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Physical training does not increase allergic inflammation in asthmatic children

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ABSTRACT: The effects of a 3-month physical training programme on airway inflammation and clinical outcomes were studied in school-aged children with asthma.

Subjects with persistent allergic asthma (aged 12.7±3.4 yrs; n=34) were randomly allocated into training and control groups. Exercise consisted of twice-weekly 50-min sessions for 12 weeks. Inflammation was assessed by levels of exhaled nitric oxide, blood eosinophils, eosinophil cationic protein, C-reactive protein, and total and mite-specific immunoglobulin (Ig)E. Lung volumes and bronchial responsiveness to methacholine were determined. The Paediatric Asthma Quality of Life Questionnaire and Paediatric Asthma Caregiver's Quality of Life Questionnaire were used to evaluate activity restrictions, symptoms and emotional stress. The efficacy of the training was assessed by accelerometry.

Following the programme, the exercise group spent twice as much time as the controls undertaking moderate-to-vigorous activities. No differences in changes were seen between groups for asthma outcomes. However, total IgE decreased more in the exercise group, as did mite-specific IgE.

Training did not increase inflammation in children with persistent asthma, and may have decreased both total and allergen-specific immunoglobulin E levels. It is concluded that there is no reason to discourage asthmatic children with controlled disease to exercise.

KEYWORDS: Asthma, exhaled nitric oxide, physical activity, quality of life, randomised controlled trial

The increase in the prevalence of asthma observed in most developed countries has been accompanied by important changes in lifestyle [1]. Reduced physical activity has been associated with increased asthma prevalence [2–4], and high levels of physical activity have been suggested to prevent disease progress [5]. Physical training may reduce breathlessness and asthma symptoms by strengthening respiratory muscles and decreasing ventilatory rate during exercise. Training programmes in asthma have not, however, shown any improvement in lung function in controlled trials [5–12]. The effects on airway inflammation are largely unknown.

Heavy physical activity has also been related to asthma occurrence and exacerbation. In elite athletes, asthma is diagnosed more frequently than in the general population [13]. This has been attributed to airway inflammation and increased bronchial responsiveness induced by high-intensity long-term exercise, such as competitive swimming or long-distance running. Asthma symptoms may attenuate after discontinuing training and competition [14, 15]. Atopy and type of sport appear to be the two major risk factors, with atopic long-distance runners having the highest risk of asthma compared to nonatopic non-athletes [16].

The effects of a 3-month physical training programme on airway inflammation and clinical outcomes were studied in school-aged children with persistent asthma. The aim of the present study was to determine a rationale for exercise and sporting guidance for children and their parents.

METHODS

Patient selection

Atopic school-aged children with controlled asthma, treated with a small-to-moderate dose of inhaled corticosteroids (ICSs) for a period of ⩾1 yr and followed in the outpatient clinic of

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University Hospital of São João (Porto, Portugal), were invited to participate. The study was explained to parents and patients, and informed consent was obtained from those willing to participate. After 131 telephone invitations, 34 children were included (fig. 1). Atopy was defined by a positive skin-prick test result (weal of $\geqslant$3 mm in diameter when the control solutions gave the expected results) to at least one aeroallergen (house dust mites, pollens, animal dander and moulds). All subjects were sensitised to *Dermatophagoides pteronyssinus*.

All 34 children used ICSs, 22 long-acting β_2-agonists, 32 short-acting β_2-agonists and nine leukotriene antagonists, and 19 had been receiving specific immunotherapy against house mites for $\geqslant$1 yr. The median (range) time since diagnosis was 4 (2–10) yrs. Controlled disease was defined as: 1) no exacerbation necessitating oral steroids or an increase in inhaled steroids during the preceding 4 weeks, 2) no more than three times weekly use of rescue short-acting β_2-agonists, and 3) no indication to change maintenance treatment.

Study design

Patients were randomly allocated to a 12-week exercise training programme or standard care by a blinded computer-generated randomisation schedule with a blocking factor of four. Allocation numbers were encoded on labels placed in each case report form by an outside researcher, and patients were assigned the next available allocation number in sequence. The baseline and final assessments each included two hospital visits, 1 week apart. The patient and research team became aware of the allocations following the second baseline visit.

