Longitudinal Evaluation of Airway Function 21 Years after Preterm Birth

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***Rationale*: There are limited longitudinal data about respiratory morbidity and lung function after preterm birth into adulthood.**

***Objectives*: To determine the evolution of respiratory symptoms, spirometry, and airway hyperresponsiveness of ex-preterm subjects from childhood into adulthood.**

***Methods*: Ex-preterm subjects (median birth weight, 1,440 g; median gestation, 31.5 wk), recruited at birth (not treated with surfactant), had excess respiratory symptoms, airway obstruction, and increased airway hyperresponsiveness in mid-childhood. At a median age of 21.7 years, 60 of these subjects (the index study group) and 50 healthy term control subjects were recruited to determine respiratory morbidity and spirometry.**

***Measurements and Main Results*: Respiratory symptom questionnaire, spirometry, and methacholine challenge test. The index study group had significantly more respiratory symptoms (16 of 60) than did control subjects (4 of 50) (odds ratio, 4.2; 95% confidence interval, 1.3 to 13.5; $P = 0.01$), but no significant difference in measured spirometry. Specifically, in the index study group and control subjects, the mean *z* scores (95% confidence interval of the group difference) for the FEV_1 were –0.60 and –0.58 (–0.44 to 0.49), respectively ($P = 0.92$); for the forced mid-expiratory flow they were –1.02 and –0.86 (–0.33 to 0.64), respectively ($P = 0.52$); and for the FVC they were –0.29 and –0.33 (–0.46 to 0.38), respectively ($P = 0.85$). Ex-preterm adults did not show evidence of increased airway hyperresponsiveness compared with control subjects, 23 and 19%, respectively ($P = 0.89$).**

***Conclusions*: There are still excess respiratory symptoms 21 years after preterm birth. Reassuringly, this longitudinal study did not show evidence of persistent airway obstruction or airway hyperresponsiveness in ex-preterm adults.**

Keywords: spirometry; respiratory symptoms; airway hyperresponsiveness

There is evidence of respiratory morbidity in ex-preterm subjects both with and without bronchopulmonary dysplasia (BPD) during childhood and adolescence (1–6). Longitudinal data suggest that neurodevelopmental sequelae also persist into young adulthood in this ex-preterm population (7). However, there are few longitudinal data regarding respiratory morbidity from childhood to adulthood.

The aim of this study was to reinvestigate in adulthood a group of ex-preterm low-birth weight subjects (the index study group) born in 1979–1980. The index study group (all $\leq$37 wk of gestation and $<$2.0 kg) born at Queen Charlotte's Hospital (London, UK) were prospectively entered into this longitudinal study at birth, and have subsequently been followed up. All subjects have extensive maternal, perinatal, and neonatal data and therapy recorded. This includes data on the duration of treatment with oxygen and positive-pressure ventilation. No subject was treated with surfactant ("presurfactant era"). All categorization of the newborns was done at birth. A diagnosis of small for gestational age (SGA) was made and was defined as less than the 10th centile on the Tanner-Thompson chart (Castlemead Publications, Ware, UK). From that era there were insufficient data to determine standard deviation scores (*z* scores) for anthropometric variables. Gestational age was determined from maternal data (date of last menstrual period) and physical assessment in the newborn period. An assessment of respiratory morbidity was made in 154 subjects in mid-childhood (7–9 yr of age). In mid-childhood, compared with a control population, these ex-preterm children had the following:

1. Excess respiratory symptoms, especially cough (2).
2. Airway obstruction, specifically a reduced forced expired volume in 0.75 seconds ($FEV_{0.75}$) (3). Low birth weight, mechanical ventilation (intermittent positive-pressure ventilation [IPPV]), oxygen therapy (O_2), and male sex were independent risk factors for airway obstruction (3).
3. Evidence of airway hyperresponsiveness (AHR) (8, 9).

The current article extends the follow-up period to 21 years of age. We hypothesized that 21 years after preterm delivery: (*1*) there would be excess respiratory symptoms in the preterm survivors, (*2*) airflow obstruction detected in mid-childhood would persist into early adult life, and (*3*) there would remain an increased prevalence of AHR.

Some of the work described herein has been published in abstract form (10–12).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The impact of preterm birth on longitudinal respiratory function in adulthood is not well understood and available data are currently limited.

What This Study Adds to the Field

Ex-preterm subjects have more respiratory symptoms in adulthood than their peers. Although impaired lung function tracks from childhood to adulthood, there is some recovery of lung function during this time period.

