

The Relationship between Infant Airway Function, Childhood Airway Responsiveness, and Asthma

Stephen W. Turner, Lyle J. Palmer, Peter J. Rye, Neil A. Gibson, Parveenjeet K. Judge, Moreen Cox, Sally Young, Jack Goldblatt, Louis I. Landau, and Peter N. Le Souëf

School of Paediatrics and Child Health, University of Western Australia, and Department of Respiratory Medicine, Princess Margaret Hospital for Children, Perth, Australia

The relationship between reduced pulmonary function in early life and persistent wheeze (PW) in school-aged children remains uncertain. In this study, $\dot{V}_{\text{maxFRC}}$ was assessed at 1 month of age, and the presence of wheeze up to 11 years of age was prospectively identified. At 11 years of age, airway responsiveness (AR) to inhaled histamine and atopy were assessed. Recent wheeze at 11 years of age was associated with a reduced mean z score for $\dot{V}_{\text{maxFRC}}$ at 1 month of age (-0.41 [SD 0.91], $n = 31$) compared with no recent wheeze (0.04 [SD 1.00], $n = 153$, $p = 0.03$). Wheeze between 4 and 6 years that persisted at 11 years (PW) was most prevalent among those with reduced $\dot{V}_{\text{maxFRC}}$ at 1 month and atopy aged 11 years ($p = 0.002$) or reduced $\dot{V}_{\text{maxFRC}}$ and increased AR aged 11 years ($p = 0.015$). When all factors were considered, reduced $\dot{V}_{\text{maxFRC}}$ at 1 month ($p = 0.03$) and increased AR aged 11 years ($p < 0.001$) were independently associated with PW ($n = 17$) compared with other outcomes ($n = 129$). Reduced airway function present in early infancy is associated with PW at 11 years of age, and this relationship is independent of the effect of increased AR and atopy in childhood.

Keywords: respiratory sounds; respiratory function tests; longitudinal study; infant

Recurrent childhood wheeze is common (1), begins in early life (2), and may then persist into later life (3). In some individuals, factors present in early life might be lifelong determinants of respiratory outcome. Factors associated with persistent childhood wheeze include male sex and a history of maternal asthma or smoking (4, 5). Atopy (4, 6) and increased airway responsiveness (AR) in young children (7–9) have also been associated with persistent wheeze (PW) in later life. The mechanism for the development of persistent childhood wheeze remains incompletely understood but appears to be complex, and in children, increased AR and atopy may be particularly important.

In addition to increased AR and atopy, abnormalities of pulmonary function are also associated with increased wheeze in children (4, 10), and these abnormalities persist into adulthood (11). What remains uncertain is whether abnormalities of pulmonary function precede the development of respiratory symptoms or, alternatively, are a consequence of the disease process responsible for respiratory symptoms. Several studies have confirmed that infants with reduced pulmonary function, as evi-

denced by reduced $\dot{V}_{\text{maxFRC}}$, before the onset of respiratory symptoms appear to be at increased risk for the development of bronchiolitis (12), pneumonia (13), and increased wheeze (4, 14–16). Two groups have followed individuals with reduced $\dot{V}_{\text{maxFRC}}$ in early infancy and have demonstrated persisting abnormalities of pulmonary function, as evidenced by reduced $\text{FEF}_{25-75\%}$ at 11 years of age (12, 13, 16). These data suggest that $\dot{V}_{\text{maxFRC}}$, in addition to increased AR and atopy, may also be an important determinant of respiratory symptoms and pulmonary function in children.

The relationship between reduced $\dot{V}_{\text{maxFRC}}$ and persistent childhood wheeze is unclear, and this is in part due to the technical and practical difficulties in undertaking a study of this nature. One study has reported that there was no association between reduced $\dot{V}_{\text{maxFRC}}$ in infancy and PW at 6 years of age (4). No study has reported outcomes at 11 years. Investigators in our department have recruited a birth cohort that underwent an assessment of pulmonary function at 1 month of age, before the onset of any respiratory symptoms. The 11-year follow-up of study subjects is now complete. We hypothesized that reduced $\dot{V}_{\text{maxFRC}}$ soon after birth would be associated with PW at 11 years of age, independent of atopy and increased AR in childhood. Some of the results of this study have been previously reported as abstracts (17, 18).

METHODS

Subjects

The cohort was enrolled before birth and was selected from a white population attending an antenatal clinic between June 1987 and November 1990 as described previously (19). There was no selection for parental asthma. Enrolled individuals who were subsequently born prematurely or who developed respiratory symptoms in the first month of life were excluded from the study. The study was approved by the Medical Ethics Committee of Princess Margaret Hospital for Children. Informed parental consent was obtained for each assessment.

Protocol

At enrollment, parents received instructions that would assist in detecting wheeze, and a parental history of smoking and/or physician-diagnosed asthma (PDA) was noted. Infant pulmonary function was assessed at 1 month of age. A history of recent wheeze or PDA was identified from monthly questionnaires completed by parents in the first year and annually on the child's second, third, fourth and fifth birthdays. Aged 6 and 11 years, individuals underwent an assessment that included questionnaire, spirometry, AR to inhaled histamine, and skin prick testing. At 11 years of age, the presence of reported previous wheeze and PDA was verified using previous questionnaire data.

Definitions

"Recent wheeze" included wheeze caused by all causes present in the past year. "Parental asthma" indicated that at least one parent had a history of PDA at enrollment. "Atopy" was defined as at least one positive skin prick test. Children were grouped according to the presence or absence of wheeze as follows: NW for no wheeze reported at any age; W0–3 for wheeze before but not after the third birthday; W4–6 for wheeze between ages 4 and 6 years but not after; W11 for wheeze at 11 years but not previously; and finally, PW for those who wheezed between 4 and 6 years and at 11 years of age.

(Received in original form July 3, 2003; accepted in final form January 25, 2004)

Supported by National Health and Medical Research Council of Australia grant number 9938107 (S.W.T.).

