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Traffic related air pollution is related to interrupter resistance in four-year old children

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Word count 2710

Abstract

Outdoor air pollution has been associated with decrements in lung function and lung function growth in school-age children. Lung function effects have not been examined in preschoolers, with the exception of one study on minute ventilation in newborns. Our goal was to assess the relationship between long- and short term exposure to traffic-related air pollution and interrupter resistance in four-year old children.

Lung function was measured using the interrupter resistance method in children participating in a Dutch birth cohort study. Long-term average air pollution concentrations of fine particulate matter, nitrogen dioxide and soot at the residential address at birth were assessed with land-use regression models. Daily average air pollution concentrations on the clinical examination day were obtained from the National Air Quality Monitoring Network.

Significant associations were found between long-term average air pollution concentrations and interrupter resistance. Interrupter resistance increased by 0.04 $kPa.l^{-1}.s$ (95% confidence interval 0.01–0.07) per interquartile range increase (3.3 $\mu g/m^3$) in fine particle concentration. Short-term exposure was not associated with interrupter resistance.

Long-term exposure to traffic-related air pollution was associated with increased interrupter resistance in 4-year old children, supporting previous birth cohort studies reporting effects of air pollution on subjectively reported respiratory symptoms in pre-school children.

Word count: 200 words

Keywords: air pollution; children; interrupter resistance; lung function; particulate matter

Introduction

Exposure to outdoor air pollution has been associated with increases in respiratory symptoms and decrements in lung function and lung function growth in children.[1-3] In a recent review of short-term exposures, the concentration of particles with a diameter less than 10 μm (PM_{10}) and nitrogen dioxide were associated with increased acute respiratory symptoms and lower peak expiratory flow [3]. Long-term average concentrations of particles smaller than 10 or 2.5 μm have also been associated with decrements in lung function and lung function growth [2]. Exposure to particulate air pollution has been associated with lower lung function growth in children between 10 and 18 year in Southern California [4-7] and 8-year old children living in Mexico city [8]. There is also evidence from cross-sectional studies that particulate matter air pollution is associated with lower lung function [2] Because most of these studies relied on spirometry and since spirometry is difficult to perform for young children, there currently is virtually no data of effects of air pollution exposure on lung function in children younger than six years. One Swiss study reported significant associations between air pollution exposure during pregnancy and minute ventilation in newborns 5 weeks old [9], but it is unclear whether these very early effects can be linked to the school-age spirometry findings. Birth cohort studies have shown effects of air pollution exposure on questionnaire reported respiratory symptoms and allergic sensitisation in the first four years of life [10-12]. It is unknown whether these effects are associated with impairment of lung function.

The Interrupter Resistance (Rint) technique is being used increasingly in preschool children to assess pulmonary function in pediatric practice and research [13-15]. This technique measures the resistance of the respiratory system, by means of a brief interruption of the airflow during tidal breathing. Because this method requires only minimal cooperation of the

patient, the Rint technique can easily be used in preschool-age children [16, 17]. Recently, reference values have been proposed [14]. To date, Rint measurements have rarely been used to investigate effects of environmental exposures such as air pollution. In a study among school- and preschool children, Rint was 7-13% higher when parents smoked at least one cigarette per day versus non-smoking parents [18].

We measured Rint at age four in a large birth cohort study in the Netherlands [19], in which we earlier reported associations between air pollution and allergic sensitisation and respiratory symptoms at ages two and four [10, 11]. The aim of this study was to assess the relationship between long- and short-term exposure to traffic related air pollution and Rint.

Materials and methods

Study population

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study is a prospective birth cohort study [20].Women were recruited in 1996–1997 during their second trimester of pregnancy from a series of communities in the North, West, and center of The Netherlands. Non-allergic pregnant women (n=2,819) were invited to participate in a ‘‘natural history’’ study arm. Pregnant women identified as allergic through the screening questionnaire were allocated primarily to an intervention arm (n=855) with a random subset (n=472) allocated to the natural history arm. The intervention involved the use of mite-impermeable mattress and pillow covers. The study started with 3,963 newborns. Yearly questionnaires completed by the parents, provided data on demographic factors, respiratory symptoms and risk factors for asthma. All children from allergic mothers (n=1,173) and a sample of the children from non-allergic mothers (n=635) were invited for a medical examination, including measurement of Rint [19]. The institutional review boards of the participating institutes approved the study protocol. Written informed consent was obtained from all participants.