METHODS

Study Groups

The attrition of the index study group (n = 60) is described in Figure 1. Definitions used in the neonatal period and mid-childhood were used

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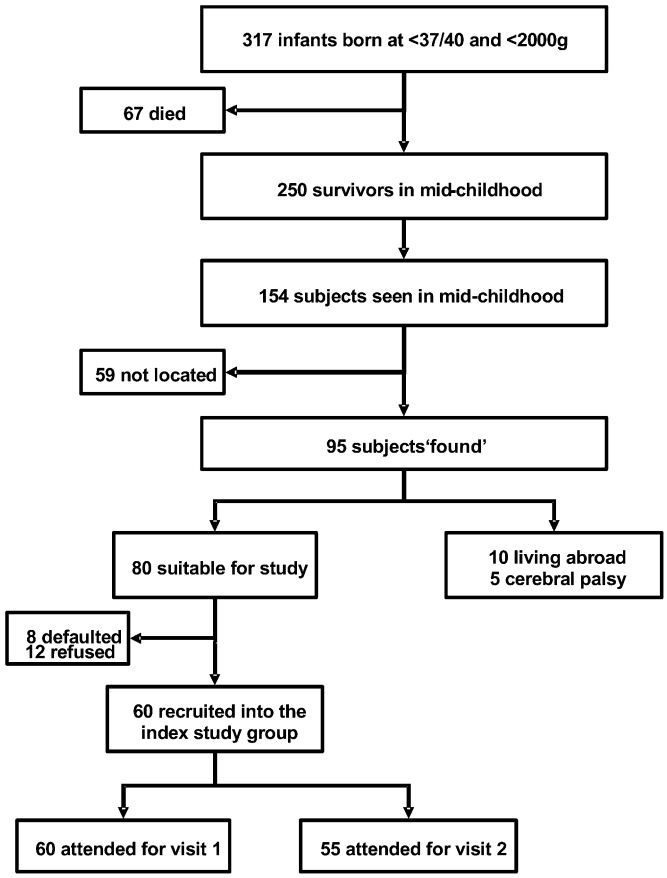

Figure 1. Recruitment of the index study group from birth to adulthood.

without revision, to avoid bias. BPD was diagnosed if subjects required oxygen at greater than 28 days' postnatal age.

A control population (n = 50) was selected in adulthood for the purpose of this study (<26 yr, birth weight > 2,000 g, and gestational age ⩾ 37 wk at birth). Recruitment took place initially from friends of the study group (each index study group subject, at the time of initial contact, was asked to bring a friend of similar age and sex to participate as a control subject), students from the local university, health staff working in the hospital, and friends of colleagues.

The exclusion criteria included a history of prematurity, chronic respiratory disease, cardiac disease, and joint or neuromuscular disease.

Methods at 21 Years of Age

The study protocol was completed during two visits.

Questionnaire

A questionnaire was used to determine respiratory symptoms. Demographic details, personal medical history, personal cigarette consumption, and respiratory symptoms of asthma, cough, and wheeze were recorded. Asthma was diagnosed if subjects reported a doctor diagnosis of asthma, treatment with inhaled medication, and a history of wheeze and/or cough. Wheeze was diagnosed if self-reported as a whistling noise from the chest any time in the previous 2 years, or diagnosed by a doctor any time in the preceding 2 years or on clinical examination at the time of the study. Cough was diagnosed if self-reported and occurred on a regular basis (at least three times per week) either during the day or night for at least 4 weeks in the preceding 2 years.

Pulmonary Function Tests

Spirometry was recorded to American Thoracic Society (ATS) standards (13), using a Compact spirometer (Vitalograph, Ltd, Birmingham, UK). FEV_1, FVC, and forced midexpiratory flow ($FEF_{25–75}$) were recorded (13). Standard deviation (z) scores for spirometry were calculated from reference values (14).

Salivary Cotinine Analysis

Salivary cotinine was collected to evaluate reported cigarette consumption.

The Cozart cotinine microplate enzyme immunoassay kit (Cozart Bioscience, Abingdon, Oxfordshire, UK) was used for salivary cotinine analysis. A concentration greater than 10 ng/ml is considered to indicate an active smoker (15). *See* the online supplement for details.

AHR

Methacholine was used to determine AHR. The methacholine challenge test was performed according to ATS guidelines (16). *See* the online supplement for details.

Statistical Methods

The index study group, its subgroups (low birth weight [LBW], > 1,500–2,000 g; and very low birth weight [VLBW], ⩽ 1,500 g), or SGA and appropriate for gestational age (AGA), and control subjects were compared by analysis of variance with Tamhane's T2 correction for multiple contrasts not assuming equal variances, with $P < 0.05$ regarded as significant. Other group comparisons used Mann-Whitney or Kruskal-Wallis nonparametric tests whereas frequency analysis employed χ^2 or Fisher's exact test if there were fewer than five subjects. t tests were used to calculate the 95% confidence interval (CI) of the group differences in the z scores of the spirometry data. Linear models were used for regression analysis. Correlation was determined using Spearman's correlation coefficient, rho (ρ). In all of the statistical tests used in this study, a P value less than 0.05 was considered significant but a P value less than 0.01 was considered a more reliable measure of significance because of the large number of potential comparisons.

