during whole pregnancy was associated with larger deficits on subsequent lung function compared to the effect we observed when investigating the effect of $PM_{2.5}$ exposure for each trimester separately. Similarly, Cai et al.[11] also described larger deficits in lung function at ages 9 and 15 years in relation to higher PM_{10} exposure during whole pregnancy compared to different trimesters. Neophytou et al. assessed lung function in 222 children at ages 6–9 and reported largest deficits in lung function for $PM_{2.5}$ exposure during the second half of pregnancy.[16] Further studies support that prenatal exposure to $PM_{2.5}$[15,17] or PM_{10}[17] is associated with lower FVC and FEV_1 growth between ~4 and 11 years, yet specific susceptibly periods during pregnancy were not reported. These findings imply that pregnancy is especially an influential window of exposure, yet it is still controversial whether the whole pregnancy or a specific trimester is most sensitive to air pollution.

We observed that $PM_{2.5}$ during the pregnancy period was negatively associated with FEV_1 and FVC at early school age. Lung development begins in utero with the formation of small airways and continues during childhood. In utero lung development is particularly sensitive to environmental exposures, and recent studies support a transplacental passage of air pollution to the fetus. In humans, it has recently been shown that small particles (black carbon) are able to pass through the placenta and accumulate on the fetal side, thereby potentially resulting in detrimental effects on in utero lung development.[19] Within a mouse model, exposure to $PM_{2.5}$ levels of around 25 $\mu g \cdot m^{-3}$ (which equates to exposure levels in our study), resulted in a suppressed early immune response, compared to mice exposed to clean air.[36] Indirect mechanisms impacting upon in utero lung development may include changes in maternal physiology such as oxidative stress or hypoxia, as well as reduced nutritional transplacental transfer which then affects lung development.[37,38] Therefore, it is plausible that exposure to air pollution results in oxidative stress, impacting upon in utero lung development of the small airways, which may reduce lung function in childhood.

Comparison with previous studies is limited, owing to the assessment of different air pollutants, higher exposure levels, different study populations (e.g., higher asthma prevalence), age at lung function assessment, and statistical models used. Five studies have investigated the association between prenatal $PM_{2.5}$ exposure and subsequent lung function.[12–15,17] Jedrychowski et al. used individual measurements during a monitoring time of 48 h during pregnancy.[13] They grouped participants according to exposure levels, and only for the subgroup of $n = 42$ subjects exposed to $PM_{2.5} > 52.6$ $\mu g \cdot m^{-3}$, a decrease of 89 mL FEV_1 and 92 mL FVC at 5 years lung function was reported. Within a follow-up sample of 294 children of the same cohort, $PM_{2.5}$ exposure during pregnancy was similarly associated with lower FEV_1 and FVC from 4 until 9 years of age.[15] Lee et al. used spatiotemporal models to estimate individual $PM_{2.5}$ and reported a significant decrease in −0.09 *z*-score FVC per 1 $\mu g \cdot m^{-3}$ unit increase. Neophytou et al. reported that an increase from 7.6 to 12.7 $\mu g.m^{-3}$ $PM_{2.5}$ for exposure from pregnancy until 3 years of age was associated with lower FVC and FEV_1 at ages 6–9 years. To summarize, we speculate that even moderate air pollution exposure may reduce the maximum attainable lung function through life,[14] which may have unfavorable long-term implications for lung health.[6]

We found that the effect of $PM_{2.5}$ during pregnancy on childhood lung function was most prominent in early school-aged children and that associations in 16-year-olds were not statistically significant. Several studies suggest that in utero lung development is especially susceptible to air pollution exposure.[4,5,10,11,13,14,16,18,26] Previous studies reported an association between air pollution exposure during early school age[2,16] and birth until adolescence with reduced FEV_1[16,39] and FVC,[16] while low-level $PM_{2.5}$ (mean 13.5 $\mu g \cdot m^{-3}$, range 10.4–19.0 $\mu g \cdot m^{-3}$) exposure during school age was not associated with reduced lung growth.[40]

Only one previous study reported the association between PM_{10} exposure during pregnancy with lung function assessed at different

