

Lung function in wheezing infants

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1. ABSTRACT

Recurrent wheeze is a very frequent disease during infancy. In many cases, this condition is a transient one, but some infants who suffer from this illness, have a persistent recurrent wheeze. During the past decades different international cohorts have been designed to answer what are the risk factors to develop recurrent wheeze and to make the condition persistent even into the adulthood. Infant lung function could explain some aspects of this pathophysiology. The aim of this article is to review the current knowledge on the relationships of recurrent wheeze with an eventual impairment in lung function, the beginning of this impairment early in life, its relationship with asthma later in life and what risk factors are related with low lung function.

2. INTRODUCTION: QUESTIONS WHICH DESERVE AN ANSWER

During the last three decades the development of new devices and software has allowed us to increase our learning about the role of infant lung function testing in respiratory diseases. With respect to recurrent wheeze infants, lung function testing should help us to understand the patho-physiology of this condition through answering four questions: 1. Do wheezing infants have impaired lung function as compared with matched healthy infants? 2. If so, does functional impairment precedes the first episode of wheeze? 3. If so, is the pre-morbid impaired lung function a risk factor for asthma later in life? And 4. What risk factors are related with this pre-morbid lung function impairment? The aim of the present review is to know how the current

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knowledge on infant lung function could answer those four questions, excluding well known respiratory diseases such as bronchopulmonary dysplasia or cystic fibrosis. Our interest is focused on infants who –apart from wheezing episodes. are considered as healthy.

3. DO WHEEZING INFANTS HAVE IMPAIRED LUNG FUNCTION AS COMPARED WITH MATCHED HEALTHY INFANTS?

Infants with recurrent wheeze have been shown to have a lower lung function as compared with healthy infants. By means of the rapid chest compression technique (RCT), it has been possible to show that the maximal flow at functional residual capacity (V'_{maxFRC}) is already diminished in wheezing infants in the first year of life (1,2), suggesting a certain degree of airway obstruction or narrowing as compared to normal airway caliber, in those infants. Additionally, both the time to achieve peak tidal expiratory flow as a proportion of total expiratory time (t_{PTEF/t_E}) and specific airways conductance (sGaw) are significantly lower in older infants with prior lower respiratory tract illnesses (LRI) as compared to a similarly aged group of healthy infants (3). Recently, again using RCT and after adjusting for sex, age, body length at the time of testing and maternal smoking, significant reductions in z-scores were observed for forced expiratory volume at 0.5 seconds ($FEV_{0.5}$), forced expiratory flow at 75% of forced vital capacity (FEF_{75}) and forced expiratory flow at 25 to 75% of forced vital capacity (FEF_{25-75}) in infants with recurrent wheeze when compared with controls. However forced vital capacity (FVC) remained comparable between groups, thus suggesting an obvious obstructive airway pattern in recurrent wheeze infants (4). Therefore the conclusion would be that lung function is reduced in infants suffering recurrent lower LRI as compared with healthy controls.

4. DOES FUNCTIONAL IMPAIRMENT PRECEDES THE FIRST EPISODE OF WHEEZE?

The first study designed to clarify whether very early LRI leads to lower lung function or low lung function is previous to the first airway infection and leads to increased risk of wheezing, was the Tucson Children's Respiratory Study. In this prospective study of 124 infants enrolled as newborns, the authors showed that the risk of having a wheezing episode was 3.7 times higher (95%CI, 0.9 to 15.5; $p=0.06$) among infants whose measurements of total respiratory conductance were in the lowest tertile, as compared with infants with values in the uppermost two tertiles. The authors concluded that diminished lung function is a predisposing factor for the development of a first wheezing illness in infants (5). Table 1 summarizes seven additional cohort studies (6-13) which, by means of different methods of assessment of lung function, have consistently shown that there is a pre-morbid lower lung function in wheezing infants.

The vast majority of those studies were performed by assessing lung function through V'_{maxFRC} . Furthermore, the recent data published from the

Southampton Women's Survey cohort (SWS study) (13) showed that decreased forced expiratory volume at 0.4 sec. ($FEV_{0.4}$), measured before 14 weeks of age, is a risk factor for later wheeze; thus further revealing an association between impaired pre-morbid lower infant lung function (V'_{maxFRC}) and preschool wheezing (both at 1 and at 3 years of age). This study also showed for the first time that lower lung function in early infancy is a risk factor for non-atopic wheeze, rather than for atopic wheeze. The pre-morbid decrease in lung function can be measured as early as in the first days of life. Those results allow only one conclusion: some children are born with an obstructive airway pattern which poses them at risk of suffering LRIs.

5. IS THE PRE-MORBID IMPAIRED INFANT LUNG FUNCTION A RISK FACTOR FOR ASTHMA LATER IN LIFE? LESSONS FROM COHORT STUDIES

The Tucson Children's Respiratory Study concludes that diminished initial airway function may be a predisposing factor, not only for the first episode of wheeze, but also for recurrent wheezing starting in the first year of life (6). As it is widely known, the results from this cohort allowed describing three phenotypes based in the existence of wheezing episodes during the first three years of life, as assessed at six years: transient wheeze (at least one wheezing LRI during the first three years of life but no wheezing at six years); persistent wheeze (wheezing both before three and at six years of life); and late wheeze (no wheezing in the first three years of life but wheezing at age six).

The most important difference between transient and persistent wheezers was that the former had decreased lung function, as assessed by means of V'_{maxFRC} , both in infancy (prior to the first episode) and at six years of age, as compared to children who never wheezed. On the other hand, persistent wheezers had early V'_{maxFRC} values that were comparable to those of children who never wheezed. However, by age six years, they had the lowest lung function, with a significant reduction in V'_{maxFRC} (14). Thus, some infants seem to have congenital decreased lung function being at risk of recurrent wheezing early in life, although they have a good prognosis; while others have normal neonatal lung function at birth which decreases during the first years of life, perhaps as a consequence of chronic airway inflammation. Those infants have a worse prognosis.