A power calculation determined that 50 subjects in each of the groups (index study group and control subjects) allowed detection of a standard deviation score difference of 0.33 in measured spirometric variables with 80% certainty at the 5% level.

A power calculation determined that 20 subjects in each of the subgroup analyses allowed detection of a standard deviation score difference of 1.0 in measured spirometric variables with 84% certainty at the 5% level.

A power calculation determined that 10 subjects in any subgroup analysis allowed detection of a standard deviation score difference of 1.0 in measured spirometric variables with 65% certainty at the 5% level.

Ethics

The Royal Brompton Hospital Ethics Committee gave approval for this study (protocol reference number 98-073). Written, informed consent was obtained from all subjects.

RESULTS

Recruited and Nonrecruited Groups

The nonrecruited group from mid-childhood (n = 94) was compared with the index study group (n = 60, 7 with BPD) (Table 1). The index study group and those of the nonrecruited group differed at birth only in the greater proportion of smoking mothers, $P < 0.01$. There were no significant differences in maternal socioeconomic status, ethnicity, or maternal age between the groups that could account for the differences observed. Furthermore, there were no statistically significant differences in asthma, cough, and wheeze in mid-childhood between these two groups (Table 1). In mid-childhood, male sex was an independent risk factor for poorer airway function (3). There were no significant differences between the males and females in measured spirometry in the index study groups and nonrecruited groups (Table 2).

TABLE 1. PERINATAL, NEONATAL, AND MID-CHILDHOOD DATA FOR INDEX STUDY GROUP IN ADULTHOOD AND NONRECRUITED GROUP

Variable	Index Study Group (*n* = 60)	Nonrecruited Group (*n* = 94)	*P* Value
M:F	32:28	52:42	0.67
White, no. (%)	50 (83)	65 (69)	0.68
Birth weight, g (range)	1,435 (790–1,990)	1,445 (730–1,990)	0.89
Gestation, wk (range)	31.5 (27–37)	32 (27–39)	0.85
Steroid therapy, no. (%)	20 (33)	38 (40)	1.0
AGA:SGA	22:38	36:58	0.89
Maternal smoker, no. (%)	8 (14)	44 (47)	<0.01
Tx with O_2 + IPPV, no. (%)	23 (38)	29 (31)	0.71
Tx with O_2 only, no. (%)	11 (18)	23 (24)	0.73
No Tx with O_2/IPPV, no. (%)	26 (44)	43 (45)	0.90
Asthma, no (%)	7 (12)	10 (11)	0.84
Cough, no (%)	15 (25)	32 (34)	0.33
Wheeze, no (%)	9 (15)	16 (17)	0.85

Definition of abbreviations: AGA = appropriate birth weight for gestational age; F = female; IPPV = intermittent positive pressure ventilation; M = male; SGA = small for gestational age; Tx = treatment.

Birth weight and gestation values are shown are medians (ranges).

Sociodemographic Status of Index Study Group and Control Subjects in Adulthood

Members of the index study group were slightly younger and shorter than the control subjects (Table 3). There were no significant differences in ethnicity between the groups. Further, there were no significant differences in socioeconomic class between the index study group and control subjects.

There were more reported smokers in the index study group (29 of 60, 48%) than among the control subjects (13 of 50, 26%) (odds ratio [OR], 2.7; 95% CI, 1.2 to 6.0; $P < 0.01$). The median numbers (range) of cigarettes smoked per week in the index study group and the control group were 50 (2–210) and 40 (2–100), respectively (P = not significant [NS]). Salivary cotinine levels were available for 55 of 60 members of the index study group and for 45 of 50 control subjects. There was agreement between self-reported smoking and salivary cotinine levels greater than 10 ng/ml in 47 of 55 members (86%) of the index study group and in 39 of 45 (87%) of the control subjects.

In the index study group and control subjects, 5 of 60 (8%) and 2 of 50 (4%) were taking inhaled therapy (β_2-agonists or corticosteroids), respectively.

