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# Relation between parental lung function and their offspring's lung function early in life.

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**Running head:** Familial lung function aggregation

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***Abstract***

Objective:

*To investigate the relation between parental lung function and their offspring's lung function measured early in life.*

Methods:

*Infants were participants of the Wheezing Illnesses Study Leidsche Rijn (WHISTLER). Lung function was measured before the age of 2 months using the single occlusion technique. Parental data on lung function (spirometry), medical history and environmental factors were obtained from the linked database of the Utrecht Health Project.*

Results:

*In 546 infants parental data on pulmonary function and covariates were available. Univariate linear regression analysis demonstrated a significant positive relation between the infant's respiratory compliance ($C_{rs}$) and parental $FEF_{25-75\%}$, $FEV_1$ and FVC. A negative significant relation was found between the infant's respiratory resistance ($R_{rs}$) and parental $FEF_{25-75\%}$ and $FEV_1$. No significant relation was found between the infant's respiratory time constant ($\tau_{rs}$) and parental lung function. Adjusting for body size reduced the significance of the observed relations partially, adjusting for shared environmental factors did not change the observed results.*

Conclusion:

*Parental lung function levels are predictors of respiratory mechanics of their newborn infants, which only partially could be explained by familial aggregation of body size. This suggests genetic mechanism in familial aggregation of lung function, which are already detectable early in life.*

## ***Introduction***

A few studies have demonstrated that parameters of lung function measured early in life are predictive for respiratory symptoms and outcome early in childhood [1]. In addition, there are many data showing a genetic trait in wheezing illnesses in childhood with a dominant maternal influence [2;3], but it is not known whether "familial small airways" play a role in the inheritance of wheezing illnesses. Investigations in diverse populations have demonstrated familial aggregation of lung function at older ages [4-6], but whether the similarities of various pulmonary function testing variables are related to common familial environmental exposures or shared genes remains unclear. Several studies have shown a lack of major genetic effects on forced expiratory volume in one second ($FEV_1$) in general populations [7-9], whereas others suggest important genetic effects [10-12]. Moreover, Chen et al illustrated that different pulmonary function indices may have different mechanisms underlying the familial aggregation, e.g., the familial aggregation for $FEV_1$ is most likely controlled by multiple loci with no major gene effect and caused by shared environmental factors whereas for forced vital capacity (FVC) major genetic mechanisms are suggested [7;13]. Whether parental lung function levels are related to early life lung function in their offspring has not been reported, nor which other factors like the age, body size and medical history of parents (asthma or allergy) as well as shared environmental factors during pregnancy and shortly after birth play a role in such relation. In addition, it would be interesting to investigate whether there is a dominant maternal or paternal influence for early life lung function of offspring.

The aim of this study was to investigate in the Wheezing Illnesses Study Leidsche Rijn (WHISTLER) whether parental lung function is related to early life lung function of their offspring and which other factors like the age, body size and medical history of parents as well as shared environmental factors during pregnancy and shortly after birth play a role in this relation.

## Methods

### *Study population*

All infants in the current study are participants of the Wheezing Illnesses Study Leidsche Rijn (WHISTLER), a prospective population-based birth cohort study on determinants (including early life lung function) of wheezing illnesses. Study design and rationale of WHISTLER were described in detail elsewhere [15]. Briefly, healthy infants born in Leidsche Rijn, a new residential area under construction near the city of Utrecht, were invited by telephone to participate in this study before the age of 2 months. Exclusion criteria were gestational age < 36 weeks, major congenital abnormalities and neonatal respiratory disease. A questionnaire filled in by one of the parents was used to gather information on gestational age, birth weight and length and exposure to tobacco smoke (active and passive maternal smoking during pregnancy and passive smoking of the child after birth). Lung function, weight and length were measured at inclusion. The paediatric medical ethics committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained from the parents.

Parental data on medical history, lung function, anthropometrics and environmental factors (smoking status, exposure to pets, socio-economic status) were obtained from the linked database of the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project), a large health monitoring study in Leidsche Rijn, which aims to generate data from all inhabitants on determinants of health and disease as described previously [15;16]. The medical ethics committee of the University Medical Center Utrecht approved the study. Written informed consent was obtained from all participants.

### Lung function tests

Infant lung function was measured before the age of two months. Measurements were performed during natural sleep without the use of any sedation. Data collection was confined to consecutive periods of quiet sleep in which posture was stable and respiration was regular. Lung function was assessed from measurement of passive respiratory mechanics (resistance ($R_{rs}$),

compliance ($C_{rs}$) and time constant ($\tau_{rs}$) of the respiratory system) using the single occlusion technique (SOT)[17]. Airflow was measured using a heated Lilly-type pneumotachometer (series 8300, dead space 1.66 ml, resistance 0.4 cm $H_2O$ at 5 L/min, Hans Rudolph Inc., Kansas City, MO, USA) attached to a face mask (infant mask, Hans Rudolph Inc., Kansas City, MO, USA). The mask was sealed to the infant's face using therapeutic silicone putty (Magic Putty, Oldelft Benelux BV, Delft, the Netherlands) to prevent air leaks and to minimize dead space. Pressure changes at the airway opening were measured with a pressure transducer (Honeywell, type 163PC01D75, Morristown, NJ, USA). Volume was obtained by electronic integration of the airflow signal. Flow, volume and pressure were digitized with a sampling rate of 200 Hz and interfaced to a computer for real-time display, storage and analysis. Before each measurement, calibration of flow and volume signals was performed using a 100-ml precision syringe (Viasys Health, Höchberg, Germany). The pressure transducer was calibrated over the expected range using a pressure transducer tester (VeriCal™, Utah Medical Products Inc., Utah, USA). To be considered acceptable, each occlusion was required to meet the criteria of the ERS/ ATS Task Force on Infant Lung Function[18]. At least three technically acceptable occlusions were used to calculate mean $C_{rs}$, $R_{rs}$ and $\tau_{rs}$ values. Lung function data were calculated offline using a custom-built software package (Luna 1.7, Utrecht, the Netherlands).