Correspondence and requests for reprints should be addressed to Stephen W. Turner, M.D., School of Medicine, Department of Child Health, Aberdeen Children's Hospital, Foresterhill, Aberdeen AB25 2ZG, Scotland. E-mail: s.w.turner@abdn.ac.uk

This article has an online supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Am J Respir Crit Care Med Vol 169, pp 921–927, 2004

Originally Published in Press as DOI: 10.1164/rccm.200307-891OC on February 5, 2004
Internet address: www.atsjournals.org

Infant Pulmonary Function Measurement

The techniques used have been described (19). After sleep was induced with chloral hydrate, $\dot{V}_{\text{maxFRC}}$ was determined from the rapid thoracoabdominal compression technique during tidal breathing. In accordance with published guidelines (20), $\dot{V}_{\text{maxFRC}}$ was expressed when appropriate as a z score, after adjustment for sex, age, length, weight, and maternal smoking during pregnancy (21). AR was determined from the response of $\dot{V}_{\text{maxFRC}}$ to doubling concentrations of nebulized histamine solutions (from 0.125 to 8 mg/ml). The airway challenge ended if a 40% reduction in $\dot{V}_{\text{maxFRC}}$ was provoked or if the final concentration had been administered. AR was expressed as the concentration of histamine provoking at least a 40% reduction in $\dot{V}_{\text{maxFRC}}$ (PC_{40}). As previously (7), those individuals in whom $\dot{V}_{\text{maxFRC}}$ did not fall by 40% after inhalation of the maximal concentration of histamine were assigned the value $\text{PC}_{40} = 16 \text{ mg/ml}$.

Childhood Pulmonary Function and AR

Childhood pulmonary function was measured with a portable spirometer (Pneumocheck Spirometer 6100; Welch-Allyn, Skaneateles Falls, NY) in accordance with published guidelines (22). Childhood pulmonary function was expressed as a z score after adjustment for height, sex, current AR, and current parental smoking status (see Table E1 on the online supplement). The rapid technique was used to determine childhood AR (23). Briefly, increasing doses of inhaled histamine were administered from a handheld dosimeter until either a 20% reduction in FEV_1 occurred or the maximal cumulative dose had been administered (7.8 μmol). The response of pulmonary function to inhaled histamine was expressed using one of two methods: first, the dose of histamine (μM) that provoked at least a 20% fall in FEV_1 (PD_{20}) (increased AR was defined as PD_{20} of less than 7.8- μM histamine) (24), and second, the dose-response slope (DRS), which was calculated as follows:

$$\left(\frac{\text{FEV}_1 \text{ prechallenge} - \text{FEV}_1 \text{ postchallenge}}{\text{FEV}_1 \text{ prechallenge}} \right) \times 100$$

cumulative dose of histamine

The DRS was adjusted for the influence of reduced $\text{FEF}_{25-75}\%$.

Skin Prick Tests

The skin prick test described by Pepys (25) was used to determine sensitivity to these allergens: cows milk, egg white, rye grass, mixed grass (No. 7), *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat dander, dog dander, *Alternaria alternans*, and *Aspergillus fumigatus* (Hollister-Stier, Elkhart, IN). The positive control was histamine sulfate (10 mg/ml), and the negative control was 0.9% saline. A positive skin test was defined as a weal of at least 3 mm in any dimension.

Statistical Analysis

The distributions of $\dot{V}_{\text{maxFRC}}$ and PC_{40} at 1 month and dose response slope at 6 and 11 years were skewed with long right-handed tails and were $\log_{10}$ transformed before analysis (a constant of three was added to DRS to allow values of zero or less to be included). Chi-square test,

Student's *t* test (equivariance not assumed), Mann-Whitney *U* test, Kruskal-Wallis test, or analysis of variance (with Bonferroni correction) were used where appropriate to compare differences between groups.

Logistic regression models were created to study the relationship between current and previous PDA at 11 years of age (outcome variables) and PC_{40} at 1 month (explanatory variable) adjusting for sex and $\dot{V}_{\text{maxFRC}}$ (used in previous analyses) (7). Longitudinal associations between measurements of $\dot{V}_{\text{maxFRC}}$ in infancy and $\text{FEF}_{25-75}\%$ in children were studied among those individuals in whom data were complete by comparing mean z scores for all measurements of pulmonary function (i.e., three measurements for each individual) between the different wheezing groups.

A Cox proportional hazards model was created to determine the relationship between $\dot{V}_{\text{maxFRC}}$ aged 1 month, atopy and DRS aged 11 years (explanatory variables), and PW (outcome variable). In this model, individuals with PW were compared with all other individuals. The following confounding variables were also considered in this model: PC_{40} aged 1 month, sex, length aged 1 month, maternal or paternal smoking during pregnancy, and parental asthma. Variables were removed in a backward stepwise manner assuming significance at the 5% level.

All reported p values were two sided. Analyses were performed using a standard statistical software package (SPSS release 10.0.7; SPSS, Chicago, IL).

RESULTS

Subjects

At 1 month of age, 243 infants underwent an assessment of pulmonary function; $\dot{V}_{\text{maxFRC}}$ was measured in all individuals and PC_{40} in 202 infants. Questionnaire data were available from 112 study subjects aged 1 year, 169 aged 2 years, 113 aged 3 years, 126 aged 4 years, and 106 aged 5 years. At 6 years of age, 117 children were assessed, and at 11 years of age, 185 cohort members were assessed, including 111 children seen at 6 years of age (see Figures E1, E2, and E3 in the online supplement for figures showing the numbers of individuals where details of wheeze, pulmonary function and AR were available during the period of follow-up). Ten individuals were recruited and not assessed aged 1 month but did participate in later assessments. One hundred fifty-seven children could be placed into one of the following groups: NW, *n* = 67; W0-3, *n* = 28; W4-6, *n* = 39; W11, *n* = 6; or PW, *n* = 17. Table 1 compares details of these 157 individuals with the original cohort. Wheeze was reported on at least one occasion during the first 3 years in 25 of the 37 (68%) individuals with W4-6 and for 13 of 16 (81%) of individuals with PW where questionnaire data were available.

