Eur Respir J 2013; 41: 1257–1263
DOI: 10.1183/09031936.00020812

Traffic-related air pollution is related to interrupter resistance in 4-year-old children

Esther Eenhuizen*, Ulrike Gehring*, Alet H. Wijga[#], Henriette A. Smit[#,¶], Paul H. Fischer[#], Michael Brauer[+], Gerard H. Koppelman[§], Marjan Kerkhof[ƒ], Johan C. de Jongste, Bert Brunekreef*,[¶] and Gerard Hoek***

ABSTRACT: Outdoor air pollution has been associated with decrements in lung function and growth of lung function 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 4-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 using land-use regression models. Daily average air pollution concentrations on the day of clinical examination were obtained from the Dutch 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·s·L^{-1} (95% CI 0.01–0.07) per interquartile range increase (3.3 μg·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 preschool children.

KEYWORDS: Air pollution, children, interrupter resistance, lung function, particulate matter

AFFILIATIONS
*Institute for Risk Assessment Sciences, Utrecht University, Utrecht,
[#]National Institute for Public Health and the Environment, Bilthoven,
[¶]Julius Center for Health Sciences and Primary Care, Utrecht University, Utrecht,
[§]Beatrix Children's hospital, University Medical Centre Groningen, University of Groningen, Groningen,
[ƒ]Dept of Epidemiology, University Medical Centre Groningen, University of Groningen, Groningen, and
**Dept of Paediatrics, Division of Paediatric Respiratory Medicine, Erasmus University Medical Center – Sophia Children's Hospital, Rotterdam, The Netherlands.
[+]University of British Columbia, Vancouver, BC, Canada.

CORRESPONDENCE
G. Hoek
PO Box 80178
3508 TD Utrecht
The Netherlands
E-mail: g.hoek@uu.nl

Received:
Feb 03 2012
Accepted after revision:
July 31 2012
First published online:
Nov 08 2012

Exposure to outdoor air pollution has been associated with increases in respiratory symptoms and decrements in lung function and growth of lung function in children [1–3]. In a recent review of short-term exposures, the concentration of particles with a diameter <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 <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 aged 10–18 years in southern California (USA) [4–7] and 8-year-old children living in Mexico City (Mexico) [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 in young children, there currently is virtually no data of the effects of air pollution exposure on lung function in children <6 years old. 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 4 years of life [10–12]. It is not known whether these effects are associated with impairment of lung function.

The interrupter resistance (R_{int}) technique is being used increasingly in preschool children to assess pulmonary function in paediatric 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 requires only minimal cooperation of the patient, the R_{int} technique can easily be used in preschool-age children [16, 17]. Recently, reference values have been proposed [14]. To date, R_{int} measurements have rarely been

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

used to investigate effects of environmental exposures such as air pollution. In a study among school-aged and preschool children, *R*int was 7–13% higher when parents smoked at least one cigarette per day *versus* nonsmoking parents [18].

We measured *R*int in children aged 4 years in a large birth cohort study in the Netherlands [19], in which we had earlier reported associations between air pollution and allergic sensitisation and respiratory symptoms at ages 2 and 4 years [10, 11]. The aim of this study was to assess the relationship between long- and short-term exposure to traffic-related air pollution and *R*int.

MATERIALS AND METHODS

Study population

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study is a prospective birth cohort study [20]. Females were recruited in 1996–1997 during their second trimester of pregnancy from a series of communities in the north, west and centre of the Netherlands. Nonallergic pregnant females (n=2819) were invited to participate in a ''natural history'' study arm. Pregnant females 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 3963 newborns. Yearly questionnaires completed by the parents provided data on demographic factors, respiratory symptoms and risk factors for asthma. All children of allergic mothers (n=1173) and a sample of the children from nonallergic mothers (n=635) were invited for a medical examination, including measurement of *R*int [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 clinical examinations at age 8 years [21] in association with air pollution are currently analysed in the framework of an international study (www.escapeproject.eu).