In contrast with the Tucson's study, the Perth (15) cohort showed an association between decreased V'_{maxFRC} at one month of age and wheeze persistence at 4-6 and even at 11 years of age. Those children with no wheeze from 3 years on (transient wheeze) had normal V'_{maxFRC} when neonates.

Using wheeze data from the SWS, children were grouped into both the Tucson and the Avon Longitudinal Study of Parents And Children (ALSPAC) phenotypes (16). According to the Tucson phenotypes, transient wheezing infants had lower premorbid V'_{maxFRC} but

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Table 1. Cohort studies showing a pre-morbid lower lung function in wheezing infants

Author	N	Age when measured	Age of LRI assessment	Type of study	Lung function assessment method	Main results
Martinez FD (1988) ⁵	124	< 6 months	1 year	Cohort (Tucson)	SBOT	The risk of having a wheezing illness was 3.7 times higher (95%CI, 0.9-15.5; p = 0.06) among infants whose values for total respiratory conductance were in the lowest tertile, as compared with infants with values in the upper two thirds of the range of values for the group.
Martinez FD (1991) ⁶	124	< 6 months	3 years	Cohort (Tucson)	RTC TFVL	V'maxFRC lower in both groups of patients having only one episode in the first year of life and in those who have, at least, another one in 2nd or 3th year of age. When compared with never wheezers, infants who wheezed during the first year of life and had at least one additional lower respiratory illness had previous levels of T _{PTEF} /T _E 22% lower
Tager IB (1993) ⁷	97	< 6 months	1 year	Cohort	RTC	Infants who developed an LRI during the first year of life had lower pre-illness length-corrected V'maxFRC than those who did not experience an LRI.
Adler A, (1995) ⁸	98	< 6 months	1 year	Cohort	TFVL	T _{PTEF} /T _E only weakly associated with the development of LRI in the first year of life.
Dezateux C (1999) ⁹	101	< 13 weeks	1 year	Cohort	SBOT TFVL	Specific airway conductance was significantly diminished in infants who subsequently wheezed. T _{PTEF} /T _E tended to be lower among infants with subsequent wheezing, and this difference between both groups, was almost statistically significant (CI 95% -20.067; 0.002)
Young (2000) ¹⁰	253	1 month	2 years	Cohort (Perth)	RTC	At the age of 1 month, prior to any lower respiratory illness, the wheezing group had impaired lung function in comparison to the never wheezing group.
Murray CS (2002) ¹¹	69	1 month	1 year	Cohort (Manchester)	RTC	Size adjusted V'maxFRC was significantly lower in infants who had recurrent wheeze during the first year of life than in those who did not.
Håland G (2007) ¹²	135	Newborn	2 years	Cohort (Oslo)	TFVL	Children with both recurrent obstructive bronchitis (rBO) and atopic eczema (AE) by 2 yr had significantly lower T _{PTEF} /T _E at birth compared with non-rBO & non-AE group. No differences among children with rBO & without AE.
Pike KC (2011) ¹³	101	8 week	1 and 3 years	Cohort (Southampton)	RTC RVRTC	Lower early infancy V'max FRC was associated with wheeze in both the first and third year of life. Lower early infancy FEV _{0.4} was associated with wheeze in the first year.

SBOT: Single-breath occlusion technique. RTC: Rapid thoraco-abdominal compression. TFVL: Tidal flow-volume loops
RVRTC: Rapid thoraco-abdominal compression with raised volume.

normal FEV_{0.4}; however, according to the ALSPAC's phenotypes, both transient and persistent wheezers had lower premorbid V'maxFRC and again normal FEV_{0.4}. Thus, authors concluded that lung function and atopy successfully differentiate persistent, late-onset and intermediate-onset wheeze (ALSPAC phenotypes) while the Tucson "early transient" phenotype could be sub-classified into two different groups (ALSPAC's early and ALSPAC's transient) that better reflect differences in early lung function. Therefore, conflicting results between different cohort studies might be due to different phenotype definitions.

Nevertheless, all this three cohort studies based their observations in very limited number of cases. In the Tucson cohort lung function was measured in 124 infants and more than 50% of them were non-wheezers (14). The Perth cohort included lung function from 157 infants, 43% of whom were non-wheezers (15); and in the SWS the total population was 95, including 39% of healthy infants (16). Hence the findings of those three cohort studies should be interpreted with caution.

More recently, the results of the Copenhagen Prospective Study on Asthma in Childhood (COPSAC

(17) have been published. This cohort followed 411 infants born from asthmatic mothers. The authors found that children who developed asthma by age 7 had reduced airflow when neonates with significant and almost significant differences in FEF₅₀ (p=0.03) and FEV_{0.5} (p=0.07), respectively. Additionally, neonates with increased bronchial responsiveness were more prone to suffer from asthma at 7 years of age. This airflow deficit worsened during the first seven years of life, suggesting that disease mechanisms are operating before and after birth.

