

Physical activity and exercise in asthma: Relevance to etiology and treatment

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There is little doubt that the cause of the increased prevalence and severity of asthma is multifactorial. Although the factors of allergen exposure and hygiene are almost certainly necessary for its development, there is a growing body of literature that implicates lifestyle change, specifically decreased physical activity, as a contributor to the increase in asthma prevalence and severity. Several literature reviews of exercise conditioning in patients with asthma have been published. These reviews and recent controlled trials emphasize that although many of the studies of exercise conditioning in asthmatic patients involved different methods and outcome measures, the overwhelming majority of studies demonstrated the capacity for asthmatic subjects to exercise safely and significantly improve their cardiovascular fitness and quality of life. There are several proposed pathophysiologic mechanisms responsible for the effects of decreased activity on the lung function of patients with asthma. A prescription for exercise has been endorsed for all asthmatic subjects by the American College of Sports Medicine and the American Thoracic Society. The allergy community has placed emphasis on medical therapy and allergen avoidance; in addition, exercise avoidance has not been formally incorporated into the National Asthma Education and Prevention Program guidelines. It is our belief that an exercise prescription should be part of the treatment for all cases of asthma. The real question is whether prolonged physical activity and, in particular, outdoor play of children plays a role in prophylaxis against persistent wheezing. If so, the decrease in physical activity might have played a major role in recent increases in asthma prevalence and severity. (*J Allergy Clin Immunol* 2005;115:928-34.)

Key words: Asthma, exercise, conditioning, etiology, pathophysiology, sedentary lifestyle, activity, therapy, incidence, severity

EPIDEMIOLOGY OF THE INCREASED PREVALENCE AND SEVERITY OF ASTHMA

Asthma prevalence, severity, and hospitalization have increased over the last 4 decades. Although there seems to

Abbreviations used

ACSM: American College of Sports Medicine
ASM: Airway smooth muscle
ATS: American Thoracic Society
BHR: Bronchial hyperreactivity
BMI: Body mass index
CF: Cystic fibrosis
EIB: Exercise-induced bronchospasm

have been a slight plateau in asthma incidence in recent years, the prevalence remains very high, and true causes of the epidemic remain an enigma. The increase has affected many different populations, but the increase has disproportionately affected African Americans and Latinos living in poverty in the United States. By contrast, rural areas that have maintained a traditional lifestyle remain unaffected: good examples have been studied in Africa, Australia, and Papua New Guinea. Many explanations for the increase have been postulated, but none of them are sufficient to explain the scale or consistency of the change. Indeed, it is becoming increasingly evident that the cause of the changes in asthma must be multifactorial, including contributions from allergen exposure, hygiene, and lifestyle.

This article will briefly review the 2 former factors and more thoroughly elaborate on lifestyle change, with a specific emphasis on the relevance of changes in physical activity. The pulmonary physiology underlying the effects of activity will be discussed as well. A prescription for exercise has been endorsed for all asthmatic subjects by the American College of Sports Medicine (ACSM)¹ and the American Thoracic Society (ATS)². Currently, the National Asthma Education and Prevention Program Guidelines for the Diagnosis and Management of Asthma³ do not include recommendations for exercise as part of the treatment for patients with asthma.

MULTIFACTORIAL EXPLANATION OF INCREASED INCIDENCE

Allergen sensitization

There have been strong and consistent associations between aeroallergen sensitization, especially to dust mites, and asthma. Supported by bronchial challenge

From the University of Virginia Asthma and Allergic Diseases Center. Supported by National Institutes of Health grants no. AI-20565 and AI/EHS-P01-AI-50989.

Disclosure of potential conflict of interest: T. A. E. Platts-Mills—none disclosed. S. R. Lucas—none disclosed.

Received for publication December 7, 2004; revised January 11, 2005; accepted for publication January 19, 2005.

Available online April 5, 2005.

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2005.01.033

and avoidance studies, these are strongly suggestive of a causal relationship between sensitization and asthma.⁴ Subsequently, many different perennial allergens from other parts of the world have been implicated as determinants of inflammation and bronchial hyperreactivity (BHR). The hygiene hypothesis proposes that decreased exposure to infections and farm animals—endotoxin or increased antibiotic use has decreased the activation of control mechanisms based on T regulator cells. The dominance of T_H2 responses in atopic individuals has been consistently demonstrated. Although there is good evidence for a change of this kind with the move from traditional lifestyle, the major changes in hygiene occurred in the United States or United Kingdom long before the increase in asthma. Furthermore, there are good reasons to believe that hay fever was epidemic in London and New York before the start of the increase of asthma.