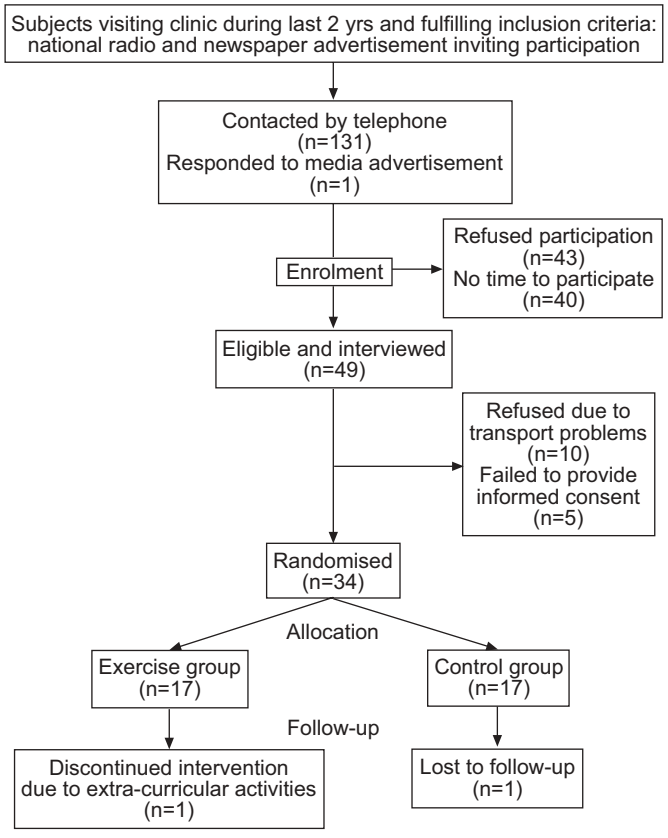

FIGURE 1. Flow chart showing participants in the study.

Training programme

The exercise group undertook submaximal aerobic exercise designed as a moderately intensive training programme including both lower and upper extremity activities. During the 12-week training programme, between February and May 2005, the sessions were held twice a week, for 50 min per session. All sessions were carried out in an indoor gymnasium. Subjects were instructed to use β_2-agonists before the training or, if necessary, during the session. A typical session started with a warm-up period (10 min) with arm and leg exercise. This was followed by submaximal training (30–35 min), including aerobic exercises, strength training, and some balance and coordination exercises, and a cool-down period (7–10 min). In order to offer an enjoyable training session, various recreational games were played. The control group subjects continued their usual daily routine.

Measurements

Exhaled nitric oxide (eNO) levels were determined using chemiluminescence in accordance with the recommendations of the American Thoracic Society (ATS), with an exhalatory flow rate of 50 $mL \cdot s^{-1}$ (NIOX; Aerocrine, Stockholm, Sweden) [17]. Blood eosinophil numbers were counted.

Serum C-reactive protein (CRP) levels were measured using a highly sensitive assay (Dade Behring CardioPhase hsCRP using the Behring Nephelometer BNII; Dade Behring, Marburg, Germany). The assay could detect a minimum CRP concentration of 0.175 $mg \cdot L^{-1}$. Serum total and mite-specific immunoglobulin (Ig)E and eosinophil cationic protein (ECP) levels were measured by fluorometric enzyme immunoassay (Phadia, Uppsala, Sweden).

Accelerometry

Compliance with the programme was assessed using an accelerometer. Physical activity was measured using an Actigraph monitor (model 7164; Computer Science and Applications, Shalimar, FL, USA) between weeks 8 and 12. The Actigraph uses a uniaxial accelerometer that measures vertical acceleration and deceleration in 1-min epochs. This accelerometer can be used to discriminate between light, moderate and vigorous levels of physical activity [18]. The monitor was affixed above the iliac crest of the right hip with an elastic belt and adjustable buckle. The subjects were instructed to wear the monitor for 1 week and to remove it for sleep. Data from days 1–7 were downloaded into a computer. Movement counts were converted into the mean time per day spent in resting or light (<3 metabolic equivalents of the task (METs)), moderate (3–6 METs), vigorous (6–9 METs) and very vigorous (>9 METs) physical activity. The time per day spent doing moderate, vigorous and very vigorous levels of activity were combined into one variable, the moderate-to-vigorous physical activity category.

