

A study of the association between exercise-induced wheeze and exercise versus methacholine-induced bronchoconstriction in adolescents

Henriksen AH, Tveit KH, Holmen TL, Sue-Chu M, Bjermer L. A study of the association between exercise-induced wheeze and exercise versus methacholine-induced bronchoconstriction in adolescents. *Pediatr Allergy Immunol* 2002; 13: 203–208. © 2002 Blackwell Munksgaard

Among asthmatics, exercise-induced wheeze (EIW) is a frequent symptom, and 40–77% of asthmatics demonstrate exercise-induced bronchoconstriction (EIB). In the North-Trøndelag population-based survey of 8,571 adolescents (YOUNG-HUNT), 26% reported wheeze during the previous 12 months (current wheeze). Of those subjects, 50% reported EIW. The aim of the present study was to investigate the association between EIW and EIB in randomly selected adolescents with EIW as the only or predominant asthma-like symptom, and to relate our findings to results from methacholine bronchoprovocation tests (MT) and measurements of exhaled nitric oxide (ENO). Sixty-three subjects with current wheeze induced by exercise, but not by allergen exposure, were investigated using a treadmill exercise test (ET) and measurements of ENO. Fifty-eight subjects completed a MT on a separate study day. EIB was defined as a fall of $\geq 10\%$ in the forced expiratory volume in 1 second (FEV_1) after exercise ($\Delta FEV_1\%_{ex}$). Twenty-one subjects (33%) had EIB and 33 (57%) had a positive MT. The degree of reported dyspnea during the ET was not correlated to the $\Delta FEV_1\%_{ex}$. The correlation between EIB and methacholine-induced bronchoconstriction (MIB) was poor, and the $\Delta FEV_1\%_{ex}$ was more pronounced in smokers than in non-smokers. Moreover, ENO was not increased in subjects with positive vs. negative ET. Hence, EIW, when reported as the only or predominant asthma-like symptom, was linked to EIB in only one-third of the patients. We conclude that EIW is a poor predictor of EIB in epidemiological studies. The poor correlation between EIB and MIB indicates that these two tests measure different mechanisms of bronchial hyper-responsiveness.

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Key words: exercise-induced wheeze; exercise test; bronchoconstriction; bronchoprovocation; exhaled nitric oxide; adolescents

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Accepted 6 October 2001

Wheeze is a cardinal symptom of asthma, and epidemiological studies of schoolchildren and adolescents report a prevalence of current wheeze of 5–30% (1–5). In asthmatics, wheeze is often induced by exercise. Moreover, exercise-induced bronchoconstriction (EIB), defined as a fall in the forced expiratory volume in 1 second (FEV_1) of at least 10% within 15 min after an exercise test, has been found in 40–77% of asthmatics (6,8). Variation in the prevalence of EIB among asthmatics may reflect differences in disease

severity as well as how asthma was defined in each study.

In several population-based studies, the association of wheeze and bronchial hyperresponsiveness (BHR) to direct stimuli, such as methacholine, or to indirect stimuli, such as exercise, as well as the association between methacholine and EIB, have been investigated (8–12). However, these studies did not differentiate between wheeze that was induced by exercise or wheeze induced by other trigger

factors. In our large-scale population-based survey of 8,751 Norwegian adolescents (13,14), exercise was a trigger factor in 50% of subjects reporting wheeze. We speculated whether those who reported exercise-induced wheeze (EIW) had EIB.

Exhaled nitric oxide (ENO) is a potential marker of lower airway inflammation, with increased levels observed in asthmatics (5,15,16). An elevated level of ENO has also been demonstrated in the exhaled air of asthmatics with EIB when compared to controls (17). Moreover, significantly increased concentrations of NO derivatives are found in induced sputum of asthmatics with EIB compared to asthmatics without EIB (18).

As physical training is usually obligatory in schools, both pupils with EIW and teachers question how to deal with this symptom. In the present study we wanted to find out whether EIW was associated with EIB or other markers of lower airway inflammation. The first aim was to characterize the association between EIW and EIB in adolescents with EIW as the only or predominant asthma-like symptom. Second, we wanted to compare the results from exercise tests with methacholine bronchoprovocation tests, and to study the relationship between EIB and ENO.