*R*int measurement

Procedures for *R*int measurement and quality criteria have been described in detail elsewhere [13, 19, 22]. Briefly, *R*int was measured using the MicroRint (Micro Medical Ltd, Rochester, 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 performed with a filter (Micro Medical Ltd) in place. Shutter closure was programmed at maximal expiratory tidal flow. *R*int values were calculated as the median of at least five valid measurements out of 10. The measurements were performed between October 18, 2000 and November 27, 2001 by trained investigators. Technicians were trained centrally to standardise the measurements in the three centres and supervised by one investigator to further standardise measurements by the three centres.

We finally included valid *R*int data for 880 (49%) out of the invited 1808 children in the analysis. A detailed flow chart of the exclusions is included in the online supplement of our earlier paper [19]. Briefly, no permission was obtained for medical examination from 529 children and no *R*int measurement was made in 34 children. *R*int measurements were not successful in a further 305 (24%) children. Rejection criteria were tachypnoea, use of the vocal cords, leakage of the mouthpiece and extreme neck flexion or extension. Tracings of flow and pressure with invisible valve closure, valve closure that was not at the peak of expiration and horizontal or decreasing mouth pressure curves were rejected. Finally, we excluded children who used inhalation medication in the 12 h before *R*int measurement, resulting in a total of 880 children for the final analysis. The children with valid *R*int data did not differ in the distribution of population characteristics from the population invited for medical examination, with the exception of small differences in pet ownership and the 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, respectively [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 Dutch 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 and *R*int 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 *R*int 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 *R*int measurements at age 4 years and the presence of wheeze symptoms and a doctor diagnosis of asthma at age 8 years using logistic regression. Wheeze and asthma referred to the past 12 months [21]. We further assessed the association of *R*int at age 4 years and forced expiratory volume in 1 s (FEV_1) at age 8 years using linear regression with the natural logarithm of FEV_1 as the dependent variable, and sex, the natural

TABLE 1 Characteristics of the study population

	Included in analysis		Invited for medical examination	
		Total		Total
Subjects		880		1808
***R*int kPa·s·L^{-1}**	0.96±0.24	880		
Age at *R*int measurement years	4.12±0.22	880		
Height cm	106.22±4.52	869		
Weight kg	18.58±2.41	875		
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#	175 (21)	853	357 (22)	1611
Use of gas for cooking#	650 (78)	829	1238 (79)	1561
Mother smoked during pregnancy	133 (15)	870	288 (16)	1776
Parental education				
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#,¶	107 (13)	849	176 (11)	1607
Geyser without outlet present in child's home#	23 (3)	824	43 (3)	1539
Pet present in child's home#,¶	393 (46)	852	790 (49)	1610
Study group				
Intervention: active cover	186 (21)	880	377 (21)	1806
Intervention: placebo cover	165 (19)	880	336 (19)	1806
No intervention	529 (60)	880	1093 (60)	1806

Data are presented as n, mean±SD or n (%). Education was defined as the highest education level of either mother or father. *R*int: interrupter resistance. #: at age 4 years; ¶: significant difference between populations (Chi-squared $p<0.05$).

logarithm of age and weight (all at age 8 years) and *R*int at age 4 years as independent variables. All analyses were performed using SAS statistical software (version 9.1; SAS Institute, Cary, NC, USA).

RESULTS

Table 1 shows the population characteristics of this study. 54% of the study population had parents with a high education level; only 11% had parents with a low education level.

TABLE 2 Distribution of air pollution substance concentrations

	n	Minimum	25th percentile	Median	Mean	75th percentile	Maximum
Annual average at birth address							
NO_2 μg·m^{-3}	880	12.58	18.62	26.04	25.45	28.93	57.46
$PM_{2.5}$ μg·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 *R*int measurements							
NO_2 μg·m^{-3}	781	1.75	15.00	28.63	30.09	43.67	90.13
PM_{10} μg·m^{-3}	828	9.25	21.73	27.31	30.88	35.78	163.12
Black smoke μg·m^{-3}	764	0.00	3.00	5.00	8.46	10.00	85.00
Day before *R*int measurements							
NO_2 μg·m^{-3}	782	1.70	13.83	27.63	28.78	43.29	79.06
PM_{10} μg·m^{-3}	827	8.89	21.33	27.12	29.97	35.16	110.96
Black smoke μg·m^{-3}	769	0.00	3.00	5.00	7.54	10.00	64.00

Long-term exposure data were available for particles <2.5 μm diameter ($PM_{2.5}$) and short-term exposure data for particles <10 μm diameter (PM_{10}). In the Netherlands, $PM_{2.5}$ is typically $0.67 \times PM_{10}$. Soot and black smoke are measures of black carbon particles measured using slightly different methods. Soot was measured as absorbance of $PM_{2.5}$. *R*int: interrupter resistance.