Prevalence of Asthma and Wheeze

Recent wheeze was reported in 37 (33%) individuals in the first year, 61 (36%) individuals aged 2 years, 40 (35%) individuals

TABLE 1. COMPARISON OF CHARACTERISTICS OF THE 156 CHILDREN WHOSE DETAILS ARE PRESENTED IN THIS STUDY WITH THE ORIGINAL COHORT

	Individuals Placed into a Wheeze Category	Individuals in whom Pulmonary Function Was Assessed on Each Occasion	Original Cohort
Male	54% (85/157)	52% (49/95)	56% (136/243)
Mother smoked during pregnancy	17% (25/157)	18% (17/95)	24% (57/242)
Parental asthma†	30% (46/153)	29% (27/93)	31% (73/232)
$\dot{V}_{\text{maxFRC}}$ z score at 1 mo of age (SD)	-0.01 (1.02), <i>n</i> = 157	0.00 (1.06), <i>n</i> = 95	-0.04 (0.99), <i>n</i> = 243
PC_{40} at 1 mo of age,‡ (95% CI)	1.01 (0.82, 1.36), <i>n</i> = 131	1.10 (0.83, 1.34), <i>n</i> = 77	1.04 (0.80, 1.14), <i>n</i> = 202

Definition of abbreviations: CI = confidence interval; PC_{40} = concentration of histamine provoking at least a 40% reduction in $\dot{V}_{\text{maxFRC}}$.

* *p* < 0.05 compared with the original cohort.

† Data missing for 11 fathers.

‡ Expressed as geometric mean and 95% confidence intervals (1.96 × SEM).

TABLE 2. DETAILS IN EARLY INFANCY FOR GROUPS DEFINED BY CHILDHOOD WHEEZE

	NW (n = 67)	W0-3 (n = 28)	W4-6 (n = 39)	W11 (n = 6)	PW (n = 17)	Trend Test (p)
Male	54% (36/67)	43% (12/28)	59% (23/39)	50% (3/6)	65% (11/17)	NS
Mother smoked						
during pregnancy	15% (10/67)	29% (8/28)	21% (8/39)	17% (1/6)	18% (2/17)	NS
Parental asthma*	23% (15/66)	30% (8/27)	26% (10/38)	50% (3/6)	63% (10/16)	0.03
$\dot{V}_{\text{maxFRC}}$ z score	0.08 (0.96),	0.36 (1.28),	-0.21 (0.94),	0.22 (0.41),	-0.59 (0.90),	
at 1 mo (SD)	n = 67	n = 28	n = 39	n = 6	n = 17	0.02
PC ₄₀ 1 mo [†]	1.05 (0.77, 1.45),	1.34 (0.82, 2.21),	0.81 (0.59, 1.10),	1.04 (0.17, 6.34),	0.73 (0.49, 1.09),	
	n = 59	n = 26	n = 30	n = 6	n = 11	NS

Definition of abbreviations: NW = no wheeze; W0-3 = wheeze before but not after the third birthday; W4-6 = wheeze between ages 4 and 6 years but not after; W11 = wheeze at 11 years but not previously; PW = those who wheezed between 4 and 6 years and at 11 years of age; PC₄₀ = concentration of histamine provoking at least a 40% reduction in $\dot{V}_{\text{maxFRC}}$.

* Data missing for 11 fathers.

[†] Expressed as geometric mean and 95% confidence interval ($1.96 \times \text{SEM}$).

aged 3 years, 34 (27%) individuals aged 4 years, 33 (31%) aged 5 years, 26 (22%) aged 6 years, and 31 (17%) aged 11 years. The incidence of wheeze was inversely related to age ($\chi^2_5 = 24.84$, $p < 0.001$). At 11 years of age, 55 (28%) children had a history of wheeze ever. A history of PDA was confirmed by questionnaires in 55 (45%) children aged 6 years of which 28 (24%) children reported current PDA; at 11 years of age, the respective figures for PDA ever and PDA currently were 73 (38%) and 28 (15%).

PC₄₀ Aged 1 Month and Respiratory Symptoms at 11 Years

Where PC₄₀ at 1 month of age was known, a history of diagnosed asthma ever by 11 years of age (n = 59) was associated with reduced PC₄₀ at 1 month of age compared with no history of diagnosed asthma (n = 106) (geometric means 0.72 [95% confidence interval [CI], 0.56, 0.94] vs. 1.09 [95% CI, 0.86, 1.38] $p = 0.04$). There was no reduction in PC₄₀ at 1 month and a history of wheeze ever (geometric mean, 0.86 [95% CI, 0.67, 1.11]; n = 97) compared with NW ever (geometric mean, 0.97 [95% CI, 0.74, 1.29]; n = 97). There was no relationship between PC₄₀ at 1 month and current wheeze and current PDA at 11 years of age.

$\dot{V}_{\text{maxFRC}}$ at 1 Month and Respiratory Symptoms between Ages 4 and 11 Years: Cross-sectional Analyses

Wheeze between 4 and 6 years of age was associated with a reduced mean $\dot{V}_{\text{maxFRC}}$ z score (-0.31 [SD 0.96], n = 64) com-

pared with NW during this period (0.16 [SD 1.06], n = 95, $p = 0.005$). Recent wheeze at 11 years of age was associated with a reduced mean $\dot{V}_{\text{maxFRC}}$ z score aged 1 month (-0.41 [SD 0.91], n = 31) when compared with no recent wheeze (0.04 [SD 1.06], n = 153, $p = 0.03$). There was no significant reduction in mean $\dot{V}_{\text{maxFRC}}$ z score aged 1 month for those individuals with current PDA when compared with other children at 6 years of age (-0.21 [SD 0.99], n = 28, vs. 0.02 [SD 1.03], n = 89) and 11 years of age (-0.21 [SD 1.00], n = 28, vs. 0.00 [SD 1.03], n = 157).