Making sense of the differences found in those four cohort studies is not an easy task, but it could be assumed that there might be two main groups of wheezing infants according to their neonatal lung function. One of them would have lower lung function and may develop recurrent wheezing with viral infections; however, their lower lung function does not get worse and they become asymptomatic during the following years (transient wheezers). A second group would have almost normal lung function (only slightly lower than that of non-wheezers) which deteriorates during the first years of life, as a consequence of chronic inflammation and/or other unknown factors. This group is at very high risk of having

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Table 2. Bronchial hyper-responsiveness in wheeze infants

Author	N	Pre/post 1st wheezing episode	Method	Main results
Stick SM, 1991 ¹	19	Post	Histamine. VmaxFRC fell by 40% (PC40)	There was no significant difference in the PC40 between wheezing infants and matched healthy infants
Clarke JR, 1992 ²	54	Post	Histamine. VmaxFRC fell by 30% (PC30)	There was no significant difference in PC30 between symptomatic infants and control infants.
Guirau LM, 1997 ¹⁸	51	Post	Methacholine (PCW)	There was a statistically significant difference between PCW for wheezing infants and for controls.
Delacourt C, 2001 ¹⁹	129	Post	Methacholine Transcutaneous oxygen tension fell by 15% (PD ₁₅ PtcO ₂)	Persistent wheezers had significantly lower PD ₁₅ PtcO ₂ than wheezers by first year of age who became asymptomatic after 1 to 3 years of follow up
Yao W, 2010 ²⁰	89 infants with 'chronic dermatitis'	Pre	Methacholine FEV ₇₅ fell by 30% (PC30)	A lower PC30 (greater reactivity) was not a significant risk factor for increased number of wheezing episodes (p>0.12).
de Mir Messa 2010 ²¹	63	Post	Methacholine (PCW) or SatO ₂ fell by 5% or respiratory rate increased by 50%	PCW was lower than the control group (≤4 mg/ml) in 43 (68%) children from the bronchitis group. The subsequent progression to transient or persistent wheezing bronchitis phenotype is not associated with bronchial hyperresponsiveness.
Debley J, 2012 ²²	76	Post	Upper limit of normal for post-bronchodilator change (FEV _{0.5} 13% and/or FEF ₂₅₋₇₅ 24%)	Approximately 1/4 of infants/toddlers with recurrent wheezing exhibited bronchodilator response at baseline. However, bronchodilator response in wheezy infants/toddlers was not associated with established asthma risk factors

PCW: Provocative concentration of methacholine causing wheeze

asthma in the future. The slight differences in lung function at the beginning of life between non-wheezers and persistent wheezers may explain the contradictory results from the different cohort studies.

However, the role of the reduction of lung function values in the first months of life in predicting the risk of asthma later in life in a specific individual is unknown; but it is probably not that high despite the associations found in epidemiological studies. Even in the case of a decreased lung function early in life, the complexity of factors that can influence the future growth and development of the lungs during infancy and childhood is enormous. Therefore, to predict lung function in adolescence and adulthood from infancy remains quite hypothetical at the individual level.

6. THE ROLE OF BRONCHIAL HYPER-RESPONSIVENESS

All studies (except one) assessing the relationship between bronchial hyper-responsiveness (BHR) and wheezing in infants (Table 2) were done after the inception of the wheezing episodes; thus we do not have information as to BHR being or not previous to wheezing. The results of those studies are quite contradictory. Two of them (1,2) -using histamine as provoking agent. found no differences between the wheezing and the control group. However, another two studies, which used methacholine (18,21), showed higher BHR among wheezers. Two additional studies (20,22) could not find any difference in BHR between the classical phenotypes. Conversely, the study from Delacourt *et a* (19) found that persistent wheezers had significantly higher BHR than transient wheezers (infants who wheezed at one year of age and became asymptomatic after a follow up period of one to three years). Differences in the age of patients and in the bronchial provocation test protocol may explain those conflicting results.

7. WHAT RISK FACTORS ARE RELATED WITH THIS PRE-MORBID LOW LUNG FUNCTION?

Excluding some well known respiratory diseases such as bronchopulmonary dysplasia or cystic fibrosis, which are beyond the scope of this review, a certain number of risk factors related to low lung function in the neonate or in the infant that may otherwise be considered as healthy, have been described. Those include preterm birth, low birth weight, prenatal tobacco exposure, certain gene polymorphisms, atopy, and very fast weight gain.

7.1. Preterm birth and intrauterine growth restriction

A very recent study based in the Swedish Medical Birth Register, showed an association between asthma and gestational age in a large population of 765,792 children, the authors concluding that both short gestational duration and intrauterine growth retardation (IUGR) appeared as risk factors for asthma, and seemed to act separately, although preterm birth showed a stronger association (23). A number of studies (Table 3) point out that infants born preterm have lower lung function (especially expiratory flows) as compared to those born at term. Some studies (27,33,34) found a diminished functional residual capacity (FRC) in infants born preterm; but others, such as the ones by Merth *et al* (26) and by Latzin *et al* (32) did not find any difference. It is not easy to explain those differences. Hjalmarsen *et al* (28) used 100% oxygen as washout gas (Merth *et al* (26) that used helium and the rest of studies used sulphur hexafluoride -SF₆) and they perform the measurement very early in life: both circumstances might have led to underestimate FRC in preterm infants. However this explanation is not valid when comparing the results from Hülskamp *et al* (33) and Latzin *et al* (32) because their methodology was very similar. Perhaps the fact that the study by Hülskamp (33) took into account not only the weight of the infants but also their postmenstrual age,

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Table 3. Pulmonary function in premature infants without BPD compared with full term neonates

