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REFERENCES

1. Charles MD, Holman RC, Curns AT, Parashar UD, Glass RI, Bresee JS. Hospitalizations associated with rotavirus gastroenteritis in the United States, 1993–2002. *Pediatr Infect Dis J* 2006;25:489–93.
2. Fischer TK, Vibound C, Parashar U, Malek M, Steiner C, Glass R, et al. Hospitalizations and deaths from diarrhea and Rotavirus among children <5 years of age in the United States, 1993–2003. *J Infect Dis* 2007;195:1117–26.
3. Malek MA, Curns AT, Holman RC, et al. Diarrhea- and rotavirus-associated hospitalizations among children less than 5 years of age: United States, 1997 and 2000. *Pediatrics* 2006;117:1887–92.
4. CDC. Delayed onset and diminished magnitude of Rotavirus activity—United States, November 2007–May 2008. *Morbidity and Mortality Weekly Report* 2008;57:1–4.
5. Payne DC, et al. Active, population-based surveillance for severe Rotavirus gastroenteritis in children in the United States. *Pediatrics* 2008;122:1235–43.
6. Tate JE, et al. Decline and change in seasonality of US Rotavirus activity after the introduction of Rotavirus vaccine. *Pediatrics* 2009;124:465–71.
7. Turcios RM, et al. Temporal and geographic trends of Rotavirus activity in the United States, 1997–2004. *Pediatr Infect Dis J* 2006;25:451–4.
8. Committee on Infectious Disease. Prevention of Rotavirus disease: updated guidelines for use of rotavirus vaccine. *Pediatrics* 2009;123:1412–20.
9. Patel NC, et al. Vaccine-acquired Rotavirus infection in two infants with severe combined immunodeficiency: late breaking abstracts. *J Allergy Clin Immunol* 2009.
10. Werther RL, et al. Rotavirus vaccine induced diarrhea in a child with severe combined immune deficiency. *J Allergy Clin Immunol* 2009;124:600 Epub 2009 Aug 5.
11. CDC. Prevention of Rotavirus gastroenteritis among infants and children—recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* 2006;55(RR12):1–13.

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Cardiorespiratory fitness, adiposity, and incident asthma in adults

To the Editor:

Available large-scale prospective studies on adiposity and asthma used body mass index as an indicator of adiposity.¹ Studies involving more accurate measures of adiposity, such as body fat percentage (BF%), are needed to confirm or contrast body mass index–related results. Cardiorespiratory fitness is a strong predictor of morbidity and mortality,² and the available literature suggests that moderate-high cardiorespiratory fitness reduces many of the health hazards associated with obesity.³ The current study aimed (1) to examine whether cardiorespiratory fitness and/or BF% are associated with subsequent acquisition of asthma in adults, and (2) to test the hypothesis that a high cardiorespiratory fitness level can reduce the risk of incident asthma in individuals with excess adiposity.

To address these issues, we selected 9810 individuals free of asthma at baseline (7712 men) age 20 to 82 years from the Aerobics Center Longitudinal Study.^{2,4} Baseline asthma was reported by the participants using a standardized medical questionnaire. Participants completed a baseline examination⁴ and a follow-up survey by which self-reported physician-diagnosed asthma was identified. The study protocol was approved annually

by the Institutional Review Board of the Cooper Institute. The endpoint was defined as a participant report of a physician diagnosis of asthma. (See this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org for further information about the study sample, design, baseline examination and ascertainment of asthma.)

Cardiorespiratory fitness was defined as the total time of a symptom-limited maximal treadmill exercise test by using a modified Balke protocol.⁴ Low fitness, moderate fitness, and high fitness were defined as the lowest 20%, the next 40%, and the remaining 40% of individuals in each age-specific and sex-specific distribution of treadmill time. BF% was assessed with hydrostatic weighing, with the sum of 7 skinfold measures, or with both assessments, following standardized protocols.⁵ On the basis of the standard clinical definitions, overfat was defined as having a BF% $\geq 25\%$ in men and $\geq 30\%$ in women.