Factors Associated with Different Wheezing Outcomes

The mean $\dot{V}_{\text{maxFRC}}$ z score aged 1 month for individuals in the NW group was 0.08 (SD 0.96, n = 67), for those in the W0-3 group was 0.36 (SD 1.28, n = 28), for those in the W4-6 group was -0.21 (SD 0.94, n = 39), for those in the W11 group was 0.22 (SD 0.41, n = 6) and -0.59 (SD 0.90, n = 17) for those in the PW group (analysis of variance, $p = 0.02$; Table 2 and Figure 1). When both $\dot{V}_{\text{maxFRC}}$ and increased AR at 11 years were considered, PW was more likely to be present for those individuals in both the lowest tertile for $\dot{V}_{\text{maxFRC}}$ z score and with increased AR, χ^2_8 for trend across groups with increased AR = 19.0, $p = 0.015$ (Figure 2), for trend across groups without increased AR $\chi^2_8 = 12.2$ ($p > 0.1$). PW was also most prevalent among those individuals in the lowest tertile for $\dot{V}_{\text{maxFRC}}$ z

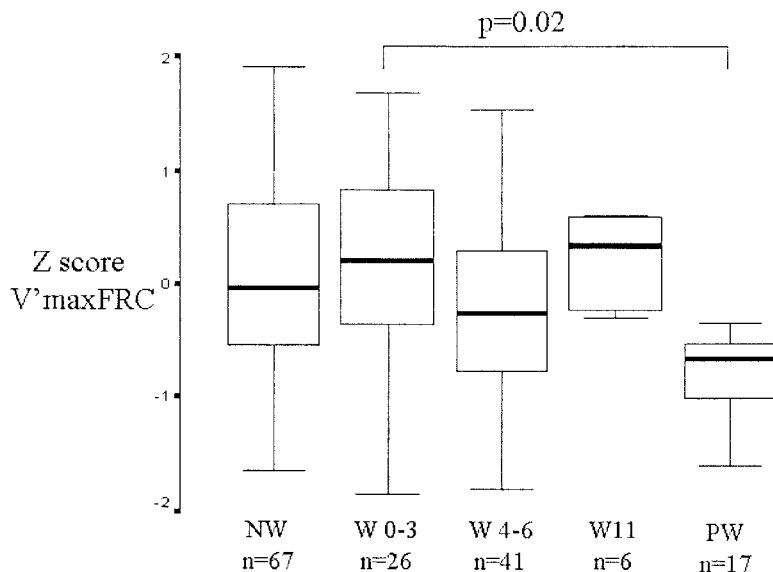


Figure 1. Box and whisker plot showing median and quartiles values for z scores of $\dot{V}_{\text{maxFRC}}$ at 1 month in groups defined by wheeze at different ages. Data from four individuals with z scores of 2.5, 3.8, 3.8, and 4.0 are not included but were included in the analysis. NW = no wheeze reported at any age; W0-3 = wheeze before but not after the third birthday; W4-6 = wheeze between ages 4 and 6 years but not after; W11 = wheeze at 11 years but not previously; PW = those who wheezed between 4 and 6 years and at 11 years of age.

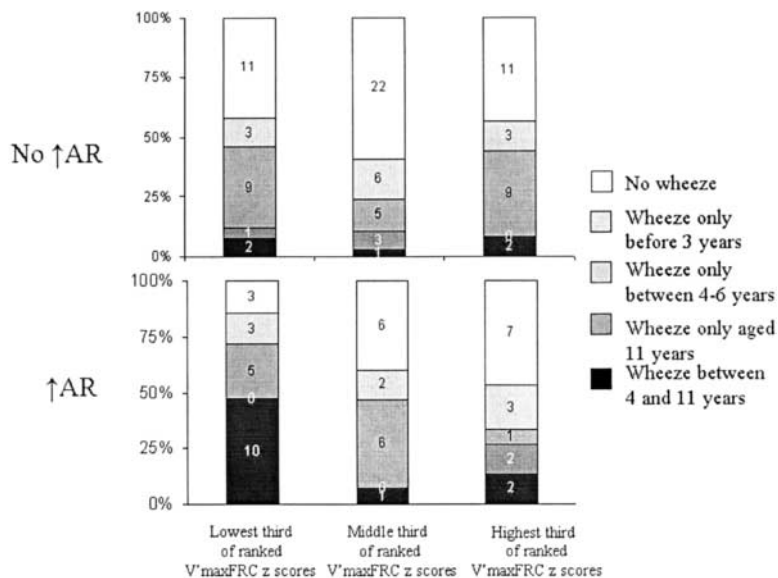


Figure 2. The relationship between tertiles of $\dot{V}_{\text{maxFRC}}$ at 1 month of age, increased airway responsiveness (AR) aged 11 years, and respiratory symptoms in childhood. The group containing individuals with z scores of $\dot{V}_{\text{maxFRC}}$ aged 1 month in the lowest tertile and increased AR aged 11 years also contained the majority of individuals with persistent wheeze (black). χ^2 for trend across groups with increased AR = 19.0, $p = 0.015$.

score aged 1 month and atopy aged 11 years (Figure 3), χ^2 for trend across groups with atopy = 25.0, $p = 0.002$, and χ^2 for trend across groups without atopy = 3.6, $p < 0.8$.

Comparisons between Wheezing Groups at 6 and 11 Years of Age

At 6 and 11 years of age, the prevalence of atopy, the dose response slope, and prevalence of PDA differed significantly between groups (Tables 3 and 4). There was also a nonsignificant trend for reduced FEF_{25-75%} at 6 and 11 years of age to be associated with PW when compared with NW. At 11 years of age, mean z scores for FEV₁ were higher for the W11 and W0-3 groups compared with W4-6 and PW groups (analysis of variance, $p = 0.005$).

Longitudinal Tracking of Pulmonary Function

Pulmonary function data were available at 1 month, 6 years, and 11 years of age in 95 individuals. Table 1 compares the details

of these individuals with the entire cohort. Figure 4 illustrates how the mean z scores for all measurements of pulmonary function (i.e., $\dot{V}_{\text{maxFRC}}$ at one month and FEF_{25-75%} at ages 6 and 11 years) within each wheezing group were consistently lower during the period of follow-up for the group with PW (−0.57, SD 0.91) compared with the NW (0.19, SD 0.88) and W0-3 groups (0.08, SD 1.04) (analysis of variance, $p = 0.001$).