Parental lung function was evaluated with a Vitalograph 2120 (Vitalograph Ltd, Buckingham, UK). At least three forced expirations were performed in accordance with the guidelines of the American Thoracic Society [19]. The maximum of the three measurements was used. The lung function variables used in the analysis were: forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$), forced expiratory volume in one second ($FEV_1$) and forced vital

capacity (FVC). The ratio of $FEF_{25-75\%}$/FVC was calculated, a relatively size-independent measure of airway calibre[20].

*Definition of variables*

The role of factors like the age, body size and medical history of parents as well as shared environmental factors during pregnancy and shortly after birth (smoking status of parents, exposure to pets, socio-economic status) in the relation with lung function of parents and their offspring was examined. A positive history of asthma or bronchitis was defined as parents having been diagnosed with of asthma or bronchitis in the last 12 months. A positive history of allergy included allergy to pollen, house dust mite, pets, drugs or food. Based on the questionnaire of the Utrecht Health Project, parents were divided in three smoking categories (never, ex- and current smoker). Based on the WHISTLER questionnaire, three additional smoking variables were available (active and passive maternal smoking during pregnancy and passive smoking of the child after birth). Socio-economic status was based on educational level and defined as low (no formal education, lower secondary education or intermediate secondary education), middle (higher secondary education) or high (higher vocational or university education). The ethnic origin was classified as Caucasian versus non-Caucasian.

*Statistical analysis*

Prior to modeling, all variables were checked for normality of distribution and when necessary logarithmic transformations were applied. Z-scores for parental lung function variables and height and weight were calculated. Linear regression analysis was used to examine the relation between parental lung function variables (sum of absolute values of paternal and maternal forced expiratory

flow between 25% and 75% of FVC ($FEF_{25-75\%}$), forced expiratory volume in one second ($FEV_1$),forced vital capacity (FVC) and sum of the ratio of $FEF_{25-75\%}$/FVC) and their offspring's respiratory resistance ($R_{rs}$), compliance ($C_{rs}$) and time constant ($\tau_{rs}$). Univariate regression models were constructed with lung function variables of the offspring as dependent (outcome) variables and the sum of maternal and paternal lung function variables as the independent variables (model I). Subsequently, five multiple linear regression models were constructed to investigate the influence of respectively age, gestational age and sex (model II), body size of the infant at the time of visit for lung function measurement (model III) and at birth (model IV), body size of parents (model V) as well as exposure to pets, parental socio-economic status (SES), parental smoking status, and parental asthma and allergy status (model VI). To further investigate the role of infant body size (weight at the time of measurement) specific $C_{rs}$ ($C_{rs}$ /kg) and specific $R_{rs}$ ($R_{rs}$ /kg) were used as dependent (outcome) variables in the last model (model VII). Analysis were repeated for maternal and paternal lung function variables separately. Normality of residuals distribution was checked to assess the fit of the models. Results are presented as linear regression coefficients and 95% confidence intervals. Intervals not including zero (p-value $\leq 0.05$) were considered statistically significant. Statistical analysis was performed using SPSS Windows, version 15.0, 2001, Chicago, USA.

**Results**

*Demographic and clinical characteristics of parents and offspring*

Figure 1 shows an overview of recruitment and inclusion of infants in the WHISTLER-study. Among the 1486 included infants, valid lung function measurements were obtained in 1184 infants (79.7%). Failure to obtain technically acceptable measurements was mainly due to failure to fall asleep naturally within 1.5 hours of study onset (14%). Of the infants with successful lung

function, maternal data on pulmonary function and major covariates could be derived from the linked database of the Utrecht Health Project in 685 (57.9%) cases (352 female infants) and paternal data in 602 (50.8%) cases (313 female infants). In 546 infants both maternal and paternal data on pulmonary function and major covariates were available. The mean and standard deviations of age, height, weight, levels of lung function, and the frequency distribution of educational level, smoking status, exposure to pets and allergy and asthma status of the parents and their newborn infant are shown in tables 1 and 2 respectively. Fathers had significantly larger values for all lung function variables, height and weight and there was a two year age difference between fathers and mothers. Among fathers there were more current smokers and education was lower compared to the mothers. Male offspring had a significantly higher birth weight and length and weight and length at the time of lung function measurement compared to female offspring.

*Lung function of parents and offspring*

Table 3 shows the results of the univariate linear regression analysis with the sum of parental lung function variables as the independent variables and their offspring's lung function variables as the dependent (outcome) variables (model I). A significant positive relation between respiratory compliance ($C_{rs}$) of the infant and parental $FEF_{25-75\%}$, $FEV_1$ and FVC was found. A significant negative relation between respiratory resistance ($R_{rs}$) of the infant and parental $FEF_{25-75\%}$ and $FEV_1$ was found. The relation between $R_{rs}$ and $FEF_{25-75\%}$/FVC was borderline significant. No significant relation was found between the respiratory time constant ($\tau_{rs}$) of the infant and parental lung function variables. Figures 2, 3 and 4 show the results of the multiple linear regression models. After adjusting for respectively age, gestational age and sex (model II) as well as exposure to pets, parental socio-economic status (SES), parental smoking status, and parental

asthma and allergy status (model VI) the observed relations remained statistically significant. The relation between $R_{rs}$ and $FEF_{25-75\%}$/FVC was statistically significant in all multiple linear regression models. Adjusting for body size explained only in part the relation between parental lung function and their offspring's lung function. The significance of the relation between $C_{rs}$ and parental FVC (ß=0.02, p=0.075) and between $R_{rs}$ and parental $FEV_1$ (ß=-0.03, p=0.073) was reduced and only showed a trend after adjusting for body size at the time of visit for lung function measurement (model III). The relation between $C_{rs}$ and parental FVC disappeared after adjusting for length and weight at birth (model IV, ß=0.02, p=0.135). Adjusting for weight and length of the parents (model V) did not change the observed results. To further investigate the role of infant body size specific $C_{rs}$ ($C_{rs}$ /kg) and specific $R_{rs}$ ($R_{rs}$ /kg) were used as dependent (outcome) variables in model VII. We found a significant relation between specific $R_{rs}$ and parental $FEF_{25-75\%}$, $FEV_1$ and FVC and between specific $C_{rs}$ and parental $FEF_{25-75\%}$ and $FEV_1$.