Information on smoking (never smoker, exsmoker, and current smoker), leisure time physical activity (physically inactive or active), and respiratory symptoms was obtained from a standardized medical questionnaire. A respiratory symptoms index was defined as the presence of 1 or more of the following respiratory symptoms: chronic cough or phlegm, tuberculosis, bronchitis, pneumonia, emphysema, coughed up blood, or unexplained shortness of breath while sleeping, sitting, or exercising. Participants had complete and valid data for all the study variables mentioned. Pulmonary function assessment was carried out in a subset of the participants (86% of the total study sample), and FEV₁ was obtained with a Collins 421 Survey spirometer (Collins, Mass). Hankinson et al⁶ predictive equations for FEV₁ specific for sex, age, and height and derived from healthy National Health and Nutrition Examination Survey (NHANES) III participants were used.

Associations of cardiorespiratory fitness and BF% at baseline with incident asthma, after adjustment for a set of confounders (ie, age, sex, height, physical activity, smoking, and respiratory symptom index) were analyzed by binary logistic regression. Interaction terms for sex were entered into the logistic regression models. No significant sex interaction was found in the associations between the exposures and the outcome. We find that cardiorespiratory fitness reduces some of the health hazards associated with obesity.³ To test this hypothesis for asthma, the associations between cardiorespiratory fitness and asthma were analyzed in the subset of overfat individuals after adjusting for the confounders. Finally, the main logistic regression models were also adjusted for FEV₁ to examine how pulmonary function could affect the associations of fitness and fatness with asthma. The analyses were performed by using SAS (Version 9.1; SAS Institute, Cary, NC). For all analyses, the statistical significance level was 5%.

We found an incidence of asthma of 5% over a mean follow-up period of 11.5 years. Both low cardiorespiratory fitness and high BF% were associated with subsequent acquisition of asthma (Table I). However, whereas BF% was associated with asthma independent of cardiorespiratory fitness, the association between cardiorespiratory fitness and asthma did not persist after adjusting for BF% (Table I). When the association between cardiorespiratory fitness and asthma was also adjusted for FEV₁ (data not shown), it became nonsignificant, suggesting that this association was also mediated by FEV₁. High adiposity remained associated with higher risk of asthma after adjustment for FEV₁ though, suggesting that factors other than pulmonary function may explain this association. Further research on this topic is needed to confirm these findings. (See the [Online Repository](http://www.jacionline.org) for further

TABLE I. Multivariate associations of cardiorespiratory fitness, BF%, and incident asthma

Predisposing factors	Cases (n)	Model 1* OR (95% CI)	Model 2† OR (95% CI)
Cardiorespiratory fitness			
Low	69 (1075)	1 (Reference)	1 (Reference)
Moderate	173 (3586)	0.77 (0.57-1.03)	0.82 (0.61-1.11)
High	218 (5149)	0.68 (0.50-0.93)	0.79 (0.57-1.09)
BF%			
Normal-fat	315 (7262)	1 (Reference)	1 (Reference)
Overfat	145 (2548)	1.45 (1.17-1.79)	1.38 (1.10-1.72)

OR, Odds ratio.

*Model 1 adjusted for age, sex, height, physical activity, smoking, and respiratory symptom index.

†Model 2 adjusted for all the variables in model 1 plus BF% (for cardiorespiratory fitness) or cardiorespiratory fitness (for BF%).

TABLE II. Associations between cardiorespiratory fitness and incident asthma stratified by normal-fat and overfat

	Cases (n)	Multiple-adjusted* OR (95% CI)
Normal-fat individuals		
Cardiorespiratory fitness		
Low	26 (473)	1
Moderate	97 (2275)	0.85 (0.54-1.33)
High	192 (4514)	0.93 (0.59-1.46)
Overfat individuals		
Cardiorespiratory fitness		
Low	43 (602)	1
Moderate	76 (1311)	0.78 (0.52-1.16)
High	26 (635)	0.51 (0.30-0.88)

OR, Odds ratio.

*Adjustment for potential risk factors: age, sex, height, physical activity, smoking, and respiratory symptoms (presence of 1 or more of the respiratory symptoms indicated in Table E1).

information about additional analyses/results [Table E1, Table E2 and Fig E1]).

One prospective study⁷ observed that a high cardiorespiratory fitness level in children was associated with a lower risk of incident asthma at late adolescence. The relationships between cardiorespiratory fitness and adult-onset asthma or the combined effect of fitness and fatness on incident asthma have not been studied. A major finding of this study was that having a high cardiorespiratory fitness level reduced by half the risk of incident asthma in overfat individuals, whereas no effect was observed in normal-fat individuals (Table II). These findings suggest that high cardiorespiratory fitness might be less beneficial in individuals with a low risk of incident asthma—that is, normal-fat adults—than in those with a higher risk of incident asthma—that is, overfat adults. Only a high level of cardiorespiratory fitness, not a moderate level, seemed to attenuate the risk of developing asthma. (See the [Online Repository](#) for further information about potential underlying mechanisms for the observed findings.)

