Air pollution exposure during pregnancy and lung function in childhood: the LUIS Study

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ONLINE SUPPLEMENTARY INFROMATION

Assessment of air pollution exposure

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 in Switzerland [1,2]. For children born before fine scale prediction models were available, individual exposure were back extrapolated using data from the pollumap dispersion model [3]. The pollumap model was used to derive annual change of the mean pollution over Switzerland for NO_2 and $PM_{2.5}$. These factors of change were then applied to the surface of the earliest fine scale model (for $PM_{2.5}$ year 2003; and for NO_2 year 2005) and back extrapolated until 1996. Values were then assigned to each participant using the extrapolated surfaces. Therefore, for each participant in the final data set, daily air pollution exposures were available during the required time period.

The NO_2 model integrates NO_2 measurements from 67 to 108 monitoring sites depending on the year, with a minimum of 30 measurements per day and site. The $PM_{2.5}$ model integrates data obtained from 10 $PM_{2.5}$ measurement sites between 2003 and 2013 and $PM_{2.5}$ 10 measurements from 89 monitoring sites that were converted to $PM_{2.5}$ concentrations using empirically derived conversion factors. In both models, satellite data, land use, and meteorological parameters were considered in a geostatistical framework. The final prediction models provide estimated daily averages of NO_2 and $PM_{2.5}$ concentrations (in micrograms per cubic meter) at a spatial resolution of 100m×100m. Validation of the NO_2 and $PM_{2.5}$ models was performed using a 10-fold cross-validation by dividing the monitoring data randomly into 10 groups of equal size.

For each of the 10 validations, in turn, the model was trained on 90% of the data and predicted NO_2 and $PM_{2.5}$ on the 10% left out. The predicted NO_2 and $PM_{2.5}$ concentrations of all the test data were then regressed against the measured NO_2 and $PM_{2.5}$ concentrations. This validation step was done to reduce measurement error. The 10-fold cross-validations of the NO_2 and $PM_{2.5}$ models were robust, predicting 57% (NO_2) and 73% ($PM_{2.5}$) of the variation in measured NO_2 and $PM_{2.5}$ concentrations at the 1km×1km level and another 73% (NO_2) and 89% ($PM_{2.5}$) of the variation in the residuals at a 100m×100m and 100m×100m resolution [1,2]. The precision of air pollution estimation in our study was comparable to previously published air pollution models, as discussed previously [1,2].

The parental questionnaire inquired about current residential address and about changes in the residential address before lung function assessment for each participant, including the past address and date of address change. Then, for each participant of the LUIS-study, addresses were geocoded using the building registry of the Swiss Federal Statistical Office (Neuchâtel). Finally, environmental exposures for NO_2 and $PM_{2.5}$ were linked to each child's home address. Address changes which occurred within the study period were considered and exposures were weighted by the time (resolution in days) spent at each address.

Lung function

Spirometry was performed using Masterlab, Jaeger, Würzburg, Germany according to American Thoracic Society (ATS) / ERS recommendations [4]. The children performed 3 to 5 forced expiratory manoeuvres. Spirometry parameters were recorded and stored digitally using the Sentry Suite software, Carefusion, Hoechberg, Germany. Spirometry parameters included forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC ratio, maximum expiratory flow at 75%, 50% and at 25% FVC (FEF_{75}, FEF_{50}, FEF_{25}) and between the 25% and 75% of FVC ($FEF_{25–75\%}$). The spirometry flow-volume curve of the best effort was printed on paper. Each flow-volume curve was reviewed by a study pulmonologist and only test results that met quality criteria standards [5] were included. The flowchart figure E2 displays the selection process from the initial to the final study sample, which only contained study participants with high-quality lung function test results. Lung function measures were all assessed pre-bronchodilation. Absolute values of spirometry parameters were expressed in millilitres (ml) and as z-scores according to Global Lung Initiative (GLI) reference values [6]. Quality control was done as described previously [7].

Risk factors

Information on potential risk and confounding variables was obtained from the parental and children questionnaires. The following factors were assessed based on previous literature: child's age, sex, weight, height, ethnicity, body mass index using WHO growth references [8], asthma of the child (defined as wheeze or use of inhaled corticosteroid use 12 months before lung function), smoking of the child (cigarette use more than 1-2 times ever), current respiratory infection (cough or cold at the day of lung function test), month of lung function, maternal and paternal smoking, smoking during pregnancy, maternal and paternal asthma (self-reported), socio-economic status (Swiss socioeconomic position index, range from 0 (lowest) to 100 (highest) [9]), maternal asthma (self-reported), pets in household. To control for confounding effects of short-term air pollution, average NO_2 and $PM_{2.5}$ concentrations were individually calculated for the 7 days preceding the lung function and also considered for analysis.

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 analysed as continuous measures. We tested for linearity between exposure and response variable, indicating that linear regression models are appropriate. Linear regression models were then fitted to assess the associations of lung function measurements with $PM_{2.5}$ and NO_2 (per 10 $\mu g \cdot m^{-3}$ increment).