Table 4 shows the results of the univariate linear regression analysis with maternal and paternal lung function variables as the independent variables and their offspring's lung function variables as the dependent (outcome) variables (model I). For the mother-infant pairs, univariate linear regression analysis demonstrated a significant positive relation between $C_{rs}$ of the infant and $FEF_{25-75\%}$, $FEV_1$ and FVC. Adjusting for body size and shared environmental factors (model II-VII) did not change the observed relations. A significant positive relation was also found between the respiratory time constant $\tau_{rs}$ and maternal $FEV_1$ and FVC. The relation between $\tau_{rs}$ and maternal $FEV_1$ and FVC however disappeared after adjusting for length and weight at visit and at birth (model III and IV). Adjustments for age, gestational age and sex (model II), maternal weight and length (model V) and exposure to pets, maternal socio-economic status (SES), maternal smoking status, and maternal asthma and allergy status (model VI) did not change the observed

results. No significant association was found between maternal lung function levels and $R_{rs}$, except after adjusting for maternal weight and length (model V) with a borderline significant relation between $R_{rs}$ and $FEF_{25-75\%}$ / FVC (ß=-0.08, p=0.070) and after adjusting for exposure to pets, maternal socio-economic status (SES), maternal smoking status, and maternal asthma and allergy status (model VI) with a borderline significant relation between $R_{rs}$ and $FEF_{25-75\%}$ (ß=-0.03, p=0.054) and $FEV_1$ (ß=-0.04, p=0.073). Specific $R_{rs}$was significantly associated with maternal $FEV_1$ (ß=-0.071, p=0.009).

For the father-infant pair (table 4), there were no significant associations between paternal lung function variables and $C_{rs}$ and specific $C_{rs}$, except after adjusting for age, gestational age and sex (model II) with a significant positive relation between $C_{rs}$ and $FEV_1$ (ß=0.03, p=0.026) and FVC (ß=0.03, p=0.033). For $R_{rs}$, $FEF_{25-75\%}$ and $FEV_1$ showed a significant negative relation which did not change after adjusting for body size and shared environmental factors (model II-VI), except for the relation between $R_{rs}$ and paternal $FEV_1$ (ß=-0.03, p=0.063) only showing a trend after adjusting for infant body size at the time of visit for lung function measurement (model III). No significant association was found between paternal lung function levels and specific $R_{rs}$ and $\tau_{rs}$.

**Discussion**

In this study, we found that parental lung function is a determinant of their offspring's lung function early in life. This relation could in part be explained by familial aggregation of body size. After adjusting for body size of parents and infants the majority of the significant relations between parental and infant lung function remained however significant. This relation could also not be explained by other factors like the age, sex, medical history of parents or shared environmental factors during pregnancy and shortly after birth. This suggests genetic mechanisms

in familial aggregation of lung function, which are already detectable very early in life. To our knowledge, this is the first study investigating the influence of parental lung function parameters in the prediction of their offspring's lung function very early in life.

Some methodological aspects need to be considered. The group of infants selected for this study was a sample from all infants participating in WHISTLER. Selection was based on whether the parents participated in the Utrecht Health Project, as this study provided the parental data. Although parental data could not be compared between included and excluded infants, the baseline characteristics and lung function variables of the excluded infants were similar to those of the infants included for this study (data not shown). Therefore, it is unlikely that selective participation has affected our results. The SOT is a suitable and non-invasive method to measure lung function, but the individual assessment, especially the reliability of the measurements needs to be critically evaluated[17;21]. Difficulties in the underlying assumptions of complete relaxation, equilibration of pressures and a single time constant for the respiratory system could have influence on the validity and accuracy of measurements  In order to ensure that only technically satisfactory data were analysed and reported, measurements were performed by trained personnel according to the criteria of the ERS/ATS Task Force [18].

Although we are comparing lung function variables assessed by two different lung function techniques, it seems reasonable to assume that genetically or environmentally mediated determinants of lung function, including the size of the airways and lungs and the lung elastic recoil and resistance properties will be detected by both techniques. The inverse relation between the sum of parental $FEV_1$, $FEF_{25-75\%}$ and $FEF_{25-75\%}$/ FVC and their offspring's $R_{rs}$ is understandable as all parameters are a reflection of airway caliber (e.g. decrease of $FEV_1$ and $FEF_{25-75\%}$ with higher resistance). In contrast no significant relation was found between the

parental lung volume parameter FVC and $R_{rs}$, For the offspring's $C_{rs}$, a significant positive relation was found with parental $FEV_1$, $FEF_{25-75\%}$ and FVC. $C_{rs}$ reflects composite elastic properties of the infant total respiratory system which apparently correlates with both airway caliber and lung volume characteristics in parents. As proposed by Tager et al, $FEF_{25-75\%}$/ FVC is a measure of airway size relative to lung size ("relative airway size") and in contrast to $R_{rs}$, $C_{rs}$ was not related to this variable. The time constant $\tau_{rs}$ is the time necessary for approximately 63% of the lung to empty and equal to the product of respiratory compliance and resistance. Parental lung function variables were negatively associated with $R_{rs}$ and positively related to $C_{rs}$, which explains that no significant relation was found between parental lung function variables and $\tau_{rs}$. Maternal lung function however showed a significant relation with their offsprings $\tau_{rs}$, most likely due to the dominant maternal effect on $C_{rs}$.

Lung function is known to aggregate in families. A familial effect on measurements of $FEF_{50}$, $FEF_{25-75\%}$, $FEV_1$ , FVC and $FEF_{25-75\%}$/ FVC at older ages has been shown [4-6;22], but there is conflicting evidence as to whether this is genetically determined or due to shared environments. In this study, we found a significant relation between several parental lung function variables and respiratory resistance and compliance of their offspring early in life. A genetic basis for the findings in our study is supported by the fact that after adjusting for shared environmental factors during pregnancy and shortly after birth, such as smoking status of the parents, exposure to pets, parental asthma and allergy status, and socio-economic status, the observed relations remained significant.

To what extent familial aggregation of lung function is primarily a reflection of familial aggregation of body size has been a source of controversy. It is generally agreed that height aggregates in families and pulmonary function measurements are dependent on height [23]. Lebowitz

et al presented strong familial aggregation for FVC, $FEV_1$ and $V_{MAX50}$, but these relations disappeared after controlling for body size [24]. In contrast, Kauffmann et al found that adjustment for body size did not affect the magnitude of the parent-child correlations for $FEF_{23-75\%}$ , $FEV_1$, or FVC [5]. In our study, we found that familial aggregation of weight and length was in part an explanatory variable for the observed relation between parental lung function variables and lung function of their offspring.

