

In asthma, the apple falls faster than the pear

Kelan G. Tantisira, MD, MPH *Boston, Mass*

Key words: Obesity, FEV₁, weight, natural history

The relationship between obesity and asthma has been consistently demonstrated in epidemiologic studies (recently reviewed by Litonjua and Gold¹ and by Ford²). Moreover, investigations into the mechanistic basis for this relationship have yielded a wealth of intriguing data (recently reviewed by Shore³), supporting the notion that excesses of body fat can indeed lead directly to many of the clinical features of asthma. What has not been emphasized in the literature, however, is how the natural history of asthma may be modified by adiposity. In this issue of the Journal, Marcon et al⁴ analyze a large cohort of patients with asthma identified via the European Community Respiratory Health Survey (ECRHS). Asthma was defined as having a doctor's diagnosis along with either asthma symptoms or having used inhaled or oral medications because of breathing difficulties in the year before assessment. Height, weight, and spirometric lung function in the selected subset of patients from the ECRHS were measured at baseline and approximately 7 to 10 years later.

Marcon et al⁴ focused on change in FEV₁ over time, evaluating a variety of factors (demographic, smoking-related, atopy, asthma characteristics, and body mass) for their association with FEV₁ decline. In the end, the strongest associations noted by the authors included body mass index (BMI) at baseline and BMI gain over time, but only in those patients with asthma without significant decrements (<0.70) in FEV₁/forced vital capacity ratio at baseline. For the relationship between BMI at baseline and subsequent FEV₁ decline, there was an inverted U-shaped relationship, with those in the extremes of body mass demonstrating the least decline in FEV₁ over time and those in the normal (BMI, 20-24.9) or overweight (BMI, 25-29.9) categories demonstrating the greatest decline. The association with intermediate body mass with larger FEV₁ decline in patients with asthma is curious, and no specific biologic rationale was proposed by the authors. Further, given that this subset of patients with asthma did not demonstrate significant evidence of airways obstruction, one would expect the FEV₁ decline in this group to parallel that of a normal population distribution. However, in several large epidemiologic studies, baseline BMI

has demonstrated a consistent inverse linear effect on longitudinal FEV₁ measures.^{5,6} The most likely reason for the association of larger FEV₁ decrements with intermediate levels of BMI in the ECRHS asthma cohort is regression to the mean. Indeed, the highest levels of baseline FEV₁ were noted in the BMI groups that demonstrated the greatest decrements in lung function over time. Although the current authors do speculate in their discussion that this might be a possibility, noting that the obese subjects had a lower baseline FEV₁, it would have been optimal if analyses specifically adjusting for measures of baseline lung function had been performed and presented.

The other significant finding, an association of FEV₁ decline with BMI increase (independent of baseline BMI), is more intriguing. Marcon et al⁴ report a 28 mL/y greater decrement in FEV₁ for every BMI unit (1 kg/m²) gained. Of further interest, this effect was stronger in men than women, with a 61.8 (95% CI, 32.0-91.7; *P* < .001) mL/y greater decrement in FEV₁ per BMI unit gained during 1 year of follow-up in men, and 20.2 (95% CI, 7.9-32.6; *P* = .001) mL/y greater decrement in FEV₁ per BMI unit gained in women. The global association of gains in BMI with subsequent decrements in FEV₁ is consistent with previous epidemiologic studies. For instance, in the Coronary Artery Risk Development in Young Adults (CARDIA) study,⁶ there was a decrease in FEV₁ in proportion with increased BMI, although this study further stratified gains in BMI by baseline BMI. The largest FEV₁ decrements occurred with BMI gain in those with the highest baseline BMI category. Overall, change in body mass has been calculated to account for ~6% of the variability in FEV₁ over time.⁷

Having established that BMI increments are associated with FEV₁ decrements in both general population cohorts and patients with asthma, is there particular relevance of this association in asthma? The decrements in FEV₁ in relation to BMI were significantly greater in the patients with asthma from ECRHS than in the CARDIA general population cohort. Moreover, the decline in the general ECRHS cohort was approximately 40% less than in the patients with asthma from ECRHS overall.⁸ Therefore, given that weight gain has been associated with asthma incidence in both children and adults,² there may be a mechanistic basis behind this association in which FEV₁ may be a causal intermediary. Decrements in the FEV₁ in association with BMI increases could certainly help to explain the increase in symptoms and exacerbations that have recently been noted in patients with severe asthma undergoing significant weight gain.⁹ This BMI-FEV₁-symptoms relationship is further substantiated by the weight loss studies that have evaluated these outcomes simultaneously. In both medical and surgical weight loss studies, significant weight loss in the obese patient with asthma has been followed by significant improvements in symptoms and need for both controller and rescue medications.² In each of the studies that have evaluated lung function, significant weight loss in the obese patient with asthma has also been associated with subsequent improvements in FEV₁. For instance, in a study of 38 obese patients with asthma randomized to a very low calorie diet regimen versus a control diet, the

From the Channing Laboratory and Pulmonary Division, Brigham and Women's Hospital and Harvard Medical School.

K.G.T. is supported by National Institutes of Health grants K23-HG3983 and U01-HL65899.

Disclosure of potential conflict of interest: K. C. Tantisira receives grant support from the National Institutes of Health.

Received for publication March 30, 2009; accepted for publication March 30, 2009.

Reprint requests: Kelan Tantisira, MD, MPH, Assistant Professor of Medicine, Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115. E-mail: kelan.tantisira@channing.harvard.edu.

J Allergy Clin Immunol 2009;123:1075-6.

0091-6749/\$36.00

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doi:10.1016/j.jaci.2009.03.037

average weight loss in the diet group was 14.5% after 8 weeks and 11.3% at 1 year (vs 0.3% loss and 2.2% gain in the control group at 8 weeks and 1 year, respectively).¹⁰ Compared with the control group, there were marked improvements in FEV₁ as a percentage of predicted (mean change vs controls of 7.2 and 6.7 at 8 weeks and 1 year), and accompanying improvements in overall asthma dyspnea score, symptoms, and need for rescue medications.

That the relationship between weight gain and decline in FEV₁ was noted to be greater in men than women is also consistent with previous epidemiologic studies^{5,8,11} and may have specific relevance to asthma. Marcon et al⁴ and others have correctly noted that men who gain weight tend to accumulate abdominal and visceral fat (ie, an apple-shaped distribution of fat), whereas women who gain weight tend to accumulate peripheral fat in the hips (ie, a pear-shaped distribution of fat), potentially accentuating the effects of weight gain in males on the thoracic cavity. The mechanical consequences related to central adiposity in relation to asthma include decreased tidal volumes and functional residual capacity leading to decreased smooth muscle stretch and to the "latch" state resulting in early airways closure, increased airways responsiveness, and persistent airflow obstruction.^{3,12,13} Certainly, these forces alone could account for the sex-specific decrements in FEV₁ noted. Nonetheless, it is intriguing to note that leptin was significantly associated with asthma and IgE levels, but only in males, in 1 recent study.¹⁴ Although these findings have not been independently replicated, they do provide a potential independent mechanistic basis for subsequent FEV₁ decline in males. The higher prevalence of obstructive sleep apnea in males,¹⁵ combined with the independent association of obstructive sleep apnea with asthma, including asthma exacerbations,¹⁶ should also be considered as a potential contributor. Although each is an intriguing possibility, none is conclusive, suggesting that gaining insights into the natural history of asthma, and how that history may be modified by changes in body mass, has only just begun.

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