Three-quarters of the children had an allergic parent and very few children had non-Dutch nationality. The *R*int test was successful in the large majority of children, indicating its feasibility at age 4 years. The mean±SD *R*int was 0.96±0.24 kPa·s·L^{-1}. 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- and short-term exposure to the air pollutants. Both long- and short-term exposure had a wide range within the study population. The modelled concentrations of NO_2, PM2.5 and soot at the birth address were highly correlated (table 3). The concentrations of PM10 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 R*int

A higher long-term average concentration of NO_2, PM2.5 and soot at the birth address was associated with a higher *R*int (table 4 and fig. 1). Adjustment for individual level confounders, season and weather on the test day reduced air pollution effect estimates only slightly. Figure 1 shows a monotonic increase of *R*int 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 *R*int (table 4) for the concentration on the test day, nor for the concentration on the day before the test day.

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

Effect modification by sex and parental allergy

No significant differences in association between PM2.5 concentration at birth address and *R*int were found between males and females (p=0.74) and between children with allergic *versus* nonallergic parents (p=0.26). Effect estimates expressed for an interquartile range increase in PM2.5±SE were 0.0251±0.0221 kPa·s·L^{-1} for males *versus* 0.0430±0.0216 kPa·s·L^{-1} for females and 0.0283±0.0178 kPa·s·L^{-1} for children from allergic parents *versus* 0.0586±0.0292 kPa·s·L^{-1} for children of non-allergic parents.

Sensitivity analyses

Associations between air pollution and *R*int 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 adjusted additionally for study region (north, centre and west) air pollution effect estimates were not affected, but confidence intervals were much wider. The wider confidence intervals are explained by a 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.

TABLE 3 Pearson correlation coefficients of short- and long-term air pollution concentrations

	PM2.5 birth address	Soot birth address	NO_2 day of *R*int measurement	PM10 day of *R*int measurement	Black smoke day of *R*int measurement	NO_2 day before *R*int measurement	PM10 day before *R*int measurement	Black smoke day before *R*int measurement
NO_2 birth address	0.93*	0.96*	0.55*	0.01	0.07	0.57*	0.03	0.09#
PM2.5 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 *R*int measurement				0.47*	0.60*	0.84*	0.25*	0.49*
PM10 day of *R*int measurement					0.86*	0.34*	0.55*	0.69*
Black smoke day of *R*int measurement						0.45*	0.52*	0.82*
NO_2 day before *R*int measurement							0.37*	0.56*
PM10 day before *R*int measurement								0.72*

PM2.5: particles with a diameter of <2.5 µm; *R*int: interrupter resistance; PM10: particles with a diameter of <10 µm. *: p<0.05; #: p<0.10.

TABLE 4 Change in interrupter resistance (*R*int) for an interquartile range (IQR) increase in long- and short-term air pollution concentration

	NO_2			$PM_{2.5}/PM_{10}$#			Soot/black smoke¶		
	n	β*IQR	SE*IQR	n	β*IQR	SE*IQR	n	β*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 *R*int 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 *R*int 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

Change in *R*int (kPa·s·L^{-1}) calculated by multiplying regression slopes (β) from multiple linear regression with IQRs (table 2). Model 1: corrected for age and sex; model 1 complete data: model 1 adjusted for age and sex with complete confounder data (same n as model 2); model 2: model 1 plus correction 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 of parents, temperature, relative humidity and season. $PM_{2.5}$: particles with a diameter of <2.5 μm; PM_{10}: particles with diameter of <10 μm; #: data were available for PM2.5 for long-term exposure; data were available for PM_{10} for short-term exposure. ¶: data were available for soot for long-term exposure; data were available for black smoke for short-term exposure. Both are measures of black carbon particles using slightly different measurement methods. *: p<0.05; **: p<0.01.

