

Lung Function, Bronchial Responsiveness, and Asthma in a Community Cohort of 6-Year-Old Children

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Children as young as 6 years old can perform spirometry, yet the relationship between current asthma, lung function, and bronchial responsiveness has not been described at this age; 2,537 children from a community-based birth cohort were assessed at 6 years of age, with history ($n = 2,141$), physical examination ($n = 1,995$), standard spirometry ($n = 1,735$), and a random sample ($n = 711$) offered methacholine challenge. Males had greater values of FVC and FEV₁ but not of mean forced expiratory flow during the middle half of the FVC or FEV₁/FVC than females. The greatest influences on lung function at 6 years were height, sex, birth weight, and wheezing in the first year of life. Children with current asthma had small but significant deficits in lung function and were more sensitive to methacholine. The optimal cutpoint for determining heightened bronchial responsiveness was found to be a 15% fall in FEV₁ at a dose of 1.8 mg/ml. A negative test could be useful in excluding a diagnosis of asthma (negative predictive value of 92%). Lung function testing, including methacholine challenge, is feasible in 5- to 7-year-old children and has the potential to contribute to the clinical management of children with asthma.

Keywords: birth cohort; spirometry; forced expiration; methacholine challenge

Measurement of lung function forms an integral part of the diagnosis, assessment, and management of lung diseases in children able to produce reliable data; however, to interpret whether an individual child's lung function is normal, population data are required. Most children at the age of 6 years are able to perform routine spirometry (1), and pediatric respiratory clinics routinely measure lung function at this age. Commercially available spirometers include normative equations, and lung function is expressed as a percentage of the predicted normal down to 6 years of age. These equations come from studies performed some time ago (2–4), and it is not apparent how many 6-year-old children were included.

The assessment of bronchial responsiveness forms an important part of the assessment of asthma in adults and older children; indeed, some have suggested that heightened bronchial responsiveness is an integral component of the definition of asthma

(5). Studies in adults with asthma define a positive challenge as one in which the provocative concentration of methacholine inducing a fall of 20% in FEV₁ (PC₂₀FEV₁) is less than 8 mg/ml (5–8). Values derived from studies in adults have also been used to classify bronchial responsiveness in children (6, 9, 10); however, this may not be appropriate. Le Souef (11) argued that children are likely to receive a larger dose of methacholine than adults if the “adult” protocol is used, and furthermore, the younger the child, the larger this “overdose” is likely to be. This phenomenon may account for the reported increased responsiveness in children when compared with adults (12–15). Despite the use of methacholine challenge as a research tool in pediatrics, the usefulness of such challenges in aiding the diagnosis of asthma in young children has never been assessed systematically.

In this study, we have measured lung function and methacholine responsiveness in a community-based birth cohort of 6-year-old children. We report the population distribution of lung function and produce normative equations. In addition, we relate lung function and methacholine responsiveness to current asthma status and examine the usefulness of using these data to aid the diagnosis of asthma in children of this age.

METHODS

A birth cohort was enrolled from the antenatal clinics of the tertiary maternity hospital in Perth, Western Australia (16), and was not selected on any criteria other than having enrolled for antenatal care at the hospital. The cohort initially consisted of 2,860 live births. Thirteen children have died. One hundred eighty-nine have withdrawn, and 121 have been lost to follow-up, leaving a cohort of 2,537 (89%) remaining in the study and potentially available at the age of 6 years. The cohort has been under active follow-up since birth, and this report focuses on data obtained when the children were approximately 6 years old. A full description of the cohort recruitment and of the methods for the 6-year follow-up is included in the online supplement.