TABLE 2. SPIROMETRIC DATA ACCORDING TO SEX IN MID-CHILDHOOD: INDEX STUDY GROUP COMPARED WITH NONRECRUITED GROUP

	Index Study Group		Nonrecruited Group	
	Males	Females	Males	Females
$FEV_{0.75}$, L	1.19 (1.11–1.36)	1.25 (1.20–1.35)	1.15 (1.05–1.20)	1.14 (1.06–1.22)
FEV_1, L	1.29 (1.24–1.51)	1.34 (1.31–1.47)	1.23 (1.15–1.32)	1.23 (1.17–1.34)
FVC, L	1.48 (1.39–1.69)	1.46 (1.41–1.60)	1.32 (1.27–1.49)	1.31 (1.26–1.46)
FEF_{25}, L/s	1.04 (0.85–1.14)	0.98 (0.98–1.28)	0.94 (0.87–1.07)	0.96 (0.89–1.13)
FEF_{50}, L/s	1.99 (1.65–2.15)	1.89 (1.85–2.30)	1.60 (1.53–1.85)	1.80 (1.67–2.05)
FEF_{75}, L/s	2.76 (2.41–3.15)	3.18 (2.81–3.40)	2.53 (2.35–2.77)	2.56 (2.44–2.90)

* All values represent medians (95% confidence interval). For spirometry, there were no significant differences between the males in the index study groups and nonrecruited males in $FEV_{0.75}$ ($P = 0.07$), FEV_1 ($P = 0.10$), FVC ($P = 0.08$), midexpiratory flow at 25% of FVC (FEF_{25}) ($P = 0.75$), midexpiratory flow at 50% of FVC (FEF_{50}) ($P = 0.12$), and midexpiratory flow at 75% of FVC (FEF_{75}) ($P = 0.46$). There were no significant differences between the females in the index study groups and nonrecruited females in $FEV_{0.75}$ ($P = 0.07$), FEV_1 ($P = 0.07$), FVC ($P = 0.18$), FEF_{25} ($P = 0.54$), FEF_{50} ($P = 0.77$), and FEF_{75} ($P = 0.08$).

TABLE 3. ADULTHOOD DATA FOR INDEX STUDY GROUP AND CONTROL SUBJECTS

Variable	Index Study Group (*n* = 60)	Control Subjects (*n* = 50)	*P* Value
Birth weight, kg (range)*	1.44 (0.79–1.99)	3.41 (2.72–5.80)	
Gestation, wk (range)*	31.5 (27–37)	40.0 (36–43)	
O_2 /+ IPPV, no. (%)	36 (60)	0 (100)	
Adulthood data			
Male:female	32:28	25:25	0.43
White, number (%)	50 (84)	45 (90)	1.0
Age, yr (range)	21.7 (20.5–22.9)	23.1 (18.8–25.1)	0.03
Height, *z* score	−0.16 (–1.2 to 0.76)	0.47 (0.00–1.19)	0.02
Weight, *z* score	0.05 (–0.20 to 0.35)	0.55 (0.21–0.27)	0.07
Smokers, no. (%)†	29 (48)	13 (26)	<0.01
Respiratory symptoms, no. (%)	16 (27)	4 (8)	0.01

Unless otherwise stated, the results shown represent medians (95% confidence interval).

* By definition, the index study group had significantly lower birth weight and gestational age than the control subjects, $P < 0.01$, as well as more intensive neonatal therapy.

† Confirmed by cotinine analysis.

Respiratory Symptoms

Adulthood data. Complete respiratory symptom data were available for all 60 members of the index study group and for the 50 control subjects. There were significantly more subjects who reported at least one occurrence of asthma, cough, or wheeze in the index study group (16 of 60, 27%) compared with control subjects (4 of 50, 8%) (OR, 4.2; 95% CI, 1.3 to 13.5; $P = 0.01$) (Table 3; and *see* Table E1 in the online supplement). Of the 16 subjects with respiratory symptoms, 9 of 16 were known to smoke.

Family histories of atopy in the index study group and among the control subjects were recorded for 39 of 60 (65%) and 29 of 50 (58%), respectively (P = NS).

Mid-childhood to adulthood. In the index study group, 27 of 60 subjects had reported respiratory symptoms (at least one of either asthma, cough, or wheeze) in mid-childhood; of these, 9 of 27 (33%) had symptoms in both childhood and adulthood. Of the 33 of 60 in the index study group who did not report any respiratory symptoms in mid-childhood, 7 of 33 did report symptoms in adulthood. There was a significant reduction in the number of subjects with respiratory symptoms from mid-childhood to adulthood ($P < 0.01$).

Neonatal factors and adulthood data. Using a linear regression model, there was no apparent association between respiratory symptoms in adulthood and birth weight, gestational age, and sex.

Airway Function

Adulthood data. Complete spirometry data are available for 58 of 60 subjects in the index study group and for 48 of 50 control subjects (Table 4); four sets of data were discarded as they did not meet ATS standards (13).