Lung function data from the clinical examination at age 8 year [21] in association with air pollution are currently analyzed in the framework of an international study (http://www.escapeproject.eu).

Rint measurement

Procedures for Rint measurement and quality criteria have been described in detail elsewhere [13, 19, 22] . Briefly, Rint was measured with the MicroRint (MicroMedical, Rochester, Kent, UK). Children were measured while breathing quietly, sitting upright and wearing a nose clip. The cheeks and chin were supported by the observer. All measurements were

carried out with a filter (Micro Medical Ltd) in place. Shutter closure was programmed at maximal expiratory tidal flow. Rint values were calculated as the median of at least 5 valid measurements out of 10. The measurements were performed between 18th of October 2000 and 27th of November 2001 by trained investigators. Technicians were trained centrally to standardize the measurements in the three centres and supervised by one investigator to further standardize measurements by the three centres.

We finally included valid Rint data for 880 of the invited 1808 children (49%) in the analysis. A detailed chart flow of the exclusions is included in the online supplement of our earlier paper [19]. Briefly, from 529 children no permission was obtained for medical examination and in 34 children no Rint measurement was made. Rint measurements were not successful in a further 305 children (24%). Rejection criteria were tachypnea, use of the vocal cords, leakage of the mouthpiece and extreme neck flexion or extension. Tracings of flow and pressure with non-visible valve closure, valve closure that was not at the peak of expiration and horizontal or decreasing mouth pressure curves were rejected. We finally excluded children who used inhalation medication in the 12 hours before Rint measurement, resulting in a total of 880 children for the final analysis. The children with valid Rint data did not differ in distribution of population characteristics from the population invited for medical examination, with the exception of small differences in pet ownership and presence of moulds in the home (Table 1).

Exposure assessment

Long-term average concentrations of NO_2, $PM_{2,5}$ and soot at the birth address were assigned using land-use regression models previously described [10, 21, 23]. Briefly, regression models were developed based on air pollution measurements and predictor variables within a Geographic Information System. Air pollution measurements were performed between

February 1999 and July 2000 at 40 sites spread over the Netherlands, including regional background, urban background and traffic sites.[10,23]. Annual average concentrations were obtained from the sampling campaign. The land use regression models included region of the country (lower concentrations in the North), population density and traffic density close to the location.[23] The models explained 73, 81 and 85% of the variability of measured concentrations of $PM_{2.5}$, soot and NO_2.[10,21, 23]. These models were applied to calculate the air pollution concentrations at the birth addresses.

Daily average concentrations of PM_{10}, Black Smoke and NO_2 on the day of and before the medical examination were obtained from the National Air Quality Monitoring Network. We used data from a background location located centrally in the three study areas. Data on daily average outdoor temperature and humidity were available from the nearest station of the Royal Netherlands Meteorological Institute.

Data analysis

The association between long and short-term exposure to air pollution with Rint was assessed by multiple linear regression, adjusting for sex, age at examination (days), height, weight, maternal smoking during pregnancy, any smoking in the child's home, use of gas for cooking, parental allergy, dampness in the home, education of the parents, season, temperature and humidity on the day of the Rint measurement. Sensitivity analyses were performed to test for the effect of cough on the test day, technician administering the test, region of the country and the (mite-impermeable mattress cover) intervention administered in part of the study population.

We further investigated the association between the Rint measurements at age four and the presence of wheeze symptoms and a doctor diagnosis of asthma at age eight using logistic regression. Wheeze and asthma referred to the past 12 months..[21] We further assessed the association of Rint at age four and $FEV_{1.0}$ at age eight using linear regression with the natural logarithm of $FEV_{1.0}$ as the dependent variable and sex, the natural logarithm of age and

weight (all at age 8) and Rint at age 4 as independent variables. All analyses were performed using SAS statistical software (SAS version 9.1, SAS Institute).