Lung function tests and bronchial responsiveness

Spirometry was performed using a calibrated computerised pneumotachograph spirometer (SensorMedics Vmax 22; SensorMedics, Yorba Linda, CA, USA) according to ATS recommendations. Bronchial responsivenss was assessed by

methacholine challenge test performed according to recommendations [19].

Recording of peak expiratory flow variability

Peak expiratory flows (PEFs) were measured using a PIKO-1 (Ferraris Respiratory, Hertford, UK). The minimum morning PEF and maximum evening PEF were determined, respectively, as the lowest and highest PEF during the 1-week monitoring period [20]. The daily amplitude of PEF variation was determined according to the following formula and expressed as a percentage: amplitude=(highest PEF – lowest PEF)/highest PEF.

Paediatric Asthma Quality of Life Questionnaire and Paediatric Asthma Caregiver's Quality of Life Questionnaire

The Paediatric Asthma Quality of Life Questionnaire (PAQLQ) is a disease-specific questionnaire for the evaluation of health-related quality of life in asthmatic children. The self-administered form of the questionnaire was used [21]. It includes 23 items in three domains, activity limitation (n=5), symptoms (n=10) and emotional function (n=8). Both the scores of the three domains and the overall score range from 1 (maximum impairment) to 7 (no impairment). Clinical changes in PAQLQ score were considered minimal or moderate if they were >0.5 and >1.0, respectively [22]. The impact of the child's asthma on the caregiver's normal daily activities and emotional functioning were assessed using the self-administered Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) [23]. This is a 13-item questionnaire that assesses caregiver burden during a 1-week recall period. It contains four items in an activities domain and nine items in an emotional function domain. Individual items are weighted equally. Total and domain scores range 1–7, with higher scores indicating a more positive response.

Statistical analysis

All analyses were conducted using the intention-to-treat approach, including all randomised patients who had at least one post-baseline efficacy variable measurement. Baseline characteristics were compared using Fisher's exact test for categorical variables or an unpaired t-test for numerical variables; changes within groups were compared using a paired t-test and differences between the exercise and control groups were compared by ANCOVA, with the baseline value as covariate. In order to detect a 25% effect of the intervention using eNO as the main outcome, the estimated sample size would be 30 subjects [24]. A p-value of <0.05 was regarded as significant.

RESULTS

At baseline, with the exception of long-acting β_2-agonist use, no significant differences were observed between the two groups (table 1). A few subjects used either short-acting β_2-agonists twice daily or long-acting β_2-agonists, according to the asthma management plan established by their doctor. However, no differences existed between the groups considering the overall use of β_2-agonists. The training programme was completed by all except for two children. In the control group, one subject was lost to follow-up because of nonadherence, and a child in the exercise group withdrew due to excessive extracurricular activities. Therefore, 32 children, 16 in each group, underwent the final examination at the end of the 12-week period. All of the children were able to maintain the intensity of the training sessions without suffering asthma exacerbations. No changes in medication occurred during the programme. In the end, the exercise group spent almost twice as much time as the controls in moderate-to-vigorous activities as assessed by accelerometry (30±13 *versus* 16±11 min; p=0.027), but showed no differences in the time spent resting (469±88 *versus* 528±44 min; p=0.073) or in light physical activity (119±60 *versus* 113±31 min; p=0.799).

Inflammation and other asthma outcomes

No differences in change in level of eNO, blood eosinophil number, serum ECP or serum CRP were observed between groups (table 2). However, in the exercise group, there was a significant decrease in serum total and mite-specific IgE compared to the controls. Changes in lung function, peak expiratory variability, airway responsiveness and quality-of-life scores were nonsignificant between groups. The percentage of subjects achieving a clinically important improvement in the PAQLQ score from baseline did not differ between groups. Individual variations for each outcome are illustrated (fig. 2 of online supplementary material).

