

Response to Reviewer Comments

Summary

We sincerely thank the Reviewer for the careful and constructive evaluation of our manuscript. We have addressed each of the comments in detail, as outlined below. All corresponding revisions have been incorporated into the revised manuscript and are marked in track changes in the re-submitted files. In addition, supplementary material has been updated to include the extended statistical analyses and detailed regression results.

1. Reviewer's comment:

The title is appropriate and the Abstract is well-constructed; however, the results are poorly presented. I believe the authors could better explore the Table and the Figure in the Abstract.

Response:

We thank the Reviewer for this suggestion. The Abstract has been revised to include the distribution of severe reactions across BMI categories, the χ^2 test result, and adjusted regression outcomes, providing a clearer summary of the results. Changes made: page 1, Abstract, Results section, lines 19–28. (tracked version)

2. Reviewer's comment:

The study's introduction lacks a clear narrative line, jumping from the prevalence of anaphylaxis to food allergens, obesity, its inflammatory mechanisms, and asthma, before finally presenting the central research question about the relationship between obesity and anaphylaxis. This long sequence with unnecessary topics confuses the reader instead of properly presenting the study's idea and relevance. The inclusion of irrelevant information exacerbates the problem: the mention of food allergens is superfluous, as the study does not investigate the triggers of the reaction, and the detailed discussion of inflammatory biomarkers like IL-6 and leptin is speculative, since the methodology does not include the measurement of such markers, making it a point better suited for the discussion section. As a result, the research question is only presented at the end of the second-to-last paragraph. This means the reader is faced with extensive generic context before understanding the true objective of the work. In other words, the introduction does not truly present what the authors want to investigate, why it is being investigated, and for what purpose. Please rewrite it, and at the end of the introduction, present the study's hypothesis.

Response:

We thank the Reviewer for this important observation. In response, we have

substantially revised the Introduction to provide a clearer and more concise narrative. We removed the mention of food allergens and streamlined the section on inflammatory mechanisms to avoid unnecessary detail, while still retaining essential context relevant to our research question. The revised Introduction first presents the clinical relevance of pediatric anaphylaxis, then highlights the rising prevalence of childhood obesity and its immunological and respiratory consequences, and finally leads directly to the rationale of our study. We now also explicitly state our hypothesis and study objective at the end of the section. We believe these changes make the Introduction more focused and accessible for readers. Changes made: page 2, Introduction, lines 59–77 and 88–90 (tracked version).

3. Reviewer's comment:

Regarding the methods, a notable methodological limitation is the absence of a sample size calculation. The study used a convenience sample based on the number of available cases. I believe there should be no issue in performing this calculation, as the number of included cases is large. However, without a power calculation, it is impossible to determine if the study had an adequate sample to detect statistically significant differences, should they truly exist. This calculation is necessary not only for the overall sample size but also for the subgroups; there are 158 normal-weight, 22 overweight, and 13 obese individuals. The study's main question is precisely the relationship between nutritional status and severe anaphylaxis. In this context, it is very important for the authors to demonstrate that the 13 (6.5%) obese and 6 (3%) underweight participants are representative enough to answer the research questions. Otherwise, the obese individuals will have to be combined with the overweight group, and the underweight individuals could be combined with the normal-weight group or excluded to increase statistical power.

Response:

We thank the Reviewer for this insightful comment. In response, we have performed post hoc power analyses and additional sensitivity analyses with aggregated BMI categories, as suggested. The results were as follows:

- Primary analysis (4 BMI groups $\times$ WAO grades 1–5): $\chi^2 = 7.06$, $p = 0.854$; post hoc power = 0.28.
- Sensitivity analysis 1 (underweight/normal weight vs. overweight/obese, full WAO grading): $\chi^2 = 3.57$, $p = 0.469$; power = 0.20.
- Sensitivity analysis 2 (underweight normal weight vs. overweight/obese, mild [1–3] vs. severe [4–5]): $\chi^2 = 0.68$, $p = 0.411$; power = 0.09.

For transparency, we also report the exploratory post hoc powers for individual BMI subgroups: underweight 0.061; normal 0.441; overweight 0.092; obese 0.074. For

aggregated subgroups, the powers were: underweight+normal 0.248; overweight+obese 0.195.

These results indicate that while our study is underpowered to detect subtle subgroup differences, especially in the smallest categories, it provides sufficient evidence to exclude large associations of the magnitude reported in adult cohorts (e.g., OR 2–3). Importantly, across all specifications (non-aggregated and aggregated), no significant association between BMI and anaphylaxis severity was observed. We have added these results to the Methods, Results, and Discussion sections, and we now explicitly acknowledge that the study excludes strong associations but cannot rule out small or moderate effects.