Results

Table 1 shows the population characteristics of this study. Fifty-four percent of the study population had parents with high education level, only 11% had parents with low education level. Three-quarter of the children had an allergic parent and very few children had non-Dutch nationality. The Rint test was successful in the the large majority of children, indicating its feasibility at age four. The mean Rint was 0.96 $kPa.l^{-1}.s$ with a standard deviation of 0.24 $kPa.l^{-1}.s$. The children included in the analysis did not differ significantly from the children invited for medical examination, with the exception of small differences in pets and moulds in the home.

Table 2 shows the distribution of long-term and short-term exposure to the air pollutants. Both long-term and short-term exposure had a large contrast within the study population. The modelled concentrations of NO_2 , $PM_{2.5}$ and soot at the birth address were highly correlated (Table 3). The concentrations of PM_{10} and Black Smoke on the test day and the day before the test had a very low correlation with the long-term exposure of the three pollutants at the birth address. NO_2 levels on the test day and the day before the test were moderately correlated with long-term exposures.

Association between air pollution and Rint

A higher long-term average concentration of NO_2, $PM_{2.5}$ and soot at the birth address was associated with a higher Rint (Table 4, Figure 1). Adjustment for individual level confounders, season and weather on the test day, reduced air pollution effect estimates only slightly. Figure 1 shows a monotone increase of Rint with increasing concentration, with no suggestion of a threshold. Because of the very high correlations between the three pollutants, we did not specify two-pollutant models.

There was no significant association between short-term exposure to air pollutants and Rint (Table 4), neither for the concentration on the test day nor for the concentration on the day before the test day.

A model with long-term and short-term exposure simultaneously in one model showed very similar associations as presented in table 4 (data not shown).

Effect modification by sex and parental allergy

No significant differences in association between $PM_{2.5}$ concentration at birth address and Rint were found between boys and girls (p=0.74) and between children with allergic versus non-allergic parents (p=0.26). Effect estimates (standard error in brackets) expressed for an interquartile range increase in $PM_{2.5}$ were 0.0251 (0.0221) for boys versus 0.0430 (0.0216) $kPa.l^{-1}.s$ for girls and 0.0283 (0.0178) $kPa.l^{-1}.s$ for children from allergic parents versus 0.0586 (0.0292) $kPa.l^{-1}.s$ for children from non-allergic parents.

Sensitivity analyses

Associations between air pollution and Rint were not affected by further adjustment for the intervention in part of the study population, technician administering the test and cough reported on the day of the test (table 5). In total, 17 technicians administered the tests. When we additionally adjusted for study region (North, centre, west), air pollution effect estimates were not affected, but confidence intervals were much wider. The wider confidence intervals are explained by reduction in exposure contrast, because region was a predictor variable used in the model that was used to calculate air pollution exposures. Confidence intervals also increased when we adjusted for technician, as different technicians were administering the tests in three study regions.

At the medical examination at age four 564 of 880 children still lived at the birth address. An analysis for the children who still lived at their birth address showed very similar effect estimates as in the full study population: effect estimates expressed per interquartile range increase in exposure were 0.0266 (0.0161) $kPa.l^{-1}.s$ for NO_2, 0.0367 (0.0194) $kPa.l^{-1}.s$ for $PM_{2.5}$ and 0.0339 (0.0173) $kPa.l^{-1}.s$ for soot.

Association between Rint and respiratory health at age eight

The Rint value at age four was a significant predictor of presence of asthma and wheeze at age eight. Odds ratios expressed for an increase of 0.05 Rint units (the approximate air pollution effect estimate) were 1.08 (95%CI 1.03-1.13) for asthma and 1.07 (95%CI 1.02-1.12) for wheeze. Odds ratios were not affected by adjustment for sex, height and weight. Rint at age four was also significantly associated with a lower $FEV_{1.0}$ at age eight, adjusting for age, sex, height and weight. A 0.05 unit higher Rint value at age four, was associated with a -0.78% (95%CI -0.94; -0.61) change in $FEV_{1.0}$ at age eight.

Discussion

Long-term exposure to traffic-related air pollution was significantly associated with Rint in four year old children. No significant association with short-term exposure to air pollution was found.

We earlier reported in this study population an association between long-term air pollution exposure at the birth address and asthma symptoms at age two [10], four [11] and eight years [21]. At age four, we also reported associations between air pollution and sensitisation to major (food) allergens [11]. The current study shows that traffic related air pollution was associated with increased Rint, an objective measure of lung function that reflects airway obstruction.