Materials and methods

Subjects

As part of a cross-sectional study conducted in Nord-Trøndelag County, Norway, 8,571 adolescents were interviewed on allergic and asthma-like symptoms – the YOUNG-HUNT Study (13,14). Twenty-six per cent reported wheeze within the preceding 12 months (current wheeze) and 13% reported EIW. In a phase II study, 722 randomly selected adolescents were investigated further (5,19,20). Of these, 150 subjects (110 females) reported current wheeze related to exercise, but not related to exposure to pollen, pets or house dust.

In the present study (the phase III study), 130 of the 150 adolescents, still residing in North-Trøndelag, were invited to undertake an exercise test (ET). Seventy-four subjects attended, and 69 subjects also completed a methacholine bronchoprovocation test (MT) on a second study day. Sixty-three of all 74 subjects, and 58 of the 69 subjects who completed a MT, reported wheeze within 12 months preceding the phase III study. Results from these subjects are presented in Table 1.

There were no significant gender differences with respect to age, body mass index (BMI), basal FEV_1 %, physical activity, cigarette smoking, or inhaled β -agonists or steroids. Cigarette smokers, however, exercised significantly less than non-smokers, mean 1.9 [95% confidence interval (CI): 1.4–2.4] vs. mean 3.6 (95% CI: 3.2–3.9) h/week, respectively ($p < 0.001$), when adjusted for age.

Written, informed consent was obtained from all participants and from parents of those ≤ 16 years of age. The study was approved by the Regional Medicine Ethical Committee in Trondheim.

Study design

Study day 1. The adolescents completed a questionnaire, performed an ET, marked their maximal degree (0–10) of breathlessness and leg pain on a Borg scale, and reported whether they had wheeze at the end of the test. Measurements of ENO and capillary lactate were taken prior to, and immediately after, the ET.

Study day 2 (2–7 days after study day 1). The adolescents underwent an MT. Measurements of ENO were taken prior to and immediately after the MT.

Methods

Flow-volume spirometry (MasterScope spirometer, software version 4.1; Erich Jaeger, GmbH-Höchberg, Germany) and the MT (tidal volume triggered equipment, Automatic Provocation System APS; Erich Jaeger) were performed using procedures identical to those previously described in detail (5,19,20). A positive MT was defined as a 20% fall in FEV_1 after a cumulative dose of inhaled methacholine ≤ 2 mg PD_{20} . The fall in FEV_1 during inhalation of methacholine (%/mg) was expressed as dose-response ratio to methacholine (DRR_{mch}).

Measurements of ENO were performed in accordance with the European Respiratory

Table 1. Subject characteristics

Subjects (females)	63 (47)
Age mean (95% CI)	17.9 (17.6–18.3)
BMI mean (95% CI) kg/height ²	23.5 (22.6–24.4)
Basal FEV_1 % mean (95% CI)	104 (100–107)
Physical activity hours/week, mean (95% CI)	3.1 (2.8–3.5)
Cigarette smokers (%)	16 (25)
Subjects (%) on inhaled β_2 -agonists weekly	11 (18)
Subjects (%) on inhaled steroids weekly	4 (6.6)

BMI, body mass index; CI, confidence interval; FEV_1 , forced expiratory volume in 1 second.

Table 2. Association between reported wheeze during the exercise test (ET), recordings on the Borg scale, the change in forced expiratory volume in 1 second ($\Delta FEV_1\%$) after exercise ($\Delta FEV_1\%_{ex}$), and rise in lactate and heart rate (HR)

Reporting wheeze during the ET	Yes*	No*
Borg scale, dyspnea mean (95%CI)	6.1 (5.3–6.8)**	4.5 (3.3–5.3)
Borg scale, leg pain mean (95%CI)	5.8 (4.9–6.6)	6.0 (5.1–7.0)
$\Delta FEV_1\%_{ex}$, median (95% CI)	6.0 (4–12)	6.0 (3–9)
Mean HR (beats/minute) during the last 4 min of the ET mean (95%CI)	191 (188–193)	193 (190–195)
Rise in lactate during the ET, mmol/l mean (95%CI)	7.4 (6.7–8.0)**	5.9 (5.3–6.6)

Results are expressed as median (95% CI).