To deal with possible misclassification of chronic obstructive pulmonary disease, we performed the analyses controlling for a respiratory symptoms index, defined as the presence of 1 or more respiratory problems associated with chronic obstructive pulmonary disease: chronic cough or phlegm, bronchitis, emphysema and/or unexplained shortness of breath while sleeping, sitting, or exercising. The associations of asthma with either

cardiorespiratory fitness or BF% persist after accounting for this index (Table I).

In this study, as in most large-scale prospective studies,⁸ asthma incidence was assessed as self-reported physician-diagnosed asthma. Although the accuracy of self-reported physician-diagnosed asthma in this study is not known, persons in this highly educated cohort have previously shown high sensitivity and specificity at reporting pathological conditions, such as hypertension (98% and 99%, respectively).⁹ We believe that large misclassification errors caused by using self-report physician-diagnosed asthma data are unlikely in this population. The current study allowed us to relate baseline cardiorespiratory fitness and BF% to subsequent acquisition of asthma. However, mechanisms by which changes in cardiorespiratory fitness and BF% levels can influence asthma risk are not known and should be addressed in future studies. Our study lacks information about the atopic status of the participants, presence of rhinitis or allergic disease, and related biomarkers such as serum IgE or leptin levels. Also, we did not collect information about wheeze at the follow-up, which is a respiratory symptom often related with asthma. On the other hand, the fact that nearly 10,000 individuals were evaluated by using objective and accurate measures of cardiorespiratory fitness and BF% and followed up for an average period of 11 years is a strength of this study.

In conclusion, the results of this prospective study suggest that the association between adiposity and the risk of incident asthma is consistent after adjustment for all the variables studied, including smoking, physical activity, cardiorespiratory fitness, and pulmonary function, whereas the association between cardiorespiratory fitness and asthma is mediated by adiposity and pulmonary function. However, we found that the higher risk of incident asthma observed in overfat men and women might be lowered by half if a high cardiorespiratory fitness level is achieved. These findings may have important implications for physicians and for future disease prevention policies.

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REFERENCES

1. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;175:661-6.
2. Blair SN, Kampert JB, Kohl HW 3rd, Barlow CE, Macera CA, Paffenbarger RS Jr, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* 1996;276:205-10.
3. Lee DC, Sui X, Blair SN. Does physical activity ameliorate health hazards of obesity? *Br J Sports Med* 2009;43:49-51.
4. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA* 1989;262:2395-401.
5. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr* 1999;69:373-80.
6. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
7. 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;16:866-70.
8. Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005;115:897-909; quiz 910.
9. Blair SN, Goodyear NN, Gibbons LW, Cooper KH. Physical fitness and incidence of hypertension in healthy normotensive men and women. *JAMA* 1984;252:487-90.

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Fetal origin of atopic dermatitis

To the Editor:

Environmental challenges during pregnancy and early life events have long been hypothesized to modulate the susceptibility to chronic diseases in later life, which is commonly referred to as “developmental programming.”¹ The unprecedented rise of allergies occurring in industrialized countries over the past 5 decades² and the recognition that prenatal and postnatal environmental factors³⁻⁵ are involved in the risk to develop allergies suggest that atopic diseases may be central in understanding mechanisms involved in developmental programming.

To date, insights on prenatal maternal biomarkers involved in developmental programming of the fetus are largely elusive. During early pregnancy, hormonal adaptations such as the secretion of progesterone and estradiol are central in establishing adaptation to pregnancy and hence set the stage for a normally progressing pregnancy.⁶ Progesterone is an upstream mediator in the cascade of maternal immune adaptation to pregnancy, and low levels of progesterone can be observed on stress challenge.⁶ Estradiol is pivotal in regulating placental steroidogenic maturation and involved in the development of functional adrenal glands.⁷

We here report an inverse association between levels of maternal progesterone during early pregnancy and the risk for atopic dermatitis in later life of the children. This association was exclusively detectable in girls (Table I), and low levels of maternal progesterone did not affect the risk to develop atopic dermatitis in boys. Interestingly, maternal levels of estradiol during pregnancy were not associated with an altered risk for atopic dermatitis in the children, irrespective of the sex. As expected from published data, parental history of atopic diseases also augmented

the risk for atopic dermatitis in all children (Table I). For additional information, such as patient selection criteria, statistical analyses, see this article’s Methods section in the Online Repository at www.jacionline.org. Additional analyses of potential risk factors considered in this study are provided in this article’s Tables E1 and E2 in the Online Repository at www.jacionline.org.

