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The Author's Response: In Response to "Is obesity paradox valid in pediatric intensive care?" by P. Zamberlan et al

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Dear Editor

We are excited that our article has elicited such interest and hope this response will continue to promote dialogue about the impact of the obesity epidemic on the care of critically ill children. While obesity is associated with numerous comorbidities and with poor health outcomes in general, our study and several adult studies have found that mortality risk from ARDS is lower in the overweight and obese categories(1–4). Our study is unique in that this reduction in mortality risk was found primarily in those with indirect lung injury (e.g. sepsis or polytrauma induced ARDS); no other study has stratified by ARDS risk factor to evaluate such a finding in adults. We hypothesize there may be a link between increased adiposity and the systemic inflammatory response in the setting of acute critical illness, although further investigation is certainly needed.

One concern raised by Zamberlan and colleagues (5) is the adequacy of the definition of obesity and other weight categories. This is indeed an issue that plagues both pediatric clinical care and research. Body mass index (BMI) z-scores are currently the most validated tool for assessment of appropriate growth for children above age 2 years through adulthood. BMI z-scores are utilized by both the Center for Disease Control (CDC) and the World Health Organization (WHO) to define weight categories. The WHO and CDC definitions are comparable for children over age 5 years but significant variance in weight category classification occurs for children less than 5 years old, as previously reported by our group(6). For our manuscript we presented CDC defined BMI categories because our cohort

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demographics are most comparable to that utilized for CDC data. To respond to Zamberlan's specific concerns, we completed an additional analysis of our data using WHO definitions. This analysis reveals the same finding, that the obese have reduced mortality risk from ARDS caused by indirect lung injury compared to their normal weight counterparts while no difference is noted between those with direct lung injury ARDS (Table 1). Zamberlan et al. also appropriately state that weight alone cannot be used to define obesity and other weight categories. Currently BMI based categorization is the best available option since it accounts for height and gender and is less affected by rapid physique changes that occur during puberty. This is an important consideration since studies using BMI have found an association between obesity and reduced mortality(1–3), while those unable to add the impact of height have shown no difference in outcome by weight category(7). Given that over 20% of hospitalized children are obese and that obesity is independently associated with mortality and other outcomes, it is imperative that the pediatric critical care community reach consensus to operationalize definitions of obesity and nutrition to advance this field.

An additional concern appropriately raised by Zamberlan et al. (5) is the accuracy of ARDS diagnosis in obese children. Both the AECC definition and the newer PALICC definition of pediatric ARDS require the presence of new pulmonary infiltrates on chest x-ray. Obese individuals have greater chest wall mass and increased risk of development of atelectasis which make reading of chest x-rays difficult and may lead to over diagnosis of mild ARDS in overweight and obese children. We agree that this is a concern and further investigations should subanalyze those of moderate and severe ARDS to test the impact of this potential misdiagnosis. With regard to our analysis, we do not believe this played a significant role as one would expect such confounding to effect both the direct and indirect lung injury ARDS groups equally and would not explain why the obesity paradox was noted only in those with indirect lung injury. As such, we believe there is a pathobiologic interplay between increased adiposity, metabolic dysfunction and systemic inflammatory response that may best explain our findings; an investigation our group hopes to assess.

Lastly, we wish to thank Zamberlan and colleagues (5) for clearly stating the importance of not implying causality from findings of association between obesity and mortality in ARDS. This is an important distinction that we, too, made in the discussion section of the manuscript. We do hope that our findings promote interest in the phenomenon and drives further study of the pathobiologic interaction between metabolism and the immune system in the children we all care for. Going forward, our team hopes to investigate such interactions prospectively.

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Table 1

Odds of in-hospital mortality in Pediatric ARDS by WHO defined BMI Categories

BMI Category	Direct Lung Injury ARDS aOR (95% CI)[a]	Indirect Lung Injury ARDS aOR (95% CI)[a]
Underweight	1.4 (0.6–3)	1.4 (0.6–3.6)
Normal Weight	Ref	Ref
Overweight	1.5 (0.3–2.6)	0.2 (0.01–3.7)
Obese	0.8 (0.3–2.6)	0.07 (0.01–0.4)
p-value	0.7	<0.001

[a]Adjusted for PRISM-III, PF ratio at ARDS onset, race, age and immunocompromised state