Associations between long-term exposure to ambient air pollution and lung function have been reported before in schoolchildren [2], but not in four-year old children. Most of the previous studies used spirometry, which cannot be reliably performed in children younger than about six years. We used the Rint technique which has been shown to be useful in objectively assessing respiratory impairment in preschool children [14, 15]. The test has a good short-term repeatability [24] and hence one measurement of Rint can be used in studies assessing long-term exposure effects. Our study suggests that some of the associations reported in cross-sectional studies between ambient air pollution and lung function in school children may already be manifest at an earlier age. A study in Germany investigated the relationship between airway resistance in six-year old children and total suspended particles (TSP) and distance of the home to a major road [25] Airway resistance was measured with a body plethysmograph. TSP was not consistently associated with airway resistance, but children living within 50m of a main road had a 7% higher airway resistance [25]. Our results

further suggest that the Rint method could be a useful tool to assess functional effects at a young age for other risk factors such as environmental tobacco smoke, gas cooking and biological contaminants as well.

The magnitude of the observed association between air pollution and Rint was moderate. An interquartile increase in the $PM_{2,5}$ concentration was associated with an increase in Rint of 0.04 $kPa.l^{-1}.s$ which corresponds to approximately 4% of the population mean Rint. Another study in the same study population showed significant differences in Rint between children with different wheezing phenotypes, which were about three times higher than the increase associated with an interquartile range of $PM_{2.5}$ observed in the current study [19]. In a study among school- and preschool children, smoking of the parents was associated with 7-13% increase in Rint [18]. In our study we did not find any association between smoking and Rint, possibly due to low smoking rates in the birth cohort. Increased Rint at age four was a significant predictor of asthma and wheeze risk and lung function at age eight, adding to the potential importance of our findings.

We did not observe an association between Rint and air pollution exposure on the day of the test or the day before the test. Hence the observed associations with long-term exposure do not reflect only a transient short-term exposure effect. Since our study design consisted of one Rint measurement per subject and hence air pollution effects had to be larger than the between subject variability, we cannot exclude the possibility that small short term effects on Rint are present. Exposure misclassification because of the use of one background site to represent short-term air pollution concentrations in the three areas may have contributed to

the lack of effect. This is unlikely a major bias, as studies have found high temporal correlations between concentrations measured at background sites.[27]

Limitations

We used the air pollution exposure at the birth address as our exposure variable as in previous analyses of this study [10, 11, 21]. Because a large fraction of our study population at age four still lived at their birth address, we cannot disentangle whether it is the exposure at birth or at a later age which drives the associations with Rint. One study in Switzerland reported significant associations between PM_{10} and NO_2 exposure of the mother during pregnancy and minute ventilation measured in newborns of five weeks old [9] We report associations between three pollutants assessed for the birth address. Because of the high correlation between modeled $PM_{2.5}$, NO_2 and soot we cannot disentangle which of the pollutants is driving the observed association, as observed before for this study population [10]. We interpret our findings as showing associations between traffic related air pollution and lung function, with the three pollutants being indicators of the complex ambient mixture.

The children included in this analysis were not a representative sample of the general population of children from the study areas, especially because children from allergic mothers were overrepresented in the selection of the cohort [20]. Children included in this analysis however did not differ in important co-variates from the cohort of children invited for medical examination. We did not find a significant difference in air pollution effect estimates between children with and without allergic parents, so the estimates for this population may apply to the general population of children.

We conclude that long-term exposure to traffic-related air pollution was associated with increased Rint and, hence, reduced airway patency in 4-year old children.

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Table 1: Characteristics of the study population (N=880).