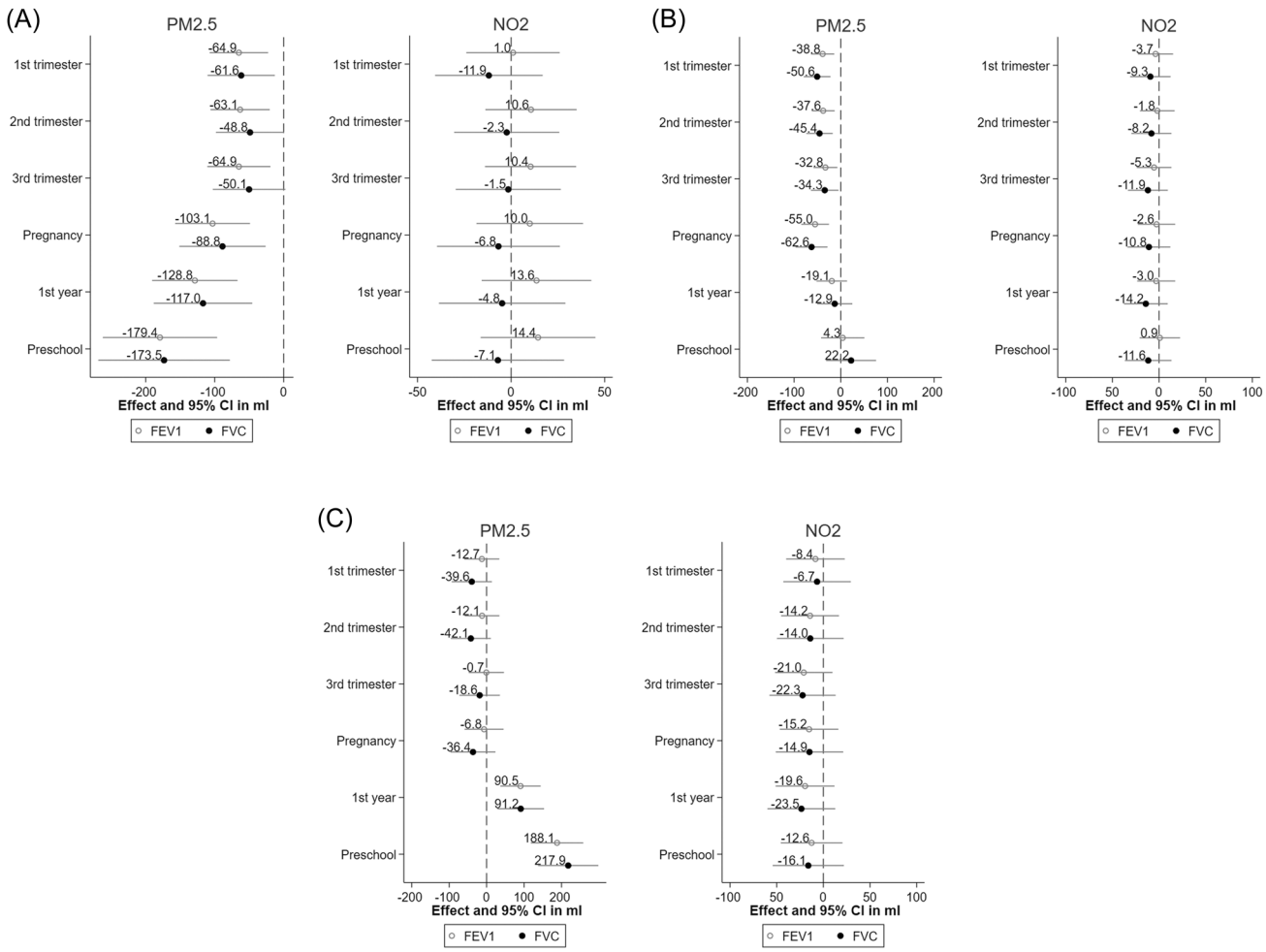

FIGURE 1 Associations of different time periods of average air pollution exposure with lung function at ages 8, 12, and 16 years. Mean changes in FEV_1 and FVC at school age per 10 $\mu g \cdot m^{-3}$ increment in $PM_{2.5}$ or NO_2. Lung function measurements are presented in mL change. The effect of air pollution exposure is presented for different ages: (A) 8 years, (B) 12 years, and (C) 16 years. All models were adjusted for the same covariates from the extended model in Tables 4 and 5, including age, height, and weight at lung function, child's sex and ethnicity, maternal smoking during pregnancy, indoor parental smoking, socioeconomic status, and short-term air pollution preceding the lung function measurement. The model includes an interaction term between the continuous air pollution exposure to $PM_{2.5}$ and NO_2 and the participant's age at lung function centered at a median of 8, 12, and 16 years. Analysis done on $n = 2127$. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm.

timepoints during childhood, and these are in line with our findings.[11] Cai et al. reported that higher PM_{10} exposure during pregnancy from traffic roads was associated with significantly lower FEV_1 at age 8 years. However, for age 15 years, these associations were no longer observed, and as in our study for $PM_{2.5}$ exposure during preschool time, associations were even positive.[11] Few other studies have examined the association between postnatal air pollution and lung function in childhood. Negative associations between air pollution exposure in infancy and lung function at age 8 years were reported in a Swedish[41] and German[42] cohort, but no significant or even better lung function with increased air pollution at 15 years was found.