CI, confidence interval.

*n=31.

**p ≤ 0.01.

Society Task Force (21) using an LR 2000 nitric gas analyzer (Logan Research Ltd, Rochester, UK). Exhalation and sampling flow rates were 250 ml/s and 250 ml/min, respectively. For each subject, the mean of three plateau levels from acceptable ENO curves were registered in parts per billion (p.p.b.).

The ET consisted of a 6–8 min standardized run without nose-clip on a motor-driven treadmill (Technogym, Fitness & Technical Equipment, Gambettola, Italy) with a 5.5% inclination. Exercise load was increased during the first 2 min by increasing the speed of the treadmill, aiming at a heart rate (HR) of 180 beats per minute. The load was further increased to obtain a HR of 90% of 220 beats per minute minus age during the last 4 min. HR (continuous electronic recordings), speed, and running time were registered. Lung function was measured before, immediately after, and 3, 6, 10 and 15 min after exercise. Assuming there was a reduction in FEV_1 after 10 min, FEV_1 was also recorded after 35 min. The mean room temperature and ambient air humidity were 22°C (range 20–24°C) and 34% (range: 33–35%), respectively. The difference between the basal FEV_1 value and the lowest FEV_1 after exercise, as a percentage of basal FEV_1 , was defined as $\Delta FEV_1\%_{ex}$. EIB was defined as a $\Delta FEV_1\%_{ex}$ value of ≥ 10% within 15 min after the ET.

Measurements of lactate were taken from capillary blood before and immediately after running on the treadmill, analyzed using a YSI

1500 Sport L-Lactate Analyzer (Yellow Springs, OH, USA), and expressed in mmol/l.

Modified Borg scale. During the last minute of the ET, the degree of dyspnea and leg pain achieved during running were registered on a scale of 0–10, where zero was ‘not at all’ and 10 was ‘extremely severe’ (22).

Questionnaire. The questionnaire in the phase II and the phase III studies were identical and contained questions on respiratory and allergic symptoms as well as asthma medication. The questions were selected from the phase I study interview that contained questions adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) (23).

Statistical analyses

Data from measurements of a decrease in the $FEV_1\%$ after exercise and the dose–response ratio to methacholine were not normally distributed and therefore non-parametric tests (Mann–Whitney *U*-test or Spearman correlation coefficient) were applied and the results presented as median with 95% CI calculated by the Bernoulli Wilcoxon procedure. Levels of ENO were close to a log-normal distribution; hence, parametric tests (independent-samples *t*-tests and Pearson’s correlation coefficient) were assessed on log values and the results are presented as geometric mean and 95% CI. Categorical data were analyzed using chi-square tests. A two-tailed *p*-value of ≤ 0.05 was regarded as statistically significant.

Results

The association between EIW and EIB

The mean (95% CI) running time was 7.7 (7.5–7.8) min and mean heart rate values during the last 4 and last 2 min were 191 (190–193) and 194 (193–196) beats/min, respectively. All but two

Table 3. Methacholine bronchoprovocation test (MT) vs. exercise-induced bronchoconstriction (EIB)

	MT ⁺ 33 (56)	MT [−] 25 (44)
Subjects*		
EIB ⁺ 19 (33)	14 (24)	5 (8.6)
EIB [−] 39 (67)	19 (33)	20 (35)

*Total no. of subjects = 58.

Results are expressed as n (% of total).

