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An exercise challenge for epidemiological studies of childhood asthma: validity and repeatability

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An exercise challenge for epidemiological studies of childhood asthma: validity and repeatability. M.M. Haby, J.K. Peat, C.M. Mellis, S.D. Anderson, A.J. Woolcock. ©ERS Journals Ltd 1995.

ABSTRACT: We assessed the validity, repeatability and practicality of a standardized exercise challenge protocol for measuring airway responsiveness in epidemiological studies of asthma in children aged 8–11 yrs.

The construct validity of the exercise challenge was assessed by comparing response to exercise with other measures of asthma, *i.e.* wheeze frequency, diagnosed asthma, asthma medication use, atopy and urgent doctor visits (n=802), and by comparison with response to histamine challenge (n=201). Repeatability was assessed by comparison of responsiveness to two exercise challenges within 3 days (n=113), and practicality was assessed by measurement of consent, compliance and throughput rates (n=802).

There was a significant relationship between frequency of wheeze attacks and % fall in forced expiratory volume in one second (FEV_1) to exercise. The correlation (r) between % fall in FEV_1 to exercise challenge and dose-response ratio to histamine challenge was 0.59. The repeatability of the exercise challenge was ±12% fall in FEV_1. Consent and compliance rates for exercise challenge were 78 and 99%, respectively, and the mean throughput rate was 45 children per school day for a team of seven researchers.

In conclusion, this exercise challenge was found to have good validity and to be reliable and practical. Thus, this challenge could be used as a standardized epidemiological tool to investigate the prevalence, aetiology and mechanisms of asthma.
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Tests of airway hyperresponsiveness (AHR) have been widely used as an objective measure of asthma in epidemiological studies. Although histamine and methacholine are currently the most widely used provoking agents, exercise challenge is also useful for studies of children, because it simulates the "real-life" circumstances of an acute episode of airway narrowing.

Exercise challenge is often used in the pulmonary function laboratory as a test of AHR, and standardized protocols are available in the literature [1–3]. Different exercise challenge protocols have been used in several epidemiological studies [4–9], but this challenge has not been standardized for use as an epidemiological tool. The results from these studies cannot be easily compared because different, non-standardized methods have been used. Furthermore, unsatisfactory methods may have decreased the sensitivity of the exercise challenge protocols used. The repeatability of these challenges is not known and their validity has not been established.

In this Journal, we previously described an exercise challenge protocol designed to overcome the methodological limitations of challenges used in previous epidemiological studies [10]. The response to this exercise challenge protocol was compared with response to histamine challenge, recent wheeze, atopy and doctor diagnosed asthma. We concluded that our exercise challenge was suitable for epidemiological studies of asthma in children but required further validation in a large random sample. Also, the repeatability of the exercise challenge needed to be determined. We now report the validity, repeatability and practicality of this standardized exercise challenge, which we have applied in a large random sample of children.

Methods

Subjects and study design

Nine schools were randomly selected from all State and Catholic primary schools within a 10 km radius of the General Post Office of Sydney, Australia. All children in grades 3, 4 and 5 (aged 8–11 yrs) were invited to attend for exercise challenge testing. A letter requesting consent for the child to have skin prick tests and exercise challenge was sent home with a questionnaire to parents/guardians for completion prior to study. Only children

with consent were tested. A total of 812 children were tested, of whom 10 children had technically unsatisfactory lung function data and were excluded from analyses. Of the 802 children included in analyses, 110 children had taken a beta-agonist aerosol at some time in the month before study, of whom 46 had taken an average of two or more puffs per day. A sodium cromoglycate aerosol had been taken by 16 children, of whom 12 reported daily use, and 74 children had taken an inhaled steroid, of whom 49 reported daily use, in the month before study.

Of the 812 children tested, 111 also underwent a histamine challenge on a separate day. In one of the nine schools, which had an enrolment of 133 children in grades 3–5, the initial letter sent to parents/guardians requested consent both for exercise and histamine challenge. Eighty two children had an exercise challenge first, followed by histamine challenge within 2 days. In a second school which had an enrolment of 209 children, children with recent wheeze, who had taken an asthma medication in the previous year, or who had a fall in forced expiratory volume in one second (FEV_1) to exercise greater than 10% were given a letter following exercise challenge which requested consent for histamine challenge. Twenty nine children underwent histamine challenge within 3 days of the exercise challenge. Four children had technically unsatisfactory data for either challenge and were excluded from analyses. In addition, data from 94 children studied at a school in Belmont, NSW, a southern suburb of Newcastle, which is 200 km north of Sydney, were included in this part of the study only, *i.e.* the comparison of exercise and histamine challenge [10]. These children had participated in a previous population study using histamine challenge. A total of 130 children whose parents/guardians had consented to histamine challenge were given a letter requesting further consent for exercise challenge, of whom 98 parents consented. Exercise challenges were administered less than 7 days later in 96 children, of whom two children had technically unsatisfactory data for either challenge and were excluded from analyses. Thus, 201 children had both exercise and histamine challenge and were included in analyses.