		Included in analysis (N=880)		Invited for medical examination (N=1808)	
Variables		**Mean (SD)**	**N**		
Rint ($kPa.l^{-1}.s$)		0.96 (0.24)	880		
Age at Rint measurement (year)		4.12 (0.22)	880		
Height (cm)		106.22 (4.52)	869		
Weight (kg)		18.58 (2.41)	875		
		n (%)	**N**	**n (%)**	**N**
Sex male		434 (49)	880	923 (51)	1806
Parental allergy		654 (74)	880	1349 (75)	1806
Older siblings		432 (49)	880	870 (48)	1801
Smoking inside child's home[1]		175 (21)	853	357 (22)	1611
Use of gas for cooking[1]		650 (78)	829	1238 (79)	1561
Mother smoking during pregnancy		133 (15)	870	288 (16)	1776
Education parents	Low	93 (11)	871	216 (12)	1757
	Medium	310 (36)	871	664 (37)	1757
	High	468 (54)	871	897 (51)	1757
Nationality Dutch		804 (94)	854	1600 (94)	1705
Mould or damp spots in living room and/or bedroom[1,2]		107 (13)	849	176 (11)	1607
Geyser without outlet present in child's home[1]		23 (3)	824	43 (3)	1539
Pet present in child's home[1,2]		393 (46)	852	790 (49)	1610
Study group					
Intervention – active cover		186 / 880	21	377 / 1806	21
Intervention – placebo cover		165 / 880	19	336 / 1806	19
No intervention		529 / 880	60	1,093 / 1806	61

Education was defined as the highest education level of either mother or father.

[1] at age 4 years

[2] Significant difference between populations (Chi-square test $p<0.05$)

Table 2: Distribution of air pollution concentrations

	N	Minimum	25th percentile	Median	Mean	75th percentile	Maximum
			Annual average at birth address				
NO_2 ($\mu g/m^3$)	880	12.58	18.62	26.04	25.45	28.93	57.46
$PM_{2.5}$ ($\mu g/m^3$)	880	13.54	14.89	17.32	16.90	18.15	24.58
Soot ($10^{-5}m^{-1}$)	880	0.88	1.35	1.78	1.72	1.92	3.27
			Day of Rint measurements				
NO_2 ($\mu g/m^3$)	781	1.75	15.00	28.63	30.09	43.67	90.13
PM_{10} ($\mu g/m^3$)	828	9.25	21.73	27.31	30.88	35.78	163.12
Black smoke ($\mu g/m^3$)	764	0.00	3.00	5.00	8.46	10.00	85.00
			Day before Rint measurements				
NO_2 ($\mu g/m^3$)	782	1.70	13.83	27.63	28.78	43.29	79.06
PM_{10} ($\mu g/m^3$)	827	8.89	21.33	27.12	29.97	35.16	110.96
Black smoke ($\mu g/m^3$)	769	0.00	3.00	5.00	7.54	10.00	64.00

For long-term exposure data were available for PM2.5 (mass of particles smaller than 2.5 µm); for short-term of PM10 (mass of particles smaller than 10 µm). In the Netherlands, $PM_{2.5}$ is typically $0.67*PM_{10.}$ Soot and Black Smoke are measures of black carbon particles using slightly different measurement methods. Soot measured as absorbance of $PM_{2.5.}$

Table 3: Pearson Correlation coefficients of the short- and long-term air pollution concentrations

	$PM_{2,5}$ birth address	Soot birth address	NO_2 day of Rint measurement	PM_{10} day of Rint measurement	BS day of Rint measurement	NO_2 day before Rint measurement	PM_{10} day before Rint measurement	BS day before Rint measurement
NO_2 birth address	0.93**	0.96**	0.55**	0.01	0.07	0.57**	0.03	0.09*
$PM_{2,5}$ birth address		0.97**	0.49**	0.00	0.07	0.51**	0.03	0.10**
Soot birth address			0.53**	0.01	0.08*	0.55**	0.04	0.10**
NO_2 day of Rint measurement				0.47**	0.60**	0.84**	0.25**	0.49**
PM_{10} day of Rint measurement					0.86**	0.34**	0.55**	0.69**
BS day of Rint measurement						0.45**	0.52**	0.82**
NO_2 day before Rint measurement							0.37**	0.56**
PM_{10} day before Rint measurement								0.72**

*p < 0,10 ** p < 0,05

Table 4: Change in Rint ($kPa.l^{-1}.s$) for an interquartile range increase in long-term and short-term air pollution concentration[a]