Table 4. Effect of cigarette smoking on the dose-response ratio to methacholine (DRR_{mch}), percentage fall in the forced expiratory volume in 1 second ($\Delta FEV_1\%$) after exercise ($\Delta FEV_1\%_{ex}$), and levels of exhaled nitric oxide (ENO)

Subjects (%) with EIW	DRR_{mch} Median (95% CI) %/mg	$\Delta FEV_1\%_{ex}$ Median (95% CI)	ENO Geometric mean (95% CI)
All subjects, n=63	12 (7.5–24)	7.6 (5–9)	6.1 (5.2–7.0)
Cigarette smokers, n=16 (25%)	20 (5.5–193)	9.5 (4–18)*	5.1 (3.8–7.0)
Non-smokers, n=47 (75%)	11.5 (7.0–23)	6.0 (4–8)	6.4 (5.4–7.6)

CI, confidence interval; EIW, exercise-induced wheeze.

subjects reached a mean heart rate of $\geq 90\%$ of 220 beats per minute minus age during the last 2 min. Among the 63 adolescents with EIW as the only or predominant asthma-like symptom, 21 (33%) had EIB, Table 2. Moreover, 16 subjects (25%) had a $\Delta FEV_1\%_{ex}$ value of $\geq 12\%$ and seven subjects (11%) had a $\Delta FEV_1\%_{ex}$ value of $\geq 15\%$.

In subjects reporting wheeze at the end of the ET, the median $\Delta FEV_1\%_{ex}$ value was not significantly greater than in those who did not report wheeze, but scores on the Borg dyspnea scale and increase in capillary lactate were significantly higher in the former group, Table 2. However, six (86%) of the seven subjects with a $\Delta FEV_1\%_{ex}$ value of $\geq 15\%$, reported wheeze ($p < 0.05$) at the end of the ET. Moreover, scores reported on the Borg dyspnea scale were not correlated to the $\Delta FEV_1\%_{ex}$, but to the increase in capillary lactate ($r = 0.091$; $p = 0.5$) and ($r = 0.35$; $p < 0.07$), respectively.

Methacholine vs. EIB

Of the 58 subjects with EIW who completed the ET and the MT, 33 (57%) had a positive MT (Table 3). Subjects with a positive MT had a significantly greater $\Delta FEV_1\%_{ex}$ value than those with a negative MT (Fig. 1). Furthermore, the DRR_{mch} was significantly increased in subjects

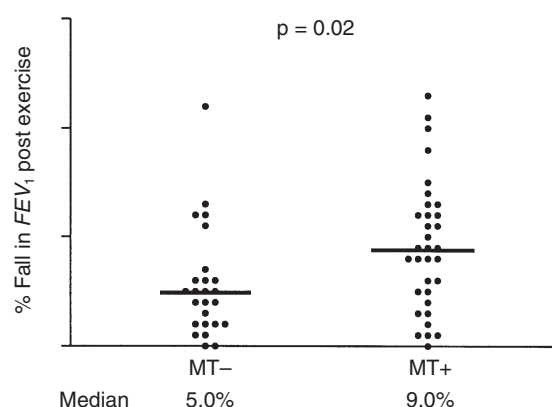


Fig. 1. Percentage fall in the forced expiratory volume in 1 second (FEV_1) after exercise test in subjects with a negative vs. a positive methacholine bronchoprovocation test (MT).

with EIB, compared to those without EIB, when cigarette smokers and subjects on inhaled steroids were excluded: median (95% CI), 28%/mg (2.0–400) vs. 8%/mg (5.5–19) $p < 0.02$.

Four (80%) of the five adolescents with EIB, but a negative MT, were habitual cigarette smokers ($p = 0.001$) (Fig. 2). In cigarette smokers, the $\Delta FEV_1\%_{ex}$, but not the DRR_{mch} , was significantly increased compared to non-smokers (Table 4). Moreover, the correlation coefficient between the DRR_{mch} and the $\Delta FEV_1\%_{ex}$ value increased from $r = 0.33$ ($p = 0.01$) to $r = 0.46$ ($p = 0.002$) when cigarette smokers were excluded from the model.