The parents/guardians of a different subsample of the study sample (n=812) from two of the nine schools were asked to consent to the child undergoing a second exercise challenge. This was administered to 116 children within 3 days of the first exercise challenge. In one school, children with a fall in FEV_1 greater than 5% on the first exercise challenge, with recent wheeze, or who had used an asthma medication in the previous month, were preferentially selected for a repeat exercise challenge to ensure our sample had representatives from the whole spectrum of abnormality. In the other school, all children with consent were tested. One child had an FEV_1 less than 75% predicted on one test and, therefore, had a bronchodilator challenge instead of exercise challenge. In addition, two children had technically unsatisfactory data for either challenge. These three children were excluded from analyses. All tests were conducted by the same team of eight research assistants.

These studies were approved by the Human Ethics Committee of the University of Sydney.

Non-attenders

To determine whether there was any selection bias in the study sample, both attenders and nonattenders for study were asked if they had used an asthma medication in the month before study. A total of 15% (95% confidence interval (95% CI) 11–20) of nonattenders had used an asthma medication in the previous month compared to 16% (95% CI 14–19) of attenders ($p>0.5$). Therefore, the children who attended are likely to be representative of the population from which they were drawn.

Lung function tests

Forced vital capacity, FEV_1 and peak expiratory flow rate were measured on the same manoeuvre with Mijnhardt VRS 2000 dry rolling seal spirometers (Mijnhardt B.V., Bunnik, Holland) connected to IBM compatible lap-top computers running Scientific and Medical data acquisition software (S&M Instrument Co. Inc., Doylestown, PA, USA). The calibration of each spirometer was checked weekly but did not need adjustment. All lung function tests were performed with the child standing and without a noseclip. Children were instructed to take a deep breath and then to blow out as hard and as fast as they could. Forced expiratory manoeuvres were repeated until two measurements of FEV_1 within 100 ml of each other were obtained. The largest FEV_1 was used in analyses. Predicted values of forced vital capacity and FEV_1 were based on height and sex, and calculated from normal values of Australian children obtained using the same equipment [11].

Airway responsiveness

Children who had taken a beta-agonist aerosol within 4–6 h of presenting for testing were asked to withhold medication before returning for testing later in the day, or the next day if possible. For exercise challenge only, children who had taken a sodium cromoglycate aerosol within 4–6 h were also asked to withhold this medication before returning for testing at a later time. Children who had an FEV_1 less than 75% of predicted prior to exercise challenge [2], or an FEV_1 less than 60% of predicted prior to histamine challenge, were excluded from the challenge test and given a bronchodilator challenge instead.

Exercise challenge. Ambient temperature and relative humidity were recorded using a HANNA HI 8564 portable thermohygrometer (HANNA instruments, Singapore) prior to each subject being tested. Testing was not begun when the absolute water content for the day was likely to be above 10 $mgH_2O \cdot L^{-1}$ [2, 12]. During the days of testing, the water content of the inspired air was <10 $mgH_2O \cdot L^{-1}$ (mean 7.4 (SD 1.5) $mgH_2O \cdot L^{-1}$) for 92% of tests, the mean temperature was 16 (4) °C and the mean relative humidity was 55 (13)%.

After baseline lung function was measured, children underwent a 6 min run on a 50 or 100 m track on a flat, grassed oval, marked with cones spaced 10 m apart. Each subject wore a noseclip to ensure mouth-breathing and a Polar Accurex heart rate monitor (Polar Electro, Hakamaantie, Finland) for the duration of the run. Heart rate was recorded at 1 min intervals. Children were encouraged to run at an intensity which gave a heart rate of 85–90% of their predicted maximum [13], which is approximately 180–190 beats·min^{-1} (bpm) for 8–11 year olds, and to maintain a heart rate of 180±10 bpm for the final 4 min of exercise. The mean heart rate over the 6 min run was 189 (10) bpm. The distance run by each child was measured so that oxygen consumption could be estimated [14]. The mean distance completed was 831 (136) m, which is equivalent to a mean oxygen consumption of 35.3 (3.8) ml·kg^{-1}·min^{-1} [14]. If children were unable to complete the 6 min run, the time and distance run was recorded and the children asked if they had symptoms of wheeze and/or chest tightness. In those children, lung function was measured as soon as possible after the child stopped running. For all other children, measurements of lung function were made at 3, 5 and 10 min following the exercise challenge.