Specifically, for the index study group and control subjects, the mean *z* scores (95% CI of the group difference) for the FEV_1 were –0.60 and –0.58 (–0.44 to 0.49), respectively; for the

TABLE 4. SPIROMETRY *z* SCORES FOR INDEX STUDY GROUP AND CONTROL SUBJECTS IN ADULTHOOD

Variable	Index Study Group (n = 58)	Control Subjects (n = 48)	95% CI of the Group Difference	*P* Value
$zFEV_1$	–0.60	–0.58	−0.44 to 0.49	0.92
$zFEF_{25–75}$	–1.02	–0.86	−0.33 to 0.64	0.52
*z*FVC	–0.29	–0.33	−0.46 to 0.38	0.85

Definition of abbreviations: CI = confidence interval; $zFEF_{25–75}$ = *z* score for $FEF_{25–75}$; $zFEV_1$ = *z* score for FEV_1; *z*FVC = *z* score for FVC.

The values given represent means and the 95% confidence interval of the difference between the means.

$FEF_{25–75}$ they were –1.02 and –0.86 (–0.33 to 0.64), respectively; and for the FVC they were –0.29 and –0.33 (–0.46 to 0.38), respectively.

The distributions of *z* scores for FEV_1 for the index study group and its subgroups (LBW and VLBW) and for control subjects were similar (Figure 2). From Figure 2, it can be observed that there is a wide distribution of FEV_1 data for the BPD group (open circles, n = 7). A similar pattern of results was also observed for FVC and $FEF_{25–75}$. However, there was an insufficient sample size to obtain valid statistical analyses for lung function data in the BPD group versus the non-BPD group.

Furthermore, there were no statistically significant differences in spirometry between smokers and nonsmokers either within the groups or between the groups (*see* Table E2).

Mid-childhood to adulthood. FVC and FEV_1 *z* scores derived from mid-childhood data, using reference values (17) (there were no measurements available for $FEF_{25–75}$ in mid-childhood), were compared with adulthood spirometry. FEV_1 and FVC values obtained in mid-childhood were weakly associated with the *z* scores in adulthood for FEV_1 ($P < 0.001$, $r^2 = 0.34$) (Figure 3) and FVC ($P < 0.01$, $r^2 = 0.20$), respectively.

Adulthood Data and Neonatal Factors

The index study group had been prospectively (at the time of initial recruitment) subdivided by birth weight for gestational age. Post hoc analyses showed that birth weight of the SGA, but not AGA, subjects may be associated with $FEF_{25–75}$ *z* scores in adulthood ($r^2 = 0.49$, $P < 0.001$) (*see* Figure E1). Interestingly, this association disappeared when birth weight *z* scores were calculated and used instead of absolute birth weight; there was no correlation between birth weight *z* scores and the $FEF_{25–75}$ ($r^2 < 0.1$, $P = 0.54$) in adulthood in the SGA group.

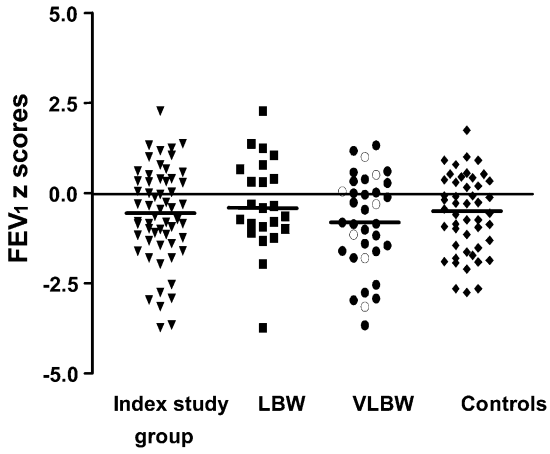

Figure 2. FEV_1 (*z* score) for the index study group, low birth weight (LBW), and very low birth weight (VLBW) subgroups, and control subjects. *Horizontal lines* indicate median values; *open circles* within the VLBW group represent subjects who had bronchopulmonary dysplasia. There were no statistically significant differences between the groups.

