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 Zhu¹ 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,² on which we authored an editorial commentary.³ 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,¹ 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 Zhu¹ could have elaborated further on the nuanced differences between these 2 factors.

The article by Tsang,⁴ “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 letter¹ 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.

Tara Karamlou, MD, MSc
Division of Pediatric Cardiac Surgery
Heart Vascular and Thoracic Institute
Cleveland Clinic
Cleveland, Ohio

References

1. Zhang Y, Zhu S. Statistical considerations for the disappeared significance in regression models. *J Thorac Cardiovasc Surg*. 2022;163:e66-7.
2. Tjoeng YL, Jenkins K, Deen JF, Chan T. Association between race/ethnicity, illness severity, and mortality in children undergoing cardiac surgery. *J Thorac Cardiovasc Surg*. 2020;160:1570-9.e1.
3. Jayaram N, Anderson BA, Karamlou T. Commentary: ode to the editorial process: healthcare disparities unmasked. *J Thorac Cardiovasc Surg*. 2020;160:1580-1.
4. Tsang T. Mediating and moderating variables explained. Available at: <https://www.psychologyinaction.org/psychology-in-action-1/2015/02/06/mediating-and-moderating-variables-explained>. Accessed November 12, 2020.

<https://doi.org/10.1016/j.jtcvs.2020.11.111>

REPLY FROM AUTHORS: MEDIATION ANALYSIS IN HEALTH DISPARITIES RESEARCH

Reply to the Editor:

We appreciate the Letter to the Editor¹ in response to our article.² 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