It is interesting to note that other studies found a greater correlation in $FEV_1$ and other lung function variables between mothers and offspring compared to fathers and offspring [5;9]. In this study, we also found differences in the relation between maternal and paternal lung function levels and lung function level of their newborn infant. Gender of the parent modifies the relation between parental lung function and lung function of their offspring with a more dominant effect of maternal lung function on their offspring's respiratory compliance and time constant and a more dominant effect of paternal lung function on their offspring's respiratory resistance. There are some interpretations found in the literature. These include exclusive exposure to maternal genetic or environmental factors during pregnancy, differences in shared postnatal environmental exposures, hormonal differences and genetic imprinting, where the genetic factors exert their effects dependent on whether they were inherited from father or mother [25]. In addition, Holberg et al observed a significant maternal-offspring correlation in $FEV_1$ in asthmatic families and suggested a connection with the maternal environment in utero, more in specific that while both parents may contribute to the susceptibility of atopic disease, additional environmental effects with a maternal influence may influence the expression of the genetic factors and subsequently affect lung function[9]. In our study, a positive maternal or paternal history of asthma or allergy did not change the observed associations between parental lung function and lung function of their offspring.

In conclusion, we demonstrated as part of a large prospective population-based birth cohort study on determinants of wheezing illnesses (Wheezing Illnesses Study Leidsche Rijn or WHISTLER) that parental lung function levels are predictors of respiratory mechanics of their newborn infants, which in part could be explained by familial aggregation of body size. This suggest genetic mechanisms in familial aggregation of lung function, which are already detectable very early in life. Although currently speculative, the findings of this study may contribute to the understanding of the genetic mechanism of lung function and subsequently the development and progression of lung disease in childhood and beyond.

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Reference List


(1) Young S, Arnott J, O'Keeffe PT et al. The association between early life lung function and wheezing during the first 2 yrs of life. Eur Respir J 2000; 15(1):151-157.

(2) Celedon JC, Wright RJ, Litonjua AA et al. Day care attendance in early life, maternal history of asthma, and asthma at the age of 6 years. Am J Respir Crit Care Med 2003 May 1;167(9):1239-43 Epub 2002 Nov 21(9):-43.

(3) Moffatt MF, Cookson WO. The genetics of asthma. Maternal effects in atopic disease. Clin Exp Allergy 1998; 28 Suppl 1:56-61; discussion 65-6.:56-61.

(4) Coultas DB, Hanis CL, Howard CA et al. Heritability of ventilatory function in smoking and nonsmoking New Mexico Hispanics. Am Rev Respir Dis 1991; 144(4):770-775.

(5) Kauffmann F, Tager IB, Munoz A et al. Familial factors related to lung function in children aged 6-10 years. Results from the PAARC epidemiologic study. Am J Epidemiol 1989; 129(6):1289-1299.

(6) Lewitter FI, Tager IB, McGue M et al. Genetic and environmental determinants of level of pulmonary function. Am J Epidemiol 1984; 120(4):518-530.

(7) Chen Y, Horne SL, Rennie DC et al. Segregation analysis of two lung function indices in a random sample of young families: the Humboldt Family Study. Genet Epidemiol 1996; 13(1):35-47.

(8) Givelber RJ, Couropmitree NN, Gottlieb DJ et al. Segregation analysis of pulmonary function among families in the Framingham Study. Am J Respir Crit Care Med 1998; 157(5 Pt 1):1445-1451.

(9) Holberg CJ, Morgan WJ, Wright AL et al. Differences in familial segregation of FEV1 between asthmatic and nonasthmatic families. Role of a maternal component. Am J Respir Crit Care Med 1998; 158(1):162-169.

(10) Redline S, Tishler PV, Lewitter FI et al. Assessment of genetic and nongenetic influences on pulmonary function. A twin study. Am Rev Respir Dis 1987; 135(1):217-222.

(11) Wilk JB, Chen TH, Gottlieb DJ et al. A genome-wide association study of pulmonary function measures in the Framingham Heart Study. PLoS Genet 2009; 5(3):e1000429.

(12) Palmer LJ, Knuiman MW, Divitini ML et al. Familial aggregation and heritability of adult lung function: results from the Busselton Health Study. Eur Respir J 2001; 17(4):696-702.

(13) Chen Y, Rennie DC, Lockinger LA et al. Major genetic effect on forced vital capacity: the Humboldt Family Study. Genet Epidemiol 1997; 14(1):63-76.

(14) Martinez FD, Wright AL, Taussig LM et al. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995; 332(3):133-138.

(15) Katier N, Uiterwaal CSPM, de Jong BM et al. The Wheezing Illnesses Study Leidsche Rijn (WHISTLER): Rationale and design. Eur J Epidemiol 2004; 19(9):895-903.

(16) Grobbee DE, Hoes AW, Verheij TJ et al. The Utrecht Health Project: optimization of routine healthcare data for research. Eur J Epidemiol 2005; 20(3):285-287.

(17) Fletcher ME, Baraldi B, Steinbrugger B. Passive respiratory mechanics. In: Stock J, Sly PD, Tepper RS et al, editors. Infant respiratory function testing. New York: Wiley-Liss, 1996: 283-327.

(18) Gappa M, Colin AA, Goetz I et al. Passive respiratory mechanics: the occlusion techniques. Eur Respir J 2001; 17(1):141-148.

(19) Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995; 152(3):1107-1136.

(20) Tager IB, Weiss ST, Munoz A et al. Determinants of response to eucapneic hyperventilation with cold air in a population-based study. Am Rev Respir Dis 1986; 134(3):502-508.

(21) Katier N, Uiterwaal CS, de Jong BM et al. Feasibility and variability of neonatal and infant lung function measurement using the single occlusion technique. Chest 2005; 128(3):1822-1829.

(22) DeMeo DL, Carey VJ, Chapman HA et al. Familial aggregation of FEF(25-75) and FEF(25-75)/FVC in families with severe, early onset COPD. Thorax 2004; 59(5):396-400.