	NO_2			$PM_{2.5}$ / PM_{10}[b]			Soot / Black Smoke[c]		
	N	**ß *IQR**	**(se *IQR)**	**N**	**ß *IQR**	**(se *IQR)**	**N**	**ß *IQR**	**(se *IQR)**
				Annual average at birth address					
Model 1	880	0.0303**	0.0108	880	0.0464**	0.0133	880	0.0383**	0.0117
Model 1 complete data	765	0.0307**	0.0117	765	0.0475**	0.0145	765	0.0396**	0.0127
Model 2	765	0.0245*	0.0123	765	0.0399**	0.0150	765	0.0337*	0.0132
				Day of Rint measurements					
Model 1	781	0.0206	0.0136	828	0.0117	0.0072	764	0.0082	0.0060
Model 1 complete data	674	0.0166	0.0147	718	0.0097	0.0074	666	0.0049	0.0062
Model 2	674	-0.0019	0.0164	718	0.0045	0.0078	666	-0.0028	0.0070
				Day before Rint measurements					
Model 1	782	0.0079	0.0147	827	0.0071	0.0088	769	0.0094	0.0079
Model 1 complete data	780	0.0067	0.0158	716	0.0034	0.0092	670	0.0055	0.0081
Model 2	780	-0.0132	0.0175	716	-0.0013	0.0094	670	-0.0026	0.0093

[a] Calculated by multiplying regression slope from multiple linear regression with interquartile ranges (Table 2). IQR= interquartile range.

[b] For long-term exposure data were available for PM2.5 (mass of particles smaller than 2.5 µm); for short-term of PM10 (mass of particles smaller than 10 µm)

[c] For long-term exposure data were available for soot, for short-term for Black Smoke. Both are measures of black carbon particles using slightly different measurement methods

Model 1: corrected for age and sex. Model 1 complete data is model adjusted for age and sex with complete confounder data (same N as model 2)

Model 2: model 1 + corrected for height, nationality, siblings, mother smoking during pregnancy, pets, mould/damp spots, smoking inside child's home, use of gas for cooking, geyser without outlet, parental allergy and education parents, temperature, relative humidity and season

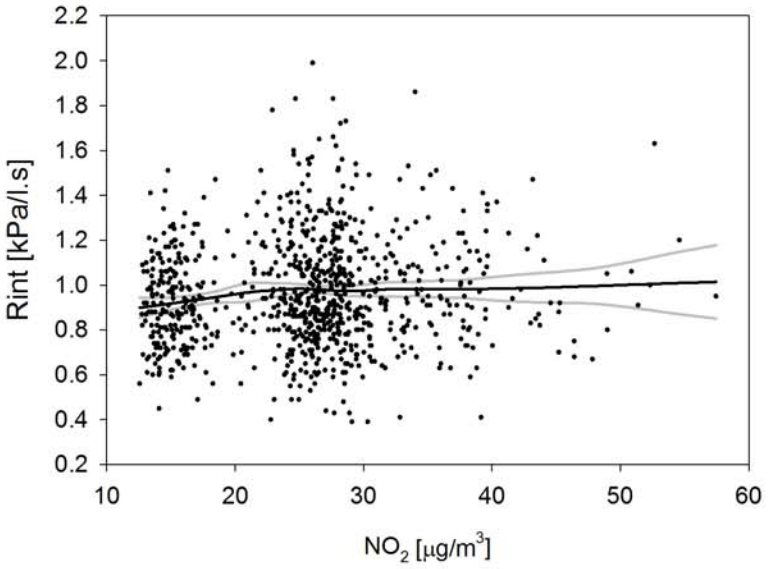
* p-value < 0.05 ** p-value < 0.01

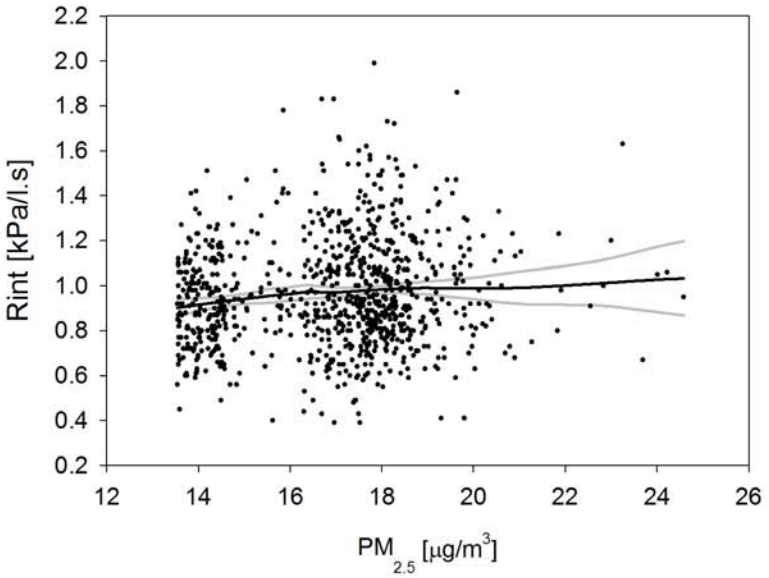
Table 5: Change in Rint ($kPa.l^{-1}.s$) for an interquartile range increase in long-term air pollution concentration: sensitivity analysis[a]