Our group has previously shown that GLI based lung function z-scores do not fit Swiss school-aged children well, and that older subjects have lower z-scores [10]. Therefore, we conducted the main analysis using ml rather than z-scores as outcome. Stata (Version 16.0, StataCorp., College Station, TX) was used for statistical analysis, and for plotting the graphs [11].

The following adjustments were *a priori* defined using a directed acyclic graph (see online supplement). The basic model was adjusted for the child's sex, ethnicity, age, and height at lung function, factors known to be associated with lung function [6]. Based on literature, in a more extended model we also included socioeconomic status, maternal smoking during pregnancy, indoor parental smoking, and short-term air pollution preceding the lung function measurement [12,13].

We investigated whether the effect of $PM_{2.5}$ and NO_2 exposure on lung function measurements is different 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 the child's sex and age at lung function measurement into the regression models. We found a significant interaction for the association between air pollution exposure and age at lung function measurement, indicating that effects of air pollution on lung function are different for different ages. Therefore, we present the estimated effect of air pollution exposure for different ages (8, 12 and 16 years).

Spearman 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. Therefore, we analyzed the association between air pollution during each exposure time period with the child's lung function in separate models.

Sensitivity analysis

As sensitivity analyses, we did a model that only included covariates associated with the outcome with a p-value < 0.1, and a model including all measured covariates (for details see directed acyclic graph figure E1 online supplement). We also conducted an analysis using lung function measured in z-scores as outcomes. Because lung function z-scores account for age, sex, height and ethnicity, these covariates were not included in that analysis.

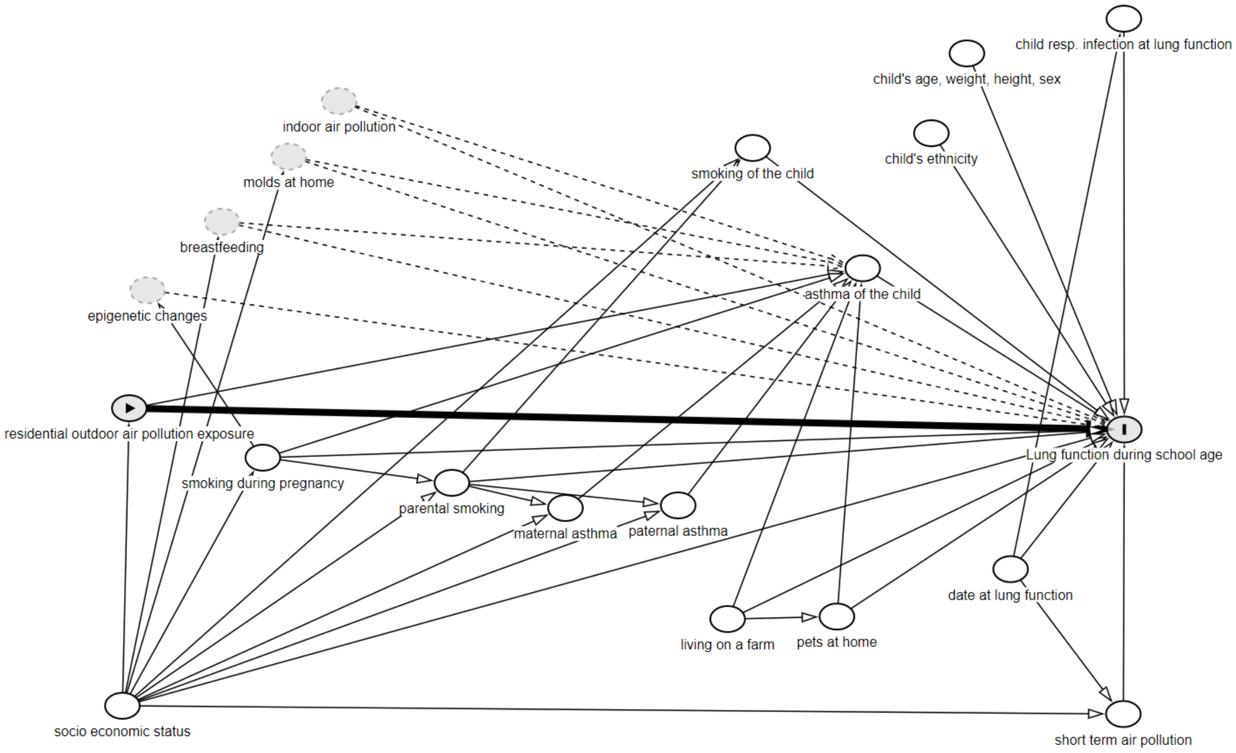

Figure E1 Directed acyclic graph of the association between residential outdoor air pollution exposure and lung function at school age. The exposure air pollution and the outcome lung function is connected with a bold black line. We performed 4 different adjustments in the statistical analysis including model 1, basic model) covariates known to affect lung functional growth model 2, extended model) covariates selected *a priori* according to the literature model 3) based on statistical reasoning, and model 4) including covariates from model 1, 2 and 3 and all other covariates. Grey, with dotted circle shown covariates were not assessed in our study.