Multiple logistic regression analyses also confirmed that increasing maternal progesterone levels during early pregnancy significantly reduced the odds to develop atopic dermatitis in girls (adjusted odds ratio, 0.83; 0.73-0.94 CI), whereas no association between maternal progesterone and the development of atopic dermatitis during the first 3 years of life could be seen in boys (adjusted odds ratio, 0.99; 0.93-1.06 CI). See this article’s Table E3 in the Online Repository at www.jacionline.org.

The phenotype of atopic dermatitis between boys and girls did not significantly differ with regard to clinical comorbidity symptoms (Table II), which allows us to exclude a sex-dependent deviation of the disease. Also, significant modulations of maternal progesterone levels by the sex of the fetus could be excluded (17.0 ± 0.8 ng progesterone/mL serum in boy pregnancies vs 17.6 ± 8.3 ng/mL in pregnant women carrying a girl). Similarly, maternal atopy did not significantly influence progesterone levels during pregnancy (16.9 ± 6.6 ng/mL in atopic mothers vs 17.3 ± 8.2 ng/mL in nonatopic mothers).

Our findings suggest that low levels of progesterone may have a predictive value as a marker for an increased risk for atopic dermatitis in girls in early childhood. Because progesterone is well accepted to promote fetal tolerance, it is conceivable that low progesterone levels during early pregnancy challenge the immune tolerance required to sustain an optimal fetal development.

Maternal levels of estradiol did not have any effect on the risk for atopic dermatitis in both sexes. Given the strong immunomodulatory properties of estradiol,⁷ it could be a worthwhile subject of future investigations to test whether maternal levels of estradiol might be involved in the fetal programming toward other diseases.

One central question arising from our observations is the identification of the causes for low maternal progesterone levels. Activation of the hypothalamic-pituitary-adrenal axis by perceived stress and increased levels of stress hormones have been reported to downregulate levels of progesterone. Hence, progesterone could be seen as an endocrine “stress-sentinel.”⁶ Unfortunately, serum progesterone level testing is rarely included in the clinical blood work during early pregnancy, which is somewhat puzzling because progesterone is a recognized adjunct marker for the prediction of early pregnancy outcome.⁶

The inverse association reported here of low levels of progesterone and a high risk for atopic dermatitis in girls in later life is not only of interest as a potential risk indicator for allergies but might also offer a therapeutic opportunity for primary prevention of atopic dermatitis in girls. In a murine experimental model of stress-induced decrease of progesterone during gestation, the supplementation of progesterone with a progesterone derivative called dydrogesterone has been shown to restore mediators of fetomaternal tolerance. Further, the increased allergic airway responsiveness seen in prenatally stressed offspring⁸ can be abrogated by supplementation with a progesterone derivative (unpublished data, Pincus, Bruenahl & Arck, August 2009). This suggests that supplementation of progesterone in women pregnant with a girl may decrease the risk for atopic dermatitis in later life of these girls. If confirmed in independent cohorts, this would evidently be a novel therapeutic intervention aiming at primary prevention of atopic

METHODS

Study sample and design

The Aerobics Center Longitudinal Study (ACLS) is a prospective follow-up study conducted on men and women.^{E1,E2} ACLS participants were mostly white (98%) and well educated, and most worked in executive or professional positions.^{E3} All participants completed a detailed questionnaire and underwent an extensive clinical evaluation, including a physical examination, fasting blood chemistry analyses, personal and family health history, anthropometry, smoking and alcohol use, and physical activity. The study protocol was approved annually by the Institutional Review Board of the Cooper Institute.