Author	N	Gestational age /birth weight	Age at measurement	Type of study	Lung function assessment	Main Results
Yuksel B (1991) ²⁴	40 LBW 5 infants with BPD/CLD	Mean 29 weeks	6-16 months postnatal	Case-control (22 symptomatic vs 18 asymptomatic)	Plethysmography HeDT	No difference in TGV between symptomatic and asymptomatic infants, but median FRC was lower, Raw higher, and FRC/TGV ratio lower in symptomatic. Changes in symptomatic infants suggestive of gas trapping
Yuksel B (1992) ²⁵	21 PT	27-33 weeks	1 st 6-11 months postnatal 2 nd 12-20 months postnatal	Subgroup of a cohort	TGV _{pleth} Raw _{pleth} FRC _{He}	Regression equations of TGV _{pleth} , FRC _{He} and Raw according to weight, height and age. No significant differences in lung function between small vs appropriated for gestational age at either the 1 st or 2 ^d measurement.
Merth IT (1995) ²⁶	26 PT vs 43 FT	26-36 weeks	PT: Mean 14.2 weeks in males & 18.5 in females (corrected age). FT: Mean 4.3 weeks in males & 3.9 in females	Case-control	HeDT SBOT	Premature and full-term infants had comparable FRC _{He} corrected for length. Crs was different, but the difference disappeared when gestational age was taken into account.
Kavvadia V (1999) ²⁷	16 PT	25-27 weeks	Measurements was made daily for the first five days and then at 1, 2 and 4 weeks	Case-Control (8 PT RDS vs 8 PT non RDS)	HeDT SBOT	Non RDS preterms, non surfactant treated infants significantly higher compliance and FRC _{He} throughout the perinatal period. Exogenous surfactant administration to RDS preterms associated with improvements in lung function.
Hjalmarson O (2002) ²⁸	32 PT vs 53 FT	25-33 weeks	PT: 38-41 weeks of postmenstrual. FT: 28-72 hours.	Case-Control	MBW (N ₂)	At same postmenstrual age preterm infants lower FRC/kg body weight, lower specific compliance, impaired gas mixing efficiency, and higher total and dead space ventilation/kg than the full-term infants.
Hoo AF (2002) ²⁹	24 PT	29-36 weeks	1 st measurement 3 weeks 2 nd 1 year after	Cohort. Subgroup of the cohort.	RTC	V _{max} FRC within normal range in all infants shortly after birth, but by 1 year, z-scores decreased significantly (consequence of dynamic elevation of end-expiratory level at so early age in 1 st measurement?)
Friedrich L (2006) ³⁰	67 PT vs 23 FT	Mean 33.4 weeks	PT: Mean 8.2 weeks (corrected age). FT: 51.6 weeks	Case-control	RVRTC	Prematurity independently associated with reduced lung function (expiratory flows) detectable in the first months of life. Male sex, lower gestational age, and weight are important predictors for reduced expiratory.
Friedrich L (2007) ³¹	26 PT vs 24 FT	30-34 weeks	PT: 1 st mean 10 weeks 2 nd 64 weeks. FT: 1 st mean 23 week 2 nd 64 weeks	Case-Control. Two separate	RVRTC	Healthy preterms decreased forced expiratory flows and normal forced vital capacities in the first and second years of life. Changes in lung function with growth parallel to full-terms: no catch up in the year of follow up.
Latzin P (2009) ³²	58 PT without BPD vs 239 FT and vs 128 PT with BPD	Mean 32 weeks	PT not BPD: 40-50 weeks (postmenstrual age) FT: 42-50 weeks (postmenstrual age)	Case-Control	MBW (SF ₆) TFVL	No differences in FRC/Kg between healthy PT and FT infants, significant differences in T _{PTEF} /T _E .
Hülkamp G (2009) ³³	59 PT not BPD vs 64 FT vs 54 RDS vs 42 BPD	Mean 33.5 weeks	~40 weeks postmenstrual age	Multicentre cohort	MBW (SF ₆)	After correcting for body size, preterms lower FRC (0.5 ml/weeks GA) and intrauterine growth restriction reduction of 1.9 ml per unit reduction of birth weight z-score. Ventilation inhomogeneity index not associated with GA.
Schulzke SM (2010) ^{33,34}	22 PT not BPD vs 16 BPD vs 20 FT	23-32 weeks	15-18 months of postnatal	Multicentre cohort	MBW (SF ₆)	After adjusting for body size, FRC at follow-up, and increment in FRC from newborn to 15-18 months corrected age positively associated with GA. Index of ventilation inhomogeneity unaltered by GA.
Schmalisch G (2013) ³⁵	386 VLBW	Less than 1500 g	Mean 49 weeks postmenstrual age	Retrospective	TFVL, SBOT, Plethysmography, MBW (SF ₆) RTC	Severe immaturity mainly associated with changes in the breathing pattern (reduced tidal volume and increased respiratory rate), reduced V _{max} FRC and lower respiratory compliance.

PT: Preterm; FT: full term; LBW: Low birth weight; VLBW: very low birth weight; BPD: Bronchopulmonary dysplasia; CLD: Chronic lung disease; GA: Gestational age; RDS: Respiratory Distress Syndrome. SBOT: Single-breath occlusion technique. RTC: Rapid thoraco-abdominal compression. TFVL: Tidal flow-volume loops RVRTC: Raised volume rapid thoraco-abdominal compression. HeDT: Helium dilution technique. MBW: Multiple breath washout method.

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length, and body mass index at the time of the test, could be of importance. In fact, after correcting for body size, preterm birth was associated with a significant decrease of 0.5 ml/week of gestational age. A prospective follow-up study (34) including the majority of neonates studied by Hülskamp (35), showed that in infants born preterm as compared with those born at term, FRC is slightly diminished at 15-18 months of corrected age. Multivariate analyses indicated that severe immaturity was mainly associated not only with lower FRC, but also with changes in the breathing pattern (reduced tidal volume and increased respiratory rate) and with lower $V'_{\max}FRC$ (35).

Forced vital capacity (FVC) has been less investigated, but the study by Friedrich *et al* (30,31) did not find any difference between preterm and full-term infants.

On the other hand, severe neonatal lung diseases requiring mechanical ventilation have been significantly and independently associated with reduced FRC_{SF_6} (33,34,35) and increased respiratory airway resistance (35). Preterm infants who suffered from bronchopulmonary dysplasia have even lower expiratory flows than preterm babies who did not suffer from BPD, especially boys (36). However we will not go deep into this topic as it exceeds the aim of the present review.