Forced expiratory manoeuvres were repeated until two measurements of FEV1 within 100 ml of each other were obtained, of which the larger value was used in analyses. If FEV1 fell by more than 20% of the baseline value, the postexercise measurements were stopped and 200 µg salbutamol aerosol administered. Children with a fall in FEV1 greater than 10% following the final reading were given 200 µg salbutamol aerosol to aid recovery. Lung function was checked at regular intervals to ensure recovery to at least 90% of the baseline FEV1 before the child was allowed to return to class.

The criteria for AHR to exercise was calculated by determining the upper limit of normal for % fall in FEV1, namely a value equal to 1.96 SD above the mean % fall in FEV1 in "normal" subjects. "Normal" was defined as children without recent wheeze or past wheeze as reported by parents, and without previous wheeze or chest tightness as reported by the child after exercise challenge.

Histamine challenge. Airway responsiveness to histamine was measured using the rapid method of YAN *et al.* [15]. After recording baseline lung function, two inhalations of saline were administered as a control dose and lung function was recorded again. Histamine acid phosphate was then administered by use of DeVilbiss handheld (No. 45) nebulizers in doubling doses ranging 0.06–3.9 µmol histamine. Lung function was measured following each dose. Forced expiratory manoeuvres were repeated until two measurements of FEV1 within 100 ml of each other were obtained, of which the larger value was used in analyses. The test was stopped if there was a fall in FEV1 of 20%, or more or when all histamine dose steps to 3.9 µmol had been administered. Children with a fall in FEV1 greater than 10% were given 200 µg salbutamol aerosol to aid recovery.

Bronchodilator challenge. Children who had an FEV1 less than 75% of predicted prior to exercise challenge, or less than 60% of predicted prior to histamine challenge, were given a bronchodilator challenge. Following measurement of resting lung function, 200 µg salbutamol was administered and, 10 min later, lung function was again measured. An increase in FEV1 of 15% or more was taken as a positive response to bronchodilator.

Respiratory Symptoms

Each child returned a questionnaire, completed by a parent or guardian, which collected demographic information and details of respiratory illness history. The questions of wheeze were "Has your child ever wheezed (wheezing is a whistling noise that comes from the chest)?"; "If yes, was this in the last 12 months?"; "Has your child ever had wheezing during or after exercise?"; "If yes, was this in the last 12 months?" Recent wheeze was defined as the presence of wheeze or exercise wheeze in the 12 months before study. Past wheeze was defined as the presence of wheeze or exercise wheeze ever but not in the 12 months before study. The question for diagnosed asthma was "Has your child ever been diagnosed as having asthma by a doctor or at a hospital?"

Skin prick tests

Atopy was measured by skin prick test reactions to eight allergens (Hollister-Stier, Miles Inc., Elkhart, IN, USA) applied to the forearm [16]. The allergens tested and the allergy units (AU) or weight/volume ratio (w/v) were *Dermatophagoides pteronyssinus* (30,000 AU·ml^{-1}) and *Dermatophagoides farinae* (1:50 w/v) (house-dust mites); house dust (1:10 w/v); rye-grass (1:20 w/v); *Cladosporium* (1:10 w/v) and *Alternaria tenuis* (1:10 w/v) (mould); cat dander (1:10 w/v); and cockroach (1:10 w/v). These allergens, together with positive (histamine 10 mg·ml^{-1}) and negative (glycerol) controls, were applied into a stencil stamped on the forearm with ink and pricked with a lancet (Long point Microlance, Becton-Dickson, Rutherford, New Jersey, USA). After 15 min, wheal size was recorded for each allergen as the largest axis and its perpendicular. A mean wheal size of 3 mm or greater was regarded as positive [17]. In the small number of children in whom the histamine skin test was negative or the control test positive, these tests were repeated. Eleven children with duplicate negative histamine or duplicate positive glycerol tests were excluded from analyses of skin prick test results only. Atopy was defined as a positive skin test reaction to one or more allergens.