(23) Xu J, Bleecker ER, Jongepier H et al. Major recessive gene(s) with considerable residual polygenic effect regulating adult height: confirmation of genomewide scan results for chromosomes 6, 9, and 12. Am J Hum Genet 2002; 71(3):646-650.

(24) Lebowitz MD, Knudson RJ, Burrows B. Family aggregation of pulmonary function measurements. Am Rev Respir Dis 1984; 129(1):8-11.

(25) Raby BA, Van Steen K, Celedon JC et al. Paternal history of asthma and airway responsiveness in children with asthma. Am J Respir Crit Care Med 2005; 172(5):552-558.

**Figure legends**

**Figure 1:** Overview of the inclusion of infants.

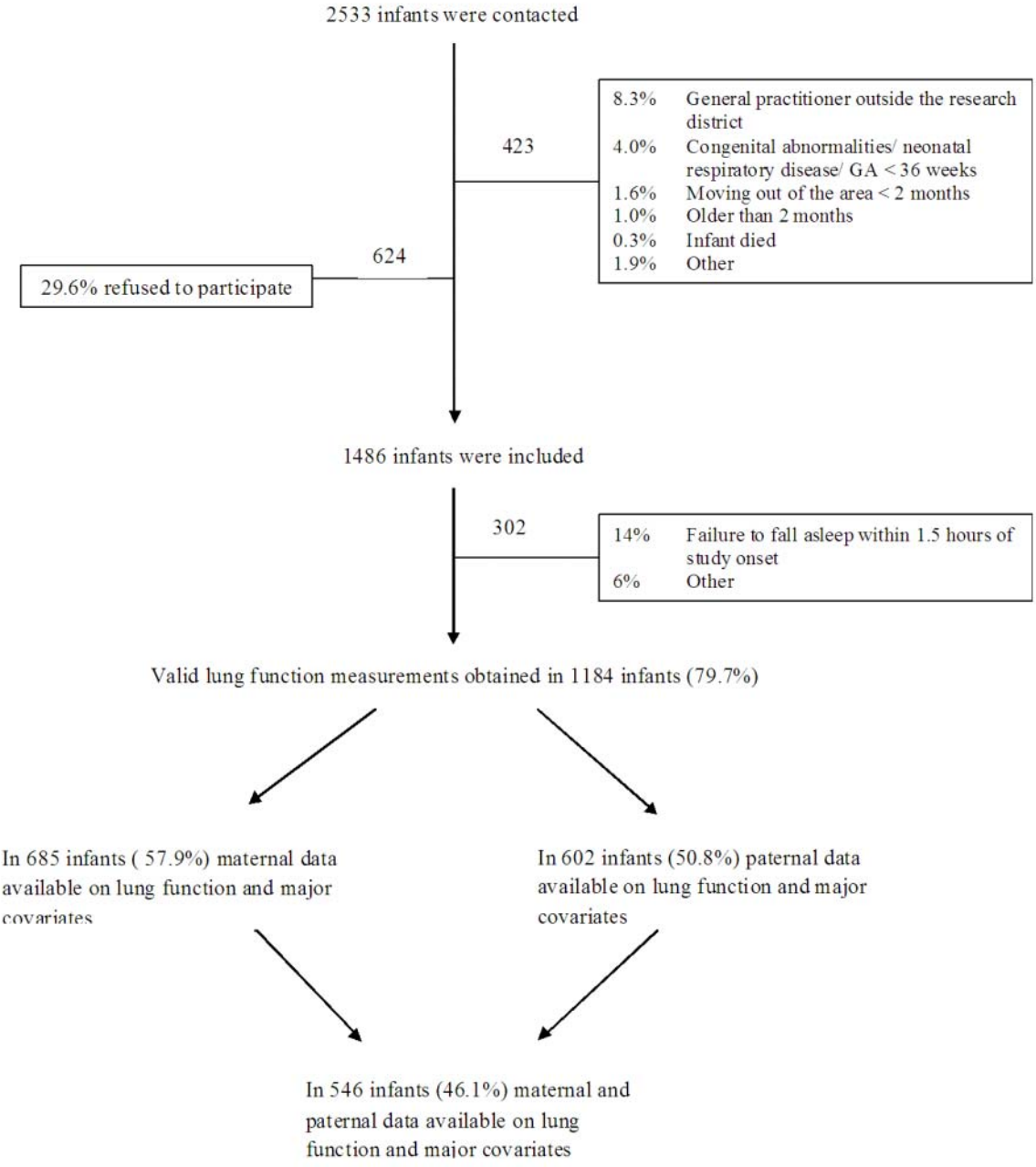
2533 infants were contacted
423
8.3% General practitioner outside the research district
4.0% Congenital abnormalities/ neonatal respiratory disease/ GA < 36 weeks
1.6% Moving out of the area < 2 months
1.0% Older than 2 months
0.3% Infant died
1.9% Other
624
29.6% refused to participate
1486 infants were included
302
14% Failure to fall asleep within 1.5 hours of study onset
6% Other
Valid lung function measurements obtained in 1184 infants (79.7%)
In 685 infants ( 57.9%) maternal data available on lung function and major covariates
In 602 infants (50.8%) paternal data available on lung function and major covariates
In 546 infants (46.1%) maternal and paternal data available on lung function and major covariates

**Figure 2:** The relation between parental lung function ($FEF_{25-75\%}$ = forced expiratory flow between 25% en 75% ; $FEV_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; ratio $FEF_{25-75\%}$ / FVC ) and compliance ($C_{rs}$) of their offspring: unadjusted and adjusted linear regression coefficients and 95% confidence interval

