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Impact of Insulin Resistance on Asthma: Is There Truly No Role of "Obesity"?

To the Editor:

Obesity reduces FRC and expiratory reserve volume, with implications for airway closure and $\dot{V}/\dot{Q}$ inequalities, especially during times of stress, such as exercise, when many asthmatics report distressing symptoms (1, 2). Obesity-related reduced FRC may offer a mechanism for increased airway hyperresponsiveness, because airway-parenchymal tethering is reduced at lower lung volumes, making it easier for the airways to constrict in response to stimuli (3). Experimentally, when the chest wall is strapped for nonobese individuals, artificially reducing the FRC, an increase in methacholine-induced airway hyperresponsiveness has been noted; conversely, increasing the FRC has been shown to reduce airway hyperresponsiveness (4). Obesity-related compression of the chest wall is also implicated in increased lung derecruitment, either by small airway closure or alveolar atelectasis, manifesting as a reduced FVC (5). Although similar degrees of lung derecruitment have been found between obese adults without asthma and obese adults with late-onset nonallergic (LONA) asthma, there is lower FVC and increased difficulty in recruiting closed alveolar units with a deep breath as well as higher airway hyperresponsiveness among obese individuals with LONA asthma (5). Mechanisms for differences in airway hyperresponsiveness between obese and nonobese individuals with LONA asthma are not fully defined but include increased airway compliance that predisposes to greater airway collapse under a higher chest wall load (3). Thus, through the mechanism of excess adipose tissue around the chest wall, breathing at lower lung volumes and lung derecruitment could be factors in physiological changes, such as airway hyperresponsiveness or collapse, and could contribute to asthma symptoms and severity.

A recent paper by Peters and colleagues (6) tested the hypothesis that insulin resistance worsens lung function among patients with asthma, independent of body mass index (BMI), using two statistical approaches. First, linear regression controlled for BMI revealed an "independent" significant effect of insulin resistance on lung function. Second, a closer look at the morbidly obese patients revealed lower FEV_1 and FVC among those with severe insulin resistance. The authors concluded that "insulin resistance independently associates with low lung function in asthma, and body mass effects on chest wall mechanics are unlikely to explain this association" (6). A strong correlation was found between BMI and insulin resistance, which warrants caution in result interpretation because of risk of multicollinearity. The authors did not share the results of the correlation matrix of BMI, insulin resistance, lung function outcomes, etc., preventing readers from gaining a preliminary understanding of the bivariate associations among the potential predictors and outcomes. Authors also did not report the standardized β coefficient and R^2 for BMI, insulin resistance, and other relevant predictors in the multiple regression model results, making it difficult to judge the relative importance of each predictor. Even if homeostatic model assessment for insulin resistance (HOMA-IR) were found to have the highest regression coefficient and R^2 value, BMI could remain significant in the final model, a finding that would support a role for chest wall mechanics in reducing lung function. Considering the wide range of BMIs in the >40 category (40–70 kg/m^2) and the heterogeneity of lung function outcomes within each HOMA-IR category, BMI could be exerting a substantial effect that was masked by the HOMA-IR categorizations. One could look at narrower ranges of BMIs (30–35, 35–40, etc.) to see if HOMA-IR continues to influence lung function. To summarize, we contend that although insulin resistance may be a plausible mechanism for worsening lung function, and randomized trials targeting insulin resistance in obese patients with asthma may very well follow to clarify causation, the role of obesity on chest wall mechanics and lung function that has been previously established through robust observational and experimental studies cannot be completely discounted as proposed by Peters and colleagues (6). ■

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Reply to Nie *et al.* and Bhammar *et al.*

From the Authors:

We thank Nie and colleagues for pointing out that insulin can promote bronchoconstriction through acetylcholine-mediated airway narrowing that occurs because insulin disrupts M2 muscarinic receptor function on airway parasympathetic nerves to increase acetylcholine release. Our paper (1) focused on insulin resistance as a predictor variable because it combines consideration of both insulin and glucose as metabolic variables that may influence lung function. We agree with Nie and colleagues that further exploration of the specific role of insulin level and decline of lung function is warranted.

Bhammar and colleagues correctly point out that obesity can increase chest wall load to decrease lung volumes, but our analyses show that asthma patients with low values for FEV_1 and FVC are more likely to be characterized by insulin resistance than obesity. Bhammar and colleagues also expressed concern about multicollinearity, as well as disappointment that we did not provide standardized β coefficients, and asked if body mass index (BMI) remained significant in our final analytical models. Our article did not provide standardized β coefficients, because we analyzed homeostatic model assessment of insulin resistance (HOMA-IR) as a categorical predictor, not as a continuous one. To address the question from Bhammar and colleagues, we generated standardized β coefficients for HOMA-IR and BMI in a model in which HOMA-IR is analyzed as a continuous variable. As shown in Table 1, these data show that the β coefficients for the effects of HOMA-IR on FEV_1 and FVC are much larger than the corresponding values for BMI. To address concerns about multicollinearity, we also calculated variance inflation factors, which quantify multicollinearity in regression analyses by measuring how much the variance of an independent variable is influenced (inflated) by its correlation with another independent variable. As shown in Table 1, the variance inflation factors generated when we explored how HOMA-IR affects FEV_1 and FVC while controlling for BMI are less than 2.0, indicating that multicollinearity is not an important issue. ■

Table 1. Standardized β Coefficients for the Effects of HOMA-IR and BMI on FEV_1 and FVC (% predicted) in Cross-Sectional Analyses

	HOMA-IR		BMI		
Outcome	**Standardized β Coefficient (95% Confidence Interval)**	***P* Value**	**Standardized β Coefficient (95% Confidence Interval)**	***P* Value**	**VIF**
FEV_1, % predicted	−0.28 (−0.41, −0.15)	<0.0001	0.09 (−0.04, 0.21)	0.18	1.38
FVC, % predicted	−0.27 (−0.40, −0.14)	<0.0001	0.02 (−0.12, 0.13)	0.97	1.38

Definition of abbreviations: BMI = body mass index; HOMA-IR = homeostatic model assessment of insulin resistance; VIF = variance inflation factor.

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