At the medical examination at age 4 years, 564 out 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±SE expressed per interquartile range increase in exposure were 0.0266±0.0161 kPa·s·L^{-1} for NO_2, 0.0367±0.0194 kPa·s·L^{-1} for $PM_{2.5}$ and 0.0339±0.0173 kPa·s·L^{-1} for soot.

Association between Rint and respiratory health at age 8 years

The *R*int value at age 4 years was a significant predictor of presence of asthma and wheeze at age 8 years. Odds ratios (95% CI) expressed for an increase of 0.05 *R*int units (the approximate air pollution effect estimate) were 1.08 (1.03–1.13) for asthma and 1.07 (1.02–1.12) for wheeze. Odds ratios were not affected by adjustment for sex, height and weight. *R*int at age 4 years was also significantly associated with a lower FEV_1 at age 8 years, adjusting for age, sex, height and weight. A 0.05-unit higher *R*int value at age 4 years was associated with a -0.78% (95%CI -0.94–0.61) change in FEV_1 at age 8 years.

DISCUSSION

Long-term exposure to traffic-related air pollution was significantly associated with *R*int in 4-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 2 [10], 4 [11] and 8 years [21]. At age 4 years, 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 *R*int, an objective measure of lung function which 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 4-year-old children. Most of the previous studies used spirometry, which cannot be performed reliably in children aged <6 years. We used the *R*int 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 *R*int 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 schoolchildren may already be manifest at an earlier age. A study in Germany investigated the relationship between airway resistance in 6-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 50 m of a main road had a 7% higher airway resistance [25]. Our results further suggest that the *R*int 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 *R*int was moderate.

An interquartile range increase in the $PM_{2.5}$ concentration was associated with an increase in *R*int of 0.04 kPa·s·L^{-1}, which