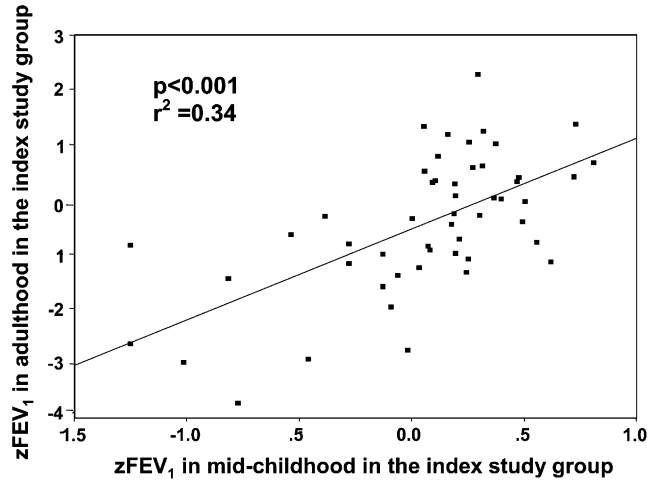

Figure 3. Relationship between *z* scores for FEV_1 in adulthood and mid-childhood in the index study group.

In mid-childhood, only the $FEV_{0.75}$ was worse in those preterm subjects who had required additional oxygen and IPPV. In adulthood, the mean *z* scores (95% CI of the group difference) for FEV_1 for those who received these treatments (n = 34) compared with those subjects who had received no oxygen or IPPV (n = 24) were –0.87 and –0.23 (–1.37 to 0.05), respectively ($P = 0.07$).

In adulthood, in the maternal steroid (n = 20) and maternal no-steroid group (n = 38), the mean *z* scores (95% CI of the group difference) for FEV_1 were –0.75 and –0.53 (–0.51 to 0.94), respectively ($P = 0.55$); for $FEF_{25–75}$ they were –0.89 and –1.08 (–0.99 to 0.62), respectively ($P = 0.64$); and for the FVC they were –0.29 and –0.30 (–0.61 to 0.59), respectively ($P = 0.97$).

Statistical analysis of the measured spirometry between the maternal smoking group (n = 8) and maternal nonsmoking group (n = 49) was not possible because of the small sample size.

AHR

Adulthood data. In the index study group and control subjects, 55 of 60 and 47 of 50, respectively, underwent a methacholine challenge test. Of these, 3 of 55 subjects in the index study group with a clinical diagnosis of asthma could not take the test because of a low FEV_1 (< 60%) at baseline. Of those who were able to do the methacholine challenge test, 12 of 52 (23%) of the index study group and 9 of 47 (19%) control subjects had a positive result defined as a PC_{20} (provocative concentration of methacholine causing a 20% fall in FEV_1) less than 16 mg/ml (OR, 1.3; 95% CI, 0.5 to 3.4; $P = 0.89$); these results are in keeping with quoted population prevalence of AHR (18).

Mid-childhood to adulthood. Of those who completed the methacholine challenge in both mid-childhood and adulthood (n = 51), 29 of 51 (57%) and 12 of 51 (23%) had evidence of AHR in mid-childhood and adulthood, respectively. The prevalence of AHR was significantly lower in adulthood compared with mid-childhood (OR, 4.3; 95% CI, 1.8 to 10; $P < 0.01$).

DISCUSSION

This is the largest longitudinal follow-up study assessing respiratory morbidity in ex-preterm, low-birth weight subjects in adulthood. The prevalence of respiratory symptoms in the ex-preterm

subjects was greater in adulthood when compared with control subjects. There was, however, no evidence of persistently low lung function or AHR from mid-childhood to adulthood in this ex-preterm group. The novel findings were that there was some tracking of FEV_1 data from mid-childhood to adulthood. There was a significantly higher smoking prevalence among the ex-preterm subjects than among the control subjects.

This study was performed at a single center, thus minimizing the variability of results. Recruitment of our own control subjects enabled direct comparison of airway function without the need for reference data. The importance of using contemporaneous control subjects tested identically to the index study group is highlighted by their spirometry z scores for FEV_1, FVC, and $FEF_{25–75}$ being lower than the population predicted values but similar to the index study group. If control data had not been obtained, a reliance on reference values would have resulted in the conclusion that survivors of preterm birth have impaired lung function in adulthood. However, the lung function z scores themselves may have been influenced at various times by the changes in the reference equations. In addition, the height z scores were greater in the control subjects compared with the index study group. However, all the spirometry data were adjusted for height, limiting any bias caused by this variable. The median age of the control population was higher than that of the index study group (23.1 vs. 21.7 yr, respectively; $P = 0.03$). However, when repeated analyses were performed with the control subjects (n = 25) who were older than the median age of the index study group, the results were unaltered, and thus the entire control group (n = 50) was used. The control group demonstrated "normal" population prevalence of smoking, asthma, atopy, and AHR; therefore we believe that the students were a representative population for their age group and could be used as control subjects.