There are various studies suggesting that the early low lung flows in infants born preterm is not recovered later in life (31,37). A recent systematic review and meta-analysis confirms this absence of catch-up of lung function between 5 and 23 years of age, and estimates that preterm babies have 10% lower FEV1 when adults (38).

Infants with IUGR have been less studied. Epidemiological studies demonstrate that in-utero growth restriction is associated with impaired lung function. The majority of those studies have been published by the group of the Great Ormond Street Hospital (39,40,41). In those studies, small for gestational age (SGA) was considered when birth weight was at or under the 10th percentile and adequate for gestational age (AGA) when it was at or over the 20th percentile. The study including the higher number of infants showed that, after adjusting for relevant maternal and infant factors, SGA infants had lower FEV_{0.4}, FVC and MEF₂₅ at 6 weeks of corrected age (39). The study by Hoo *et al* (41) obtained similar results: both FVC and FEV_{0.4} z-scores were significantly diminished at 8-9 months of corrected age. The authors suggested that a reduced lung function is present during the first year of life in SGA infants, which is independent of somatic growth during infancy.

Greenhough *et al* (42) found an increase in Raw and a comparable FRC between SGA and AGA, as measured by means of body plethysmography and by the helium-dilution method. Conversely, a more recent study (33) showed that IUGR was associated with a reduction in FRC. The first study included only infants born preterm and measurements were done at about 9 to 10 months of age; while the second included both term and preterm infants and measurements were carried out very early in

life (preterm infants at approximately 44 weeks postmenopausal age, and term infants within 4–8 weeks after birth).

In summary, the effects of prenatal and perinatal factors on lung function during the first months of life are very complex even excluding specific respiratory diseases, which are relatively frequent and severe in neonates. A number of epidemiological studies provide evidence suggesting that both prematurity and IURG play an important role in lung development probably through the interaction of at least two mechanisms: disruption of lung development and restriction of airway growth.

7.2. Prenatal tobacco exposure

A very recent and large pooled analysis of eight birth cohorts with data on more than 21,000 children showed that maternal smoking during pregnancy is associated with wheeze and asthma in preschool children, and the likelihood of developing wheeze and asthma increased significantly in a linear dose-dependent manner in relation to maternal daily cigarette consumption during the first trimester of pregnancy (43).

The methodology of studies focusing on the influence of tobacco exposure on lung function in infancy is quite variable in distinguishing prenatal from postnatal exposure, in “smoker” definitions; in the assessment of the exposure (mainly by questionnaires), and even in the list of confounders (44). Even though, there is strong evidence that exposure to parental smoking is associated with impaired lung function during infancy, which is likely to persist. Maternal smoking during pregnancy and in the early months of life remains the most significant source of such exposure. The most consistent finding is the existence of reduced flows at low lung volumes, which may reflect extensive underlying pathological and functional alterations in the distal airways (44).

Table 4 summarizes the main studies dealing with the association between prenatal or pre & postnatal exposure to tobacco smoke and lung function in infancy. The great majority of them found lower lung function values in infants exposed to tobacco in uterus (including or not postnatal exposure). Most of them described significant decrease in expiratory flows [$V'_{\max}FRC$ (46,47,50,51,53), FEV_{0.5} (57), FEF₅₀ (52,56), FEF₇₅ (52), FEF₈₅ (52) and FEF₂₅₋₇₅ (52,56)]. It is very difficult to separate the influence of pre versus postnatal exposure to tobacco, because the great majority of mothers who smoke during pregnancy continue smoking after delivery. As some studies (46,48,49,50,56) were performed very early in life (in the first weeks) it could be assumed that they assessed mostly the prenatal effect. Two of those studies found decreased $T_{PTEF/TE}$. However, another one (48), which also showed that maternal smoking during pregnancy (including active and passive exposure) adversely affected $T_{PTEF/TE}$, found that this effect disappeared if the analysis was limited to active (as opposed to passive) maternal smoking. The study by Hanrahan *et al* (46) found a diminished $V'_{\max}FRC$, but the study by Hoo *et al* (50), who obtained a similar result, this reduction in $V'_{\max}FRC$ disappeared

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Table 4. Major studies on the influence of tobacco smoke exposure prenatally on lung function in infants