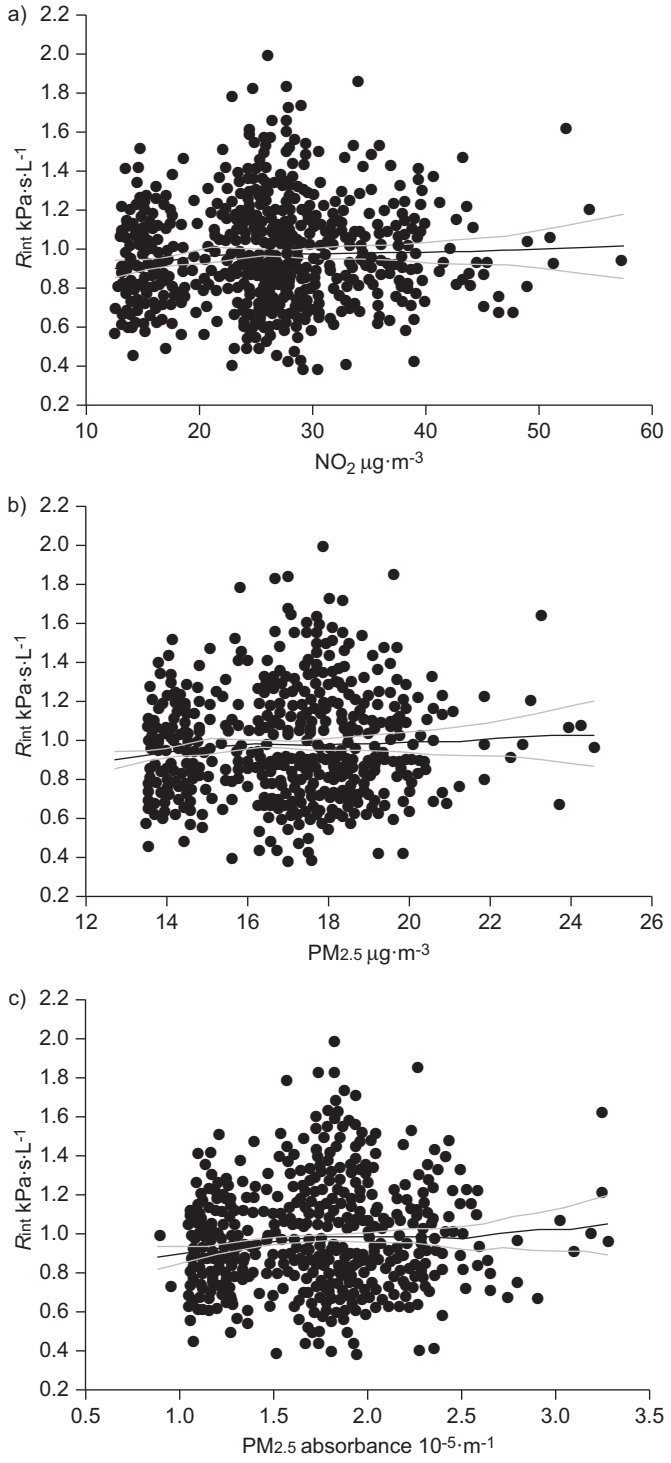

FIGURE 1. Scatter plot of the relationship between interrupter resistance (R_{int}) and a) annual average concentration of NO_2; b) particles with a diameter of <2.5 µm ($PM_{2.5}$); and c) soot at the birth address. Solid lines are Loess smoothers (span=0.6) with 95% CI (point-wise 1.96 SE bands).

corresponds to ~4% of the population mean R_{int}. Another study in the same study population showed significant differences in R_{int} 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 a 7–13% increase in R_{int} [18]. In our study we did not find any association between smoking and R_{int}, possibly due to low smoking rates in the birth cohort. Increased R_{int} at age 4 years was a significant predictor of asthma and wheeze risk and lung function at age 8 years, adding to the potential importance of our findings.

We did not observe an association between R_{int} 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 R_{int} measurement per subject and air pollution effects had to be larger than the between-subject variability, we cannot exclude the possibility that small short-term effects on R_{int} 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 to be a major bias, as studies have found high temporal correlations between concentrations measured at background sites [26].

Limitations

We used 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 4 years 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 R_{int}. 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 5 weeks of age [9]. We report associations between three pollutants assessed for the birth address. Because of the high correlation between modelled $PM_{2.5}$, 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]. However, children included in this analysis did not differ in important covariates 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 R_{int} and, hence, reduced airway patency in 4-year-old children.

SUPPORT STATEMENT

This study was funded by the Netherlands Organisation for Health Research and Development; the Netherlands Organisation for Scientific Research; the Netherlands Asthma Fund; the Netherlands Ministry of Spatial Planning, Housing and the Environment; and the Netherlands Ministry of Health, Welfare and Sport.

TABLE 5 Change in interrupter resistance (R_{int}) for an interquartile range (IQR) increase in long-term air pollution concentration: sensitivity analysis

	NO_2			$PM_{2.5}$			Soot		
	n	β*IQR	SE*IQR	n	β*IQR	SE*IQR	n	β*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	0.0246*	0.0123	765	0.0403*	0.0151	765	0.0339*	0.0132
Model 2 + cough on test day	765	0.0227#	0.0124	765	0.0379*	0.0151	765	0.0318*	0.0132
Model 2 + technician R_{int}	765	0.0283	0.0184	765	0.0432#	0.0247	765	0.0376#	0.0198
Model 2 + region of the country	765	0.0248	0.0192	765	0.0400	0.0271	765	0.0368#	0.0210