Lifestyle

If we assume that the real increase in asthma has occurred between 1960 and 2000, what are the lifestyle changes that match this increase? The obvious candidates are diet and physical activity. Obesity, however, is the product of these changes that is easiest to measure. Obviously, these three are strongly interrelated, but there are good arguments for a primary role of either obesity itself, changes in diet, or decreased physical activity in the increase in asthma.

Obesity. Adult and pediatric obesity has become an epidemic in industrialized nations over the past 2 decades. The prevalence of childhood obesity in the United States increased 100% between 1980 and 1994.⁵ In the 1990s, obesity came under scrutiny for its potential contribution to the increase in asthma. Obesity has been associated with reduction in deep breathing, contributing to airway narrowing through smooth muscle latching,⁶ decreased forced expiratory flow at 25% to 75% of forced vital capacity,⁷ reflux-induced bronchoconstriction,⁸ shortness of breath, increased wheezing,^{9,10} and increased release of inflammatory mediators.^{11,12} Perzanowski and colleagues¹³ evaluated the relationship between body mass index (BMI) and asthma among rural and urban children in Kenya and the United States. They found that urban American children had significantly higher BMIs and increased prevalence of asthma (Table I). They also found that despite having larger lung volumes and being taller and heavier than the African children, the children in Atlanta had an FEV₁ as a percentage of predicted value that was significantly lower (Table I). One randomized controlled trial demonstrated improved lung function in asthmatic subjects with dietary weight loss.¹⁴ Although there is an abundance of literature demonstrating the association of asthma and obesity, there is only one study that has established that obesity precedes asthma independent of activity level.¹⁵ Could it be that increased sedentary lifestyle has more influence on asthma prevalence and severity than obesity and diet? Certainly the association between obesity and asthma is not comparable with the association between obesity and diseases, such as

Box 1. Salter (1882) on exercise as a treatment for asthma

Exercise—I have seen several cases in which prolonged bodily exertion has been of great benefit, indeed, some in which it has been the best remedy to which the asthmatic could resort.

This treatment is, of course, rather prophylactic than curative—it must be taken in the intervals of the attacks: but when so taken it seems to have a marvelous efficacy in keeping them off, and in giving to the asthmatic a lightness and freedom of respiration to which at other times he is a stranger.

The following cases are good examples illustrative of this point:

Case I.—“Of all remedies,” writes a confirmed asthmatic to me, “there is none for me so complete and lasting as a day of severe walking exercise—five-and-twenty miles over hilly ground, or across heaths. The strain must never be great. I begin slowly, almost saunteringly, and only increase my pace when it is pleasanter to do so than not.

Case II—The following extract from an interesting case sent me by a medical friend: “For the last twenty years, in fact ever since I can recollect, my father has been running the gauntlet of medical men in England and Scotland, without any sort of benefit, so much so that about eight years ago he gave this plan up, and took the treatment into his own hands—I ought to say legs, perhaps, for his only curative measure consisted in walking exercise; about twenty miles a day was, he considered, an average dose, and the result is that he is now comparatively free from attacks.

type II diabetes. It is our view that there is a more logical case related to changes in physical activity and also a more convincing explanation for the effects of exercise on asthma than the effect of obesity on increased asthma.

Sedentary lifestyle. There has been a steady decrease in the levels of physical activity of adults and children in America over the last 3 decades. This decrease corresponds in time course to the increased prevalence of asthma. Rasmussen et al,¹⁶ in their 10.5-year prospective study of 757 children, concluded that decreased physical fitness in childhood was significantly ($P < .01$) correlated with the development of adolescent asthma. Huovinen et al,¹⁷ in their 17-year study of 262 twin pairs, showed that the twin who participated in exercise conditioning had a decreased risk of asthma.