model 1 basic model) age and height at lung function, child's sex and ethnicity.

model 2 extended model) 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.

model 3 statistically significant covariates) sex, child's age, height, and weight at lung function, ethnicity, asthma of the child, smoking of the child, current respiratory infection, maternal asthma, pets at home.

model 4 all measured covariates) month at lung function, living on a farm, maternal and paternal asthma and additionally all covariates included in model 1, 2, and 3.

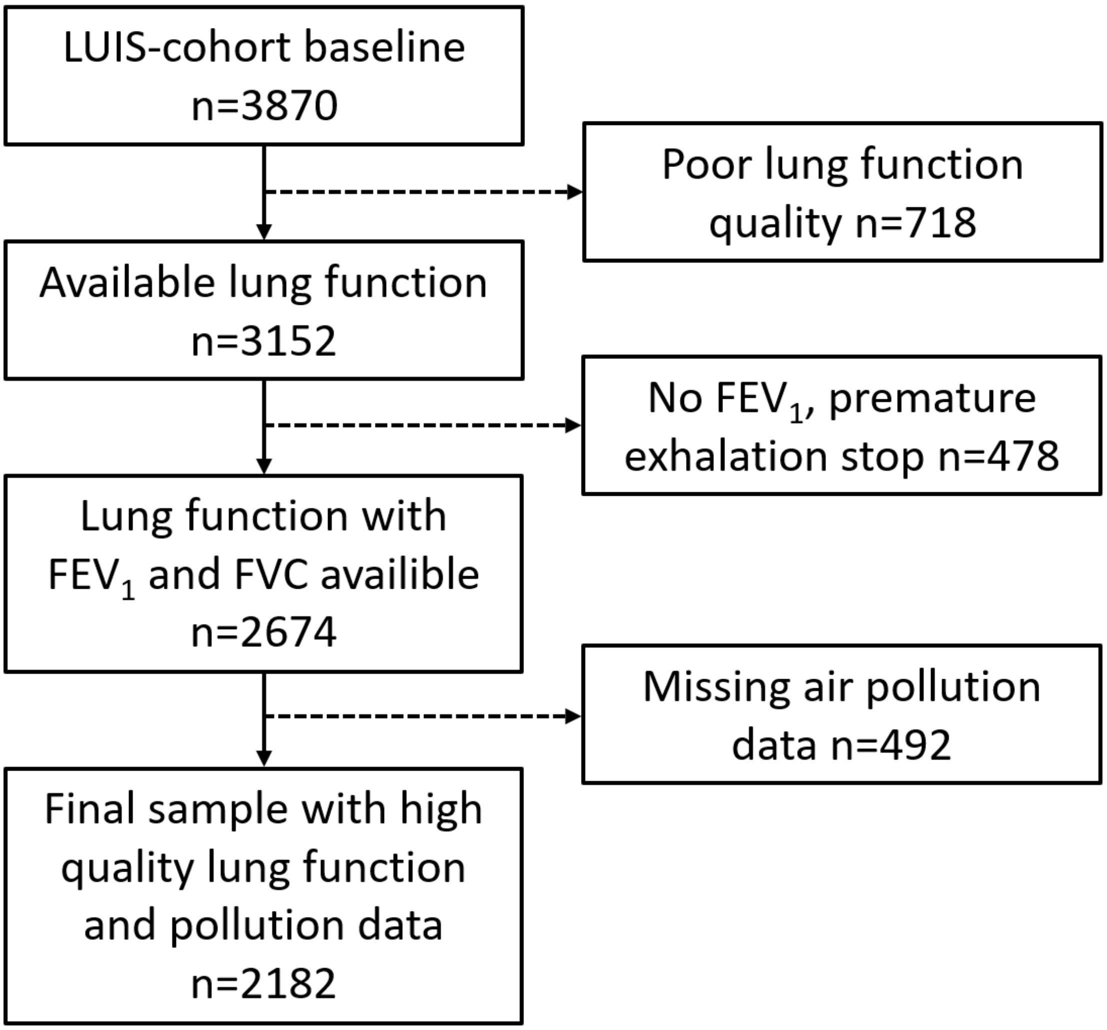

Figure E2 Flow chart of the study population.