Change in R_{int} ($kPa \cdot s \cdot L^{-1}$) calculated by multiplying regression slope (β) from multiple linear regression with IQRs (table 2). 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 of parents, temperature, relative humidity and season. $PM_{2.5}$: particles with a diameter of <2.5 μm. *: $p<0.05$; #: $p<0.10$.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Brunekreef B, Holgate ST. Air pollution and health. *Lancet* 2002; 360: 1233–1242.
2 Götschi T, Heinrich J, Sunyer J, *et al.* Long-term effects of ambient air pollution on lung function: a review. *Epidemiology* 2008; 19: 690–701.
3 Weinmayr G, Romeo E, De Sario M, *et al.* Short-term effects of PM_{10} and NO_2 on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. *Environ Health Perspect* 2010; 118: 449–457.
4 Gauderman WJ, Vora H, McConnell R, *et al.* Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. *Lancet* 2007; 369: 571–577.
5 Gauderman WJ, Avol E, Gilliland F, *et al.* The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004; 351: 1057–1067.
6 Gauderman WJ, McConnell R, Gilliland F, *et al.* Association between air pollution and lung function growth in southern California children. *Am J Respir Crit Care Med* 2000; 162: 1383–1390.
7 Gauderman WJ, Gilliland GF, Vora H, *et al.* Association between air pollution and lung function growth in southern California children: results from a second cohort. *Am J Respir Crit Care Med* 2002; 166: 76–84.
8 Rojas-Martinez R, Perez-Padilla R, Olaiz-Fernandez G, *et al.* Lung function growth in children with long-term exposure to air pollutants in Mexico City. *Am J Respir Crit Care Med* 2007; 176: 377–384.
9 Latzin P, Röösli M, Huss A, *et al.* Air pollution during pregnancy and lung function in newborns: a birth cohort study. *Eur Respir J* 2009; 33: 594–603.
10 Brauer M, Hoek G, Van Vliet P, *et al.* Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am J Respir Crit Care Med* 2002; 166: 1092–1098.
11 Brauer M, Hoek G, Smit HA, *et al.* Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur Respir J* 2007; 29: 879–888.
12 Gehring U, Cyrys J, Sedlmeir G, *et al.* Traffic-related air pollution and respiratory health during the first 2 years of life. *Eur Respir J* 2002; 19: 690–698.
13 Merkus PJ, Mijnsbergen JY, Hop WC, *et al.* Interrupter resistance in preschool children: measurement characteristics and reference values. *Am J Respir Crit Care Med* 2001; 163: 1350–1355.
14 Merkus PJ, Stocks J, Beydon N, *et al.* Reference ranges for interrupter resistance technique: the Asthma UK initiative. *Eur Respir J* 2010; 36: 157–163.
15 Beydon N, Davis SD, Lombardi E, *et al.* An official American Thoracic Society/European Respiratory Society Statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med* 2007; 175: 1304–1345.
16 Caudri D, Wijga AH, Hoekstra MO, *et al.* Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, R_{int} and specific IgE. *Thorax* 2010; 65: 801–807.
17 Child F. The measurement of airways resistance using the interrupter technique (R_{int}). *Paediatr Respir Rev* 2005; 6: 273–277.
18 Kooi EM, Vrijlandt EJ, Boezen HM, *et al.* Children with smoking parents have a higher airway resistance measured by the interruption technique. *Pediatr Pulmonol* 2004; 38: 419–424.
19 Brussee JE, Smit HA, Koopman LP, *et al.* Interrupter resistance and wheezing phenotypes at 4 years of age. *Am J Respir Crit Care Med* 2004; 169: 209–213.
20 Brunekreef B, Smit J, de Jongste J, *et al.* The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002; 13: Suppl. 15, 55–60.
21 Gehring U, Wijga AH, Brauer M, *et al.* Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med* 2010; 181: 596–603.
22 Beelen RM, Smit HA, van Strien RT, *et al.* Short and long term variability of the interrupter technique under field and standardised conditions in 3–6 year old children. *Thorax* 2003; 58: 761–764.
23 Brauer M, Hoek G, van Vliet P, *et al.* Estimating long-term average particulate air pollution concentrations: application of traffic indicators and geographic information systems. *Epidemiology* 2003; 14: 228–239.
24 Beydon N, M'Buila C, Bados A, *et al.* Interrupter resistance short-term repeatability and bronchodilator response in preschool children. *Respir Med* 2007; 101: 2482–2487.
25 Sugiri D, Ranft U, Schikowski T, *et al.* The influence of large-scale airborne particle decline and traffic-related exposure on children's lung function. *Environ Health Perspect* 2006; 114: 282–288.
26 Hoek G, Brunekreef B, Verhoeff A, *et al.* Daily mortality and air pollution in the Netherlands. *J Air Waste Manag Assoc* 2000; 50: 1380–1389.