Extensive historical data were obtained, including sociodemographic factors (housing, family structure, employment, income); family and child's history of asthma, hay fever, eczema, and allergies; respiratory illnesses ever and current (past 12 months); exposures (smoking, pets, etc.); and family functioning and cognitive and psychosocial factors. Physical examination was performed. Lung function was measured, and skin prick tests were conducted. Spirometry (Model 6100; Welch Allyn, Skaneateles Falls, NY) was performed to American Thoracic Society standards with the children standing. Bronchial responsiveness testing was offered to a random sample of the cohort. Within this sample, children were eligible if they could perform reproducible spirometry, had an FEV₁ at least 80% of predicted (2), had no respiratory tract infections for 14 days, and had withheld asthma medication for the standard periods. Methacholine challenge was performed using a modified Yan and colleagues (17) technique. PC₂₀FEV₁, PC₁₅FEV₁, and PC₁₀FEV₁ were calculated by linear interpolation from log-concentration response curves. The dose-response slope was calculated as the two-point slope of the entire curve regardless of the fall in FEV₁ (18). Ethics permission was obtained from the institutional committee, and parents gave written consent.

A child was considered to have current asthma if he or she had a doctor diagnosis of asthma ever and had asthma symptoms (wheeze and/or nocturnal cough in the absence of an obvious respiratory infec-

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tion) in the past 12 months and had been taking asthma medications in the past 12 months (19).

One-way analysis of variance and independent *t* tests for equality of means were used to compare lung function between sexes and asthma status groups. Multiple regression analyses estimated predictive models of lung function, and residual analysis was used to validate the final models. Receiver-operator characteristic (ROC) analyses were used to investigate associations between asthma status and methacholine responsiveness. Optimal cutoff points for each outcome measure were selected as giving the maximum sum of sensitivity and specificity (Youden's *J*). Sensitivity, specificity, positive predictive value, and negative predictive value associated with these cutoff levels were determined, and for 3.9 mg/ml, a commonly used cutoff in adults.

Relationships between lung function, methacholine responsiveness, and asthma were investigated using regression analyses. Prediction equations were based on data from white children only, and other lung function analyses were adjusted for race.

RESULTS

Questionnaires were obtained for 2,147 children (1,095 males and 1,052 females), and physical examination was performed in 1,995 (1,017 males and 978 females), representing 84.4% and 78.6%, respectively, of those potentially available for follow-up at the age of 6 years. The proportions of the original cohort potentially available for the 6-year follow-up and those participating in the various components of the follow-up are shown in Table E2 in the online supplement. As might be expected for a cohort recruited from a tertiary maternity hospital, complex pregnancies and deliveries and socially disadvantaged families were overrepresented in the cohort. There were no important differences between the characteristics of the children who participated in the 6-year follow-up (Table E3 of the online supplement) or who completed spirometry (Table E4 of the online supplement) compared with those who did not. The sample that completed the methacholine challenge was slightly older (71.4 vs. 70.8 months) and had slightly better lung function (FVC, 99.2% vs. 96.5%; FEV₁, 105.9% vs. 101.5%) than those not offered or not able to complete the test (Table E5 of the online supplement). Current asthma status was available for 2,147 children, with 18%, that is, 387 (229 males), satisfying the study definition.

Lung function was obtained from 1,735 children (Table 1), ranging in age from 60 to 86 months and in height from 1.01 to 1.30 m. This group consisted of 1,558 (89.8%) white children, 21 (1.2%) Aboriginal children, and 156 (9.0%) children of other races, predominantly Asian. In the total population, males had greater values of FVC ($p < 0.001$) and FEV₁ ($p < 0.001$) than

females, with these differences remaining after controlling for height and race. These differences were accounted for by sex. There were no differences in mean forced expiratory flow during the middle half of the FVC (FEF₂₅₋₇₅) ($p = 0.212$) or FEV₁/FVC ($p = 0.379$). The influence of height and sex on lung function variables is shown in Table 2 for both the white population as a whole and for the white population, excluding children with current asthma.

After allowing for age, current height, sex and race, birth weight and gestational age, but not birth length had additional effects on FVC and FEV₁. Only gestational age had a significant effect on FEF₂₅₋₇₅, increasing 9 ml/seconds with each additional week of gestational age (95% CI, 0–17) (Table 3). Allowing interactions between current height and sex, current age and sex, or body mass index and height did not improve the model fits.