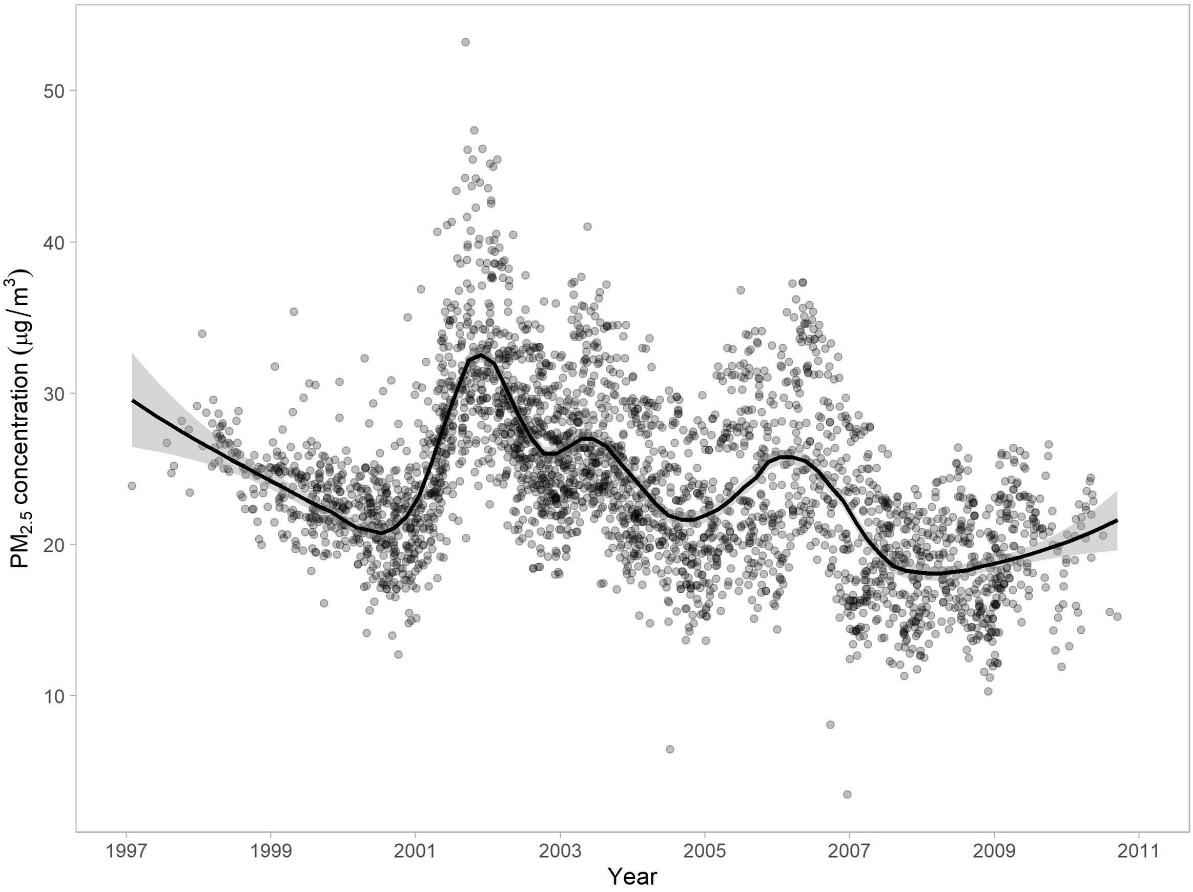

Figure E3 Distribution of air pollution levels over time. Depicted are the individual mean levels with an aerodynamic diameter <2.5 µm (PM$_{2.5}$) during pregnancy. The trend line was computed by a LOWESS smoother using locally weighted polynomial regression with a smoother span of 0.25. Abbreviation: PM$_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 µm.