Accordingly, we have revised the Methods (page 5, section 2.5, 2.6), Results (page 7, section 3.2), and Discussion (page 11, lines 391-396 of the tracked version) to include these additional analyses and to explicitly acknowledge that the study excludes strong associations but cannot rule out small or moderate effects.

4. Reviewer's comment:

It is also necessary to describe the purpose of certain measurements. The results mention asthma and dermatitis, which are not part of the EAACI 2021 diagnostic criteria. In this regard, the authors need to be more detailed about the diagnosis; as it is not a very common topic, readers may find it difficult to understand the manuscript. As the methods are currently written, it is not possible to reproduce the study or even understand how the authors arrived at their results. Finally, the exclusion criteria are also not clear.

Response:

We appreciate the Reviewer's observation and agree that the Methods section required clarification. In the revised version we therefore:

specified that asthma and atopic dermatitis were collected as comorbidities to describe the study population, rather than as part of the EAACI 2021 diagnostic criteria for anaphylaxis. These data were obtained from caregiver-reported medical history and, when available, verified with hospital records;

expanded the description of how anaphylaxis was diagnosed, explicitly stating the application of the EAACI 2021 criteria and the process of independent review by two investigators;

revised the exclusion criteria to clearly indicate that patients were excluded if hospitalization was for conditions other than anaphylaxis, if clinical data were insufficient to apply the EAACI 2021 criteria or to classify severity, or if anthropometric measurements required for BMI calculation were unavailable.

These details have been added to the Methods (sections 2.3 and 2.4) to ensure that the study can be fully understood and reproduced.

5. Reviewer's comment:

Regarding the statistics, I have another suggestion for the authors, as the chosen tests are not sufficient for the desired answers. Although the univariate analysis presented shows no association between BMI and anaphylaxis severity, the absence of a multivariate analysis prevents a robust conclusion. In Table 1, asthma and dermatitis are presented as confounding variables that were controlled for. However, to state with greater confidence that nutritional status is not an independent predictor of reaction severity, it is essential to perform a logistic regression analysis that simultaneously adjusts for variables such as age, sex, asthma, and atopic dermatitis. This approach would isolate the specific effect of BMI, and the persistence of a non-significant odds ratio after this adjustment would greatly strengthen the validity of the main result. Therefore, I suggest the authors implement a model that dichotomizes the outcome into "severe anaphylaxis" (WAO 4-5) versus "non-severe" (WAO 1-3) or that uses the full ordinal scale of the WAO. The results, presented as adjusted odds ratios with confidence intervals, would allow for a clearer and more causally informative interpretation of the relationship under investigation.

The results are adequate for the current statistical model but will need to be redone based on my suggestion above.

Response:

We thank the Reviewer for this valuable suggestion. In response, we have performed multivariate logistic regression analyses to adjust for potential confounders, including age, sex, asthma, and atopic dermatitis. Two approaches were applied, as recommended: (i) ordinal logistic regression across the full WAO 5-grade severity scale and (ii) binary logistic regression with severity dichotomized into non-severe (grades 1–3) versus severe (grades 4–5). Each model was estimated both with BMI as a continuous percentile variable and as categorical nutritional status.

Across analytic approaches, BMI was not significantly associated with anaphylaxis severity. In the ordinal model with BMI categories, the adjusted OR was 1.58 (95% CI: 0.96–2.59, $p = 0.07$), while in the binary model the adjusted OR was 1.48 (95% CI: 0.86–2.54, $p = 0.15$). Comparable results were obtained when BMI was modeled as a continuous percentile variable. Other covariates, including age, sex, and asthma, were not significantly associated with severity, whereas atopic dermatitis was associated with slightly lower severity in the ordinal model with BMI categories (OR = 0.54, 95% CI: 0.31–0.95, $p = 0.03$) and approached significance in the corresponding binary model (OR = 0.55, 95% CI: 0.30–1.00, $p = 0.05$).

These findings confirm that the main results are robust and that nutritional status was not an independent predictor of anaphylaxis severity in this cohort. We have incorporated the regression analyses into the Methods (section 2.6 lines 182-184), Results (section 3.2, lines 235-245), and Discussion sections of the manuscript (lines 286- 295), and the full set of adjusted odds ratios with 95% confidence intervals is reported in Supplementary Table S3.

6. Reviewer's comment:

The discussion should also be reworked. I recommend that the authors avoid in-depth discussion of variables that were not measured in the present study. There is a long paragraph discussing pro-inflammatory cytokines. I recommend that this be revised.

Response:

We acknowledge this important point. The Discussion has been revised to limit speculation and to avoid detailed descriptions of variables not assessed in the present study. Specifically, the paragraph on cytokines has been condensed into a brief reference to the general pro-inflammatory state associated with obesity (lines 328-334).