A weakness of the study is that the current index study group represents only 40% of the subjects who were recruited in mid-childhood, and 20% of the total number eligible at birth. The final number of subjects recruited into the study limited the number of valid statistical analyses that could be undertaken for some of the subgroups of the index study group, such as the BPD, maternal smoking groups (n = 8), and those who were born SGA. A further weakness is that there were limited data on the neonatal course of some patients, including the duration of oxygen therapy and number of ventilated days. That is, the study was not powered to evaluate the impact of some important neonatal variables on adulthood lung function.

Another weakness is that most of the attrition occurred among the subjects of mothers who smoked during pregnancy, which may have impacted on the results. However, there were no statistically significant differences in lung function between the recruited and nonrecruited groups from mid-childhood.

At the time of recruitment there were insufficient data, and allocation to SGA status relied on back extrapolation of the Tanner growth charts. We have used subsequently acquired data retrospectively to calculate z scores (19). However, there is the risk of introducing bias by retrospectively recategorizing the babies; and further, secular changes in birthweight mean that more modern data may not have been relevant to the babies born in 1979.

Another relative weakness is that the results precede surfactant therapy and these results may not apply to babies born today.

Although, reassuringly, the prevalence of respiratory symptoms in the ex-preterm population was lower in adulthood than mid-childhood, it was still higher than in the control population. Excess respiratory symptoms have been reported in some (1, 20) but not all (21) larger studies, although these studies did not extend into adulthood. In one of the few reported studies examining preterm survivors in early adulthood, 6 of 26 subjects (23%) with moderate to severe BPD in infancy had respiratory symptoms (22); similar to our study, these symptoms were not attributable to specific neonatal factors. The higher rate of respiratory symptoms might be due to a sustained increased vulnerability of the immature airways secondary to a host of factors related to preterm birth. It is also possible that with lung growth, neonatal factors such as positive-pressure ventilation become less important and that environmental influences dominate on more "vulnerable" airways.

FEV_1, FVC, and $FEF_{25–75}$ were similar in the index study group and control subjects. This implies that there is catch-up growth and normalization of lung function from mid-childhood to adulthood. This may be a result of increased lung volumes in line with somatic growth and/or physiologic airway remodeling, but the mechanisms cannot be delineated by this study. However, some evidence of tracking was seen, in that mid-childhood spirometry was predictive of adult values. The low incidence of BPD and maternal smokers, both risk factors for poorer airway function (22, 23), may have created a bias toward improved airway function in adulthood. Although smoking is known to be detrimental to airway function (24), smoking in the index study group did not appear to affect airway function.

One explanation is that there were many potential confounding variables in the index study group and that the effects of smoking in a relatively small group may be hard to tease out. That is, the small sample sizes may have precluded the obtaining of significant results. Further, smoking as an independent risk factor may also be related to the duration of smoking (25). Because the median age of the index study group was 21 years, the effects of smoking may not be seen until late in adult life, when the effects of smoking are established (24, 26).

Finally, there was no statistically significant difference in lung function between the maternal steroid and no-steroid groups. However, the dose and duration of steroids administered are unknown. Information regarding the indications for steroids during pregnancy and its administration to some mothers in preterm labor, but not all, is not available. This apparent differential use of steroids and the relatively small sample sizes may be possible explanations for the lack of relationship between steroids, respiratory symptoms, and airway function in both mid-childhood and adulthood; however, a larger study concurs with these findings (27).

Other longitudinal studies of ex-preterm subjects have demonstrated improvement in lung function from childhood to adolescence (21, 28). In one such longitudinal study, Doyle and coworkers (21) examined lung function in a preterm cohort (n = 152; mean gestation, 28 wk; mean birth weight, 1.08 kg) both at 8 and 14 years of age. Similar to the current study, no infants received surfactant or high-frequency ventilation. Their study also showed normalization of FEV_1, FVC, and $FEF_{25–75}$ from childhood to age 14 years. The same authors more recently reported lung function data on 147 VLBW ($\leqslant$1,500 g) survivors at 18 years of age (29). These subjects had been born at about the same time as the current cohort and had also not received surfactant treatment. Some of these 147 subjects had lung function recorded at 8, 11, and 14 years of age. In the VLBW cohort, 33 of 147 had BPD (BPD group) and 114 of 147 did not have BPD (no-BPD group). The major finding of that study was that lung function was reduced in the BPD group compared with the no-BPD group (no data comparisons were shown between the BPD group and control subjects). However, overall lung function in the no-BPD group was within the reference range at 18 years of age and not dissimilar from that of the normal birth weight control subjects

(n = 37). This is similar to our data, where the majority of our subjects did not have BPD and had lung function similar to that of control subjects, and further they also showed that active smoking had little effect on any respiratory variable. However, there was no longitudinal assessment of either respiratory symptoms (specifically, asthma, cough, and wheeze) or airway hyperresponsiveness to fully evaluate respiratory morbidity.