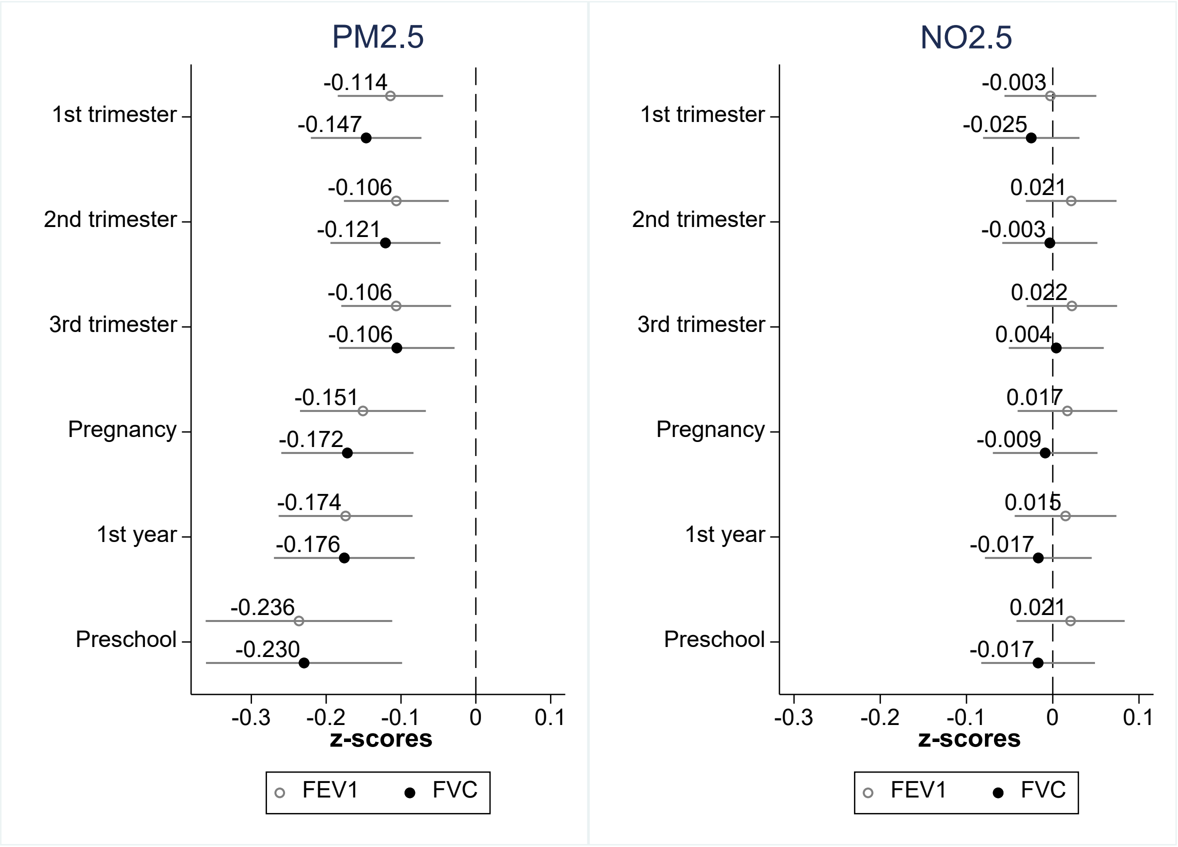

Figure E4 Associations of different time windows of average exposure air pollution exposure with lung function z-scores at school age. Mean changes in FEV_1 and FVC at school age in relation to 10 µg·m^{-3} increase of $PM_{2.5}$ or NO_2. Lung function measurements are presented in z-scores according to Quanjer et al. [14]. Extended model adjusted for weight at lung function, maternal smoking during pregnancy, indoor parental smoking, socioeconomic status, and average air pollution concentrations for the 7 days preceding the lung function measurement. Analysis done on n=212**5**, without interaction terms.

Table E1 Spearman's correlation (rho.) between average modelled $PM_{2.5}$ exposures for the pregnancy trimesters, whole pregnancy, infancy (months 1 to 12), and preschool (pregnancy until age 6.5 years)

	Trimester 1	Trimester 2	Trimester 3	Pregnancy	First year	Preschool
Trimester 1	1					
Trimester 2	0.715	1				
Trimester 3	0.489	0.682	1			
Pregnancy	0.835	0.916	0.835	1		
First year	0.571	0.631	0.704	0.728	1	
Preschool	0.618	0.651	0.667	0.740	0.848	1

All correlations two-tailed with a significance of $p<0.001$.

Table E2 Spearman's correlation (rho.) between average modelled NO_2 exposures for the pregnancy trimesters, whole pregnancy, infancy (months 1 to 12), and preschool (pregnancy until age 6.5 years)

	Trimester 1	Trimester 2	Trimester 3	Pregnancy	First year	Preschool
Trimester 1	1					
Trimester 2	0.905	1				
Trimester 3	0.809	0.878	1			
Pregnancy	0.942	0.971	0.937	1		
First year	0.936	0.929	0.928	0.977	1	
Preschool	0.941	0.928	0.918	0.975	0.9845	1

All correlations two-tailed with a significance of $p<0.001$.

Table E3 Comparison of study participants characteristics form the original cohort and those with available lung function and air pollution exposure

	Original cohort	Final sample	p-value
Subjects n	n=3870	n=2180	
Characteristic at lung function			
Age (years)	12.11±2.71	11.99±2.63	0.004
Body mass index (z-score)	0.06±1.15	0.08±1.16	0.348
Height (cm)	153.75±16.13	152±15.9	<0.001
Weight (kg)	45.88±1.01	45.22±16.01	0.003
Asthma of the child	477 (13.5)	303 (13.9)	0.189
Child smoking	150 (4.31)	69 (3.2)	0.254
Current respiratory infection	1344 (37.9)	799 (36.6)	0.608
Living characteristics			
Socio-economic status (0-100) *	69.22 (10.9)	69 (10.8)	0.952
Smoking during pregnancy	230 (6.7)	149 (6.8)	0.738
Maternal smoking	567 (16.6)	362 (16.6)	0.624
Paternal smoking	1256 (32.9)	747 (34.3)	0.095
Maternal asthma	290 (9.02)	193 (8.9)	0.413
Paternal asthma	218 (6.94)	146 (6.7)	0.490
Pets in the household	1469 (42.9)	936 (42.9)	0.271
Living on a farm	85 (2.3)	50 (2.3)	0.848

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 [8]. The Swiss-socio-economic scores ranges from 0 (lowest) to 100 (highest) [9].

