purposes in chronic lung disease appear to be reasonable and important paths of investigation. Hassan and colleagues present a novel study suggesting that miRNAs may play a central role. ■

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Weight Gain and Lung Disease: The Vagary of Body Mass Index and the Dilemma of the Obese Smoker

With the rising tide of obesity worldwide, clinicians and researchers alike find themselves struggling to understand not only what this means to human health, but also how we should best analyze and characterize weight gain (or loss) itself. Obesity as a disease modifier in vascular disease and diabetes has often been simplified to the concept of "risk factor"; yet, as we are learning in lung disease, our understanding must be far more nuanced to capture the complex effects associated with weight change. This is highlighted by the growing number of clinical "paradoxes" associated with obesity in which weight gain appears to confer not only health risks but health benefits, often in an unpredictable fashion (1). The issues that frame these paradoxes typically reflect our inability to explain these divergent associations mechanistically.

Traditionally, our understanding of weight gain and its effects has centered on the concept of obesity as an inflammatory disease (2). However, although useful in the context of vascular disease, this concept often fails to predict the effects of changes in body mass index (BMI) on the lung and lung disease. For example, recent reports have demonstrated that in acute lung injury, obese patients have *lower* levels of circulating inflammatory cytokines (3) (and improved outcomes [4]) compared with lean patients, and in obese individuals with asthma, surgically induced weight loss is accompanied by evidence of *increased* airway inflammation (5, 6). These findings speak to a far more complicated relationship

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between weight change and lung function than can be ascribed solely to proinflammatory effects or even, for that matter, to immune modulation at all, and growing evidence suggests that an interplay of adipokine disarray (6–8), mechanical perturbations (9), and changes in muscle mass (10, 11) is likely to also influence lung disease and its manifestations. In this wider context, let us consider the interesting study by Sood and colleagues (pp. 274–281) in this issue of the *Journal* (12).

These investigators report an examination of 1,641 current and former smokers at risk for or with mild to moderate chronic obstructive pulmonary disease (COPD), followed for a median of 6 years as part of the Lovelace Smokers' Cohort in New Mexico, and present both cross-sectional and longitudinal data relating subjects' BMI to spirometric variables and health status (as assessed by the St. George Respiratory Questionnaire [SGRQ]). Stratifying their cohort by World Health Organization BMI category, they found that at baseline, higher BMI in obese (BMI $>$ 30 kg/m^2) smokers was associated with worse health status and lower FEV_1, yet in the lean (BMI $<$ 25 kg/m^2) smokers, the association between BMI and these variables was reversed. The authors report that these findings delineate a "U-shaped" association between BMI and the extreme weight categories, such that both the morbidly obese *and* the lean to underweight subsets of their cohort had the lowest FEV_1 and worst health status. Even more interestingly, in longitudinal analyses, they found that these opposing relationships appear to be real since they applied to weight gain over the duration of the study as well: rising BMI was associated with worsening health status and falling FEV_1 in obese smokers, yet improvement in these outcomes in lean smokers. Interestingly, the authors found no association between IL-6, IL-10, or leptin and outcomes. Do these findings present yet another "paradox" or do they underscore a complex dichotomy between BMI, lung function, and respiratory symptoms in smokers?

Given the methods of analysis, these findings might be more intuitively understood as follows: *weight loss is better tolerated by the obese than the lean* in their cohort. The authors attempt to dissect weight gain from weight loss in their supplemental data (Table E2), which reveal roughly equal numbers of subjects gaining and losing weight within each BMI category. In the obese cohort, both weight gain and weight loss are strongly associated with inverse changes in FEV_1 and SGRQ. However, in the lean cohort, although SGRQ appears similarly bidirectional in it association, only weight loss is significantly associated with FEV_1, and in a markedly downward manner. These findings suggest that in smokers without severe COPD, weight change signifies something quite different in lean versus obese patients. But what?

To answer that question, let's consider the contrast between the Lovelace Smokers' cohort findings and those of The Copenhagen City Heart Study (13). The latter study found that weight loss was associated with increased COPD-related mortality across the BMI spectrum of their cohort, whereas weight gain was protective. Further examination of this cohort and others suggests that much of this effect may be related to low or decreasing fat-free body mass—presumed here to indicate sarcopenia (10, 14, 15). Further studies by Marquis and colleagues (16) and Rutten and colleagues (11) have gone further to prove this association. It is understandable that loss of muscle mass as a consequence of worsening COPD, inflammation, poor nutrition, or other comorbidities might compromise pulmonary physiology and overall health status. The same effect is seen with falling BMI in the lean (BMI $<$ 25) subset of the Lovelace cohort. How does this explain the findings in the rest of this cohort?