Analysis

Data were analysed using the statistical package SAS (SAS Institute Inc., Cary, NC, USA). Exercise response was recorded as the greatest fall in FEV1 following exercise, expressed as a percentage of the baseline FEV1 measured immediately before exercise, *i.e.* exercise response = (fall in FEV1 / baseline FEV1) × 100.

Histamine response was expressed as dose-response ratio (DRR) calculated as the percentage fall in FEV1 at last dose divided by the total dose administered [18], *i.e.* DRR = (% fall in FEV1 (last dose) / total dose histamine (µmol)). Because DRR values are log normally distributed [19], they were converted to base 10 logarithms prior to analyses. In order to have a positive value for logarithmic conversion, DRR values had a constant of 3 added and are indicated by units %fall FEV1/µmol+3 [19]. The higher the DRR value, the greater the severity of AHR. Both % fall in FEV1 following exercise and DRR to histamine are continuous measures which were calculated for all subjects. Pearson's correlation coefficient and linear regression were used to compare the continuous measures of response to the exercise and histamine challenges.

Mean values were calculated for % fall in FEV1 and are shown with the 95% confidence interval (CI). Prevalence rates (population proportions) were calculated for the categorical variables (recent wheeze, atopy, medications in previous 12 months, urgent doctor visit in previous 12 months for breathing problems, diagnosed asthma, AHR) and are shown with their 95% CI. The Chi-squared statistic was used to measure differences in prevalence rates (population proportions) between defined groups. Analysis of variance (ANOVA) was used to compare mean values of % fall in FEV1.

The repeatability of % fall in FEV1 following exercise challenge was assessed by the calculation of a 95% CI within which the difference between any single measurement and the true value for the subject is expected to lie [20, 21].

The practicality of exercise challenge was assessed by measurement of consent, compliance and throughput rates. The consent rate was calculated as the percentage of the sample base which returned a signed consent form to their school, *i.e.* consent (%) = (number of signed consent forms returned / total number of children selected for the study) × 100.

The compliance rate was calculated as the percentage of children who completed satisfactory exercise challenge tests, *i.e.* compliance (%) = (number of satisfactorily completed exercise challenge tests / number of children tested) × 100. The throughput rate was calculated as the average number of children who underwent a complete test in a normal school day. This included measurement of height and weight, a skin-prick test, a lung function test and an exercise challenge.

Results

Of the 812 children who were studied, 802 children had technically satisfactory tests. Figure l shows the frequency distribution of % fall in FEV1 values in 435 "normal" children, *i.e.* children without recent wheeze or past wheeze as reported by parents and without previous wheeze or chest tightness as reported by the child. Five children with extreme values were excluded. A visual examination both of the frequency distribution (fig. 1) and the cumulative frequency distribution showed no systematic deviation from normal [22]. A Shapiro-Wilk test

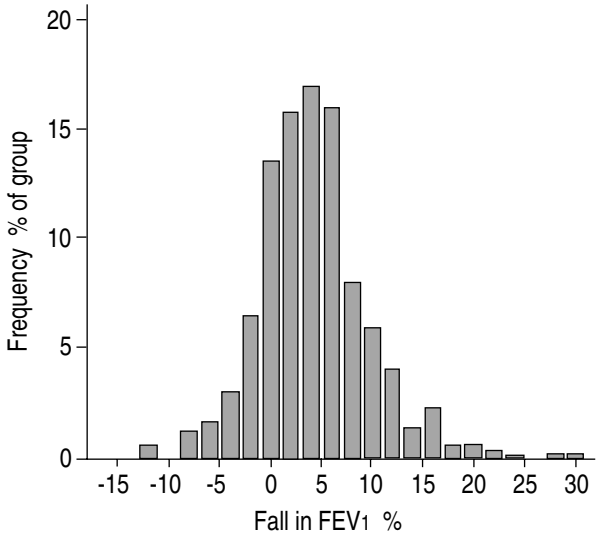

Fig. 1. – Relative frequency distribution of % fall in FEV1 in 435 "normal" children. FEV1: forced expiratory volume in one second.

of normality [23] was also used to compare the distribution of % fall in FEV1 with a normal distribution. The distribution deviated slightly from normal (w=0.96; p=0.0001). Although % fall in FEV1 values did not have an absolutely normal distribution according to the Shapiro-Wilk test, the distribution was close enough to normal to warrant the use of parametric summary statistics. In addition, the distribution was symmetrical, so that the mean was a reliable measure of the central position.

