The author reported no conflicts of interest. The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

**REPLY: 3M—MULTICOLLINEARITY, MEDIATORS, AND MODERATORS**

**Reply to the Editor:**

Zhang and Zhu addressed limitations of multivariable modeling in their Letter to the Editor titled, “Statistical Considerations for the Disappeared Significance in Regression Models.” The letter refers to the study recently published in the Journal by Tjoeng and colleagues, on which we authored an editorial commentary. Zhang and Zhu discuss potential statistical reasons why the association between race (the aforementioned authors above incorrectly use the term ethnicity for black race) and greater risk of mortality is mitigated by disease severity—a phenomenon they refer to as “disappeared statistical significance.” These reasons include multicollinearity (when one predictor variable is highly linearly related to another predictor variable), moderating effects (when a variable influences the strength of a relationship between 2 other variables), and mediation effects (when a variable explains how or why there is a relationship between 2 other variables). Multicollinearity is distinct from collinearity, which also could have been mentioned by Zhang and Zhu, in that collinearity refers to a linear association between 2 variables (a bivariable phenomenon), whereas multicollinearity is a multivariable phenomenon. Multicollinearity is problematic because it can undermine (or even nullify) the statistical significance of other variables in the model, can lead to overfitting, and can result in large standard errors such that the probability of Type II error increases. Luckily, there are widely accepted diagnostic tests, such as variable inflation factors and correlation matrices, that can assess whether a multivariable model contains a prohibitive amount of highly multicollinear variables. Mediator and moderator variables are less-well understood, and are difficult to detect, and so I would argue that Zhang and Zhu could have elaborated further on the nuanced differences between these 2 factors.

The article by Tsang, “Mediating and Moderating Variables Explained,” is an excellent reference for readers to explore this concept in more detail. Tsang explains that, “a mediating variable can be a potential mechanism by which an independent variable can produce change on a dependent variable. When you fully account for the effect of the mediator, the relation between independent and dependent variables may go away.” She uses the example of how the number of hours spent studying can “mediate” the positive relationship between note-taking and improved exam performance. In contrast, moderator variables, which are commonly referred to as interaction terms, usually impact the strength of a relationship and may deflect the relationship in a positive or negative direction. In cardiac surgery, it is well known that income can interact with race, such that white patients may have reduced adverse effects (including morbidity and mortality) at similar income levels compared with black patients. Zhang and Zhu’s letter is an important contribution that highlights the importance of understanding the limitations of statistical models and the need to involve experienced biostatisticians when constructing and interpreting multivariable regression results.

It is heartening to see the visibility that Tjoeng and colleagues’ paper has received—the lens of our nation and our specialty ought to be focused on recognizing and addressing health care inequities based on socioeconomic factors and race/ethnicity.

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**REPLY FROM AUTHORS:**

**MEDIATION ANALYSIS IN HEALTH DISPARITIES RESEARCH**

**Reply to the Editor:**

We appreciate the Letter to the Editor in response to our article. We concluded that African-American children admitted postoperatively had 40% higher odds of mortality compared with White children, but that this survival advantage was eliminated after taking into account severity of illness on admission, suggesting that severity of illness is