Author	N	Age of measurement	Method	Main results	Comments
Young S (1991) ⁴⁵	63	4.5 weeks	BHR by RTC.	V'maxFRC fell by 40% with histamine. Airway responsiveness may be present early in life. Maternal smoking contributes to airway responsiveness at an early age.	Assessment of smoking by means of questionnaire (no cotinine). No differences in basal lung function between groups. Subsequent paper ⁴² including 237 infants does not confirm BHR.
Hanrahan JP (1992) ⁴⁶	80	4.2±1.2 weeks	RTC HeDT	V'maxFRC in infants born to smoking mothers lower than in infants whose mothers did not smoke. Differences remained significant when flow was corrected for lung size (V'maxFRC/FRC).	Mothers classified by urinary cotinine level. Measurements of lung function made very early in life. Passive environmental exposure to tobacco smoke accounted for.
Tager IB (1995) ⁴⁷	159	18 months	RTC HeDT	Maternal smoking associated with lower FRC and V'maxFRC after controlling for growth (length). Higher effect in females.	Mothers classified by urinary cotinine level. Postnatal smoke exposure did not add further effect.
Stick SM (1996) ⁴⁸	461	26-159 hours of life	TFVL	Lower values of T _{PTEF} /T _E independently associated with maternal smoking (more than 10 cigarettes daily).	Mothers classified by questionnaire. Measurements very early in life: prenatal effects mainly.
Lødrup Carlsen KC (1997) ⁴⁹	803	1-9 days	TFVL SBOT	Maternal smoking during pregnancy (active and passive) adversely affected T _{PTEF} /T _E in healthy newborn babies, as well as Crs in girls, independently of reduced body size (known effect of maternal smoking)	Mothers classified by questionnaire. No effect on T _{PTEF} /T _E , Crs or Rrs was found if analyses limited to active maternal smoking.
Hoo AF (1998) ⁵⁰	108 PT	Mean 21 days	RTC TFVL	T _{PTEF} /T _E and V'maxFRC significantly lower in infants exposed to tobacco in utero.	Mothers classified by urinary cotinine. Significant reduction in V'maxFRC disappeared when adjusted by ethnic group, postnatal age, sex, and length.
Dezateux C (1999) ⁹	101	Less than 13 weeks	Plethysmography	Expiratory Raw significantly elevated in infants exposed to prenatal tobacco smoke; no differences in sGaw, FRC _{pleth} , Crs, and T _{PTEF} /T _E .	Mothers classified by urinary cotinine. 89% of mothers smoking during pregnancy continued to smoke afterwards (pre and postnatal effect intermingled).
Young S (2000) ⁴²	237	1-12 months	RTC	Maternal smoking associated with a lower V'maxFRC in both genders.	Mothers classified by questionnaire. Association between BHR and smoke exposure not reported.
Jones M (2000) ⁵²	155	3-149 weeks	RVRTC	Lower FEF ₅₀ , FEF ₇₅ , FEF ₈₅ and FEF ₂₅₋₇₅ in infants exposed. After correcting for smoking during pregnancy, postnatal exposure not significant.	Prenatal and postnatal assessment of tobacco exposure by questionnaire. Urinary cotinine not measured.
Dezateux C (2001) ⁵³	100	1 year. Previous measurement at 8 weeks	Plethysmography	In a multivariate model only maternal postnatal smoking and diminished premorbid sGawEE were independently associated with decreased sGawEE at 1 year of age.	Prenatal assessment of exposure made by questionnaire and postnatally by urinary cotinine. 37/38 mothers who smoked at 1 year of age of their infants, smoked during pregnancy too (postnatal vs prenatal effect of difficult to separate).
Adler A, 2001 ⁵⁴	86 infants RSV. LRI vs 78 controls	Mean approx. 6 months	RTC V'maxFRC fell by 40% (PC40) with methacholine	Exposure to maternal or paternal environmental tobacco smoke predictive of decreased length-corrected V'maxFRC. Same in infants with and without RSV-LRI. However, there was no further effect of tobacco smoke exposure on BHR.	Exposure to tobacco smoke measured by questionnaire.
Tepper RS (2005) ⁵⁵	76	Mean approx. 10 months	RVRTC	Exposure to parental smoking associated with lower airway function (FEF ₅₀ and FEF ₂₅₋₇₅) but not increased airway reactivity	Mothers classified by questionnaire. Exposure in infants measured by hair cotinine. Not possible to separate exclusive postnatal exposure from pre and postnatal exposure. Significant higher level of hair cotinine in non caucasian infants.
Bisgaard H (2009) ⁵⁶	411	6 weeks	RVRTC	Neonates of mothers smoking during the third trimester 7% lower baseline FEV _{0.5} .	Mothers classified by urine cotinine. Measurements made very early in life. Study only includes infants born from mothers with doctor's diagnosed asthma.

SBOT: Single-breath occlusion technique. RTC: Rapid thoraco-abdominal compression. TFVL: Tidal flow-volume loops
RVRTC: Rapid thoraco-abdominal compression with raised volume. HeDT: Helium dilution technique. MBW: Multiple breath washout method.

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Table 5. A summary of studies on the association between infant lung function and genetic polymorphisms