Fifty-six percent of these children were exposed to maternal smoking during gestation, and 23% of mothers were still smoking when the children were 6 years old. Neither maternal smoking during pregnancy nor maternal smoking when the child was 6 years old had any influence on lung function (Table 3). Wheezy lower respiratory illnesses in the first year of life were associated with a reduced FEF₂₅₋₇₅ (71 ml/second [95% CI, 11–131], a lower FEV₁ [37 ml, 95% CI, 15–59], and a reduced FVC [47 ml; 95% CI, 19–75] (Table 3).

Methacholine challenge was offered to a random sample of 711 children. Of these, 34 were unable to perform the number of forced expiratory maneuvers required, despite being able to perform reliable baseline spirometry, and 112 (7 with current asthma) were excluded with a low baseline FEV₁, leaving a test sample of 565. The challenge was successfully completed in 537 (95% of the test sample), with 28 unable to finish for technical reasons. Of those completing the challenge, FEV₁ fell by at least 20% in 420 (78%), by at least 15% in 457 children (85%), and by at least 10% in 495 (92%) children. Children who did not reach the desired fall in FEV₁ did not have a value for the corresponding PCxFEV₁ (i.e., values were not assigned for these children). There were no differences in methacholine responsiveness between males and females, regardless of which index was examined (Table 2).

Children with current asthma had lower lung function, adjusted for age, height, sex, and race, than those without asthma (Table 4), with small but significant deficits in FEV₁, FEF₂₅₋₇₅, and FEV₁/FVC. FVC was not different between the two groups. The children with current asthma were also more sensitive to methacholine than those without asthma, regardless of which index was used (Table 4).

TABLE 1. LUNG FUNCTION AND METHACHOLINE RESPONSIVENESS AT 6 YEARS OF AGE

	Total Population*	Male*	Female*	p Value (male vs. female)
Height, cm	115 (5.01)	116 (5.17)	115 (4.75)	< 0.001
Age, mo	71.2 (2.47)	71.2 (2.45)	71.2 (2.49)	0.757
FVC, L	1.16 (0.23)	1.20 (0.23)	1.12 (0.20)	< 0.001
FEV ₁ , L	1.09 (0.19)	1.12 (0.20)	1.05 (0.17)	< 0.001
FEF ₂₅₋₇₅ , L/sec	1.50 (0.46)	1.52 (0.47)	1.49 (0.44)	0.212
FEV ₁ /FVC	0.94 (0.07)	0.93 (0.07)	0.94 (0.07)	0.379
DRS	0.21 (90.56)	0.20 (0.44)	0.22 (0.67)	0.784
PC ₁₀ FEV ₁ , mg/ml	1.34 (1.45)	1.39 (1.58)	1.32 (1.31)	0.597
PC ₁₅ FEV ₁ , mg/ml	1.81 (1.67)	1.81 (1.66)	1.80 (1.70)	0.562
PC ₂₀ FEV ₁ , mg/ml	2.07 (1.61)	1.98 (1.57)	2.11 (1.64)	0.562

Definition of abbreviations: DRS = dose-response slope; FEF₂₅₋₇₅ = mean forced expiratory flow during the middle half of the FVC; PC₁₀FEV₁ = provocative concentration of methacholine inducing a fall of 10% in the forced FEV₁; PC₁₅FEV₁ = provocative concentration of methacholine inducing a fall of 15% in the forced FEV₁; PC₂₀FEV₁ = provocative concentration of methacholine inducing a fall of 20% in the forced FEV₁.

* Data presented are mean and (SD).

TABLE 2. INFLUENCE OF HEIGHT AND SEX ON LUNG FUNCTION FOR THE ALL-WHITE CHILDREN AND WITH THOSE WITH CURRENT ASTHMA EXCLUDED (POPULATION WITHOUT ASTHMA)