A cross-sectional study in adulthood (18–25 yr old) by Northway and coworkers (22) compared both BPD (n = 26) and ex-preterm subjects (no BPD) with healthy term control subjects and showed excess respiratory symptoms and impairment of airway function in the BPD group only. However, neither of the control groups was randomly selected; none of the ex-preterm control subjects were ventilated and the term control subjects had no lung disease and were nonsmokers. These selection filters reduce the generalizability of the results of such a study and cause a bias in favor of finding a difference in the BPD group, in contrast to the current study. Further, the current index study group was born on average 10 years later than Northway's group, during a period when neonatal intensive care was rapidly evolving. A larger cross-sectional study by Anand and coworkers (1) compared 128 VLBW (<1,500 g) subjects (8 of 128 had BPD) with 128 term control subjects born in the same years as the current index study group. Like the current study, their VLBW group showed a significant increase in the prevalence of chronic cough, wheezing, and asthma (not defined), but this was associated with a reduction in the $FEF_{25–75}$. Possible explanations for the differing results with the current study included different mean ages of the subjects (21 vs. 15 yr) and the possibility that airway function continues to normalize beyond adolescence, especially in males, in whom lung and thoracic development is thought to occur at least until the end of puberty (30). Other confounding variables in their study (1) may include the higher prevalence of maternal smoking during pregnancy, 45% compared with only 14% in the current study, and the larger numbers requiring respiratory support, 65% compared with 41% in the current study. In a more recent cross-sectional, population-based study (consisting of 1,338 subjects; gestational age, 32 wk; birth weight, 1,500 g or less), Vrijlandt and coworkers (31) reported on 42 of these ex-preterm subjects (mean age, 19 yr), who had mean values of FVC, FEV_1, and FEV_1/FVC in the normal range (98, 95, and 82%, respectively), but these values were lower when compared with 48 control subjects (106, 110, and 87%, respectively). However, their study group had a higher incidence of BPD and lower gestational age than their own much larger nonrecruited group, which may have caused a bias toward finding a difference compared with control subjects. Further, it is difficult to appreciate whether their study group always demonstrated "normal lung function" because no longitudinal data are available.

Regarding birth weight for gestational age and lung function, Barker and coworkers hypothesized that an adverse environment *in utero* may affect fetal growth and have lasting effects on lung function in adulthood and old age (32). We found that birth weight in the SGA group, but not in the AGA group, was a predictor of FEF_{50} and $FEF_{25–75}$ *z* scores in mid-childhood and adulthood, respectively. However, this was a post hoc analysis, albeit on prospectively determined categories. Interestingly, Lima and colleagues (33) monitored a group of 18-year-old males recruited into the Brazilian army. In their subgroup analyses, those born preterm and SGA (defined as <37 wk of gestation and <10th centile, n = 11) did have a reduction in both FEV_1 and FVC, 263 and 302 ml, respectively, when compared with those born at term and with birth weights greater than 2,500 g. However, the small sample size of the current study, the fact that we do not know what maternal and other factors caused the babies to be SGA, and the lack of accurate charts to classify babies of this size at the time of initial study recruitment preclude more meaningful analyses, and the fact that this association disappeared when birth weight *z* scores were used means this observation is only hypothesis generating, and testing in other cohorts is mandatory before it is accepted. Thus the current data suggest that defining the relationship of impaired fetal growth and adult lung function is an important area for future research.

The finding of a decrease in AHR prevalence in this study is similar to that of a larger longitudinal study with more than 800 subjects, in which AHR declined from childhood to adolescence, paralleling the increase in lung function during this period (34).

Finally, the high prevalence of smoking observed in the index study group, which was verified by biochemical markers, could not be explained; it did not appear to reflect a lower socioeconomic background for these individuals. Future research is necessary to evaluate the causes of "risk-taking behaviors" of such individuals.

In conclusion, this study has highlighted that there is an increased prevalence of respiratory symptoms in adult subjects who were born preterm. Reassuringly, from mid-childhood to adulthood, there was normalization of lung function and no persistence of AHR. However, it is feasible that the age-related decline in respiratory function that commences in mid-adult life may be more rapid or reach a critical threshold at an earlier age in these subjects (35) and, indeed, in those with respiratory symptoms. In a study by Edwards and coworkers (36), a group of adults aged 45–50 years with childhood wheezy bronchitis, having achieved normal lung function in earlier adulthood, had a more rapid decline in lung function than did control subjects with an increased risk of developing chronic obstructive airway disease. Because impaired airway function in adult life is an important and independent indicator of mortality risk (32), continued surveillance of these subjects into late adulthood, particularly of the active smokers, will be vital.

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