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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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Polymorphisms and Severity of COVID-19

To the Editor:

We would like to share ideas on the publication "A *MUC5B* gene polymorphism, rs35705950-T, confers protective effects against COVID-19 hospitalization but not severe disease or mortality" (1). Verma and colleagues conducted the current investigation to determine whether the Million Veteran Program participants' rs35705950-T genotype confers differential risk for clinical outcomes related to coronavirus disease (COVID-19) infection (1). According to this study, the rs35705950-T allele was associated with fewer COVID-19 hospitalizations (1). The MUC5B variant rs35705950-T, according to Verma and colleagues, may provide protection in COVID-19 hospitalizations (1).

We are all in agreement that the genetic mutation under examination has a strong therapeutic potential. It should be mentioned that the presence of particular diseases might be influenced by a range of factors. Because the current study is expected to diminish or eliminate environmental influences, confounding genetic variants should be addressed. Angiotensinogen, angiotensin-converting enzyme, angiotensin-II receptor 1, PNPLA3, TLL-1, HADHA, and DRC1 polymorphisms may also be linked to the occurrence of COVID-19 in children (2, 3). The likelihood of COVID-19 infection was reduced by the II genotype of ACE rs4646994 and the I allele (2). PNPLA3 and TLL-1 polymorphisms are proven potential predictors of disease severity in patients with COVID-19 (3). Genetic variations in HADHA and DRC1 have been linked to severe COVID-19 results (4). As a result, many unstudied genetic variations may be related to how severe COVID-19 is. Multiple genetic variations may have an impact; however, Verma and colleagues' current study (1) does not investigate this possibility. As a result, more research into the potential repercussions of newly discovered genetic variations would be beneficial. ■

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