Cox Proportional Hazards Model

When all variables were considered, $\dot{V}_{\text{maxFRC}}$ aged 1 month (hazards ratio = 0.18; 95% CI, 0.00, 0.73; $p = 0.03$) and DRS aged 11 years (hazards ratio = 8.68; 95% CI, 3.27, 23.1; $p < 0.001$) were independently associated with PW.

DISCUSSION

This study was designed to determine the relationship between lung function in early life and respiratory outcome in later childhood, and the data suggest that airway function in early infancy was associated with persistent childhood wheeze. Cross-sectional

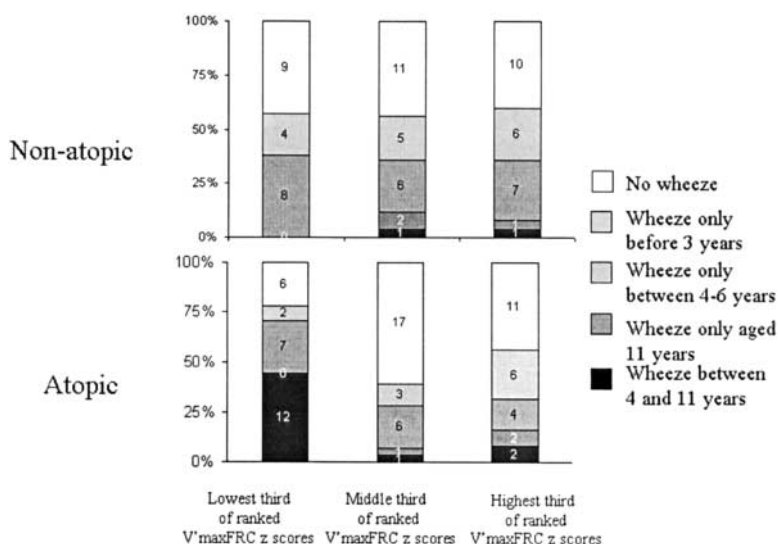


Figure 3. The relationship between tertiles of $\dot{V}_{\text{maxFRC}}$ at 1 month of age, atopy aged 11 years, and respiratory symptoms in childhood. The group containing individuals with z scores of $\dot{V}_{\text{maxFRC}}$ aged 1 month in the lowest tertile and atopic aged 11 years also contained the majority of individuals with persistent wheeze (black). χ^2 for trend across groups with atopy = 25.0, $p = 0.002$.

TABLE 3. DETAILS AT 6 YEARS OF AGE IN CHILDREN GROUPS DEFINED BY CHILDHOOD WHEEZE

	NW	W0-3	W4-6	W11	PW	Trend Test
Atopic	31% (13/39)	24% (4/20)	32% (8/25)	0% (0/5)	77% (9/12)	p = 0.009
Dose response slope*	2.8 (1.8, 4.3), n = 38	4.1 (2.0, 7.0), n = 18	3.3 (2.0, 5.0), n = 22	3.2 (0.2, 9.0), n = 4	18.9 (7.1, 44.3), n = 12	p < 0.001
Mean FEF ₂₅₋₇₅ z score (SD)	0.28 (0.85), n = 38	0.03 (1.11), n = 18	-0.01 (0.84), n = 24	-0.41 (0.51), n = 4	-0.43 (0.80), n = 12	NS
Mean FEV ₁ z score (SD)	0.09 (0.79), n = 40	-0.14 (0.91), n = 19	-0.09 (0.73), n = 25	-0.32 (0.29), n = 4	-0.19 (0.72), n = 12	NS
Diagnosed asthma	5% (2/44)	10% (2/21)	36% (10/28)	20% (1/5)	72% (11/15)	p < 0.001

Definition of abbreviations: NW = no wheeze; W0-3 = wheeze before but not after the third birthday; W4-6 = wheeze between ages 4 and 6 years but not after; W11 = wheeze at 11 years but not previously; PW = those who wheezed between 4 and 6 years and at 11 years of age.

* Expressed as geometric mean $\pm$ 95% confidence interval (1.96 $\times$ SEM).

analyses demonstrated a relationship between reduced $\dot{V}_{\text{maxFRC}}$ aged 1 month and wheeze between ages 4 to 6 and also at 11 years of age. Longitudinal analysis revealed that reduced neonatal lung function was associated with wheezing at age 4 to 6 years that persisted to 11 years of age. In the final analysis, reduced $\dot{V}_{\text{maxFRC}}$ at 1 month of age was shown to be associated with PW, and this relationship was independent of atopy and increased AR in infancy and childhood and, additionally, factors that may influence $\dot{V}_{\text{maxFRC}}$. Individuals with atopy or increased AR at 11 years of age who also had reduced $\dot{V}_{\text{maxFRC}}$ aged 1 month were most likely to have PW, but the influence of increased AR subsumed that of atopy. Because the group with PW has the usual phenotype for childhood asthma, the data suggested that for many children asthma is associated with both reduced $\dot{V}_{\text{maxFRC}}$ at 1 month of age and increased AR at 11 years of age (Figure 5).

Current understanding of the relationship between infant pulmonary function and childhood asthma has been mostly influenced by a study from Tucson, which demonstrated an association between reduced $\dot{V}_{\text{maxFRC}}$ and transient and not PW (4). The findings of this study are in contrast to the previous study because we have found individuals with transient wheeze to have normal pulmonary function at 1 month of age. The techniques used to determine infant pulmonary function in the two studies were very similar. The wheeze outcomes at 11 years of age cannot be compared between the two studies because the Tucson group has not published the relationship between $\dot{V}_{\text{maxFRC}}$ in infancy and wheeze at 11 years of age for their cohort. In keeping with our findings, a study of young children with recurrent wheeze with a follow-up to 6 years of age has reported that individuals with persisting wheeze had reduced $\dot{V}_{\text{maxFRC}}$ at 17 months of age when compared with individuals with transient wheeze (8). Both our study and the Tucson study agree that reduced $\dot{V}_{\text{maxFRC}}$ in infancy is associated with reduced FEF_{25-75%} at 11 years of age (12, 13, 16). We are not able to account for the different outcomes that we have observed from our cohort compared with the cohort in Tucson.