Here it is worth noting that in the previously cited studies, mean BMIs of the cohorts were in the range of 24–25, whereas in the Lovelace cohort, the mean was nearly 28. Furthermore, unlike previous studies, the Lovelace cohort is predominantly women (>70%). Although the ratio of fat mass (FM) to fat-free mass (FFM) generally rises with BMI, it is well known that both sex and age significantly affect FM/FFM balance. For any given BMI, women have a significantly higher percentage of FM compared with men (Figure 1), and FM/FFM ratio rises with age for both sexes (17). Thus, the differences seen between overall BMI/outcome associations in the current study compared with previous studies, including the Copenhagen, are likely to reflect the effects of greater FM on the higher BMI subsets. What are these effects?

In this study, obese smokers had a markedly lower incidence of Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria–defined COPD (17% vs. 35% in lean smokers) despite having a higher incidence of wheeze and dyspnea and a nearly 20% rate of bronchodilator response at baseline. Although this may in part reflect a notable failure of the GOLD criteria to capture early COPD in the obese (likely due to obesity-driven elevation of the FEV_1/FVC ratio), it may also suggest the presence of an additional, discrete syndrome in the obese (female) smoker. This is underscored by the *salutary effects* of weight loss in this subset—a distinctly different finding than reported for subjects in the Copenhagen Study and others. As Sood and others have shown previously, weight gain and obesity are associated with an increased incidence of airway obstruction and wheezing in the general population, particularly among women, irrespective of smoking status (18, 19), whereas weight loss improves these symptoms, particularly in the nonatopic obese (5). Although generally described as "patients with asthma," this group of patients has recently been recognized as a distinct phenotype within this syndrome (20). The current work therefore begs the question, what is this form of obese obstructive lung disease that variously appears as difficult-to-treat asthma or the dyspneic, wheezing smoker? As the authors find no association between these findings and a (limited) panel of cytokines and adipokines, it is tempting to invoke the mechanical effects of obesity in this patient subset that hopefully future studies will delineate. The only thing we know for sure is that smoking cessation and weight loss are likely the

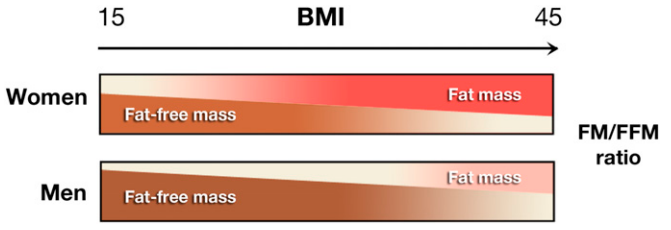

Figure 1. Percentages of total body mass from fat mass (FM) and fat-free mass (FFM) in males and females across the body mass index (BMI) range. Data shown are for subjects 45 years of age (16).

most effective (and only?) treatments for this rapidly growing population of patients. ■

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Dual Inhibition of Interleukin-1β and Interleukin-18: A New Treatment Option for Sepsis?

In this issue of the *Journal*, a report by Vanden Berghe and colleagues (pp. 282–291) appears in which the therapeutic value of simultaneous inhibition of IL-1β signaling and another member of the IL-1 family, IL-18, is examined in experimental models of systemic inflammation and sepsis (1). The results of these experiments show some unexpected findings that might have significant ramifications for the further preclinical and clinical development of inflammasome inhibitors and combination immunotherapies targeting both IL-1β and IL-18.

Both IL-1 and IL-18 belong to subfamilies of the rapidly expanding family of IL-1–like cytokines that now has at least 11 members (2). The subfamilies are recognized by their structural homology and differentiated by the length of the precursor pro-pieces that are covalently linked to the amino termini of the mature cytokines before final processing. The IL-1 subfamily consists of IL-1α, IL-1β, and IL-33, which have the longest pro-pieces of the entire IL-1 family. IL-18 and IL-37 are in the IL-18 subfamily and have smaller pro-pieces than the IL-1 subfamily. IL-37 binds to the IL-18 receptor α component and attenuates IL-18 signaling and therefore belongs to the IL-18 family. The IL-36 family consists of the Th1-inducing cytokines IL-36α, -β, and -γ, as well as IL-36 receptor antagonist. In