ENO vs. exercise- or methacholine-induced bronchoconstriction

ENO was not increased in subjects with EIB, or in subjects with a positive MT, compared to subjects with negative tests, and there was no significant correlation between ENO and DRR_{mch} or $\Delta FEV_1\%_{ex}$ ($r = 0.18$ and $r = 0.09$, respectively).

Discussion

In this study we demonstrated that EIW, as the only or predominant asthma-like symptom, was associated with EIB only in 33% of the adolescents when EIB was defined as a decrease in FEV_1

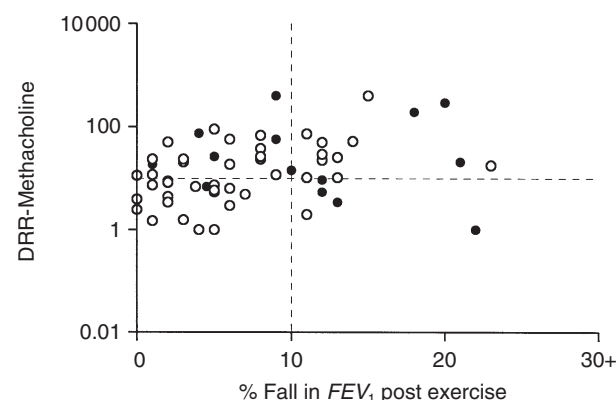


Fig. 2. Association between the dose-response ratio to methacholine (DRR-METHACHOLINE) and percentage fall in the forced expiratory volume in 1 second (FEV_1) after exercise in cigarette smokers (•) vs. non-smokers (○).

after exercise of at least 10%. Moreover, four of the five subjects with EIB, but a negative MT, were cigarette smokers. No agreement was found between the percentage fall in FEV_1 after exercise ($\Delta FEV_1\%_{ex}$) and reported wheeze at the end of the ET or scores on the Borg dyspnea scale.

West and colleagues found EIB in 57% of a random sample of children aged 12–13 years with reported wheeze within the preceding 12 months, i.e. current wheeze (11). In comparison, we found EIB in only 33% of adolescents with EIW. In contrast to West et al., we had excluded subjects with wheeze related to allergen exposure. As a result, we may have excluded a group of patients with severe asthma. This assumption was further supported by the finding that MT was positive only in 57% of the subjects, which contrasts with our previous study of adolescents with allergy-related wheeze, where 75% had a positive MT (5). Thus, compared to current wheeze, it appears that EIW is a very non-specific symptom when reported as the only or predominant asthma-like symptom. This is further underlined by the fact that scores on the Borg dyspnea scale were significantly correlated to a rise in lactate, but not to $\Delta FEV_1\%_{ex}$, indicating that the scores on the Borg scale merely reflected the degree of exhaustion rather than bronchoconstriction.

As EIW was explained by EIB in only 33% of the cases, other potential causes of EIW should be considered. This was a cross-sectional study aimed to investigate whether there existed a point-by-point correlation between exercise-induced symptoms and EIB. However, we are aware of a certain variation in the degree of BHR over time. Thus, if the exercise tests were repeated, an increase in the percentage of subjects with at least one positive test would be expected. Moreover, a variety of disorders arising in the structures of the upper respiratory tract, such as infections, congenital anomalies and vocal cord dysfunction (VCD), can cause coughing, wheezing, and dyspnea (24,25). As VCD is most common in females, the preponderance of girls among adolescents with EIW may indicate that VCD is an important differential diagnosis to EIB. However, the subjects were carefully observed during the ET, and no indications of such conditions were found. Furthermore, it is known that hyperventilation may be associated with hypocapnia without bronchospasm and lead to chest discomfort perceived as dyspnea (7,26). Although this is a plausible explanation for EIW in some cases, we believe that exhaustion was the most common explanation for sensation of wheeze or dyspnea during exercise in subjects where EIB could not be confirmed.