Table E4 Average $PM_{2.5}$ and NO_2 in each time period shown for the child's sex and different ages

	Sex			Mean age			
	boy	girl	p-value	8 years	12 years	14 years	p-value
First trimester							
$PM_{2.5}$ $\mu g \cdot m^{-3}$	23.1	23.6	0.824	21.3	25.3	26.1	<0.001
NO_2 $\mu g \cdot m^{-3}$	24.1	24.3	0.408	29.5	25.5	24.6	<0.001
Second trimester							
$PM_{2.5}$ $\mu g \cdot m^{-3}$	23.5	23.1	0.350	21.2	24.9	25.9	<0.001
NO_2 $\mu g \cdot m^{-3}$	24.5	23.6	0.690	29.7	26.6	24.4	<0.001
Third trimester							
$PM_{2.5}$ $\mu g \cdot m^{-3}$	23.4	23.2	0.463	21.1	24.7	26.1	<0.001
NO_2 $\mu g \cdot m^{-3}$	23.4	23.9	0.463	29.9	25.8	24.2	<0.001
Pregnancy							
$PM_{2.5}$ $\mu g \cdot m^{-3}$	23.7	23.5	0.425	21.2	24.9	25.9	<0.001
NO_2 $\mu g \cdot m^{-3}$	24.3	23.6	0.822	29.7	25.6	24.4	<0.001
1st year of life							
$PM_{2.5}$ $\mu g \cdot m^{-3}$	22.9	22.8	0.615	20.3	23.7	26.5	<0.001
NO_2 $\mu g \cdot m^{-3}$	24.1	23.8	0.837	29.4	25.2	24.5	<0.001
Preschool							
$PM_{2.5}$ $\mu g \cdot m^{-3}$	20..4	20.3	0.648	18.3	20.6	23.3	<0.001
NO_2 $\mu g \cdot m^{-3}$	23.2	23.1	0.813	28.6	24.8	24.1	<0.001

Air pollutants are given in $\mu g \cdot m^{-3}$ $PM_{2.5,}$ particulate matter with an aerodynamic diameter of <2.5 µm. NO_2, nitrogen dioxide. For comparison of air pollution between different ages, we defined three similarly sized groups of 727, 727 and 726 subjects with a mean age (range) of 8.8 (6.0 to 10.9), 12.4 (10.8 to 13.6) and 14.7 (13.6 to 17.5) years. Air pollution levels between sexes were compared with the Mann-Withney test, between different ages with a Kruskal-Wallis test.

Table E5 Sensitivity analysis of the association of average $PM_{2.5}$ exposure during pregnancy with lung function at school-age, basic model additionally adjusted

	$PM_{2.5}$ exposure during pregnancy					
	FEV_1			FVC		
	Coef	95% CI	p-value	Coef	95% CI	p-value
Basic model$^+$	-60.6	(-89.7, -31.4)	**<0.001**	-69.9	(-106.4, -33.5)	**<0.001**
Basic model$^+$ separately additionally adjusted for						
Weight at lung function	-57.2	(-85.8, -28.6)	**<0.001**	-72.1	(-106.2, -37.9)	**<0.001**
Smoking of the child§	-49.3	(-79.2, -19.3)	**<0.001**	-55.7	(-91.8, -19.6)	**<0.001**
Respiratory infection$^\%$	-56.1	(-86.1, -26.2)	**<0.001**	-69.5	(-105.9, -33.1)	**<0.001**
Asthma of the child*	-55.9	(-85.8, -26.1)	**<0.001**	-70.4	(-106.8, -34.1)	**<0.001**
Month at lung function	-59.3	(-89.3, -29.3)	**<0.001**	-74.5	(-110.9, -37.9)	**<0.001**
Maternal asthma	-62.3	(-89.3, -29.3)	**<0.001**	-69.9	(-106.4, -33.5)	**<0.001**
Pregnancy smoking	-52.6	(-82.9, -22,3)	**<0.001**	-69.9	(-106.4, -33.5)	**<0.001**
Parental smoking	-56.8	(-86.8, -26.9)	**<0.001**	-70.3	(-106.7, -33.9)	**<0.001**
Socio economic status	-60.1	(-90.2, -29.9)	**<0.001**	-69.8	(-106.6, -33.1)	**<0.001**
Living on a farm	-53.9	(-84.3, -23.7)	**<0.001**	-69.2	(-105.7 -32.7)	**<0.001**
Pets in the household	-55.1	(-85.4, -24.7)	**<0.001**	-73.5	(-110.1, -36.8)	**<0.001**
Short term air pollution	-59.6	(-90.6, -28.6)	**<0.001**	-67.1	(-105.7, -30.2)	**<0.001**

Linear regression for the association per 10 µg·m^{-3} increase of $PM_{2.5}$ with lung function measurements in milliliter. The basic model is equivalent to the model in table 4 and 5. The basic model$^+$ is adjusted for age and height at lung function, child's sex and ethnicity. § Binary categorized in non-smoking if never or only tried 1-2 times a cigarette, more often smoking considered as smokers. * Defined as wheeze or inhaled corticosteroid use in the 12 months preceding the lung function test. Due to missing data in covariates, analysis done on n=1840. $^\%$ Defined as cough or cold at the day of lung function. Coef, Coefficient; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; $PM_{2.5,}$ particulate matter with an aerodynamic diameter of <2.5 µm.