A relationship between reduced $\dot{V}_{\text{maxFRC}}$ in infants, increased AR in childhood, and PW might explain why early wheeze is transient in some children but persistent in others. Reduced $\dot{V}_{\text{maxFRC}}$ in infancy in the absence of increased AR in later childhood has, in our cohort, been associated with transient wheeze (12). This study reports that persistent childhood wheeze was, for the majority of cases, present for those individuals with both reduced $\dot{V}_{\text{maxFRC}}$ at 1 month and greater levels of AR at 11 years of age. Our data are consistent with other studies that have reported associations between abnormalities of lung function and wheeze in early childhood (4, 14) and between increased AR and PW or asthma in later childhood (24). Childhood asthma is commonly considered to be a complex, multifactorial condition, and the increased likelihood of persistent symptoms for individuals with both reduced $\dot{V}_{\text{maxFRC}}$ in infancy and increased AR in childhood is plausible.

The findings of this study suggested that increased AR in infancy and childhood is associated with different wheezing phenotypes. Increased AR present at 1 month of age was associated with future asthma that often resolved, whereas increased AR present at 11 years of age was associated with persisting asthma. There was a trend for individuals in groups W4-6 and PW to have increased AR at 1 month of age compared with other groups, and there is a possibility that with larger numbers of study subjects this trend may have become significant. In this cohort, at 4 weeks of age, increased AR was not influenced by atopy (7), and therefore, increased AR present in infancy may be a nonatopic mechanism for wheeze in younger children. At 11 years of age, increased AR was associated with persistent respiratory symptoms and atopy. Stein and colleagues (26) have proposed that childhood wheeze could be considered as early nonatopic wheeze and later atopic wheeze. Our data would support this concept of wheeze and suggest that the presence of increased AR in either or both infancy or childhood may be an important determinant of wheezing phenotype.

In a previous report, we have reported an association between reduced $\dot{V}_{\text{maxFRC}}$ at 1 month of age, as evidenced by flow

TABLE 4. DETAILS AT 11 YEARS OF AGE IN CHILDREN GROUPS DEFINED BY CHILDHOOD WHEEZE

	NW	W0-3	W4-6	W11	PW	Trend test
Atopic	53% (34/64)	46% (13/28)	42% (15/36)	50% (3/6)	88% (15/17)	p = 0.03
Dose-response slope* (95% CI)	1.6 (1.2, 2.1), n = 66	2.3 (1.4, 3.4), n = 29	1.7 (1.2, 2.4), n = 34	2.4 (1.4, 3.6), n = 6	8.2 (3.2, 17.4), n = 17	p < 0.001
Mean FEF ₂₅₋₇₅ z score (SD)	0.08 (0.74), n = 64	-0.28 (0.60), n = 28	0.08 (0.86), n = 37	0.06 (0.73), n = 6	-0.46 (1.01), n = 16	NS
Mean FEV ₁ z score (SD)	-0.03 (0.97), n = 65	0.41 (0.97), n = 28	-0.21 (0.96), n = 37	1.10 (0.88), n = 6	-0.28 (1.0), n = 17	0.005
Diagnosed asthma	3% (2/67)	4% (1/28)	10% (4/39)	50% (3/6)	82%* (14/17)	p < 0.001

Definition of abbreviations: CI = confidence interval; NW = no wheeze; W0-3 = wheeze before but not after the third birthday; W4-6 = wheeze between ages 4 and 6 years but not after; W11 = wheeze at 11 years but not previously; PW = those who wheezed between 4 and 6 years and at 11 years of age.

* Expressed as geometric mean $\pm$ 95% confidence interval (1.96 $\times$ SEM).

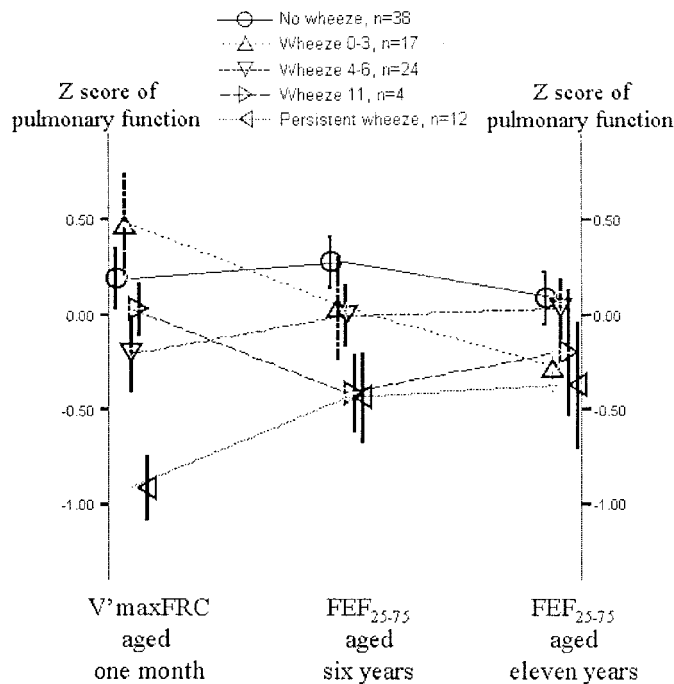


Figure 4. Chart demonstrating mean z scores for $\dot{V}_{\text{maxFRC}}$ at 1 month and $\text{FEF}_{25-75\%}$ at 6 and 11 years of age for groups determined by wheeze outcome.

limitation during tidal expiration, transient wheeze, and increased AR in childhood (16). In this study, we report that reduced $\dot{V}_{\text{maxFRC}}$ and increased AR in childhood were independently related to PW. These outcomes, taken from the same cohort, appear to be contradictory. However, at 11 years of age, the formerly flow-limited individuals were no more likely to be atopic than other cohort members (16), whereas in this study, those individuals with PW were mostly atopic. The data from our study therefore suggest that persistent respiratory symptoms are not associated with increased childhood AR per se but increased childhood AR associated with atopy.