Unlike BMI, levels of physical activity are difficult to measure. Recently, when compared with healthy peers, statistically significantly lower levels of activity have been documented in low-income preschool children with a history of asthma and wheezing by using Actiwatchs (Mini Mitter Company, Inc, Bend, Ore).¹⁸ The Actiwatchs that measure movement were worn on the wrist

TABLE I. Anthropometric and spirometric measurements on children in rural and urban Kenya and Atlanta, Georgia

	Kabiti (rural)	Thika (urban)	Atlanta
No. enrolled	136	129	112
Age (y)	11.5 (9-15)	10.0 (8-13)	10.8 (10-12)
Height (cm)†	137 (120-159)	135 (123-154)	150 (112-168)
Weight (kg)†	31 (20-51)	30 (20-45)	46 (22-112)
Body fat (%)*	15.5 (6-23)	17.4 (12-31)	19.8 (14-32)
Initial LFTs			
FVC (L)†	1.99 (1.27-3.08)	1.93 (1.06-2.58)	2.49 (1.41-5.92)
FEV ₁ (L)†	1.66 (0.97-2.53)	1.6 (0.92-2.19)	2 (1.19-4.16)
% Predicted†‡	95.6	96.4	89.2
PEF (L/m)†	242 (91-426)	228 (102-358)	292 (174-692)

Values are presented as means (ranges).

LFT, Lung function test; FVC, forced vital capacity; PEF, peak expiratory flow.

* $P < .01$ between all locations (Mann-Whitney U test).

† $P < .01$ between children from Kenya and Atlanta.

‡Percent predicted FEV₁ values were race adjusted.

for 6 to 7 days, and children with a history of wheezing or a recent emergency department visit for wheezing demonstrated lower levels of vigorous and prolonged activity. There were no significant correlations between BMI and physical activity or wheezing, suggesting that activity level could have played a role in the development or persistence of wheezing independent of obesity.

Most studies have shown that asthmatic subjects have a lower aerobic fitness level than their nonasthmatic peers. However, this limited fitness level in asthmatic subjects seems not to be related to their degree of obstruction but rather to their decreased levels of habitual activity.¹⁹ Although seemingly counterintuitive given the potential for exercise-induced bronchospasm (EIB), exercise has long been recognized as a possible method of improving subjective and objective asthma indices. The possibility that exercise could be a treatment for asthma was recognized in 1882 by Henry Hide Salter.²⁰ However, the regimens he proposed were slightly “unrealistic” (see Box 1).

It is well documented that the incidence of EIB after proper medical prophylaxis is extremely low.²¹ Several recent literature reviews have supported the benefits and safety of exercise in asthmatic subjects.^{19,21-23} Although studies vary in terms of design, outcome measures, exercise mode, duration, intensity, and outcome variables, the majority of studies on pediatric and adult asthmatic subjects have demonstrated improved objective and subjective markers of disease.

EXERCISE CONDITIONING FOR PATIENTS WITH ASTHMA

Orenstein's 2002 literature review of exercising patients with pulmonary disease concluded that asthmatic subjects can improve cardiopulmonary fitness with exercise conditioning.²¹ In addition to decreased risk of cardiovascular disease and diabetes, the benefits of conditioning on asthma are both subjective (increased participation in activities, improved emotional status, and decreased intensity of wheezing attacks) and objective

(improved running performance and increased aerobic fitness). He, however, also points out it is unclear whether improved fitness influences the severity of underlying asthma. Several studies have reported that exercise conditioning does not influence inflammation as judged on the basis of preconditioning and postconditioning methacholine challenges.^{24,25} Orenstein²¹ suggested that some older studies erroneously concluded that underlying asthma was less severe after exercise conditioning because when challenged with the same preconditioning workload in the fit state, asthmatic patient's minute ventilation was lower, making the stimulus for EIB less intense. Regardless, it seems to us, any measure that makes doing the same workload less asthmogenic seems prudent, irrespective of the mechanism. He concluded that “exercise conditioning is good for patients with asthma, but probably does not lead to decreased underlying airway reactivity.”

In Satta's 2000 review of 48 articles on exercise training for patients with asthma,²³ he draws attention to the fact that “much of the research suffers from methodological problems such as small sample size, the lack of adequate control groups, incomplete outcome measures, lack of prospective data collection.” However, his literature review highlighted the health benefits of exercise conditioning on asthmatic subjects, including improved fitness level and quality of life. He also highlighted positive outcomes, including reductions in the need for medications, fewer visits to the emergency department, decreased exercise-related fear and anxiety, and less absenteeism from school. Some studies have documented improvement in spirometry (decreased peak flow variability and increased FEV₁), whereas others did not. He also cited several studies that failed to demonstrate an improvement in nonspecific BHR.

Another thorough literature review of 90 articles on exercise conditioning for asthma by Clark¹⁹ identified that the categories of patients chosen, the control groups, the disease severity, and the type of physiologic measurements of the studies varied greatly. Furthermore, there were few studies on adult asthmatic patients before 1993.