	$[NO_2]$			$[PM_{2.5}]$			Soot		
	N	**ß *IQR**	**(se *IQR)**	**N**	**ß *IQR**	**(se *IQR)**	**N**	**ß *IQR**	**(se *IQR)**
Model 2 (main model)	765	0.0245*	0.0123	765	0.0399*	0.0150	765	0.0337*	0.0132
Model 2 + intervention	765	0.0244*	0.0122	765	0.0390*	0.0146	765	0.0321*	0.0125
Model 2 + cough on test day	765	0.0225#	0.0123	765	0.0418*	0.0239	765	0.0301*	0.0125
Model 2 + technician Rint	765	0.0281	0.0183	765	0.0418#	0.0239	765	0.0356#	0.0188
Model 2 + region of the country	765	0.0248	0.0192	765	0.0400	0.0271	765	0.0368#	0.0210

[a] Calculated by multiplying regression slope from multiple linear regression with interquartile ranges (Table 2). IQR= interquartile range.
Model 2: corrected for age, sex, height, nationality, siblings, mother smoking during pregnancy, pets, mould/damp spots, smoking inside child's home, use of gas for cooking, geyser without outlet, parental allergy and education parents, temperature, relative humidity and season
* p-value < 0.05 # p<0.10

0.0248 (0.0192) for NO_2, 0.0400 (0.0271) for $PM_{2.5}$ and 0.0368 (0.0210) $kPa.l^{-1}.s$ for soot.


Rint [kPa/l.s]
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
10
20
30
40
50
60
NO2 [µg/m3]


Rint [kPa/l.s]
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
12
14
16
18
20
22
24
26
PM2.5 [µg/m3]

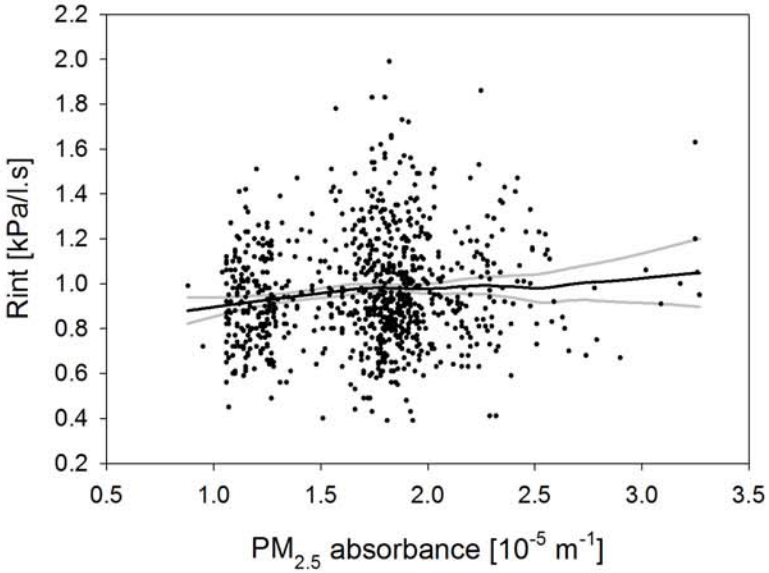

Rint [kPa/l.s]
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.5
1.0
1.5
2.0
2.5
3.0
3.5
PM2.5 absorbance [10-5 m-1]

Figure 1: Scatter plot of the relationship between Rint and annual average concentration of NO_2, $PM_{2.5}$ and soot at the birth address. Solid lines are Loess smoothers (span=0.6) with 95% confidence interval (point-wise 1.96 standard error bands)

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