This study has confirmed previous observations that measurements of $\dot{V}_{\text{maxFRC}}$ in infancy correlate with measurements of $\text{FEF}_{25-75\%}$ in childhood (12, 13, 16). Maximal flow at functional residual capacity and $\text{FEF}_{25-75\%}$ are flow-related measurements with relatively large intrasubject variability and as such a strong

interrelationship might not be expected. The coefficient of variation for $\dot{V}_{\text{maxFRC}}$ in infants may vary between 11% and 36% (27), although measurement of $\dot{V}_{\text{maxFRC}}$ becomes less variable in older infants (28), and the coefficient of variation for $\text{FEF}_{25-75\%}$ in 7 year olds is 15% (29). Children with wheeze have reduced $\text{FEF}_{25-75\%}$ but not reduced FEV_1 or FVC, suggesting that $\text{FEF}_{25-75\%}$ is a sensitive measurement of pulmonary dysfunction despite increased variability (10).

There are at least two separate mechanisms that may explain the relationship between reduced $\dot{V}_{\text{maxFRC}}$ at 1 month and reduced $\text{FEF}_{25-75\%}$ and increased wheeze throughout childhood. First, wheeze may be the result of narrow, small airways. This hypothesis is supported by studies of infant pulmonary function that have reported reduced total respiratory conductance in children that subsequently developed wheeze (30, 31). Alternatively, altered airway compliance may result in increased wheezing; abnormal airway wall properties have been demonstrated in infants with a history of wheeze (32). $\dot{V}_{\text{maxFRC}}$ does not distinguish between reduced airway caliber and altered airway compliance; therefore, this study is not able to determine the specific underlying abnormality of pathophysiology.

The main findings of this study are based on a proportion of the original cohort with a relatively lower level of *in utero* smoke exposure, and this loss to follow-up may have affected the outcomes because antenatal exposure to tobacco products has been associated with reduced $\dot{V}_{\text{maxFRC}}$ in our cohort (21) and another (33). Despite adjusting $\dot{V}_{\text{maxFRC}}$ for exposure to *in utero* smoke exposure, this study may not be able to exclude definitively a relationship between exposure to *in utero* tobacco products and increased childhood wheeze. Two recent studies involving large numbers of 6- and 11-year old Perth children (34, 35) have reported prevalences of wheeze very similar to that reported in this study, and this suggests that the symptom frequency reported by cohort members was representative of the general population.

Compared with our findings, two other studies have reported a larger proportion of individuals with wheeze in the first 3 years of life compared with the second 3 years (4, 5). One possible explanation for this apparent difference between our study and other is that wheeze in the first 3 years was underreported in our study because questionnaire data were not available for all study subjects. A second consequence of incomplete questionnaire data is that we cannot exclude the possibility that wheeze was present in the first 3 years but not reported for some children with W4-6 and PW.

In summary, this study demonstrated that reduced $\dot{V}_{\text{maxFRC}}$ at 1 month was associated with PW at 11 years of age. The data suggested that the mechanism for PW in many children involves both an intrinsic abnormality in pulmonary function, as evidenced by reduced $\dot{V}_{\text{maxFRC}}$, determined at an early age and the later onset of increased AR associated with atopy. Our data

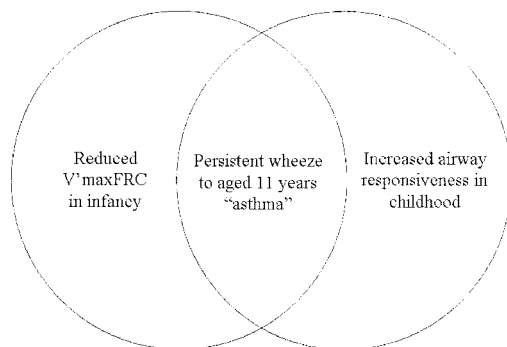


Figure 5. Schematic representation of the relationship between reduced $\dot{V}_{\text{maxFRC}}$ in infancy and AR in childhood, which appears to be important to persistent childhood wheeze and asthma.

TABLE 5. THE FINAL OUTPUT FROM A COX PROPORTIONAL HAZARDS REGRESSION MODEL IN WHICH THE OUTCOME VARIABLE WAS CODED PERSISTENT WHEEZE (= 1) AND NO WHEEZE (= 0)

	RR	95% CI for RR	p Value
Dose-response slope aged 11 yr	8.68	3.27, 23.1	< 0.001
$\dot{V}_{\text{maxFRC}}$ aged 1 mo	0.18	0.00, 0.73	0.03

Definition of abbreviations: CI = confidence interval; RR = relative risk.

Predictive variables included log $\dot{V}_{\text{maxFRC}}$ and log PC_{40} aged 1 month, log dose response slope aged 11 years, atopy aged 11 years, sex, maternal smoking during pregnancy, age (weeks), length (cm), and weight (kg) at 1-month assessment.

may therefore help to explain why asthma does not develop in all atopic children and why early childhood wheeze does not persist in some individuals. The incidence of childhood wheeze is increasing (36), and mechanisms responsible for reduced $\dot{V}_{\text{maxFRC}}$ in early life and increasing atopy in childhood require further study.

Conflict of Interest Statement: S.W.T. has no declared conflict of interest; L.J.P. has no declared conflict of interest; P.J.R. has no declared conflict of interest; N.A.G. has no declared conflict of interest; P.K.J. has no declared conflict of interest; M.C. has no declared conflict of interest; S.Y. has no declared conflict of interest; J.G. has no declared conflict of interest; L.I.L. received airfares, accommodation and honorarium (\$1500) from GSK for speaking at approximately two conferences/workshops each year; P.N.L. has no declared conflict of interest.

Acknowledgment: The authors acknowledge the contribution of many colleagues over the last 15 years and are indebted to the families involved in the Osborne Park family asthma study.