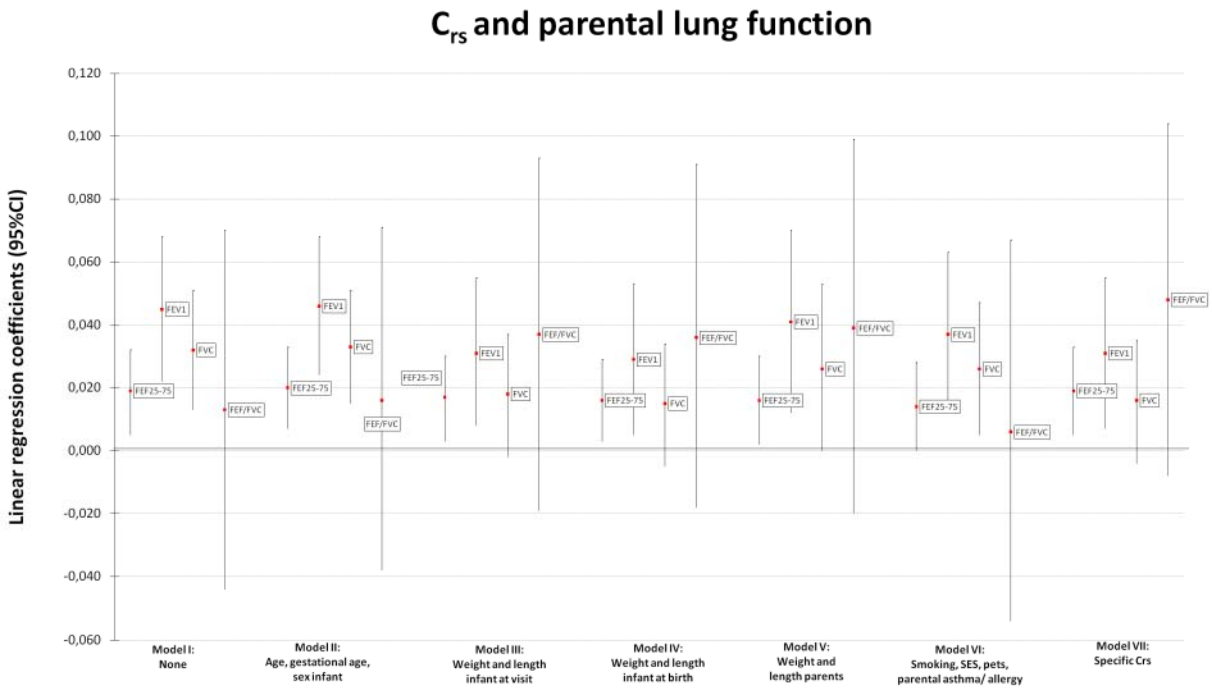


**Figure 3:** The relation between parental lung function ($FEF_{25-75\%}$ = forced expiratory flow between 25% en 75% ; $FEV_1$ forced expiratory volume in 1 second; FVC = forced vital capacity; ratio $FEF_{25-75\%}$ / FVC) and resistance ($R_{rs}$) of their offspring: unadjusted and adjusted linear regression coefficients and 95% confidence interval

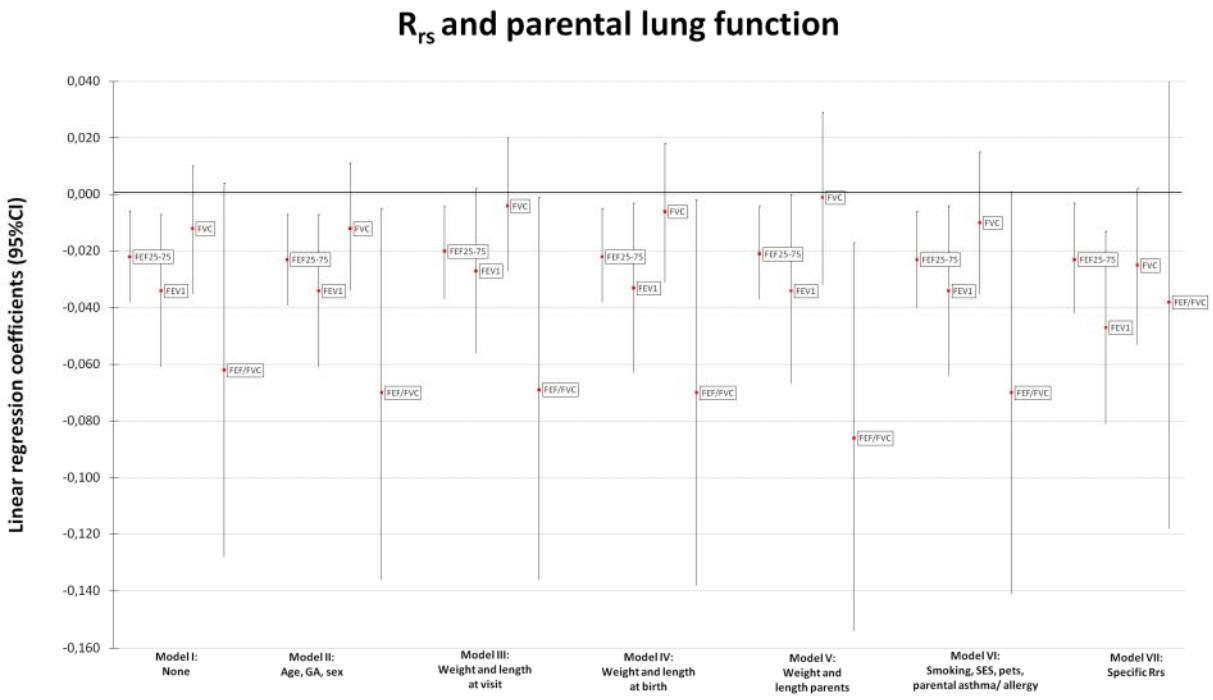


**Figure 4:** The relation between parental lung function ($FEF_{25-75\%}$ = forced expiratory flow between 25% en 75% ; $FEV_1$ forced expiratory volume in 1 second; FVC = forced vital capacity; ratio $FEF_{25-75\%}$ / FVC) and time constant ($\tau_{rs}$) of their offspring: unadjusted and adjusted linear regression coefficients and 95% confidence interval