The current study includes ACLS participants who were examined between 1974 and 1994, and who responded to at least 1 mail survey during 1990 or 1995 ($n = 20,252$). Participants were excluded if at baseline they reported a personal history of asthma ($n = 911$), had missing data or achieved less than 85% of their age-predicted maximal heart rate during graded Balke treadmill exercise testing ($n = 985$), or had missing data on BF% ($n = 1007$), age, sex, smoking, physical activity, or respiratory symptoms ($n = 942$). Participants with missing body mass index data or body mass index below 18.5 kg/m^2 ($n = 2218$) also were excluded because of the increased likelihood of chronic illness in this group.^{E4} Finally, participants who had a follow-up time shorter than 1 year also were excluded ($n = 4380$). The final sample consisted of 9810 participants, 7712 men and 2098 women, age 20 to 82 years at the time of their clinical examination.

Baseline examination

Previous reports have described the baseline examination in detail.^{E2} Briefly, height and weight were measured on a standard doctor's scale at the baseline clinic visit. It has been suggested that short height is associated with adult-onset asthma,^{E5} so a sex-specific and age-specific tertile variable was created for height and used in the analysis to examine this hypothesis. Body mass index (kg/m^2) was calculated as weight in kilograms divided by height in meters squared. BF% was assessed with hydrostatic weighing, with the sum of 7 skin-fold measures, or with both assessments, following standardized protocols.^{E6} BF% was further dichotomized on the basis of standard clinical definitions for men (normal-fat <25%; overfat $\geq 25\%$) and for women (normal-fat <30%; overfat $\geq 30\%$).^{E7}

Cardiorespiratory fitness was defined as the total time of a symptom-limited maximal treadmill exercise test by using a modified Balke protocol.^{2,8} Total time of the test on this protocol correlates highly with measured maximal oxygen uptake ($\text{VO}_{2\text{max}}$) in both men ($r = 0.92$)^{E9} and women ($r = 0.94$).^{E10} The test endpoint was volitional exhaustion or when the physician stopped it for medical reasons. $\text{VO}_{2\text{max}}$ was calculated from the final treadmill speed and grade.^{E11} Previous ACLS reports have shown that low fitness is an independent predictor of mortality and morbidity.^{E1,E2,E12} To be consistent with previous reports, the same established age-specific and sex-specific cut points were used in this study: low, moderate, and high cardiorespiratory fitness as the lowest 20%, the middle 40%, and the upper 40%, respectively, of the age-specific and sex-specific distribution of treadmill duration in the overall ACLS population.^{E12}

Information on smoking (never smoker, ex-smoker, and current smoker), leisure time PA (physically inactive or active), and respiratory symptoms was obtained from a standardized medical questionnaire. Participants were defined as physically inactive if they reported no leisure-time PA in the 3 months before baseline examination. A respiratory symptoms index was defined as the presence of 1 or more of the following respiratory symptoms: chronic cough or phlegm, tuberculosis, bronchitis, pneumonia, emphysema, coughed up blood, or unexplained shortness of breath while sleeping, sitting, or exercising.

Pulmonary function assessment was carried out in a subset of the participants (86% of the total study sample), and FEV₁ was obtained with a Collins 421 Survey spirometer (Collins, Mass) as described elsewhere.^{E3} All procedures were administered by trained technicians who followed standardized protocols. Hankinson et al.^{E13} predictive equations for FEV₁ specific for sex, age, and height and derived from healthy National Health and Nutrition Examination Survey (NHANES) III participants were used. The FEV₁ was expressed both as raw values and as percentage of the predictive values.

Ascertainment of asthma

The incidence of asthma was ascertained from responses to mail-back follow-up health surveys in 1990 or 1995. The aggregate survey response rate across these 2 survey periods in the ACLS is $\approx 65\%$. Nonresponse bias is a concern in epidemiologic surveillance. This issue has been investigated in the ACLS,^{E14} and no major source of bias was found. Baseline health histories and clinical measures were similar between responders and nonresponders and between early and late responders.^{E14} The endpoint was defined as a participant report of a physician diagnosis of asthma.

RESULTS

Baseline characteristics of the participants are shown in Table E1. The prevalence of overfat in men and women was 25% and 31%, respectively. Mean cardiorespiratory fitness levels (maximal oxygen consumption) were 42 and 34 mL/kg/min for men and women, respectively. Less than one third of the participants reported no leisure-time PA in the 3 months before baseline examination. A higher percentage of women (60%) compared with men (45%) reported never having smoked, and most of the participants (93% and 87% of men and women, respectively) were free of any respiratory symptoms. Over a mean follow-up period of 11.5 years, 460 (5%) new cases of asthma, 358 (5%) men and 102 (5%) women, were identified.