Author	Gen	Sample	SNPs or haplotypes	Main results
Wilson NM, 2004 ⁵⁷	β2-Adrenoceptor	73 normal, healthy full-term infants who had at least one atopic parent	Gln ²⁷ vs Glu ²⁷ Any Arg ¹⁶ vs Gly ¹⁶ Gly ¹⁶	V ^{max} FRC in Gln ²⁷ Gln ²⁷ < Gln ²⁷ Glu ²⁷ < Glu ²⁷ Glu ²⁷ ; V ^{max} FRC in any Arg ¹⁶ vs Gly ¹⁶ Gly ¹⁶
Zhang G, 2006 ⁵⁸	β2-Adrenoceptor	Perth's cohort	Arg ¹⁶ Gln ²⁷ vs Gly ¹⁶ Gln ²⁷ vs Gly ¹⁶ Glu ²⁷ vs Gly ¹⁶ Gln ²⁷ in homo or heterozygosis	Multivariate analyses did not show a significant association neither in V ^{max} FRC nor in BHR at 1 month of age with any SNP after adjustment for height, weight, exact age, gender, and maternal smoking in pregnancy.
Torjussen TM, 2013 ⁵⁹	β2-Adrenoceptor	Oslo's cohort	rs1042711, rs1042713, rs1042714 and rs1800888. Three most common haplotypes: CGGC, TACC and TGCC	No association between lung function at birth (t _{PEF} /t _E) and any of haplotype studied.
Bisgaard H, 2009 ⁶⁰	Chromosome 17q21 locus gene variants	COPSAC cohort	rs7216389 and 19 additional SNPs in the region.	Baseline lung function values not significantly associated with rs7216389 or specific SNPs. Bronchial responsiveness significantly increased by 1 month of age.
Torjussen TM, 2012 ⁶²	Alpha-nicotinic acetylcholine receptor (CHRNA)	ECA study	CHRNA SNP rs8034191	rs8034191 genotypes not associated with lung function at birth. Stratifying according to tobacco exposure did not alter the results.
Murdzaska J, 2010 ⁶³	Glutathione S-Transferase Genes	Perth' cohort	GSTT1, GSTP1 and GSTM1 genotyped in infants and mothers,	Infant and/or maternal GST polymorphisms associated with BHR at 1, 6 and 12 months of age as measured by V ^{max} FRC. Association between BHR and lung function with GST polymorphisms different when prenatal exposure to tobacco smoke was taken into account. GSTT1 and GSTP1 genes may be especially important during fetal development as it may modify, through proficient detoxification, the effects of maternal smoke exposure on BHR and lung function.
Simpson A, 2012 ⁶⁴	Vascular Endothelial Growth Factor-A	Tucson Children's Respiratory Study (TCRS) cohort and a sample of a study of infants lung function from Indianapolis ^{42bis}	rs3025038; rs833068; rs833070; rs2146323; rs3025028 and rs10434	CC homozygotes of rs3025028 had significantly higher V ^{max} FRC compared with other genotypes. Similar trend for AA homozygotes of SNP rs10434. Similarly, in Indiana, mean z-scores for FEF ₅₀ and for FEF ₂₅₋₇₅ significantly higher among CC homozygotes of rs3025028 and AA homozygotes of rs10434 than among carriers of the other two genotypes.
Laing IA, 2009 ⁶⁵	Secretoglobin 1A1	Perth's cohort	A38G	Significant association with the SCGB1A1 A38G genotype with airway reactivity to histamine at 1 month of age. Multiple regression analyses did not show associations were found between SCGB1A1 A38G and V ^{max} FRC.
Collins SA, 2013 ⁶⁶	Hedgehog interacting protein (HHIP). Retinoic acid receptor b (RARb). Natural cytotoxicity triggering receptor 3 (NCR3). Histone deacetylase 4 (HDAC4)	Southampton Women's Survey Study (SWS)	rs11100860 and rs1032296 in HHIP rs1529672 in RARB rs2857595 in NCR3 and rs12477314 in HDAC4	rs11100860 in HHIP associated with increased compliance and rs1032296 associated with decreased compliance. rs1529672 in RARB associated with increased V ^{max} FRC. rs2857595 in NCR3 associated with a lower respiratory rate. rs12477314 HDAC4 associated with both increased compliance and V ^{max} FRC.

SNP: Single nucleotide polymorphism.

after adjustment for ethnic group, postnatal age, sex, and length. This situation shows the complex interaction of genetic and environmental factors in lung function, even so early in life. Finally the Danish cohort (56) found a reduction of FEV_{0.5} in infants whose mothers smoked in the 3rd trimester of gestation (this cohort included only infants born from mothers diagnosed of asthma).

Two studies have explored the role of tobacco exposure in BHR tests. The study by Young *et al* (9) found that parental smoking could contribute to an increased airway responsiveness at an early age; but a subsequent paper (51), including 237 infants, did not confirm those results. The study from Adler *et al* (44) showed no effect of tobacco smoke exposure on the PC40 or on the slope of the

dose-response curve to methacholine. Environmental tobacco smoke may act as a trigger, aggravating symptoms and causing transient hyperresponsiveness, rather than inducing permanent changes in bronchial smooth muscle tone (44).

7.3. Gene polymorphisms (GP)

The association between certain polymorphisms in specific genes and lung function, and even the interaction of the association with tobacco smoke exposure, has recently been studied in adults. However, there is much less information on infants, and the number of studies are very limited currently (Table 5).

Probably the most extensively studied is the β2-adrenergic receptor gene. Wilson *et al* (57) found lower

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V_{max}FRC in homozygosis in the single nucleotide polymorphism (SNP) Gln27 in that gene. However, further studies with larger cohorts have not confirmed those results (58,59)⁹. In the Perth cohort (58), multivariate analyses could not show any significant association of the two haplotypes Arg¹⁶Gly and Gln²⁷Glu with neither V_{max}FRC nor BHR at 1, 6 and 12 months of age. Furthermore, no SNP showed any association after adjusting for height, weight, exact age, gender, and maternal smoking in pregnancy. Moreover, the Oslo cohort (59), did not find any association between lung function at birth (as measured by t_{PTEF}/t_E) and any of the studied haplotypes; and failed to find any significant interaction between tobacco smoke exposure and the haplotype-lung function relationship.

The study by Bisgaard *et al* (60) was designed to look for an eventual association between GPs in the chromosome 17q21 locus which contains the ORMDL3 gene. Baseline lung function values were not significantly associated with rs7216389 SNPs, although bronchial responsiveness was significantly increased by 1 month of age in infants who had that SNP. Breslow *et al* (61) identified the ORM proteins as critical mediators of sphingolipid homeostasis and suggested the possibility that sphingolipid misregulation may contribute to the development of childhood asthma.

The rs8034191 SNP of the alpha-nicotinic acetylcholine receptor was not associated with lung function at birth and stratification according to tobacco exposure did not alter the results (61).

Different SNPs in Glutathione S-Transferase genes (GSTT1, GSTP1) both in mothers and in infants were associated with lower V_{max}FRC and bronchial hyper-responsiveness in infants exposed to tobacco smoke *in utero*, suggesting that the presence of the GSTT1 and GSTP1 genes may be especially important during fetal development as it may modify, through proficient detoxification, the effects of maternal smoke exposure on BHR and lung function in infants (62).

CC homozygotes in rs3025028 in the Vascular Endothelial Growth Factor-A (VEGF-A) gene, had significantly higher V_{max}FRC compared with other genotypes. Similarly, in a population from Indiana (USA), the mean z-scores of FEF₅₀ and FEF₂₅₋₇₅ were significantly higher among CC homozygotes in rs3025028 (63). Interestingly, the ratio VEGF-A_{165a}/ VEGF-A_{165b} was significantly higher among the CC group as compared with the GG group. The authors proposed that this variant in VEGF-A might alter the relative ratio of stimulating VEGF-A_{165a} versus inhibitory VEGF-A_{165b} in angiogenesis, resulting in differences in lung function.