Table E6 Sensitivity analysis for the association of average air pollution exposure during pregnancy with lung function at school-age, analysis adjusted for statistically significant covariates and for all measured covariates

	Statically significant covariates[+]			All covariates[*]		
			$PM_{2.5}$ exposure during pregnancy			
Outcome	Coef	95% CI	p-value	Coef	95% CI	p-value
FEV_1 (ml)	-54.5	(-84.8, -24.3)	**<0.001**	-57.6	(-89.2, -26.1)	**<0.001**
FVC_1 (ml)	-60.1	(-94.5, -25.6)	**0.001**	-53.7	(-89.6, -17.8)	**0.003**
$FEF_{25-75\%}$ (ml/sec)	-71.9	(-135.9, -7.7)	**0.028**	-97.5	(-164.3, -30.5)	**0.004**
FEV_1/FVC	-0.004	(-0.009, 0.002)	0.226	-0.006	(-0.012, 0.001)	0.055
			NO_2 exposure during pregnancy			
Outcome	Coef	95% CI	p-value	Coef	95% CI	p-value
FEV_1 (ml)	-7.3	(-22.5, 7.8)	0.346	-14.6	(-36.7, 7.1)	0.185
FVC_1 (ml)	-6.9	(-24.3, 10.3)	0.429	-21.1	(-45.9, 3.8)	0.098
$FEF_{25-75\%}$ (ml/sec)	-4.1	(-36.2, 28.1)	0.804	2.6	(-43.8, 49.1)	0.491
FEV_1/FVC	-0.001	(-0.003, 0.002)	0.800	0.002	(-0.002, 0.007)	0.307

Linear regression for the association per 10 $\mu g \cdot m^{-3}$ increase of $PM_{2.5}$ and NO_2 with lung function measurements in milliliter. The model includes an interaction term between the continuous exposure variable $PM_{2.5}$ and the participants age at median at 12 years.

[+] Statically significant covariates: Adjusted for age height and weight at lung function, child's sex and ethnicity, smoking of the child, respiratory infection at lung function, asthma of the child, maternal asthma, pets in household.

[*] All covariates: Adjusted for age height and weight at lung function, child's sex and ethnicity, smoking of the child, respiratory infection at lung function, asthma of the child, maternal asthma, pets in household, month of assessment, smoking during pregnancy, parenteral smoking, socioeconomic status, living on a farm, and average air pollution concentrations for the 7 days preceding the lung function measurement. Due to missing data in covariates, analysis done on n=1840. Coef, Coefficient; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 μm; NO_2, nitrogen dioxide.

Table E7 Association of average air pollution exposure during pregnancy with lung function at school-age, analysis with lung function in z-scores (n=2125)

	Univariate model			Multivariable model*		
	$PM_{2.5}$ exposure from pregnancy until lung function assessment					
Outcome	Coef	95% CI	p-value	Coef	95% CI	p-value
FEV_1 (z-scores)	-0.12	(-0.19, -0.05)	**0.001**	-0.15	(-0.23, -0.06)	**<0.001**
FVC (z-scores)	-0.13	(-0.21, -0.06)	**0.001**	-0.17	(-0.26, -0.08)	**<0.001**
$FEF_{25-75\%}$ (z-scores)	-0.05	(-0.13, 0.02)	0.160	-0.11	(-0.19, 0.03)	0.012
FEV_1/FVC	-0.02	(-0.11, 0.06)	0.555	-0.01	(-0.9, 0.9)	0.393
	NO_2 exposure from pregnancy until lung function assessment					
Outcome	Coef	95% CI	p-value	Coef	95% CI	p-value
FEV_1 (z-scores)	0.04	(0.01, 0.08)	0.050	0.02	(-0.04, 0.07)	0.554
FVC (z-scores)	0.04	(0.01, 0.08)	0.055	-0.01	(-0.07, 0.05)	0.806
$FEF_{25-75\%}$ (z-scores)	0.03	(-0.01, 0.07)	0.150	0.05	(-0.02, 0.11)	0.142
FEV_1/FVC	-0.02	(-0.6, 0.03)	0.471	0.03	(-0.03, 0.09)	0.347

Univariable and multivariable linear regression models for the association per 10 $\mu g \cdot m^{-3}$ increase of $PM_{2.5}$ and NO_2 with lung function measurements in z-scores according to Quanjer et al. [14]. The multivariable model is equivalently adjusted to the extend model in table 4 and 5, excluding those parameters are already used to generate z-scores (age, height, sex, ethnicity). * Adjusted for weight at lung function, maternal smoking during pregnancy, indoor parental smoking, socioeconomic status, and average air pollution concentrations for the 7 days preceding the lung function measurement. Due to missing data in covariates, analysis done on n=2125.Coef, Coefficient; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; $PM_{2.5}$, particulate matter with an aerodynamic diameter of <2.5 µm; NO_2, nitrogen dioxide.