The fall in FEV1 value for 1.96 SD above the mean in this "normal" group was 15.3%. Thus, a value of 15% fall in FEV1 has been used as the criteria for AHR. In this "normal" group, 21 children (4.8%) were classified as having AHR.

The prevalence of AHR, defined as a fall in FEV1 of 15% or more following exercise challenge was 20% (157 out of 802). Of the 157 children classified as positive, 152 had a fall in FEV1 which was 15% or greater following exercise challenge (range 15–72%) and five had a positive response to bronchodilator.

Validity

Construct validity is defined as the extent to which a test agrees with other tests or other measures of the disease. The construct validity of exercise challenge was assessed by comparing it with other measures of asthma and allergic severity. Children with AHR to exercise challenge were more likely to have experienced recent wheeze, to be atopic, to have used an asthma medication in the previous 12 months, to have visited a doctor urgently for breathing problems in the previous 12 months, and to have ever been diagnosed as having asthma by a doctor or at a hospital (table 1). Chi-squared analyses showed that the differences in proportion of each of these measures between AHR negative and AHR positive children were all significant at the p<0.001 level.

Response to exercise, expressed both as a continuous measure (% fall in FEV1) and as a categorical measure

Table 1. – Prevalence and 95% confidence intervals (95% CI) of symptoms, atopy, asthma medication use, morbidity and diagnosed asthma in children with and without AHR to exercise

	AHR -ve	AHR +ve	Significance
Subjects n	645	157	
Recent wheeze			
%	15	54	χ^2=108.2
95% CI	12–18	46–61	p<0.001
Atopy			
%	32	82	χ^2=126.4
95% CI	29–36	76–88	p<0.001
Used an asthma medication in previous 12 months			
%	16	57	χ^2=122.2
95% CI	13–18	49–65	p<0.001
Urgent doctor visit in previous 12 months for breathing problems			
%	3	22	χ^2=64.6
95% CI	2–5	15–28	p<0.001
Diagnosed asthma			
%	17	57	χ^2=109.1
95% CI	14–20	50–65	p<0.001

AHR negative (-ve): <15% fall in FEV1; AHR positive (+ve): ≥15% fall in FEV1. AHR: airway hyperresponsiveness; FEV1: forced expiratory volume in one second.

(AHR), was able to discriminate between asymptomatic children and children with past or recent wheeze (table 2). Tests of analysis of variance (for mean % fall in FEV1), Chi-squared (for percentage of group with AHR to exercise) and comparison of 95% CI all showed that there was a significant difference in responsiveness to exercise between groups.

There was also a significant positive relationship between % fall in FEV1 and number of wheeze attacks in the last year (fig. 2). Mean % fall in FEV1 increased with the number of wheeze attacks in the last year from 6% in children who had never wheezed to 27% in children who had wheezed 12 or more times in the last year. Analysis of variance for the difference between the five groups was significant at the level of p=0.0001 (F=50.5; DF=4,791). Duncan's multiple-range *post hoc* test showed that the

Table 2. – Mean % fall in FEV1 and percent with airway hyperresponsiveness to exercise challenge in groups of children categorized according to wheeze history

	Asymptomatic	Past wheeze	Recent wheeze	Significance
Subjects n	528	94	180	
% fall in FEV1				
Mean	6.1	8.9	18.4	F=69.4
95% CI	5.3–6.9	6.5–11.3	15.7–21.0	DF=2,793
				p=0.0001
AHR				
%	10	22	47	χ^2=117.1
n	52	21	84	DF=2
95% CI	7–12	14–31	40–54	p<0.0001

AHR: ≥15% fall in FEV1. 95% CI: 95% confidence interval. For further abbreviations see legend to table 1.