A significant association of the secretoglobin 1A1 (SCGB1A1) A38G genotype with airway reactivity to histamine, but not with V_{max}FRC, at one month of age has been found in one study (64).

The Southampton Women's Survey Study (65) has recently showed associations of five SNPs, in four

different genes, with infant lung function: Hedgehog interacting protein (HHIP) had one SNP (rs11100860) that was associated with increased lung compliance; while another one (rs1032296) was associated with decreased lung compliance; retinoic acid receptor b (RARb) (rs1529672) was associated with increased V_{max}FRC; the natural cytotoxicity triggering receptor 3 (NCR3) (rs2857595) was associated with lower respiratory rate; and the histone deacetylase 4 (HDAC4) (rs12477314) was associated with both increased compliance and V_{max}FRC.

We are now starting to know the genetic regulation of infant lung function and the future will probably bring complex interactions between genes and between genes and the environment associated to lung function parameters.

7.4. Atopy and inflammation

Atopy has been shown to be another risk factor for reduced lung function in the early years of life. The study by Håland *et al* (12) showed that children less than 2 years of age with both recurrent LRI and atopic eczema had significantly lower t_{PTEF}/t_E at 2 years and at birth, as compared to children with no recurrent LRI or atopic eczema. In the COPSAC cohort, levels of fractional exhaled nitric oxide (FeNO) were unrelated to neonatal lung function, although increased neonatal FeNO levels were significantly associated with the development of recurrent wheeze in the first year of life, but not thereafter. The authors concluded that an elevated FeNO level in asymptomatic neonates born to mothers with asthma preceded the development of transient early wheezing, but not persistent wheezing during preschool age, and was unrelated to atopy (67). The study conducted by Debley *et al* (68) found no correlation between single breath eNO at enrollment and lung function at the same time point, but was associated with a decline in FEV_{0.5}, FEF₂₅₋₇₅ and FEF₇₅ over 6 months: a 10ppb increase in single breath eNO was associated with a 0.4 z-score decline in FEV_{0.5}, a 0.4 z-score decline in FEF₂₅₋₇₅, and a 0.42 z-score decline in FEF₇₅. This suggests an association between the decrease of expiratory flows and the degree of eosinophilic inflammation. A study by Malmström *et al* (69) assessed lung function and obtained endobronchial biopsies in 53 infants submitted to a tertiary center for investigation of recurrent lower respiratory symptoms, including dyspnoea, cough and wheeze. The authors found that a reduced baseline lung function in those symptomatic infants was significantly associated with the persistence of lower airway symptoms and furthermore, both reticular basement membrane thickness and the density of bronchial mucosal mast cells in infancy are associated with amount of use of inhaled corticosteroids at age 3 years. However the study fails to show any association between lung function and histological findings, what might be due to the small sample size. Atopy, as assessed by a positive skin prick test, was not more frequent in patients with abnormal lung function.

Another similar study (70) performed in 23 infants who had failed empiric anti-asthma and/or anti-reflux therapy and underwent flexible bronchoscopy, found

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that, as compared to subjects without lower airway abnormalities, subjects with lower airway abnormalities (defined as anatomical defects below the vocal cords) had significantly elevated FRC values. Furthermore, as compared to subjects without neutrophilic inflammation, subjects with neutrophilic inflammation had significantly higher FVC values. Conversely, there was no significant association between the remaining lung function parameters (FEV_{0.5}, FEF₇₅, FEF₂₅₋₇₅ and RV/TLC) and the five clinical covariates (airway inflammation, positive bacterial culture, lower airway abnormality, visible bronchitis, and hyperinflation on chest radiograph). Furthermore, in a selected cohort of 116 infants with chronic dermatitis enrolled prior to the first episode of wheeze, milk and/or egg sensitization was associated with higher airway reactivity prior to wheezing and after the onset of wheezing; however, these factors were not associated with an increased risk of wheezing (20).

Some studies have tried to clarify the role of atopy in lung function, considering whether asthma or allergy in parents is a risk factor to lower lung function. The study by Borrego *et al* (4) showed a reduction in FVC and FEF₂₅₋₇₅ in wheezing children with risk factors for asthma (parental asthma, personal history of allergic rhinitis, wheezing without colds and/or eosinophil level >4%), as compared with those without such risk factors. A later study (71) found that V_{max}FRC was significantly lower in wheezing infants with a positive predictive index of asthma (72). Family history of asthma has been shown to be related with an increase in bronchial hyper-responsiveness (45,51,55).

7.5. Other risk factors

A few years ago, a study in 154 infants assessed at ages 1 and 12 months showed that the change in V_{max}FRC was inversely associated with the change in weight. The authors suggested that these associations could be relevant to the clinically recognized “fat, happy wheezer” syndrome (71). More recently the COPSAC cohort (56) has shown that newborns in the upper quartile of body mass index had 14% lower FEV_{0.5}.

Adler *et al* (54) indicated that respiratory syncytial virus (RSV) infection was not associated with V_{max}FRC (measured after the first infection), and their data do not support a role for RSV as a risk factor for bronchial hyper-responsiveness. Unfortunately, there is no information whether early virus infection has a deleterious effect on lung function early in life. Currently we just know that infants with poor lung function are at risk of lower airway viral illness. However, and very interestingly, a study by Mallol (58) *et al.* showed a transient reduction in lung function (especially in expiratory flows) during common colds in young children.

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Key Words: Infant lung Function, Asthma, Recurrent Wheeze, Review

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