In general, air quality improved over the study period in our (Supporting Information S1: Figure 3), and previous studies.[26,42,43] Within our study area, the annual mean of $PM_{2.5}$ was about 20 $\mu g \cdot m^{-3}$ in 1998, and in 2020 about 8 $\mu g \cdot m^{-3}$ $PM_{2.5}$.[44] Therefore, children with younger ages at lung function were exposed to lower air pollution levels compared to the older. However, it is unlikely that the decreasing exposure levels biased our results since we found an association between prenatal air pollution exposure and lung function in younger children who were exposed to even lower air pollution levels.

A potential explanation for nonsignificant association between air pollution exposure during pregnancy and lung function at age 16 years could be that the negative effects of higher air pollution levels during early lung development are compensated through catch-up growth during times of lower exposure levels. Other influencing factors relevant for the older study participants are, for example, active smoking and higher cumulative air pollution amounts, which may negatively affect lung function and, therefore, render the overall effects of prenatal air pollution exposure. The cross-sectional

TABLE 4 Association of average $PM_{2.5}$ exposure (per 10 μg·m^{-3} increment) during pregnancy with lung function at median age 8, 12, and 16 years (n = 2125).

	Basic model[b]			Extended model[a]		
	Coef	95% CI	*p* Value	Coef	95% CI	*p* Value
$PM_{2.5}$ exposure during pregnancy						
Outcome at 8 years						
FEV_1 (mL)	−156.1	(−211.3 to −100.8)	**<.001**	−103.1	(−157.5 to −48.8)	**<.001**
FVC (mL)	−163.9	(−228.9 to −98.9)	**<.001**	−88.7	(−151.3 to −26.2)	**.005**
$FEF_{25\%-75\%}$ (mL/s)	−228.9	(−341.1 to −116.8)	**<.001**	−185.8	(−300.3 to −71.4)	**.001**
FEV_1/FVC	−0.012	(−0.023 to −0.001)	**.016**	−0.015	(−0.026 to −0.005)	**.004**
Outcome at 12 years						
FEV (mL)	−65.7	(−94.9 to −36.6)	**<.001**	−54.9	(−84.7 to −25.2)	**<.001**
FVC_1 (mL)	−82.3	(−116.6 to −47.9)	**<.001**	−62.2	(−96.8 to −28.3)	**<.001**
$FEF_{25\%-75\%}$ (mL/s)	−58.3	(−117.5 to 0.9)	.054	−64.5	(−127.1 to −1.8)	**.044**
FEV_1/FVC	−0.001	(−0.007 to 0.004)	.642	−0.002	(−0.008 to 0.003)	.362
Outcome at 16 years						
FEV_1 (mL)	24.7	(−26.4 to 75.7)	.343	−6.7	(−58.7 to 45.2)	.779
FVC (mL)	−0.7	(−60.6 to 59.4)	.984	−36.4	(−96.3 to −23.5)	.234
$FEF_{25\%-75\%}$ (mL/s)	112.4	(8.8 to 215.9)	**.034**	56.9	(−52.9 to 166.4)	.308
FEV_1/FVC	0.010	(0.001 to 0.019)	**.038**	0.010	(0.001 to 0.020)	**.047**

Note: Numbers in bold indicate significant association with $p < 0.05$.

Abbreviations: Coef, coefficient; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75% at exhalation; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm.

Note: Linear regression for the association per 10 μg·m^{-3} increase in $PM_{2.5}$ with lung function measurements in milliliters. The model includes an interaction term between the continuous exposure variable $PM_{2.5}$ and the participant's age centered at a median at 8, 12, and 16 years. The analysis for each age group was done on the entire study sample, including the interaction term; no stratification was done.

[a]Adjusted for age, height, and weight at lung function, child's sex and ethnicity, maternal smoking during pregnancy, indoor parental smoking, socioeconomic status, and short-term air pollution preceding the lung function measurement. Due to missing data in covariates, analysis was done on n = 2125.