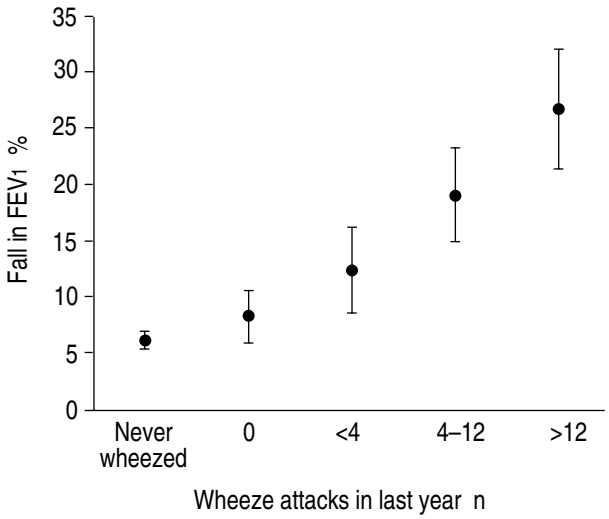

Fig. 2. – Mean % fall in FEV1 and 95% confidence intervals in groups of children categorized according to frequency of wheeze attacks. Five hundred and twenty eight children had never wheezed, 94 had not wheezed in the last year, 71 had wheezed less than four times in the last year, 55 wheezed 4–12 times and 48 children wheezed more than 12 times in the last year. FEV1: forced expiratory volume in one second.

mean % fall in FEV1 of children who had never wheezed was not significantly different from that of children who had not wheezed in the last year. All other means were significantly different from each other (p<0.05).

Responsiveness to exercise and to histamine were compared using continuous measures of % fall in FEV1 (fig. 3). For the histamine challenge, responsiveness was adjusted for dose of histamine administered. Although regression analysis and the correlation coefficient are not appropriate for method comparison studies when the two methods have the same units of measurement [20], we

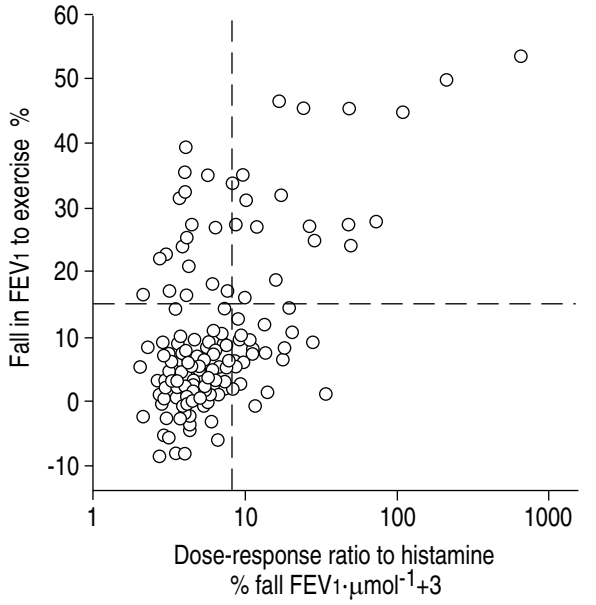

Fig. 3. – Relationship between dose-response ratio to histamine (log scale) and % fall in FEV1 to exercise in 201 children (r=0.59; p=0.0001). The dashed lines separate AHR positive and AHR negative children for each challenge. AHR: airways hyperresponsiveness, ≥15 % fall in FEV1; FEV1: forced expiratory volume in one second.

have used them to compare results from these two challenges which have different units of measurement. Linear regression shows that 35% of the variation in % fall in FEV1 can be explained by the base 10 logarithm of DRR (F=106.4; DF=1,195, p=0.0001). Pearson's correlation coefficient (r) was 0.59 (p=0.0001), which shows that there is a significant positive association between % fall in FEV1 and DRR.

Repeatability

The exercise challenge protocol had good short-term repeatability. Figure 4 shows the average % fall in FEV1 to the two exercise challenges plotted against the difference in % fall in FEV1 [20]. A regression line between these points is a straight line with no slope (t=-0.11; DF=1, p=0.91), thus, the difference in % fall in FEV1 is not related to the magnitude of % fall in FEV1. This indicates that the mean and standard deviation of the difference between the two days can be used to assess repeatability.

The mean difference in % fall in FEV1 between the two days was -0.4, which is not significantly different from zero (t=0.57; DF=112; p>0.5), and, thus, the measurements from the two days were not significantly different. The standard deviation of a single measurement, calculated by dividing the standard deviation of the differences by the square root of 2 [21], is 6.0% fall in FEV1, from which we have calculated a 95% CI of ±12% fall in FEV1. The meaning of this interval is that there is a 95% probability that the difference between any single measurement and the true value for the subject is within the range ±12% fall in FEV1.

Practicality

The mean consent rate for exercise challenge and skin-prick tests was 78% (844 out of 1080). However, 32 children were not tested because they were absent from school at the time of the study (n=23), or because of time constraints (n=9). Thus 812 children out of 1,080 were included in the study (75%).