In the present study, levels of ENO were not increased in adolescents with EIW. Furthermore, there was no difference in the ENO levels between subjects with EIB and those without EIB, either in cigarette smokers or in non-smokers. In a study by Scollo and colleagues, 24 asthmatic children and 18 healthy controls were investigated using the ET (17). Twenty of the asthmatics and none of the controls had positive skin-prick tests. Baseline levels of ENO were significantly increased in asthmatic children with EIB compared to healthy controls, but not compared to asthmatic children without EIB. Scollo and colleagues also demonstrated a correlation between baseline ENO and the maximal fall in FEV_1 after exercise. In previous work, a close correlation was found between an increase in ENO and confirmed sensitization to airborne allergens (5,19,20). Thus, the normal ENO levels found in the present study may be the result of exclusion of subjects with allergy-related wheeze.

Surprisingly, there was a significant association between cigarette smoking and bronchoconstriction caused by exercise, but not by methacholine. We are not aware of any previous reports of such a finding. Furthermore, in a former study of the association between wheeze and methacholine-induced bronchoconstriction (MIB), no significant association between smoking and MIB was found (5). However, it is known that both active and passive smoking increase the inflammatory burden of the lower respiratory tract through a number of mechanisms. An association between maternal smoking during pregnancy and impaired fetal airway development, as well as altered lung function during early childhood, have been demonstrated (27). In Norway, an increasing number of girls tend to take up cigarette smoking (13,14). As girls reported EIW more frequently than boys, girls may be at a greater risk of developing EIW and EIB, as a result of smoking, than boys.

In summary, we demonstrated that EIW, as the only or predominant asthma-like symptom, was associated with EIB in only 33% of the subjects. Bronchoprovocation caused by exercise, but not by methacholine, was significantly increased in cigarette smokers. Furthermore, ENO was not increased in subjects with EIB.

We conclude that when wheeze is experienced mainly during exercise, it is easily confused with exercise-induced exhaustion and is not a reliable indicator of EIB. Furthermore, the relatively poor correlation between response to exercise and response to methacholine indicates that these two tests reflect different mechanisms of reactivity in the lower airways.

Acknowledgments

The skilful technical assistance of T. Skaland is greatly appreciated. A.H.H. is funded by a research grant from The Norwegian Research Council. The study was sponsored by The Norwegian Asthma and Allergy Association and by GlaxoWellcome.