	FVC ($R^2 = 0.28$) Value (95% CI)	FEV ₁ ($R^2 = 0.34$) Value (95% CI)	FEF ₂₅₋₇₅ ($R^2 = 0.06$) Value (95% CI)
Constant	-1.579 (-1.816, -1.342)*	-1.451 (-1.639, -1.264)*	-1.014 (-1.510, -0.518)
Height, m	2.344 (2.139, 2.549)*	2.169 (2.007, 2.332)*	2.194 (1.767, 2.621)*
Sex	0.062 (0.042, 0.082)*	0.054 (0.038, 0.069)*	N/A
Total population, n = 1,558			
	FVC ($R^2 = 0.28$) Value (95% CI)	FEV ₁ ($R^2 = 0.35$) Value (95% CI)	FEF ₂₅₋₇₅ ($R^2 = 0.06$) Value (95% CI)
Constant	-1.612 (-1.879, -1.344)*	-1.431 (-1.641, -1.221)*	-0.840 (-1.412, -0.268)†
Height, m	2.377 (2.146, 2.609)*	2.156 (1.974, 2.338)*	2.062 (1.569, 2.555)*
Sex	0.060 (0.001, 0.078)*	0.06159 (0.044, 0.078)*	N/A
Population without asthma, n = 1,221			

Definition of abbreviations: CI = confidence interval; FEF₂₅₋₇₅ = mean forced expiratory flow during the middle half of the FVC.

*p < 0.001.

†p = 0.004.

When considering methacholine responsiveness in the asthma population as a whole and comparing it with that in the non-asthma population, the area under the ROC curve was 0.672 for PC₂₀FEV₁, 0.661 for PC₁₅FEV₁, and 0.660 for PC₁₀FEV₁. For all outcome variables, the optimal cutoff for binary results (i.e., negative vs. positive tests) was 1.8 mg/ml. The best balance between sensitivity and specificity was obtained at a PC₂₀FEV₁ of 3.9 mg/ml, at PC₁₅FEV₁ of 1.8 mg/ml, or at PC₁₀FEV₁ of 1.8 mg/ml. At these cutoff values, the negative predictive values of the tests were 93.6%, 92.0%, and 93.1%, respectively, with positive predictive values of 19.8%, 21.6% and 19.1%, respectively. The sensitivities and specificities were 0.863 and 0.364 for a PC₂₀FEV₁ of 3.9 mg/ml, 0.763 and 0.495 for a PC₁₅FEV₁ of 1.8 mg/ml, and 0.863 and 0.364 for a PC₁₀FEV₁ of 1.8 mg/ml.

DISCUSSION

This study reports the most comprehensive assessment of lung function and bronchial responsiveness to inhaled methacholine in 6-year-old children available. These data show the normal values for a community-based population of Australian children, including the differences between males and females and children with current asthma compared with children without asthma at the age of 6 years. These data provide the basis for determining abnormal lung function at this age.

The use of spirometry in young children is increasing, with the realization that younger children can perform adequate forced expiratory maneuvers required for reproducible spirometry (1). Reference equations in current use do include values for children down to the age of 6 years (2, 3, 20); however, although the authors did not report the number of children 6 years old included, it

is likely that few subjects of this age were in the original data sets. One limitation of our study that needs to be acknowledged is that the age range of our children is quite narrow, with a mean age of 71.2 (SD, 2.47) months. This does limit the use of the equations that we have produced; however, they still represent an advantage over the currently available normative equations for children in the age range that we have studied, with smaller standardized residual errors than those in current use (see Table E6 in the online supplement).

The equations presented in Table 2 are suitable for use in children ranging from 60 to 86 months old and 0.86 to 1.30 m in height. In this table, we have provided data for the total white population and for the white population with the children with current asthma excluded. There does not appear to be a consensus regarding whether normative data should reflect the entire population or only those without disease. Wang and colleagues (4) specifically excluded data from children who smoked or who had a doctor diagnosis of asthma from their analyses, whereas Dockery and colleagues (3) recruited their study sample from "all first and second grade children in both public and private school within each of the study communities." Although they recorded personal smoking habits from older children, they did not exclude children's data from their analyses or growth curves based on smoking status. They did not appear to have access to the children's asthma status. The differences in prediction equations reported in this study by including or excluding data from children with a diagnosis of current asthma are small and would not result in clinically important differences in predicted lung function (1, 3, 4, 21–23).