TABLE II. Review of controlled trials after 1990 on the benefits of exercise conditioning in asthmatic patients

Reference	Asthmatic patients	Control subjects	Fitness measures	Fitness trend	Time (wk)	Other
Hallstrand et al ²⁶	5 A	5 A, H	↑ VO2max*, ↓ AT*, ↓ VE*	↑	10	↑ Fitness = in H and asthmatic subjects
Cambach et al ²⁷ §	43 A	23 COPD	↑ ET‡, ↓ f _c ‡, ↑ WD‡	↑	12	↑ QOL‡ Multidisciplinary rehab program
Robinson et al ²⁴	8 A	8 A, H	↑ VO2max*, ↓ VE	↑	12	↑ QOL‡
Varray et al ²⁸	7 C	7 C Asthma	↑ VO2max‡, ↑ V _{th} ‡	↑	12	↓ Intensity of wheeze
Cochrane and Clark ²⁵ §	18 A	18 A Asthma	↑ VO2max‡, ↓ VE‡, O2pulse‡, AT‡, ↓ VCO2‡	↑	12	↓ Lactate*, ↓ breathlessness

A, Adult; H, healthy; VO2max, maximal oxygen consumption; AT, anaerobic threshold; VE, minute ventilation; COPD, chronic obstructive pulmonary disease; ET, endurance time; f_c, cardiac frequency; WD, walking distance; QOL, quality of life; C, children; V_{th}, ventilatory threshold; VCO2, CO₂ output.
*P < .05.
‡P < .01.
§P < .001.
§Randomized controlled trial.

The training programs varied with respect to mode, frequency, duration, and intensity, and the use of prophylactic β-agonists for EIB was often not specified. He concluded that despite these methodological differences, “almost universally the clinical studies have shown major improvement in exercise performance in patients after participation in rehabilitation programs.”

There are several more recent controlled trials that provide sound data to support incorporating exercise into asthma management (Table II).²⁴⁻²⁸ In these studies and the remainder of the studies reviewed above there were no major adverse reactions to conditioning programs. There are, however, some recent studies that have reported increased asthma symptoms among children involved in vigorous sports.^{29,30} Although the literature is replete with studies demonstrating the benefits of conditioning asthmatic subjects, there is a relative dearth of physiologic explanations for these positive outcomes.

PATHOPHYSIOLOGY BEHIND THE BENEFITS OF CONDITIONING

Deep inspiration and smooth muscle

There are many factors influencing the patency of bronchioles (Fig 1). There has been a lot of speculation that collagen deposition or airway remodeling plays a significant role in decreased airway patency or compliance. Some authors have speculated that increased smooth muscle is the cause of excessive bronchoconstriction or changed compliance. Thomson and colleagues,³¹ however, evaluated cross-sectional airway muscle in axial airway sections at high resolution and found no evidence of increased airway smooth muscle (ASM).

The key component of acute airway narrowing is constriction of ASM. This acute bronchoconstriction is shown in Fig 2, a hyperpolarized helium scan demonstrating regional ventilation defects of an asthmatic subject with EIB. The effect of deep inspiration on ASM and acute bronchoconstriction was first studied in 1961 by Nadel and Teirney.³² They demonstrated decreased airway resistance after deep inspiration in patients with

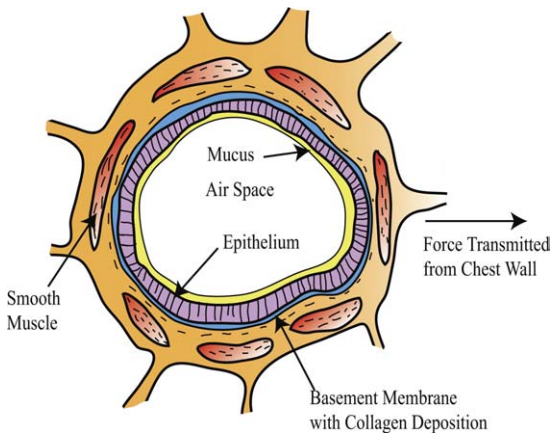


FIG 1. Proposed factors influencing the patency of bronchioles. Excess mucus and edema caused by poor mucociliary clearance from decreased epithelial stimulation secondary to decreased activity. Smooth muscle latching and decreased chest wall force from decreased deep inspiration and sigh rate. Collagen deposition from chronic inflammation. Adapted from a slide by R. R. Schellenberg.