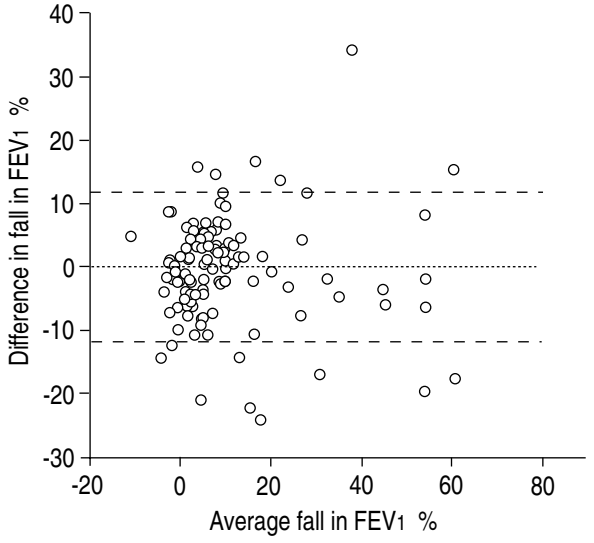

Fig. 4. – Repeated measures of % fall in FEV1 in 113 children, shown with the line of no difference (dotted line) and 95% confidence interval (dashed line). FEV1: forced expiratory volume in one second.

Of the 812 children who were studied, 10 children were unable to perform spirometry satisfactorily and were excluded from all analyses. In addition, six children had a baseline FEV1 less than 75% predicted, and so had a bronchodilator challenge instead of exercise challenge. Of the 796 children who participated in exercise challenge, 12 children did not complete the 6 min run. When their lung function was tested after stopping running, four of these children did not have a fall in FEV1 greater than 15% and were considered noncompliant to exercise, *i.e.* they stopped running for reasons other than wheeze or chest tightness, such as hyperventilation or poor fitness. Thus, compliance with the exercise challenge was 99% (792 out of 796). The four noncompliant children were classified as AHR negative and were included in analyses.

The main study (*i.e.* excluding histamine challenge and repeat exercise challenge) of 812 children required 18 days of data collection. The mean throughput rate was 45 per school day (9 a.m. until 3 p.m.). That is, a team of seven trained researchers (four to conduct exercise challenge, one to measure height and weight and distribute forms, one to measure atopy, and one doctor to review each child's results) tested an average of 45 children daily.

Discussion

The exercise challenge protocol which we have standardized had good validity against other markers of asthma and allergy, and was both reliable and practical in this epidemiological study in children. The results of the comparison of response to exercise challenge with wheeze, atopy, asthma medication use, urgent doctor visits for breathing problems, diagnosed asthma, and histamine challenge support the hypothesis that exercise challenge has good construct validity against other widely-accepted epidemiological measures of asthma. A significant association was found between response to exercise challenge and other measurements of asthma severity (table 1, fig. 3). Furthermore, both % fall in FEV1 and % of sample with AHR, when used as measures of response to exercise, were able to discriminate clearly between asymptomatic children and children with recent wheeze (table 2). There was also a dose-response relationship between % fall in FEV1 and frequency of wheeze attacks (fig. 2).

The questionnaire used in this study to measure symptoms and the skin prick test method to measure atopy have good repeatability [24, 25]. There was no selection bias in the sample of children in the current study, in that there was no significant difference in the proportion of children who had used an asthma medication in the month before study between those attending or not attending for testing. There was no significant between-observer variability, *i.e.* the variation in % fall in FEV1 values obtained did not differ between testers (F=1.34; DF=5,686; p=0.24), and the distribution of % fall in FEV1 was close enough to normal to allow the use of parametric statistics.

Forty nine children had taken daily inhaled corticosteroids in the month before study, of whom 20 children did not have AHR at the time of study. These children were classified as AHR negative but, because preventive medication can return AHR to the normal range [26], the prevalence of AHR could have been as high as 22% (177 out of 802). Inclusion of these 20 children as AHR positive in the analyses of the validity of exercise challenge would have increased the significance of the differences between AHR negative and AHR positive children shown in table 1.

The finding that not all children who had AHR to exercise had recent symptoms of wheeze is consistent with population studies which have used histamine challenge to measure AHR [19, 24]. Although both AHR and recent wheeze are associated with a clinical diagnosis of asthma, different aetiological factors may be involved in the presence of respiratory symptoms and of AHR [24]. It was interesting that only 57% of children with AHR to exercise had ever been diagnosed as having asthma by a doctor or at a hospital. However, the diagnosis of asthma by a doctor can be affected by labelling patterns, by diagnostic criteria, and by the willingness of parents to take their children for assessment.