[b]Adjusted for age and height at lung function, child's sex, and ethnicity.

assessment of lung function in our study did not allow the investigation of catch up-growth. However, the hypothesis is supported by the Southern California Children's Health Study, where long-term air quality improvements resulted in increased FEV_1 and FVC in children aged 11–15 years.[45]

4.3 | Comparison with literature: Prenatal NO_2 exposure and lung function

Compared to previous studies, we did not find an association between prenatal or early childhood NO_2 exposure with subsequent lung function. These findings were robust for different time windows and during several sensitivity analyses. A previous study including 208 Swiss children from the general population reported a −0.16 z-score reduction in FEV_1 per 8 μg·m^{-3} increase in NO_2.[18] Within another study of 232 children with asthma aged 6–11 years, a per IQR increase in NO_2 resulted in FEV_1 and FVC deficits of 1.2% and 7.1%, though the effect size is difficult to quantify since the IQR is not reported.[5] In a Spanish cohort of 620 children, lung function testing was completed at 4.5 years, and a 16 μg·m^{-3} increase in NO_2 during the second trimester was significantly associated with a 28 mL reduction in FEV_1 and a 33 mL reduction in FVC.[4] Recently, two studies were performed, including 788 and 2942 children with lung function at ages 8.5 and 17.5 years.[10,12] Although NO_2 levels during pregnancy in these studies were much higher compared to all previous studies, Bougas et al. found significant associations with FEV_1 and FVC only in a subgroup of children with repeated lower respiratory tract infections during childhood,[10] while He et al.[12] found an association with reduced FEV_1 and FVC in the entire study

TABLE 5 Association of average NO_2 exposure (per 10 $\mu g \cdot m^{-3}$ increment) during pregnancy with lung function at median age at 8, 12, and 16 years ($n = 2125$).

	Basic model[b]			Extended model[a]		
	Coef	95% CI	*p* Value	Coef	95% CI	*p* Value
NO_2 exposure during pregnancy						
Outcome at 8 years						
FEV_1 (mL)	9.6	(−14.4 to 33.5)	.433	9.9	(−18.5 to 38.4)	.493
FVC (mL)	5.4	(−22.7 to 33.5)	.705	−6.7	(−39.6 to 26.1)	.686
$FEF_{25\%-75\%}$ (mL/s)	20.7	(−27.7 to 69.1)	.402	45.8	(−14.1 to 105.7)	.133
FEV_1/FVC	0.001	(−0.003 to 0.005)	.550	0.005	(−0.001 to 0.010)	.068
Outcome at 12 years						
FEV_1 (mL)	3.1	(−11.7 to 17.8)	.683	−2.6	(−22.6 to 17.3)	.795
FVC (mL)	7.9	(−9.4 to 25.3)	.371	−10.8	(−33.8 to 12.2)	.357
$FEF_{25\%-75\%}$ (mL/s)	5.3	(−24.5 to 35.2)	.726	17.2	(−33.8 to 12.2)	.357
FEV_1/FVC	−0.001	(−0.003 to 0.001)	.578	0.003	(−0.001 to 0.001)	.127
Outcome at 16 years						
FEV_1 (mL)	−3.4	(−32.3 to 25.4)	.817	−15.3	(−46.6 to 16.2)	.341
FVC (mL)	0.62	(−23.5 to 44.3)	.548	−14.8	(−51.1 to 21.3)	.420
$FEF_{25\%-75\%}$ (mL/s)	−10.1	(−68.3 to 48.4)	.737	−11.1	(−77.1 to 54.8)	.741
FEV_1/FVC	−0.002	(−0.003 to 0.001)	.287	0.003	(−0.005 to 0.007)	.773

Note: Linear regression for the association per 10 $\mu g \cdot m^{-3}$ increase in NO_2 with lung function measurements in milliliters. The model includes an interaction term between the continuous exposure variable NO_2 and the participant's age centered at a median of 8, 12, and 16 years. The analysis for each age group was done on the entire study sample, including the interaction term; no stratification was done.

Abbreviations: Coef, coefficient; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75% at exhalation; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm.

[a]Adjusted for age, height, and weight at lung function, child's sex and ethnicity, maternal smoking during pregnancy, indoor parental smoking, socioeconomic status, and short-term air pollution preceding the lung function measurement. Due to missing data in covariates, analysis was done on $n = 2125$.

[b]Adjusted for age and height at lung function, child's sex, and ethnicity.

population. To summarize, effect sizes of prenatal NO_2 on lung function strongly differ between studies, potentially due to different population characteristics, air pollution assessment, and exposure levels.