Table E8 Association of average $PM_{2.5}$ exposure (per 10 $\mu g \cdot m^{-3}$ increment) during different trimesters with lung function at median age at 8, 12, and 16 years (n=2125), adjusted additionally for $PM_{2.5}$ exposure during other pregnancy trimesters

	Extended model*			Extended model adjusted for $PM_{2.5}$ exposure during other trimesters^{+}		
			$PM_{2.5}$ exposure during first trimester			
Outcome at 8 years	Coef	95% CI	p-value	Coef	95% CI	p-value
FEV_1 (ml)	-64.9	(-107.4, -22.5)	**0.003**	-61.5	(-104.1, -18.9)	**0.005**
FVC (ml)	-61.6	(-110.4, -12.7)	**0.013**	-58.9	(-108.1, -0.9)	**0.018**
Outcome at 12 years						
FEV_1 (ml)	-38.8	(-63.6, -13.9)	**0.002**	-29.1	(-56.2, -1.8)	**0.037**
FVC (ml)	-50.6	(-79.2, -22.1)	**0.001**	-43.1	(-74.5, -11.8)	**0.007**
Outcome at 16 years						
FEV_1 (ml)	-12.7	(-59.3, 34.1)	0.595	3.5	(-46.7, 53.7)	0.892
FVC (ml)	-39.6	(-93.3, 14.1)	0.149	-27.3	(-85.1, 30.4)	0.354
			$PM_{2.5}$ exposure during second trimester			
Outcome at 8 years	Coef	95% CI	p-value	Coef	95% CI	p-value
FEV_1 (ml)	-63.1	(-106.1, -20.2)	**0.004**	-56.1	(-100.9, -11.1)	**0.014**
FVC (ml)	-48.8	(-98.2, 0.64)	**0.053**	-45.1	(-96.8, 6.6)	0.087
Outcome at 12 years						
FEV_1 (ml)	-37.6	(-62.2, -13.1)	**0.003**	-26.8	(-58.5, -4.4)	0.097
FVC (ml)	-45.4	(-73.7, -17.2)	**0.002**	-39.8	(-76.3, -3.2)	**0.033**
Outcome at 16 years						
FEV_1 (ml)	-12.1	(-58.2, 34.2)	0.608	2.3	(-51.3, 55.9)	0.932
FVC (ml)	-42.1	(-95.5, 11.3)	0.122	-34.5	(-96.2, 27.2)	0.273
			$PM_{2.5}$ exposure during third trimester			
Outcome at 8 years	Coef	95% CI	p-value	Coef	95% CI	p-value
FEV_1 (ml)	-64.9	(-110.6, -19.2)	**0.005**	-56.9	(-103.1, -10.8)	**0.015**
FVC (ml)	-50.1	(-102.8, 2.5)	0.062	-40.3	(-93.3, 12.8)	0.137
Outcome at 12 years						
FEV_1 (ml)	-32.8	(-58.5, -7.2)	**0.012**	-17.9	(-45.9, 9.8)	0.206
FVC (ml)	-34.3	(-63.9, -4.8)	**0.023**	-15.2	(-47.3, 16.8)	0.352
Outcome at 16 years						
FEV_1 (ml)	-0.7	(-47.6, 46.2)	0.975	21.1	(-28.5, 70.5)	0.406
FVC (ml)	-18.6	(-72.6, 35.5)	0.487	9.7	(-47.2, 66.8)	0.737

Linear regression for the association per 10 $\mu g \cdot m^{-3}$ increase in $PM_{2.5}$ with lung function measurements in milliliter. 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. [*]Adjusted for age, height and weight at lung function, child's sex and ethnicity, maternal smoking during pregnancy, indoor parental smoking, socio-economic status, and short-term air pollution preceding the lung function measurement. [+] In addition to the adjustment from the extended model, first and second trimester was adjusted for $PM_{2.5}$ exposure during the third trimester, while the third trimester was adjusted for $PM_{2.5}$ exposure during the first trimester. Due to missing data in covariates, analysis done on n=2125. Coef Coefficient; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; $FEF_{25-75\%}$: forced expiratory flow between 25-75% at exhalation. NO_2, nitrogen dioxide.

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