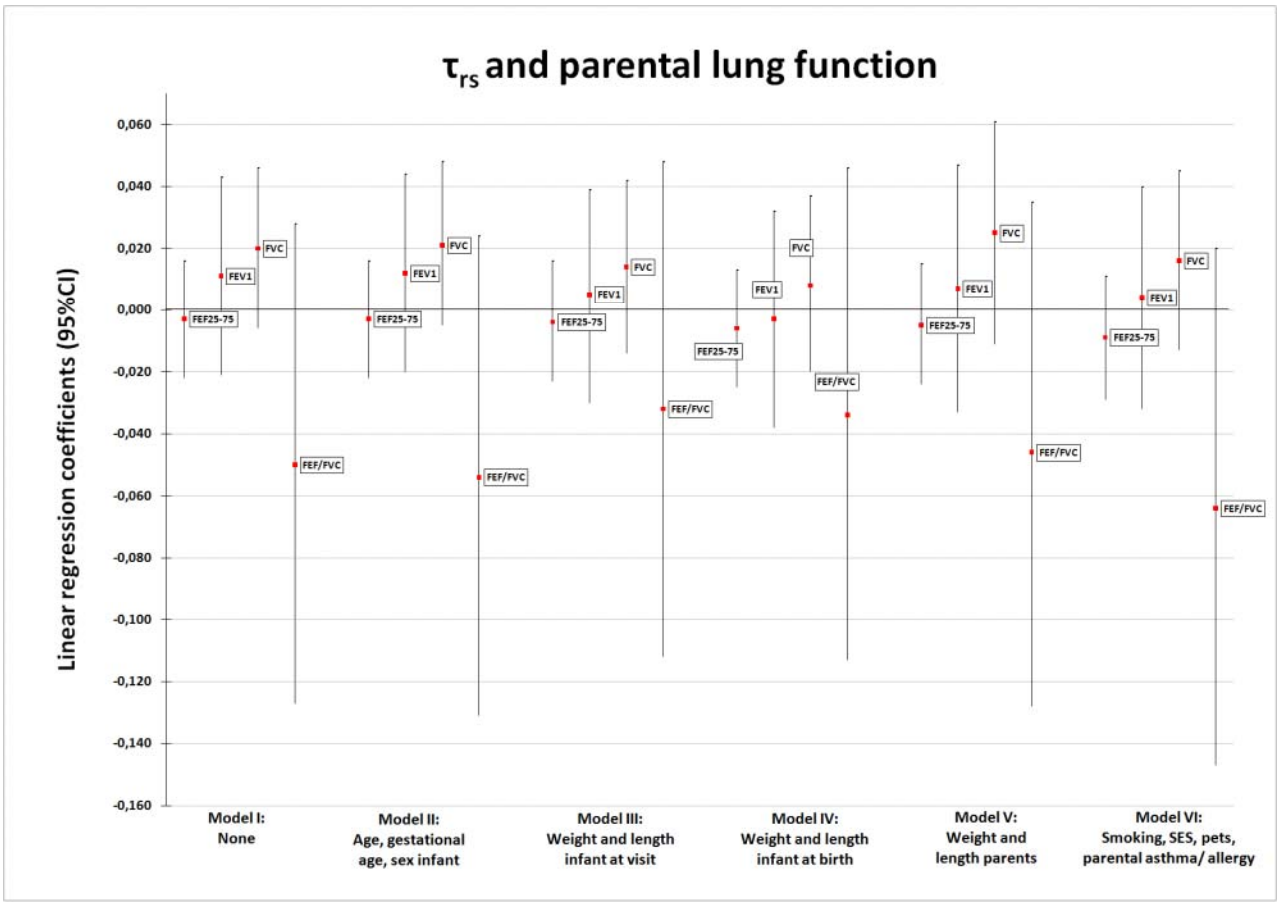
τrs and parental lung function
Linear regression coefficients (95%CI)
0,060
0,040
0,020
0,000
-0,020
-0,040
-0,060
-0,080
-0,100
-0,120
-0,140
-0,160
FEF25-75
FEV1
FVC
FEF/FVC
Model I: None
Model II: Age, gestational age, sex infant
Model III: Weight and length infant at visit
Model IV: Weight and length infant at birth
Model V: Weight and length parents
Model VI: Smoking, SES, pets, parental asthma/ allergy

**Table 1**: Demographic and clinical characteristics of parents

| Variable | Mother n=685 | Father n=602 |
|---|---|---|
| **General characteristics (mean ± SD)** | | |
| Age (yrs) | 30.8 ± 4.1 | 32.9 ± 4.4 |
| Height (m) | 169.9 ± 7.0 | 183.3 ± 8.3 |
| Z-score | 0 (-3.34 – 2.98) | 0 (-7.21 – 2.96) |
| Weight (kg) | 70.8 ± 12.5 | 84.6 ± 11.4 |
| Z-score | 0 (-2.50 – 4.32) | 0 (-2.42 – 4.87) |
| $FEF_{25-75\%}$ (l/s) | 3.91 ± 0.91 | 4.97 ± 1.21 |
| Z-score | 0 (-2.72 – 3.89) | 0 (-2.46 – 4.31) |
| $FEV_1$ (l) | 3.27 ± 0.50 | 4.38 ± 0.69 |
| Z-score | 0 (-2.98 – 3.13) | 0 (-3.11 – 3.08) |
| FVC (l) | 3.79 ± 0.60 | 5.23 ± 0.83 |
| Z-score | 0 (-2.70 – 3.89) | 0 (-3.49 – 2.90) |
| $FEF_{25-75\%}$/FVC | 1.05 ± 0.25 | 0.96 ± 0.25 |
| Z-score | 0 (-2.40 – 3.67) | 0 (-2.30 – 3.56) |
| **Questionnaire data** | | |
| History of asthma/ bronchitis (%) | 6.8 | 6.5 |
| History of allergy (%) | 42.9 | 41.5 |
| Smoking status (%) | | |
| Never | 61.5 | 55.1 |
| Ex-smoker | 28.3 | 27.7 |
| Current smoker | 10.2 | 17.2 |
| Socio-economic status (%) | | |
| Low | 4.1 | 4.7 |
| Moderate | 30.0 | 36.3 |
| High | 65.9 | 59.0 |
| Ethnicity (%) | | |
| Caucasian | 81.1 | 83.6 |
| Non-Caucasian | 18.9 | 16.4 |
| Exposure to pets (%) | 43.1 | 43.8 |

* Data presented as mean and standard deviation or percentages
** Z-scores expressed as mean and range
*** $FEF_{25-75\%}$ = forced expiratory flow between 25% en 75% ; $FEV_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity;