DISCUSSION

A physical training programme of moderate intensity did not affect inflammatory or other clinical outcomes in children with good asthma control. The present results are valid for subjects permitted to use effective medication against exercise-induced asthma symptoms.

A recent Cochrane review [25] pooled data from 13 studies and 455 subjects, and could not show physical training to improve lung function or decrease wheezy episodes. However, physical training improved cardiopulmonary fitness and maximum expiratory ventilation. In the present programme, children started their physical activity at an almost recreational level,

TABLE 1 Baseline characteristics of randomised patients by intervention group

	Exercise	Control	Total	p-value
Subjects n	17	17	34	
Age yrs	12.9±3.4	12.5±3.5	12.7±3.4	0.695
Females:males n	6:11	8:9	14:20	0.486
Height cm	152±12	152±13	152±13	0.947
Weight kg	46.8±13.4	46.3±13.0	46.6±13.0	0.928
Allergic rhinoconjunctivitis	17 (100)	17 (100)	34 (100)	
Time since diagnosis yrs	4.4±2.2	4.9±1.8	4.7±2.0	0.507
Inhaled short-acting β_2-agonists	16 (94)	17 (100)	33 (97)	0.310
Inhaled long-acting β_2-agonists	7 (41)	15 (88)	22 (65)	0.004
Inhaled corticosteroid dosage μg	402±117	400±61	401±93	
Leukotriene antagonist	3 (18)	6 (35)	9 (27)	0.244
Immunotherapy	12 (71)	8 (47)	20 (59)	0.163

Data are presented as mean±SD or n (%), unless otherwise indicated.

TABLE 2 Changes in biomarkers, lung function, bronchial responsiveness, body mass index (BMI), and quality of life related to asthma at baseline and after 12 weeks

Outcomes	Exercise				Control				p-value¶
	Subjects n	Baseline	Change#	p-value	Subjects n	Baseline	Change#	p-value	
Inflammatory									
eNO ppb	16	48.9±39.5	-5.8 (-18.5–6.9)		16	56.8±30.5	-17.9 (-31.8– -4.0)	0.015	NS
hsCRP mg·dL^{-1}	15	0.15±0.23	-0.06 (-0.20–0.07)		15	0.07±0.06	-0.01 (-0.04–0.02)		NS
Eos %	15	6.2±2.4	-0.2 (-1.2– 0.9)		15	7.5±2.8	-0.3 (-1.3–0.7)		NS
ECP μg·L^{-1}	15	34.0±19.6	8.9 (-3.2–21.1)		15	33.6±27.7	11.5 (-5.9–28.9)		NS
IgE kUA·L^{-1}	15	498.2±411.6	-120.7 (-198.5– -42.9)	0.005	15	898.8±789.8	-75.1 (-168.4–18.1)		0.003
Dp IgE kUA·L^{-1}	15	68.6±37.2	-9.5 (-16.0– -3.0)	0.007	15	64.1±40.9	-1.2 (-2.6–0.3)		0.014
Functional									
FEV_1 % pred	16	86.0±10.9	1.68 (-3.02–6.40)		15	86.0±10.7	4.13 (-0.22–8.48)		NS
$FEF_{25–75}$ % pred	16	82.9±30.1	0.87 (-10.0–11.78)		15	79.0±29.2	-0.42 (-12.00–11.10)		NS
Highest PEF amplitude %	11	20.6±13.0	-2.8 (-6.2–0.5)		13	18.0±9.7	-5.0 (-10.4–0.3)		NS
PD_{20}	14	1.20±1.76	-0.23 (-0.67–0.21)		13	2.08±1.93	-0.51 (-1.53–0.49)		NS
BMI	16	20.0±3.2	-0.2 (-0.6–0.2)		16	20.8±3.6	-0.23 (-0.6–0.2)		NS
Quality of life									
PAQLQ Activity	16	4.56±1.14	1.16 (0.58–1.73)	0.001	15	4.92±1.02	0.77 (0.28–1.26)	0.004	NS
PAQLQ Symptom	16	5.50±0.99	0.48 (0.19–0.78)	0.003	15	5.46±1.33	0.40 (-0.13–0.93)	0.133	NS
PAQLQ Emotion	16	5.98±1.16	0.44 (0.12–0.77)	0.011	15	5.93±0.94	0.30 (-0.13–0.75)	0.160	NS
PAQLQ Total	16	5.46±0.96	0.61 (0.29–0.95)	0.001	15	5.50±1.00	0.45 (0.03–0.86)	0.035	NS
PACQLQ Total	16	5.69±0.93	0.21 (-0.16–0.59)		15	4.89±1.48	0.28 (-0.21–0.77)		NS