bronchoconstriction. Fish et al³³ later confirmed these findings in nonasthmatic subjects. Induced bronchoconstriction was transiently reduced or abolished with deep inspiration. These bronchoprotective effects, however, were minimal in patients with asthma. They suggested that the primary problem in asthma, hyperresponsiveness, occurs after a failure of inspiration to stretch ASM, as it does in nonasthmatic subjects. Together the findings suggested that stretch of constricted ASM causes a transient decrease in smooth muscle tone.^{34,35}

This theory of failure of inspiration to stretch ASM was further explored by Skloot et al,³⁶ who conducted methacholine challenges on asthmatic and nonasthmatic subjects while prohibiting deep inspiration; after 20 minutes of shallow breathing, the response to methacholine was similar in both groups. In nonasthmatic subjects a single deep inspiration abolished the increased response to methacholine. However, deep inspiration had no effect

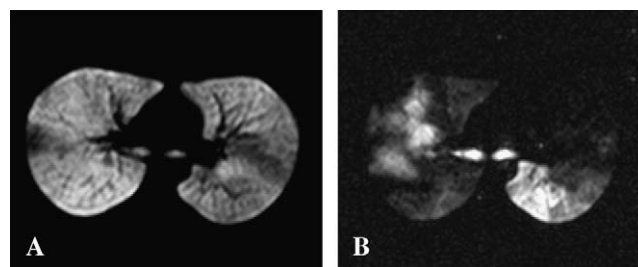


FIG 2. Axial chest hyperpolarized helium magnetic resonance scan of a patient with mild asthma before (A) and after (B) exercise, demonstrating acute bronchoconstriction and ventilation defects.

on methacholine-induced bronchoconstriction in asthmatic subjects. The results suggest either that inflammation could interfere with normal ASM stretching or that there is an intrinsic abnormality of asthmatic ASM.³⁷

Perturbed equilibriums

Fredburg et al³⁸ addressed the relationship between ASM length and tidal lung inflation and its molecular basis. They showed that ASM length is determined by lung tidal movement that acts to “perturb the interactions of myosin and actin” and will bias the muscle toward bronchodilation, the implication being that low tidal volumes result in the conversion of ASM from rapid to slow-cycling actin-myosin cross-bridges. This slow cycling results in a latch state that in turn leads to chronic bronchoconstriction. Their data suggested that physical extension of ASM is imperative to maintain normal tone. They concluded, on the basis of *in vitro* experiments, that this full lung expansion was a more potent bronchodilator than isoproterenol. They also suggested that spontaneous sighs (periodic deep inspirations) are the first line of defense against bronchospasm, citing other evidence that showed deep inspiration to be protective in the face of bronchoprovocation with leukotrienes.³⁹

Sigh rate

More recently, our group has speculated that a decrease in these sighs or periodic expansion of the lungs while sedentary could contribute to nonspecific BHR in children.⁴⁰ Our study demonstrated significantly lower sigh rates in asthmatic and nonasthmatic students while watching a video than while reading. Given that many people watch 5 or more hours of television or other screens a day, their breathing pattern could affect lung function. The combination of decreased exercise coupled with increased hours in front of a screen both contribute to decreased deep inspiration. Whether the real problem is prolonged, sedentary periods or the lack of physical activity is not clear.

Cyclic compressive stress and epithelial cells

There are of course many other mechanisms by which activity could influence lung pathophysiology or mechanics. Mechanically stimulating airway epithelial cells from patients with cystic fibrosis (CF) with cyclic compression (variable transepithelial pressures) increases the height of

the periciliary liquid layer and rate of mucociliary clearance.⁴¹ Recently, there have been *in vitro* data demonstrating that cyclic compressive stress acting on CF airway epithelial cells increases endothelial nitric oxide synthase and S-nitrosylated proteins.⁴² This endothelial nitric oxide synthase is located in the basal body of the cilia in epithelial cells, and it stimulates ciliary beat frequency. S-nitrosylated proteins are signaling molecules in vascular endothelial response to mechanical stress. Increases in these two could contribute to the improved mucociliary clearance and therapeutic benefit of exercise on airway clearance and patency in both patients with CF and patients with asthma (Fig 1).

