The author reported no conflicts of interest.

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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

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<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

Dr Jenkins has received industry research grant support from Numed for projects unrelated to this work. VPS data were provided by Virtual Pediatric Systems, LLC. No endorsement or editorial restriction of the interpretation of these data or opinions of the authors has been implied or stated. All other authors reported no conflicts of interest.

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a mechanism for this observed health disparity. Zhang and colleagues¹ identify additional statistical methods that have the potential to make the conclusions more stable, which we will address below.

To test for multicollinearity, a variance inflation factor analysis was performed on the logistic regression models examining the association between race and mortality, which included each of the 3 severity of illness [SOI] scores. We did not find signs of multicollinearity, with low mean variance inflation factors ≤ 2 and tolerance values for race/ethnicity approaching 1.

Logistic regression mortality models were then constructed for postoperatively admitted patients, stratified by SOI tertile. These models did not demonstrate a consistent trend of a higher odds of mortality for African-American patients in the higher tertiles of illness, suggesting that there is no modulating effect. Additionally, there were no significant interactions between African-American race and SOI.

We conducted additional mediation analysis to obtain total, indirect, and direct effects between race/ethnicity and mortality, with SOI as a mediator. For postoperatively admitted patients, the proportion of the relationship explained by SOI was 24% using the Pediatric Index of Mortality 2, 15% using the Pediatric Risk of Mortality 3, and 41% using Pediatric Index of Cardiac Surgical Intensive Care Mortality models. This finding reached significance ($P \leq .05$) in the Pediatric Index of Mortality 2 and Pediatric Index of Cardiac Surgical Intensive Care Mortality models.

Zhang and colleagues¹ have raised valid epidemiological considerations, and we appreciate the suggestions to strengthen our finding that severity of illness is among the mechanisms for disparities in congenital heart surgery.

However, it does not explain the entirety of the relationship between race/ethnicity and mortality. The relationship among SOI, race/ethnicity, and outcomes must be considered in the appropriate social context.

Although we traditionally refer to additional covariates—such as insurance, income, primary language, and parental education—as confounders, in the case of health disparities, it may be more appropriate to view them as interlinked variables due to systemic and structural racism. These so-called confounders should not simply be considered elements that need to be adjusted for, but rather mechanisms by which health disparities exist. This study did not find collinearity between race/ethnicity and SOI, yet it would not be surprising if we had found such a relationship. Furthermore, a finding of modulation or interaction effect between race/ethnicity and SOI should be considered as further characterization of the disparities that we have documented. Our article² suggests that lowering severity of illness on admission may be an area of intervention, but further research is needed to identify additional mechanisms that contribute to racial disparities in congenital heart surgery patients.

Yuen Lie Tjoeng, MD, MS^{a,b}

Kathy Jenkins, MD, MPH^c

Jason F. Deen, MD^{b,d}

Titus Chan, MD, MS, MPP^{a,b}

^aDivision of Critical Care Medicine

Seattle Children's Hospital

University of Washington

Seattle, Wash

^bDivision of Cardiology

Seattle Children's Hospital

University of Washington

Seattle, Wash

^cDepartment of Cardiology

Boston Children's Hospital

Harvard Medical School

Boston, Mass

^dCenter of Health Equity

Diversity, and Inclusion

University of Washington School of Medicine

Seattle, Wash

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