TABLE 3. EARLY LIFE PREDICTORS OF CHANGE (REGRESSION COEFFICIENTS AND 95% CONFIDENCE INTERVALS) IN LUNG FUNCTION AT AGE 6, WITH EACH VARIABLE SINGLY IN TURN ADJUSTED FOR HEIGHT, SEX, AGE, AND RACE

	FVC (ml)	FEV ₁ (ml)	FEF ₂₅₋₇₅ (ml/s)
Birth weight, g	20 (4, 36)*	15 (3, 28)*	28 (-6, 61)
Birth length, cm	4 (0, 8)	3 (0, 6)	6 (-2, 13)
Gestational age, wk	5 (4.1, 7.7)*	4 (1, 8)*	9 (0, 17)*
Wheeze in first year	-47 (-75, -19)*	-37 (-59, -15)*	-71 (-131, -11)*
Maternal smoking in pregnancy	-6 (-26, 14)	-2 (-18, 14)	-25 (-68, 18)
Maternal smoking at a child age 6	-4 (-15, 7)	-5 (-13, 4)	-14 (-37, 10)

Definition of abbreviation: FEF₂₅₋₇₅ = mean forced expiratory flow during the middle half of the FVC.

*p < 0.05.

TABLE 4. LUNG FUNCTION AND METHACHOLINE RESPONSIVENESS FOR CHILDREN WITH AND WITHOUT ASTHMA

	Subjects without Asthma	Subject with Asthma	Difference between Groups	p Value
Spirometry	n = 1,365	n = 308		
FVC, L	1.17 (0.22)	1.16 (0.23)	-0.013 (-0.037, 0.010)	0.271
FEV ₁ , L	1.09 (0.19)	1.06 (0.20)	-0.032 (-0.050, -0.013)	0.001
FEF ₂₅₋₇₅ , L/s	1.52 (0.46)	1.42 (0.44)	-0.109 (-0.160, -0.059)	0.001
FEV ₁ /FVC	0.94 (0.07)	0.93 (0.08)	-0.016 (-0.026, -0.007)	0.001
MCh challenge	n = 440	n = 80		
DRS	0.19 (0.59)	0.34 (0.42)	0.141 (0.008, 0.274)	0.037
PC ₁₀ FEV ₁ , mg/ml	1.44 (1.49)	0.94 (1.32)	-0.530 (-0.889, -0.171)	0.004
PC ₁₅ FEV ₁ , mg/ml	1.93 (1.71)	1.27 (1.48)	-0.658 (-1.078, -0.239)	0.002
PC ₂₀ FEV ₁ , mg/ml	2.18 (1.65)	1.37 (1.23)	-0.811 (-1.220, -0.403)	0.001

Definition of abbreviations: DRS = dose response slope; FEF₂₅₋₇₅ = mean forced expiratory flow during the middle half of the FVC; MCh = methacholine; PC₁₀FEV₁ = provocative concentration of methacholine inducing a fall of 10% in the forced FEV₁; PC₁₅FEV₁ = provocative concentration of methacholine inducing a fall of 15% in the forced FEV₁; PC₂₀FEV₁ = provocative concentration of methacholine inducing a fall of 20% in the forced FEV₁.

Data are shown as raw data (mean and SD) and as the differences between the groups (mean, 95% confidence intervals), adjusted for age, height, sex, and race.

Although standard spirometry is technically possible in 6-year-old children, FEV₁ may not be the most appropriate outcome variable. The mean FEV₁/FVC ratio reported in this study of 94% for boys and 93% for girls is consistent with the 93% reported by Viložni and colleagues (24) and the 80% to 97% reported by Eigen and colleagues (1). FEV₁ has stood the test of time as a robust measure of lung function because, provided a reasonably effort is made during forced expiration, it occurs on the flow-limited portion of the forced expiratory flow-volume curve and its value is independent of effort. There is, however, considerable doubt that flow limitation can be maintained on the lower portion of the curve. A FEV₁/FVC ratio of more than 90% indicates that 6-year-old children effectively empty their lungs in a little over 1 second. It is extremely unlikely that children of this age will possess sufficient expiratory muscle strength to maintain flow limitation during forced expiration and that their lung volume approaches residual volume. This problem will be most evident in children with normal lungs, whereas those with obstructive airway diseases may be able to maintain flow limitation for longer than 1 second during forced expiration. If FEV₁ is not an appropriate outcome variable for children 6 years old and younger, what should be used? Recalculating the data presented by Viložni and colleagues (24) shows that the ratio of FEV_{0.5}/FVC is approximately 75 to 86.5%, depending on which data set is used. These values are closer to those considered to be normal in older children and adults. A systematic study performed in children with normal lungs and those with various diseases, using equipment capable outputting flow-volume and volume-time data as calibrated signals, will be required before we can determine the appropriate lung function variable for use in young children. In the mean time, one must exhibit caution when using variables validated in adults and older children in preschool children.