EXERCISE PRESCRIPTION FOR ASTHMATIC SUBJECTS

Both the ACSM¹ and the ATS² guidelines recommend exercise for patients with asthma. Exercise training is the key component to pulmonary rehabilitation. The ACSM guidelines state that “current evidence suggests that the standard principles of exercise prescription (mode, frequency, intensity, and duration) can be applied to patients with respiratory diseases, including asthma.” The recommended mode of aerobic exercise is walking or any mode of aerobic exercise with large muscles. The optimal frequency is 3 to 5 days a week. They conclude there is no consensus on the optimal intensity of exercise but recommend exercising at 50% of peak oxygen uptake or at limits as tolerated by symptoms. Optimal duration of exercise is 20 to 30 minutes of continuous activity, although they admit this will be unrealistic for some patients at the beginning of an exercise program. Subjects with severe asthma refractory to typical EIB prophylaxis might require optimal air conditions (ie, heated humidified air) to exercise safely. The ACSM guidelines endorse exercise prescription for asthmatic subjects, but they mention that the majority of published data relate to chronic obstructive pulmonary disease.

The ATS recommends pulmonary rehabilitation for patients whose lung disease results in loss of independence, anxiety or breathlessness with activities, or limitations in social, leisure, indoor, or outdoor activities. They list asthma as one of the non-chronic obstructive pulmonary disease indications for pulmonary rehabilitation

and emphasize that symptoms, disability, and handicap and not the severity of physiologic impairment of the lungs dictate the need for rehabilitation. The ATS recommends training at 60% to 75% of maximal work rate, ideally for 20 to 30 minutes 2 to 5 times per week. For patients who cannot tolerate 20 minutes of sustained activity, they suggest as an alternative 2 to 3 minutes of high-intensity intervals.

The modes of exercise reported in asthmatic conditioning studies that demonstrated improved fitness in patients with asthma included walking, swimming, cycling, running, rowing, calisthenics, and gymnastics. The frequency of exercise sessions in most studies was 3 to 5 times a week. Intensity of sessions is perhaps the most variable component among the published conditioning studies, ranging from patient-determined intensity to 60% to 75% of predicted maximal heart rate. The duration of conditioning programs averaged 18 weeks, with a range of 6 to 80 weeks. In Clark's review²⁹ he concluded that regardless of the mode of exercise used, one can follow intensity by monitoring heart rates.

Although the ACSM and ATS recommend formal exercise prescription for asthmatic subjects as above, it is important to distinguish between formal exercise defined by objective physiologic changes and routine gradual, moderate-intensity physical activities, such as walking or playing. Some authors have claimed that the move from traditional lifestyle to urban living can be seen as the progressive loss of a lung-specific protective effect against asthma,⁴³ the implication being that routine walking or playing might be more protective against asthma than brief, high-intensity exercise. One author found that short periods of vigorous activity did not have much effect on overall activity level, the factor by which total energy expenditure exceeds resting energy expenditure, the implication being that those involved in traditional, brief, high-intensity exercise actually overcompensate and might have lower overall activity levels.⁴⁴ It is possible that a more frequent (ie, daily) moderate-intensity activity like walking is what conferred the protective effects against asthma. There are, however, no long-term, prospective, controlled trials evaluating the effects of consistent, moderate-intensity activity on the development or persistence of asthma.

CONCLUSION

There is little doubt that the cause of increased prevalence and severity of asthma is multifactorial. Although allergen exposure and some levels of hygiene might be necessary for its development, there is a growing body of literature that implicates decreased physical activity as a contributor to the increase in asthma prevalence and severity.

Exercise conditioning of asthmatic subjects has been endorsed in the literature for decades. Although it is true that fitness levels are lower among patients with asthma than among their nonasthmatic peers, this is a function of

their levels of habitual activity rather than their degree of obstruction. Although many of the studies of exercise conditioning in asthmatic patients involved different methods and outcome measures, the overwhelming majority of studies demonstrated the capacity for asthmatic subjects to exercise safely and to significantly improve their cardiovascular fitness and quality of life. Outcomes in many studies are as good as those achieved with many of the pharmaceutical drugs recommended for asthma.

Although asthma severity is variable, a prescription for exercise has been endorsed for all asthmatic subjects by both the ACSM and the ATS. However, the allergy community has largely placed emphasis on medical therapy and allergen avoidance, and exercise has not been formally incorporated into the National Asthma Education and Prevention Program guidelines. The exact age at which to start conditioning asthmatic subjects is unclear, but it appears, given recent data, that conditioning of children with a family history of atopy should be initiated as early as preschool age or earlier. It is our belief that an exercise prescription should be part of the management-treatment for all cases of asthma. The real question is whether prolonged physical activity and, in particular, outdoor play of children played an important role in prophylaxis against persistent wheezing. If so, the decrease in physical activity might have played a role in recent increases in asthma prevalence and severity.

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