**Table 2**: Demographic and clinical characteristics of male and female offspring

| Variable | Female offspring n=352 | Male offspring n=333 |
|---|---|---|
| **General characteristics (mean ± SD)** | | |
| Gestational age (wks) | 40.0 ± 1.2 | 39.8 ± 1.4 |
| Age at time of visit (wks) | 4.7 ± 1.3 | 4.6 ± 1.2 |
| Birth weight (gr) | 3460 ± 450 | 3593 ± 507 |
| Birth length (cm) | 50.6 ± 2.0 | 51.5 ± 2.2 |
| Weight at visit (gr) | 4275 ± 544 | 4555 ± 660 |
| Length at visit (cm) | 54.3 ± 2.3 | 55.1 ± 2.8 |
| **Lung function data (mean ± SD)** | | |
| Compliance $C_{rs}$ (ml/kPa) | 44.4 ± 11.1 | 44.2 ± 10.9 |
| Resistance $R_{rs}$ (kPa/l/s) | 7.0 ± 2.2 | 7.3 ± 2.2 |
| Time constant $\tau_{rs}$ (s) | 0.308 ± 0.116 | 0.319 ± 0.114 |
| **Questionnaire data** | | |
| Active maternal smoking during pregnancy (%) | 5.4 | 4.8 |
| Passive maternal smoking during pregnancy (%) | 14.5 | 13.2 |
| Passive smoking infant after birth (%) | 2.3 | 2.4 |

**Table 3:** The relation between lung function of parents and offspring: unadjusted linear regression coefficients and 95% confidence interval

| | Ln $C_{rs}$ (ml/kPa) ß-coefficient (95% CI) p-value | $R^2$ | | Ln $R_{rs}$ (kPa/l/s) ß-coefficient (95% CI) p-value | $R^2$ | | Ln $\tau_{rs}$ (s) ß-coefficient (95% CI) p-value | $R^2$ | |
|---|---|---|---|---|---|---|---|---|---|
| **$FEF_{25-75\%}$ (L/s)** | 0.019 (0.005- 0.032 | 0.013 | ***0.007*** | -0.022 (-0.038- -0.00 | ***0.014*** | ***0.006*** | -0.003 (-0.022 - 0.01 | 0.000 | 0.749 |
| **$FEV_1$ (L)** | 0.045 (0.022 - 0.06 | 0.027 | ***<0.001*** | -0.034 (-0.061- -0.01 | ***0.011*** | ***0.013*** | 0.011 (-0.021 - 0.043 | 0.001 | 0.492 |
| **FVC (L)** | 0.032 (0.013 - 0.05 | 0.020 | ***0.001*** | -0.012 (-0.035 - 0.01 | 0.002 | 0.278 | 0.020 (-0.006 - 0.046 | 0.004 | 0.140 |
| **$FEF_{25-75\%}$/FVC** | 0.013 (-0.044 - 0.07 | 0.003 | 0.662 | -0.062 (-0.128 - 0.00 | 0.006 | ***0.064*** | -0.050 (-0.127 - 0.02 | 0.003 | 0.210 |

$FEF_{25-75\%}$ = sum of paternal and maternal forced expiratory flow between 25% en 75% ; $FEV_1$ = sum of paternal and maternal forced expiratory volume in 1 second; FVC = sum of paternal and maternal forced vital capacity; $R_{rs}$= resistance of the respiratory system; $C_{rs}$= compliance of the respiratory system, $\tau_{rs}$ = time constant of the respiratory system.

**Table 4:** The relation between lung function of mother, father and offspring: unadjusted linear regression coefficients and 95% confidence interval

| | Ln $C_{rs}$ (ml/kPa) ß-coefficient (95% CI) | $R^2$ | p-value | Ln $R_{rs}$ (kPa/l/s) ß-coefficient (95% CI) | $R^2$ | p-value | Ln $\tau_{rs}$ (s) ß-coefficient (95% CI) | $R^2$ | p-value |
|---|---|---|---|---|---|---|---|---|---|
| **$FEF_{25-75\%}$ (L/s)** | | | | | | | | | |
| Mother | 0.033 (0,012- 0,054 | 0.014 | ***0.002*** | -0.018 (-0,042- 0,00 | 0.003 | 0.130 | 0.014 (-0,014- 0,043) | 0.00 1 | 0.31 9 |
| Father | 0.009 (-0,008- 0,02 | 0.002 | 0.299 | -0.024 (-0,043 - -0,005) | 0.010 | ***0.015*** | -0.015 (-0,038 - 0,008) | 0.003 | 0.191 |
| **$FEV_1$ (L)** | | | | | | | | | |
| Mother | 0.085 (0,047 - 0,12 | 0.028 | ***0.001*** | -0.032 (-0,075- 0,01 | 0.003 | 0.143 | 0.053 (0,001 - 0,104 | 0.006 | ***0.045*** |
| Father | 0.026 (-0,003- 0,05 | 0.005 | 0.075 | -0.045 (-0,078 - -0,011) | 0.011 | ***0.010*** | -0.018 (-0,058 - 0,021 | 0.001 | 0.368 |
| **FVC (L)** | | | | | | | | | |
| Mother | 0.062 (0,030 - 0,09 | 0.021 | ***0.001*** | -0.009 (-0,045- 0,02 | 0.000 | 0.627 | 0.053 (0,010 - 0,096 | 0.008 | ***0.016*** |
| Father | 0.020 (-0,004- 0,04 | 0.004 | 0.111 | -0.022 (-0,050 - 0,005) | 0.004 | 0.114 | -0.003 (-0,036 - 0,030) | 0.0001 | 0.862 |
| **$FEF_{25-75\%}$ / FVC** | | | | | | | | | |
| Mother | 0.012 (-0.065 – 0.0 | 0.000 | 0.757 | -0.052 (-0.139 - 0.03 | 0.002 | 0.244 | -0.040 (-0.144 - 0.06 | 0.001 | 0.455 |
| Father | -0.047 (-0.039 – 0.133) | 0.002 | 0.280 | -0.059 (-0.154 – 0.035) | 0.003 | 0.215 | -0.062 (-0.173 – 0.048) | 0.002 | 0.269 |

$FEF_{25-75\%}$ = forced expiratory flow between 25% en 75% ; $FEV_1$ forced expiratory volume in 1 second; FVC = forced vital capacity; $R_{rs}$= resistance of the respiratory system; $C_{rs}$= compliance of the respiratory system, $\tau_{rs}$ = time constant of the respiratory system