Data are presented as mean±SD or mean (95% confidence interval). eNO: exhaled nitric oxide; hsCRP: C-reactive protein (measured using a highly sensitive assay); Eos: eosinophil; ECP: eosinophil cationic protein; Ig: Immunoglobulin; UA: allergen-specific unit; Dp: *Dermatophagoides pteronyssinus*; FEV_1: forced expiratory volume in one second; % pred: % predicted; $FEF_{25–75}$: forced expiratory flow between 25 and 75% of vital capacity; PEF: peak expiratory flow; $PD_{20}M$: PD_{20}: provocative dose of methacholine causing a 20% fall in FEV_1; PAQLQ: Paediatric Asthma Quality of Life Questionnaire; PACQLQ: Paediatric Asthma Caregiver's Quality of Life Questionnaire; NS: nonsignificant. #: paired t-test; ¶: ANCOVA with baseline value as covariate (exercise *versus* control).

and a more intense and vigorous programme could have produced greater improvements. However, it has been shown that the best way of increasing activity level is spending more time on moderate-intensity exercise and less on high-intensity activity [26]. Short periods of vigorous physical activity do not influence overall activity, probably due to decreased compensatory activity outside the training sessions [27].

The intervention period was 12 weeks in the present study, which is the longest among published studies of controlled randomised design [25]. It is possible that a longer intervention, or more frequent sessions, might have created differences between the groups. It could also be argued that children in the training programme were supervised by health professionals, which could limit the possible negative effects of exercise. It is unlikely that increased awareness of the disease affected the outcomes, since no additional medical visits were paid by the intervention group. If any unlikely benefit existed with the use of long-acting β_2-agonists, this would have been in favour of the control group. Other strengths of the present study include the use of validated tools for the measurement of physical activity and quality of life, and the assessment of inflammation.

Regular exercise has induced various degrees of airway inflammation, depending on type of sport and the medical history of the athlete [16]. In contrast with asthmatics, the increased numbers of inflammatory cells in healthy athletes' airways do not correlate with exercise-induced symptoms or bronchial responsiveness [28]. Recently, it has been observed that healthy children undertaking outdoor recreational activities exhibit a significant increase in eNO, dependent on ambient ozone levels, but with no changes in lung function test results [29]. Neither of these effects was observed in the present study with asthmatic subjects. Although the decrease in eNO was larger in the non-exercising group following the programme, no significant differences between groups were observed. All of the present children were treated with ICSs, which may have suppressed the exercise effect.

In the present study, performed between late winter and early spring, significant differences between groups were observed in change in total and mite-specific IgE. Seasonal variations in mite allergen exposure may account for changes in total and specific IgE in mite-sensitive asthmatics [30], but exercise seemed to boost this effect. This has been observed in a mouse model of allergic asthma, in which moderately intense aerobic exercise attenuated lung inflammatory responses [31, 32]. In ovalbumin-sensitised mice, exercise reduced mucus production, lung epithelial cell hypertrophy, secretion of type-2 T-helper cell-type cytokines, expression of adhesion molecules and production of ovalbumin-specific IgE [31]. In another recent animal study, moderate training decreased numbers of bronchoalveolar eosinophil and peribronchial cells expressing interleukin-4 and -5 but had no effect on total IgE levels [32].