Repeatability

This exercise challenge protocol had good short-term repeatability of ±12 % fall in FEV1. It is difficult to judge this value, because the repeatability of exercise challenge has not previously been measured under field conditions. Most laboratory studies report the coefficient of variation (calculated as the SD of differences as a percentage of the overall mean). However, comparisons of studies with different mean values may not be valid, because differences are dependent upon the mean and the standard deviation [27]. The coefficient of variation for this epidemiological exercise challenge was 81%, calculated from a mean % fall in FEV1 of 10.6 and SD of difference of 8.5. A laboratory study by ANDERSON *et al.* [28] using subjects with exercise-induced asthma found a coefficient of variation of 19% when the interval between tests was 7–28 days. This was derived from a similar SD of differences (8.4% fall in peak expiratory flow rate) but a much larger mean of 43.5% fall in peak expiratory flow rate. Obviously, the larger coefficient of variation in the current study is due to the lower mean % fall, which is a direct result of inclusion of both normal and asthmatic subjects. However, the SD of a single measurement from the study of ANDERSON *et al.* [28] is 5.9, which is very close to the value of 6.0 obtained in the current study. Thus, the short-term repeatability of exercise challenge in the field seems to be similar to that obtained in Anderson's pulmonary function laboratory.

Practicality

The consent and compliance rates for this exercise challenge were 78 and 99%, respectively. This consent rate is similar to that for histamine challenge, which is generally in the range of 75–85% [29, 30]. The consent rate may have been different if skin-prick tests had not been included in the protocol. Compliance to the exercise challenge protocol was excellent and is similar to that achieved with histamine challenge, which is generally in the range 97–99% [19]. It takes one tester about 5 min to conduct a histamine challenge in a nonresponsive child and 10 min in a responsive child. In contrast, an exercise challenge in a responsive or nonresponsive child takes one tester about 17 min. Thus, the mean throughput rate for exercise challenge (45 children per school day) was lower than can be achieved by the same researchers when using histamine challenge (80–100 children per school day), but is still acceptable.

The positive aspects of the exercise challenge over histamine or methacholine challenges are that exercise is a natural activity, and both the children and the researchers enjoyed the exercise challenge, which was conducted outdoors. The major negative aspect was the reliance on weather conditions. The ability of the exercise challenge to provoke airway narrowing is maximized when the absolute water content of the inspired air is below 10 $mgH_2O \cdot L^{-1}$ [2, 12]. Thus, the study was conducted during winter because this is generally the driest and coolest part of the year in Sydney. A total of 6 out of 30 days were lost due to rain or high relative humidity and/or temperature. This would be less of a problem in other countries or regions where the temperature and/or humidity is lower, but may limit the usefulness of exercise challenge in some countries. The other potential drawback is that all children were run at the same "maximal dose" of exercise, so that 21 children experienced a fall in FEV1 of greater than 50%. Emergency equipment and personnel were available to help these children recover quickly. However, it could be argued that there is a potential for such falls in FEV1 to occur at any time.

The criteria used to define AHR to exercise was a fall in FEV1 of 15% or more. This was calculated by determining the upper limit of normal for % fall in FEV1, namely a value equal to 1.96 standard deviations above the mean % fall in FEV1 in the "normal" subjects. In clinical studies, GODFREY *et al.* [31] and KATTAN *et al.* [32] used the same statistical method, although their subjects were not a random population sample, and obtained values of 8.2 and 10% fall in FEV1, respectively. The higher value obtained in the current study is due to the higher standard deviation of % fall in FEV1 which is likely to have been because children from the full spectrum of responsiveness were included as subjects. In the clinical studies, known asthma clinic patients were compared with known normals and representatives from the large group of children between these extremes were excluded. Other authors have chosen arbitrary values of 10% [6], 15% [7], or 20% [33] fall in FEV1 or in peak expiratory flow rate.

Thus, we conclude that this exercise challenge has good construct validity and good repeatability, and is practical for epidemiological studies of asthma in children. This exercise challenge protocol could be adopted as a standardized epidemiological tool for measuring AHR in population studies of children designed to measure prevalence or to investigate the aetiology and mechanisms of

asthma. Furthermore, because exercise is a physiological stimulus, it more closely resembles "real-life" circumstances than a pharmacological stimulus and may be more clinically relevant.

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