Measures of bronchial responsiveness have been used as part of the definition of asthma for determining the prevalence of clinically important asthma in populations (5) and form part of the clinical assessment of asthma in some adult clinics (8). When taken as a group, the children in this study with current asthma were more responsive to inhaled methacholine (Table 4). The cutoff values commonly used in adults and older children to determine a positive test range from 4 to 16 mg/ml (8, 10). These values have also been used in children (10) without any dose adjustment. Le Souef (11) argued that this practice was inappropriate, as smaller children were likely to receive a larger dose, relative to their lung size, and that the increased responsiveness

reported in younger children was likely to be a consequence of this relatively increased dose rather than to increased intrinsic responsiveness. He further showed (25) that both male and female children in the upper quartile for height in a longitudinal study had lower airway responsiveness, as assessed by dose response slope, than children in the lowest height quartile, independent of age. The results of this study support Le Souef's arguments, in that 78% of the children who completed the methacholine challenge, including 60.1% of the group without asthma, had a fall in FEV₁ of at least 20% with a dose of methacholine up to 7.8 mg/ml, a proportion that far exceeds that which would be expected if a fall of 20% in FEV₁ was indicative of heightened airway responsiveness. These data strongly argue that the doses of methacholine used in adults and older children are inappropriate for use in 6-year-old children as too many will have "positive" reactions.

The use of methacholine challenge as an aid to the diagnosis of asthma was examined in our study and showed that determining a 10% fall in FEV₁ with methacholine gives as much information, on a population basis, in 6-year-old children as does pushing the test to achieve a 20% in FEV₁. However, one would need to caution against taking this approach in an individual child, as the variability of spirometry is greater in young children and a 10% fall in FEV₁ would be expected to be close to the limits of reproducibility achievable by children 5 to 7 years old. As the prognostic statistics for a 15% fall in FEV₁ with 1.8 mg/ml of methacholine are almost the same as for a 10% fall in FEV₁ at this dose, using a 15% fall in FEV₁ at this age as a cutoff point would seem appropriate. The ROC analyses demonstrate that a cutoff dose of 1.8 mg/ml provides the best balance between sensitivity and specificity for the diagnosis of current asthma. The area under the ROC curve reported here varied between 0.62 and 0.67. A test with no diagnostic utility would have an area under the ROC curve of 0.5, and a "perfect" test would have an area of 1.0. Although the area under the ROC curves for each of the indices of bronchial responsiveness was significantly greater than 0.5, these analyses show that the methacholine challenge test is far from an ideal test for diagnosing asthma in children of this age. Despite this caveat, examination of the positive and negative predictive values of methacholine testing strongly suggests that the most clinically useful feature would be in excluding a diagnosis of asthma. A 6-year-old child who fails to show a fall of 15% in FEV₁ at a dose of 1.8 mg/ml (or a fall in FEV₁ of 20% at a dose of 3.9 mg/ml) is unlikely to have current asthma; the negative predictive value exceeds 90%.

There has been a recent recognition that “indirect” challenges, such as inhaled adenosine monophosphate may be more specific for the diagnosis of asthma, at least in adults (26–29). Thus, the fact that our data show that methacholine challenge is not useful for diagnosing asthma in 6-year-old children does not preclude a role for indirect challenges in children with asthma.

In summary, we have presented a comprehensive assessment of lung function, bronchial responsiveness, and their relationships to current asthma in 6-year-old children. Lung function testing is feasible at this age and has the potential to contribute to clinical management of children with lung diseases.

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