4.4 | Strengths and limitations

This study is the first to investigate the effect of moderate $PM_{2.5}$ exposure during pregnancy and thereafter on subsequent lung function within a large study sample, extending our understanding of the effects of smaller, more harmful particles on childhood lung development. This study further benefits from novel fine-scale prediction models incorporating information from several monitoring stations as well as satellite data, land use, and meteorological parameters[21,22] enabling us to define precise and individual air pollution estimates.

We acknowledge that the age range at lung function measurement was wide, and hence, children were assessed at different developmental stages. As we further found an interaction between air pollution and age in lung function, we thus reported age-specific results. Air pollution exposure was weighted according to the time spent at each address. However, information on past residential addresses was collected retrospectively, and a recall bias may exist. Address information of the mothers' place of work or from daycare was not assessed; therefore, air pollution for these locations could not be estimated. For older study participants, air pollution estimates were back-extrapolated since the prediction models were not available at this time. However, several studies have shown stable spatial distribution for NO_2 and $PM_{2.5}$, giving us confidence to use back-extrapolation for historical exposures.[46,47] The observed age-dependent susceptibility to air pollution exposure is unlikely to be due to a cohort effect since associations were stronger in those who

were born later and who were exposed to lower air pollution exposure compared to those participants born earlier. The study is limited by the cross-sectional design and only spirometry-based assessment of lung function, which did not allow us to assess the adverse effects of air pollution on lung growth or on static lung volumes. Furthermore, in this field study, objective measures of second-hand smoking or active smoking were not obtained.

5 | CONCLUSION

In conclusion, higher levels of $PM_{2.5}$ exposure during in-utero lung development may lead to airflow limitation and reduced lung volume at school age, most prominently when assessed at a younger age. Compared to previous studies, air pollution exposure levels in our study were rather low, yet we found adverse effects of exposure during pregnancy on lung function. Therefore, our results support that there is no safe level of air pollution, and further stringent air pollution policies emissions are required to protect the respiratory health of children and adults.

AUTHOR CONTRIBUTIONS

Alexander Moeller, Claudia E. Kuehni, and Philipp Latzin conceptualized and designed the study. Jakob Usemann analyzed the data and drafted the manuscript. Rebecca Mozun and Florian Singer supported the analysis. Benjamin Flueckiger and Kees de Hoogh provided the air pollution measurements. Marcel Zwahlen assisted with the statistical analysis. All authors gave input for the interpretation of the data. All authors critically revised and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

Jakob Usemann received funding from the Lungenliga Schweiz, the Palatin Foundation, the University of Basel, and the Swiss Cancer League paid to the institution; and payments or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events received from Vertex Pharmaceuticals and Lunge Zurich, outside the submitted work. Philipp Latzin reports grants or contracts from Vertex Pharmaceuticals and OM Pharma paid to the institution; personal payment or honoraria and payments or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events received from Vertex Pharmaceuticals, Vifor, and OM Pharma; three personal fees and fees paid to the institution for participation on a data safety monitoring or advisory board for Polyphor, Vertex Pharmaceuticals, OM Pharma, and Vifor; personal fees for participation on data safety monitoring or advisory board for Santhera (DMC) and Sanofi Aventis. Alexander Möller reports receiving consulting fees from Vertex Pharmaceuticals and Vifor Pharma; payments or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events received from Vertex Pharmaceuticals and Vifor Pharma; participation on a data safety monitoring or advisory board for Vertex Pharmaceuticals; and leadership or fiduciary roles in other boards, societies, committees or advocacy groups, paid or unpaid, held for European Respiratory Society Assembly 7, Swiss Society of Pulmonology board, Swiss Society of Pediatric Pulmonology board, Swiss Working Group for Cystic Fibrosis and Swiss Society for Sleep Research, Sleep Medicine and Chronobiology. Receipt of medical writing from Vertex Pharmaceuticals. All disclosures made outside the submitted work. Florian Singer reports grants or contracts from the Medical University of Graz and the Lungenliga Bern paid to the institution; personal payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Novartis Pharma, Vertex Pharmaceuticals, and nonfinancial support from Chiesi Pharmaceuticals outside the submitted work. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The ethics committee of the canton of Zurich, Switzerland, approved the study (KEK-ZH-Nr: 2014-0491). Parents signed the informed consent and completed a detailed questionnaire. Children assented orally, and those aged 15 years or older also signed their consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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