References

1. Park ES, Golding J, Carswell F, Stewart-Brown S. Preschool wheezing and prognosis at 10. *Arch Dis Child* 1986;61:642–646.
2. Yunginger JW, Reed CE, O'Connell EJ, Melton LJ III, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma: incidence rates, 1964–1983. *Am Rev Respir Dis* 1992;146:888–894.
3. Kelly WJ, Hudson I, Phelan PD, Pain MC, Olinsky A. Childhood asthma in adult life: a further study at 28 years of age. *Br Med J (Clin Res Ed)* 1987;294:1059–1062.
4. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life: the Group Health Medical Associates. *N Engl J Med* 1995;332:133–138.
5. Rusconi F, Galassi C, Corbo GM, Forastiere F, Biggeri A, Ciccone G, Renzoni E. Risk factors for early, persistent, and late-onset wheezing in young children: SIDRIA Collaborative Group. *Am J Respir Crit Care Med* 1999;160:1617–1622.
6. Clough JB, Keeping KA, Edwards LC, Freeman WM, Warner JA, Warner JO. Can we predict which wheezy infants will continue to wheeze? *Am J Respir Crit Care Med* 1999;160:1473–1480.
7. Palmer LJ, Rye PJ, Gibson NA, Burton PR, Landau LI, Le Souëf PN. Airway responsiveness in early infancy predicts asthma, lung function, and respiratory symptoms by school age. *Am J Respir Crit Care Med* 2001;163:37–42.
8. Delacourt C, Benoist MR, Waernessyckle S, Rufin P, Brouard JJ, de Blic J, Scheinmann P. Relationship between bronchial responsiveness and clinical evolution in infants who wheeze: a four-year prospective study. *Am J Respir Crit Care Med* 2001;164:1382–1386.
9. Lombardi E, Morgan WJ, Wright AL, Stein RT, Holberg CJ, Martinez FD. Cold air challenge at age 6 and subsequent incidence of asthma: a longitudinal study. *Am J Respir Crit Care Med* 1997;156:1863–1869.
10. Gold DR, Wypij D, Wang X, Speizer FE, Pugh M, Ware JH, Ferris BG Jr, Dockery DW. Gender- and race-specific effects of asthma and wheeze on level and growth of lung function in children in six US cities. *Am J Respir Crit Care Med* 1994;149:1198–1208.
11. Oswald H, Phelan PD, Lanigan A, Hibbert M, Carlin JB, Bowes G, Olinsky A. Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1997;23:14–20.
12. Turner SW, Young S, Landau L, Le Souëf PN. Reduced lung function both before bronchiolitis and at 11 years. *Arch Dis Child* 2002;87:417–420.
13. Castro-Rodriguez JA, Holberg CJ, Wright AL, Halonen M, Taussig LM, Morgan WJ, Martinez FD. Association of radiologically ascertained pneumonia before age 3 yr with asthmatic symptoms and pulmonary function during childhood: a prospective study. *Am J Respir Crit Care Med* 1999;159:1891–1897.
14. Clarke JR, Salmon B, Silverman M. Bronchial responsiveness in the neonatal period as a risk factor for wheezing in infancy. *Am J Respir Crit Care Med* 1995;151:1434–1440.
15. Murray CS, Pipis SD, McArdle EC, Lowe LA, Custovic A, Woodcock A, National Asthma Campaign-Manchester A and Allergy Study Group. Lung function at one month of age as a risk factor for infant respiratory symptoms in a high risk population. *Thorax* 2002;57:388–392.
16. Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge P, Young S, Landau LI, Le Souëf PN. Infants with flow-limitation at 4 weeks: outcome at 6 and 11 years. *Am J Respir Crit Care Med* 2002;165:1294–1298.
17. Le Souëf PN, Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge P, Young S, Landau LI. Pulmonary function at four weeks correlates with pulmonary function at 6 and 12 years [abstract]. *Am J Respir Crit Care Med* 2001;163:A541.
18. Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge V, Young S, Landau LI, Le Souëf PN. Reduced lung function at one month is associated with asthma at eleven years [abstract]. *Arch Dis Child* 2002;86:A37.
19. Young S, Le Souëf PN, Geelhoed GC, Stick SM, Turner KJ, Landau LI. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991;324:1168–1173.
20. Sly PD, Tepper R, Henschen M, Gappa M, Stocks J. Tidal forced expirations: ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. *Eur Respir J* 2000;16:741–748.
21. Young S, Sherrill DL, Arnott J, Diepeveen D, Le Souëf PN, Landau LI. Parental factors affecting respiratory function during the first year of life. *Pediatr Pulmonol* 2000;29:331–340.
22. Standardisation of spirometry: 1987 update: Statement of the American Thoracic Society. *Am Rev Respir Dis* 1987;136:1285–1298.
23. Yan K, Salome C, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983;38:760–765.
24. Salome CM, Peat JK, Britton WJ, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren: I: relation to respiratory symptoms and diagnosed asthma. *Clin Allergy* 1987;17:271–281.
25. Pepys J. Skin tests for immediate, type I, allergic reactions. *Proc R Soc Med* 1972;65:271–272.
26. Stein RT, Holberg CJ, Morgan WJ, Wright AL, Lombardi E, Taussig L, Martinez FD. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax* 1997;52:946–952.
27. Le Souëf PN. Forced expiratory manouevres: infant respiratory function testing. New York: Wiley-Liss; 1996. p. 379–402.
28. Henschen M, Stocks J. Assessment of airway function using partial expiratory flow-volume curves: how reliable are measurements of maximal expiratory flow at FRC during early infancy? *Am J Respir Crit Care Med* 1999;159:480–486.
29. Strachan DP. Repeatability of ventilatory function measurements in a population survey of 7 year old children. *Thorax* 1989;44:474–479.
30. Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. *Am J Respir Crit Care Med* 1999;159:403–410.
31. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988;319:1112–1117.
32. Frey U, Makkonen K, Wellman T, Beardsmore C, Silverman M. Alterations in airway wall properties in infants with a history of wheezing disorders. *Am J Respir Crit Care Med* 2000;161:1825–1829.
33. Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy: effects on lung function during the first 18 months of life. *Am J Respir Crit Care Med* 1995;152:977–983.
34. The ISAAC Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;12:315–335.
35. Oddy WH, Holt PG, Sly PD, Read AW, Landau LI, Stanley FJ, Kendall GE, Burton PR. Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *Br Med J (Clin Res Ed)* 1999;319:815–819.
36. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? *Lancet* 2001;357:1821–1825.