The odds ratios and 95% CIs of asthma developing according to different baseline levels of cardiorespiratory fitness, BF%, and a set of potential confounders, after controlling for sex and age, are shown in Table E2.

The results from the main analyses shown in Tables I and II did not materially change when the analyses were performed using cardiorespiratory fitness and BF% as continuous variables (data not shown). Therefore, we elected to focus on the categorical analyses.

Analyses of spirometry data in a subset of the participants showed that the pulmonary function, as assessed by FEV₁, was significantly lower in both overfat and unfit individuals (Fig E1).

DISCUSSION

Potential underlying mechanisms for the observed findings

Asthma is well known to be linked to a chronic systemic inflammation state.^{E15} The fact that high cardiorespiratory fitness is inversely associated with low-grade systemic inflammation^{E16,E17} may partially explain the associations between cardiorespiratory fitness and asthma developing. Mechanical factors, such as a decreased lung function, also may play an important role in the pathogenesis of asthma.^{E18} It has been reported that a lower lung function in FEV₁ predicts airway hyperresponsiveness later in life, a key characteristic of asthma phenotype.^{E19} We studied pulmonary function in a subset of the participants (86% of the total study sample), and our data showed that both low cardiorespiratory fitness and high fatness at baseline are associated with a lower FEV₁, which in turn could be related to future airway responsiveness and asthma. This finding is in accordance with previous studies.^{E20} In high-fit athletes, especially in sports like swimming, this higher capacity seems to be a result of the development of physically wider chests, containing an increased number of alveoli.^{E21} Greater fitness includes a higher ventilatory threshold,^{E22} and a relatively lower ventilation means a smaller ventilatory stimulus to asthma.^{E23} Moreover, when the association between cardiorespiratory fitness and asthma was also adjusted for FEV₁, it became nonsignificant, suggesting that this association was mediated by

FEV₁. High adiposity remained associated with higher risk of asthma after adjustment for FEV₁, suggesting that factors other than pulmonary function may explain this association. Further research on this topic is needed to confirm these findings.

The deep inspiration hypothesis must also be considered. The key component of acute narrowing is constriction of the airway smooth muscle, and it has been demonstrated that this constriction is reduced after deep inspiration.^{E24,E25} The primary problem in asthma, hyperresponsiveness, seems to occur after a failure of deep inspirations to stretch the airway smooth muscle and the consequent reduction of the airway resistance. It is important to take into account that this is a theory and has little data that support it. Nevertheless, exercise increases the frequency of deep inspirations significantly, yielding a bronchoprotective effect. Although PA and fitness are not interchangeable concepts, 90% of the high cardiorespiratory fitness participants were active, compared with only 39% of the low cardiorespiratory fitness participants. This means that the high cardiorespiratory fitness group in this study can be considered a physically active group, having a lower risk of developing asthma, according to the PA–deep inspiration hypothesis.

Finally, the sensation of respiratory symptoms and their report could be influenced by a person's fitness.^{E26} High fitness could raise the person's threshold to respiratory symptoms and raise the level at which respiratory discomfort develops. Mahler et al^{E27} proposed that these effects are induced by alterations in brain ventilatory chemosensitivity.