References

1. SENNAUSER FH, KUHN CE. Prevalence of respiratory symptoms in Swiss children: is bronchial asthma really more prevalent in boys? *Pediatr Pulmonol* 1995; 19: 161–6.
2. NYSTAD W, MAGNUS P, ROKSUND O, SVIDAL B, HETLEVIK O. The prevalence of respiratory symptoms and asthma among school children in three different areas of Norway. *Pediatr Allergy Immunol* 1997; 8: 35–40.
3. PEAT JK. The epidemiology of asthma. *Curr Opin Pulm Med* 1996; 2: 7–15.
4. KUEHNI CE, BROOKE AM, SILVERMAN M. Prevalence of wheeze during childhood: retrospective and prospective assessment [In Process Citation]. *Eur Respir J* 2000; 16: 81–5.
5. HENRIKSEN AH, LINGAAS-HOLMEN T, SUE-CHU M, BJERMER L. Combined use of exhaled nitric oxide and airway hyperresponsiveness in characterizing asthma in a large population survey. *Eur Respir J* 2000; 15: 849–55.
6. FORESI A, MATTOLI S, CORBO GM, POLIDORI G, CIAPPI G. Comparison of bronchial responses to ultrasonically nebulized distilled water, exercise, and methacholine in asthma. *Chest* 1986; 90: 822–6.
7. LOWHAGEN O, ARVIDSSON M, BJARNEMAN P, JORGENSEN N. Exercise-induced respiratory symptoms are not always asthma. *Respir Med* 1999; 93: 734–8.
8. NYSTAD W, STENSRUD T, RUCKEN B, HAGEN J, MAGNUS P, CARLSEN KH. Wheezing in school children is not always asthma. *Pediatr Allergy Immunol* 1999; 10: 58–65.
9. JENKINS MA, CLARKE JR, CARLIN JB, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996; 25: 609–16.
10. TOELLE BG, PEAT JK, VAN DEN BERG RH, DERMAND J, WOOLCOCK AJ. Comparison of three definitions of asthma: a longitudinal perspective. *J Asthma* 1997; 34: 161–7.
11. WEST JV, ROBERTSON CF, ROBERTS R, OLINSKY A. Evaluation of bronchial responsiveness to exercise in children as an objective measure of asthma in epidemiological surveys. *Thorax* 1996; 51: 590–5.
12. BACKER V, ULRIK CS. Bronchial responsiveness to exercise in a random sample of 494 children and adolescents from Copenhagen. *Clin Exp Allergy* 1992; 22: 741–7.
13. HOLMEN TL, BARRETT-CONNOR E, HOLMEN J, BJERMER L. Health problems in teenage daily smokers versus nonsmokers, Norway, 1995–97: The Nord-Trøndelag Health Study. *Am J Epidemiol* 2000; 151: 148–55.
14. HOLMEN TL, BARRETT-CONNOR E, HOLMEN J, BJERMER L. Adolescent occasional smokers, a target group for smoking cessation? The Nord-Trøndelag Health Study, Norway, 1995–97. *Prev Med* 2000; 31: 682–90.
15. KHARITONOV SA, YATES D, ROBBINS RA, LOGAN-SINCLAIR R, SHINEBOURNE EA, BARNES PJ. Increased nitric oxide in exhaled air of asthmatic patients. *Lancet* 1994; 15: 133–5.
16. SALOME CM, ROBERTS AM, BROWN NJ, DERMAND J, MARKS GB, WOOLCOCK AJ. Exhaled nitric oxide measurements in population sample of young adults. *Am J Respir Crit Care Med* 1999; 159: 911–6.
17. SCOLLO M, ZANCONATO S, ONGARO R, ZARAMELLA C, ZACCHELLO F, BARALDI E. Exhaled nitric oxide and exercise-induced bronchoconstriction in asthmatic children. *Am J Respir Crit Care Med* 2000; 161 (3 Part 1): 1047–50.
18. KANAZAWA H, HIRATA K, YOSHIKAWA J. Role of endogenous nitric oxide in exercise-induced airway narrowing in patients with bronchial asthma [In Process Citation]. *J Allergy Clin Immunol* 2000; 106: 1081–7.
19. HENRIKSEN AH, SUE-CHU M, LINGAAS-HOLMEN T, LANGHAMMER A, BJERMER L. Exhaled and nasal NO levels in allergic rhinitis: relation to sensitization, pollen season and bronchial hyperresponsiveness. *Eur Respir J* 1999; 13: 301–6.
20. HENRIKSEN AH, HOLMEN TL, BJERMER L. Sensitization and exposure to pet allergens in asthmatics versus non-asthmatics with allergic rhinitis. *Respir Med* 2001; 95: 122–9.
21. KHARITONOV S, ALVING K, BARNES PJ. Exhaled and nasal nitric oxide measurements: recommendations. The European Respiratory Society Task Force. *Eur Respir J* 1997; 10: 1683–93.
22. BURDON JG, JUNIPER EF, KILLIAN KJ, HARGREAVE FE, CAMPBELL EJ. The perception of breathlessness in asthma. *Am Rev Respir Dis* 1982; 126: 825–8.
23. ASHER MI, KEIL U, ANDERSON HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483–91.
24. CHRISTOPHER KL, WOOD RP II, ECKERT RC, BLAGER FB, RANEY RA, SOUHRADA JF. Vocal-cord dysfunction presenting as asthma. *N Engl J Med* 1983; 308: 1566–70.
25. GOLDBERG BJ, KAPLAN MS. Non-asthmatic respiratory symptomatology. *Curr Opin Pulm Med* 2000; 6: 26–30.
26. HAMMO AH, WEINBERGER MM. Exercise-induced hyperventilation: a pseudoasthma syndrome. *Ann Allergy Asthma Immunol* 1999; 82: 574–8.
27. HANRAHAN JP, TAGER IB, SEGAL MR, et al. The effect of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis* 1992; 145: 1129–35.