In the present study, the lack of effect on other outcomes besides IgE may suggest that the balance between the pro- and anti-inflammatory effects of exercise in asthma would be null in respect to markers of airway inflammation, such as eNO. However, since physiological changes during the training were not addressed, this may represent a random effect. This can only be clarified in further studies. Seasonal variations in mite allergen load may also account for the eNO changes in both groups. In children who are sensitised to indoor allergens, higher dust mite allergen exposure has been associated with increased eNO levels [33].

The exercise group showed significant improvements in all domains of asthma-related quality of life, even with a moderate increase in activity, whereas changes in the control children were only significant for the activities domain. Failure to achieve a significant difference between groups could be due to the inclusion of subjects that are already well-controlled, leaving little room for improvement, and to a type II error due to small sample size. This is in contrast with the trial of BASARAN *et al.* [34], in which a significant improvement occurred in the exercise group compared to control group. However, in that study, a significant baseline difference in symptom scores was observed between groups.

In a physical intervention programme for school-aged children, an extra burden is placed upon the family. Additional to medication administration, ongoing care and disease monitoring, the caregiver is required to drive the child to a sports training centre and stay there until the session ends several times weekly for 12 weeks. Nevertheless, the additional burden introduced to the family did not have a negative impact on caretakers' quality of life.

Currently, Global Initiative for Asthma guidelines do not include recommendations for exercise as part of the treatment of patients with asthma [35]. Exercise is a powerful trigger for asthma symptoms. For this reason, caretakers may be reluctant to permit their asthmatic children to engage in sports practice, fearing an exacerbation of the disease. Every child with asthma should be questioned about exercise performance, tolerance and symptoms. It is concluded that there is no reason for discouraging asthmatic children with controlled disease from exercise.

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REFERENCES

1 Lucas SR, Platts-Mills TA. Paediatric asthma and obesity. *Paediatr Respir Rev* 2006; 7: 233–238.
2 Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M. Social predictors of adult asthma: a co-twin case–control study. *Thorax* 2001; 56: 234–236.
3 Nystad W, Stigum H, Carlsen KH. Increased level of bronchial responsiveness in inactive children with asthma. *Respir Med* 2001; 95: 806–810.
4 Rasmussen F, Lambrechtsen J, Siersted HC, Hansen HS, Hansen NC. Low physical fitness in childhood is associated with the development of asthma in young adulthood: the Odense schoolchild study. *Eur Respir J* 2000; 16: 866–870.
5 Swann IL, Hanson CA. Double-blind prospective study of the effect of physical training on childhood asthma. *In*: Oseid S., Edwards AM., eds. The Asthmatic Child in Play and Sport. London, Pitman Books, 1983; pp. 318–325..
6 Sly RM, Harper RT, Rosselot I. The effect of physical conditioning upon asthmatic children. *Ann Allergy* 1972; 30: 86–94.
7 Ahmaidi SB, Varray AL, Savy-Pacaux AM, Prefaut CG. Cardiorespiratory fitness evaluation by the shuttle test in asthmatic subjects during aerobic training. *Chest* 1993; 103: 1135–1141.
8 Girodo M, Ekstrand KA, Metivier GJ. Deep diaphragmatic breathing: rehabilitation exercises for the asthmatic patient. *Arch Phys Med Rehabil* 1992; 73: 717–720.
9 Cochrane LM, Clark CJ. Benefits and problems of a physical training programme for asthmatic patients. *Thorax* 1990; 45: 345–351.
10 Varray AL, Mercier JG, Terral CM, Prefaut CG. Individualized aerobic and high intensity training for asthmatic children in an exercise readaptation program. Is training always helpful for better adaptation to exercise? *Chest* 1991; 99: 579–586.
11 Varray AL, Mercier JG, Prefaut CG. Individualized training reduces excessive exercise hyperventilation in asthmatics. *Int J Rehabil Res* 1995; 18: 297–312.
12 Fitch KD, Blitvich JD, Morton AR. The effect of running training on exercise-induced asthma. *Ann Allergy* 1986; 57: 90–94.
13 Helenius I, Haahtela T. Allergy and asthma in elite summer sport athletes. *J Allergy Clin Immunol* 2000; 106: 444–452.
14 Helenius I, Rytila P, Sarna S, *et al.* Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: a 5-year prospective follow-up study of 42 highly trained swimmers. *J Allergy Clin Immunol* 2002; 109: 962–968.
15 Helenius I, Lumme A, Ounap J, *et al.* No effect of montelukast on asthma-like symptoms in elite ice hockey players. *Allergy* 2004; 59: 39–44.
16 Helenius IJ, Tikkanen HO, Sarna S, Haahtela T. Asthma and increased bronchial responsiveness in elite athletes: atopy and sport event as risk factors. *J Allergy Clin Immunol* 1998; 101: 646–652.
17 American Thoracic Society, Recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children – 1999. *Am J Respir Crit Care Med* 1999; 160: 2104–2117.
18 Puyau MR, Adolph AL, Vohra FA, Zakeri I, Butte NF. Prediction of activity energy expenditure using