REFERENCES

- E1. Blair SN, Kampert JB, Kohl HW 3rd, Barlow CE, Macera CA, Paffenbarger RS Jr, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* 1996;276:205-10.
- E2. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA* 1989;262:2395-401.
- E3. Cheng YJ, Macera CA, Addy CL, Sy FS, Wieland D, Blair SN. Effects of physical activity on exercise tests and respiratory function. *Br J Sports Med* 2003;37:521-8.
- E4. Stanley AH, Demissie K, Rhoads GG. Asthma development with obesity exposure: observations from the cohort of the National Health and Nutrition Evaluation Survey Epidemiologic Follow-up Study (NHEFS). *J Asthma* 2005;42:97-9.
- E5. Huovinen E, Kaprio J, Koskenvuo M. Factors associated to lifestyle and risk of adult onset asthma. *Respir Med* 2003;97:273-80.
- E6. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr* 1999;69:373-80.
- E7. Bray GA. Fat distribution and body weight. *Obes Res* 1993;1:203-5.
- E8. Balke B, Ware RW. An experimental study of physical fitness of Air Force personnel. *U S Armed Forces Med J* 1959;10:675-88.
- E9. Pollock ML, Bohannon RL, Cooper KH, Ayres JJ, Ward A, White SR, et al. A comparative analysis of four protocols for maximal treadmill stress testing. *Am Heart J* 1976;92:39-46.
- E10. Pollock ML, Foster C, Schmidt D, Hellman C, Linnerud AC, Ward A. Comparative analysis of physiologic responses to three different maximal graded exercise test protocols in healthy women. *Am Heart J* 1982;103:363-73.
- E11. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription, 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2005.
- E12. Sui X, LaMonte MJ, Blair SN. Cardiorespiratory fitness as a predictor of nonfatal cardiovascular events in asymptomatic women and men. *Am J Epidemiol* 2007;165:1413-23.
- E13. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
- E14. Macera CA, Jackson KL, Davis DR, Kronenfeld JJ, Blair SN. Patterns of non-response to a mail survey. *J Clin Epidemiol* 1990;43:1427-30.
- E15. Renaud JC. New insights into the role of cytokines in asthma. *J Clin Pathol* 2001;54:577-89.
- E16. Church TS, Barlow CE, Earnest CP, Kampert JB, Priest EL, Blair SN. Associations between cardiorespiratory fitness and C-reactive protein in men. *Arterioscler Thromb Vasc Biol* 2002;22:1869-76.
- E17. Jae SY, Heffernan KS, Lee MK, Fernhall B, Park WH. Relation of cardiorespiratory fitness to inflammatory markers, fibrinolytic factors, and lipoprotein(a) in patients with type 2 diabetes mellitus. *Am J Cardiol* 2008;102:700-3.
- E18. Weiss ST. Obesity: insight into the origins of asthma. *Nat Immunol* 2005;6:537-9.
- E19. Grol MH, Postma DS, Vonk JM, Schouten JP, Rijcken B, Koeter GH, et al. Risk factors from childhood to adulthood for bronchial responsiveness at age 32-42 yr. *Am J Respir Crit Care Med* 1999;160:150-6.
- E20. Cooper KH, Pollock ML, Martin RP, White SR, Linnerud AC, Jackson A. Physical fitness levels vs selected coronary risk factors: a cross-sectional study. *JAMA* 1976;236:166-9.
- E21. Armour J, Donnelly PM, Bye PT. The large lungs of elite swimmers: an increased alveolar number? *Eur Respir J* 1993;6:237-47.
- E22. Londeree BR. Effect of training on lactate/ventilatory thresholds: a meta-analysis. *Med Sci Sports Exerc* 1997;29:837-43.
- E23. 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;16:866-70.
- E24. Nadel JA, Tierney DF. Effect of a previous deep inspiration on airway resistance in man. *J Appl Physiol* 1961;16:717-9.
- E25. Fish JE, Ankin MG, Kelly JF, Peterman VI. Regulation of bronchomotor tone by lung inflation in asthmatic and nonasthmatic subjects. *J Appl Physiol* 1981;50:1079-86.
- E26. Clark CJ. The role of physical training in asthma. *Chest* 1992;101:293S-8S.
- E27. Mahler DA, Cunningham LN, Skrinar GS, Kraemer WJ, Colice GL. Beta-endorphin activity and hypercapnic ventilatory responsiveness after marathon running. *J Appl Physiol* 1989;66:2431-6.