accelerometers in children. *Med Sci Sports Exerc* 2004; 36: 1625–1631.
19 Sterk PJ, Fabbri LM, Quanjer PH, *et al.* Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *Eur Respir J* 1993; 6: Suppl. 16, 53–83.
20 Fonseca JA, Costa-Pereira A, Delgado L, *et al.* Pulmonary function electronic monitoring devices: a randomized agreement study. *Chest* 2005; 128: 1258–1265.
21 Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Qual Life Res* 1996; 5: 35–46.
22 Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol* 1994; 47: 81–87.
23 Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in the parents of children with asthma. *Qual Life Res* 1996; 5: 27–34.
24 Kharitonov SA, Gonio F, Kelly C, Meah S, Barnes PJ. Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. *Eur Respir J* 2003; 21: 433–438.
25 Ram FS, Robinson SM, Black PN, Picot J. Physical training for asthma. *Cochrane. Database Syst Rev 2005; Issue*, 4: CD001116.
26 Westerterp KR. Pattern and intensity of physical activity. *Nature* 2001; 410: 539.
27 Kempen KP, Saris WH, Westerterp KR. Energy balance during an 8-wk energy-restricted diet with and without exercise in obese women. *Am J Clin Nutr* 1995; 62: 722–729.
28 Karjalainen EM, Laitinen A, Sue-Chu M, Altraja A, Bjermer L, Laitinen LA. Evidence of airway inflammation and remodeling in ski athletes with and without bronchial hyperresponsiveness to methacholine. *Am J Respir Crit Care Med* 2000; 161: 2086–2091.
29 Nickmilder M, Carbonnelle S, de Burbure C, Bernard A. Relationship between ambient ozone and exhaled nitric oxide in children. *JAMA* 2003; 290: 2546–2547.
30 Nahm DH, Park HS, Kang SS, Hong CS. Seasonal variation of skin reactivity and specific IgE antibody to house dust mite. *Ann Allergy Asthma Immunol* 1997; 78: 589–593.
31 Pastva A, Estell K, Schoeb TR, Atkinson TP, Schwiebert LM. Aerobic exercise attenuates airway inflammatory responses in a mouse model of atopic asthma. *J Immunol* 2004; 172: 4520–4526.
32 Vieira RP, Claudino RC, Duarte AC, *et al.* Aerobic exercise decreases chronic allergic lung inflammation and airway remodeling in mice. *Am J Respir Crit Care Med* 2007; 176: 871–877.
33 Spanier AJ, Hornung R, Lierl M, Lanphear BP. Environmental exposures and exhaled nitric oxide in children with asthma. *J Pediatr* 2006; 149: 220–226.
34 Basaran S, Guler-Uysal F, Ergen N, Seydaoglu G, Bingol-Karakoc G, Ufuk AD. Effects of physical exercise on quality of life, exercise capacity and pulmonary function in children with asthma. *J Rehabil Med* 2006; 38: 130–135.
35 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. www.ginasthma.org/Guidelineitem.asp??l1=2&l2=1&intId=60 Date last updated: 19 December 2007. Date last accessed: 22 September 2008.