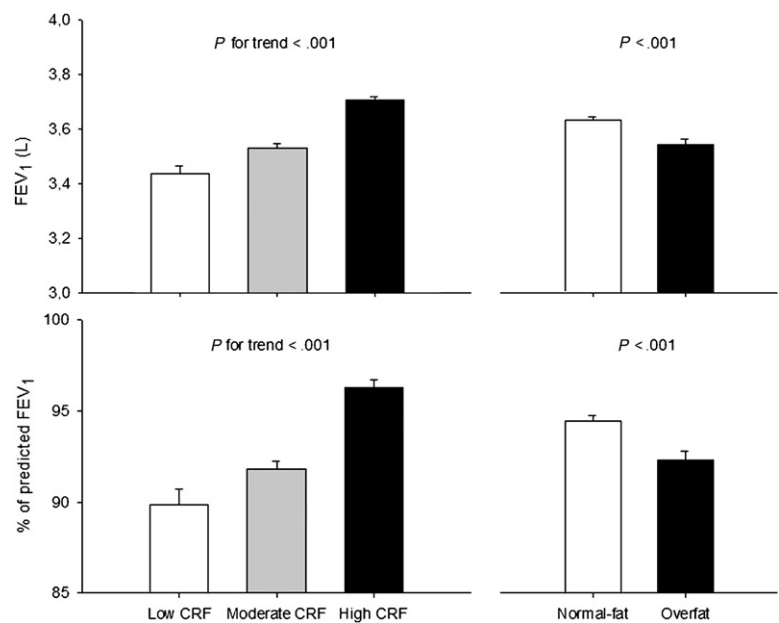


FIG E1. Baseline associations between pulmonary function, as measured by FEV₁ and levels of cardiorespiratory fitness (CRF) and BF%. Adjusted means and SEs are shown. Data were analyzed by 1-way analysis of covariance, adjusting for potential risk factors (variables from Model 1, Table I, except for predictive values' analyses, where age, sex, and height were not adjusted for, because these factors are already accounted for when using the predictive equations).

TABLE E1. Baseline characteristics of the participants

	Men (N = 7712)	Women (N = 2098)	All (N = 9810)
Age (y)	46.0 (9.5)	45.7 (10.3)	45.9 (9.7)
Height (cm)	178.6 (6.4)	164.3 (6.0)	175.5 (8.6)
Weight (kg)	82.1 (11.9)	60.8 (9.3)	77.6 (14.4)
Body mass index (kg/m ²)	25.7 (3.3)	22.5 (3.2)	25.0 (3.5)
BF%	20.6 (6.4)	26.6 (6.8)	21.9 (7.0)
Normal-fat	5822 (75.5)	1440 (68.6)	7262 (74.0)
Overfat	1890 (24.5)	658 (31.4)	2548 (26.0)
VO _{2max} (mL/kg/min)	41.8 (8.8)	33.9 (7.7)	40.1 (9.2)
Treadmill time (min)	18.5 (5.0)	13.8 (4.7)	17.5 (5.3)
Cardiorespiratory fitness levels			
Low	892 (11.6)	183 (8.7)	1075 (11.0)
Moderate	2850 (36.9)	736 (35.1)	3586 (36.5)
High	3970 (51.5)	1179 (56.2)	5149 (52.5)
Leisure time physical activity			
Inactive	2045 (26.5)	523 (24.9)	2568 (26.2)
Active	5667 (73.5)	1575 (75.1)	7242 (73.8)
Smoking			
Never smoker	3469 (45.0)	1260 (60.1)	4729 (48.2)
Ex-smoker	3202 (41.5)	678 (32.3)	3880 (39.6)
Current smoker	1041 (13.5)	160 (7.6)	1201 (12.2)
Respiratory symptoms index*			
Presence	554 (7.2)	282 (13.4)	836 (8.5)
Absence	7158 (92.8)	1816 (86.6)	8974 (91.5)

Data are shown as mean (SD) for continuous variables and as frequency (%) for nominal variables.

*Respiratory symptoms index was defined as the presence of 1 or more of the following respiratory symptoms: chronic cough or phlegm, tuberculosis, bronchitis, pneumonia, emphysema, coughed up blood, or unexplained shortness of breath while sleeping, sitting, or exercising.

TABLE E2. Univariate association of cardiorespiratory fitness, BF%, and other risk factors for asthma, after adjusting for age and sex

Predisposing factors	Cases (n)	Age and sex-adjusted OR (95% CI)
Cardiorespiratory fitness		
Low	69 (1075)	1 (Reference)
Moderate	173 (3586)	0.75 (0.56-1.00)
High	218 (5149)	0.65 (0.49-0.86)
BF%		
Normal-fat	315 (7262)	1 (Reference)
Overfat	145 (2548)	1.48 (1.20-1.82)
Height		
Tertile 1	152 (3298)	1 (Reference)
Tertile 2	152 (3219)	1.02 (0.81-1.28)
Tertile 3	156 (3293)	1.02 (0.81-1.29)
Leisure time physical activity		
Inactive	134 (2568)	1 (Reference)
Active	326 (7242)	0.86 (0.70-1.06)
Smoking		
Never smoker	208 (4729)	1 (Reference)
Ex-smoker	188 (3880)	1.20 (0.97-1.47)
Current smoker	64 (1201)	1.25 (0.94-1.67)
Respiratory symptoms index*		
Presence	417 (8974)	1 (Reference)
Absence	43 (836)	0.87 (0.63-1.21)

OR, Odds ratio.

*Presence of 1 or more of the respiratory symptoms indicated in [Table E1](#).