Peer-Review comments and author responses

Reviewer 1

Comment: Firstly, discussing zinc and vitamin D and its association with obesity requires a more physiological and detailed explanation. While the zinc-related evidence appropriately addresses inflammatory pathways, the specific mechanisms by which the mentioned inflammatory markers (IL-6 and C-reactive protein) are related and/or contribute to obesity pathogenesis warrant a more detailed discussion.

Response: *We appreciate this comment and have added a detailed explanation of the mechanisms linking IL-6 and CRP to obesity pathogenesis, emphasizing their role in inflammatory and metabolic pathways. Additionally, the discussion on vitamin D has been enriched to include its biological mechanisms related to metabolic function and fat storage. These revisions are reflected in the "Introduction" section.*

Comment: the exclusion of participants with incomplete data may introduce selection bias, potentially affecting sample representativeness, generalizability, and validity of the findings

Response: *We drop initially the variables that present missing values, for conducted this study since the variables of interest were Obesity, Vitamin D and Zinc as NHANES data base were self reported the missing value were considered missing not at random so it would increase way too much the bias risk. The only data that refers "Dont remember" hast 9 responses with the referred value being a drop of 9 of 1042 (<0.01%)*

Comment: Furthermore, the measurement of variables key requires additional considerations. The discrepancy between measurement of the zinc (24-hour dietary recall) and assessment of vitamin D (supplement use in the last 30 days) introduceand temporal inconsistencies that could confuse comparisons.

Response: *The authors understand and appreciate this point; that is why it is included among the limitations.*

Comment: A more robust approach to variable selection would involve a systematic process based on theoretical justifications or model evaluations using criteria such as the AIC, potentially incorporating hierarchical models to ensure stable and interpretable results. Relying solely on univariate statistical significance, as opposed to a theoretically driven framework, risks overfitting the model, producing unstable parameter estimates, and excluding critical confounders such as total fat intake that may influence obesity outcomes in multivariate analyses.

Response: *The variable selection process was carried out based on both clinical judgment and the observed p-value, with priority given to clinical judgment, as the goal is not to develop the best*

predictive model. The authors believe that using AIC as a selection criterion for the best predictive model whether through forward, backward, or stepwise methods would not be the most appropriate approach to address the research question. The focus of the study is on examining the existence of a relationship rather than identifying the best predictive model for the outcome.

Comment: First, multiple univariate analysis of nutrient intake variables introduce a risk of type I error inflation, which could be addressed by appropriate adjustments such as: Multiple comparisons, such as Bonferroni controls or the false discovery rate.

Response: *We appreciate the reviewer's feedback regarding the risk of type I error inflation from univariate analyses. In our study, univariate analyses were conducted solely to evaluate the potential association of covariates with the outcome variable (obesity), with the goal of identifying variables to include as potential confounders in the multivariable model. These analyses were not intended to statistically assess relationships within subcategories of the variables of interest, as evaluating intra-association was not the study's objective. Therefore, methods to adjust for multiple comparisons, such as Bonferroni or FDR, were not deemed necessary in this context.*

Comment: The statistical data from Orces et al. regarding supplement usage patterns among obese individuals, while relevant, needs some contextual positioning regarding socio-economic, behavioral, and metabolic factors

Response: *We have contextualized the data by discussing socio-economic, behavioral, and metabolic factors that may influence supplement usage patterns, as suggested. This information has been included in the "Discussion" section.*

Comment: While the authors correctly identify a gap in understanding zinc and vitamin D's role in obesity among women, the precise nature of this gap, whether about supplementation efficacy, dosage optimization, or broader metabolic effects, requires clarification.

Response: *We have revised the introduction to clarify the precise gap, focusing on supplementation efficacy, dosage optimization, and broader metabolic effects. This revision highlights how our study aims to address these aspects.*

Comment: The absence of sensitivity analyses and alternative model specifications, particularly regarding the dichotomization of nutrient intake variables, may oversimplify potentially complex dose-response relationships that are not addressed in the discussion.

Response: *We add the sensitivity analysis and its explained in the results sections.*

Comment: The hypothesis, though clearly stated, would benefit from a more detailed explanation of the expected outcomes as well as its underlying mechanisms, particularly regarding whether the anticipated weight regulation stems from direct metabolic effects, inflammatory modulation, or alternative pathways.

Response: *We have expanded the hypothesis section to specify the expected outcomes and the proposed mechanisms, including the potential pathways for weight regulation via metabolic effects, inflammatory modulation, and alternative mechanisms.*

Comment: The cross-sectional design of this study presents significant methodological considerations. While the approach appropriately explores associations between nutrients and obesity, it precludes causal inference and temporal relationships. that must be addressed in the discussion

Response: *We acknowledge the limitations of a cross-sectional design, particularly its inability to establish causal relationships. This has been explicitly addressed in the "Discussion" section, alongside an acknowledgment of selection bias due to excluding participants with incomplete data. A comparative analysis of included versus excluded participants has also been conducted, and the results are now included in the manuscript.*

Comment: Address the temporal inconsistencies in nutrient measurement and the limitations of dichotomizing variables.

Response: *We acknowledge the temporal inconsistency between zinc and vitamin D measurements and have expanded the discussion to address the potential confounding effects. Additionally, we have included an analysis of the limitations of dichotomizing nutrient intake variables and their impact on dose-response relationships.*

Comment: Incorporate model fit assessments and validation procedures.

Response: *We have conducted Hosmer-Lemeshow tests to validate model assumptions. These assessments, along with calibration and discrimination metrics such as ROC curve, are now included in the "Statistical Analysis" section.*

Comment: Address the inflation of Type I error due to multiple comparisons.

Response: *We appreciate the reviewer's suggestion regarding the use of multiple comparison adjustments. However, in this analysis, we evaluate the association of a single nutrient with obesity at a time, adjusting for potential confounders in a multivariable model. Therefore, methods for correcting multiple comparisons, such as Bonferroni adjustment or FDR, are not deemed necessary in this context..*

We sincerely thank the reviewers for their valuable feedback, which has greatly contributed to enhancing the quality of our manuscript. We believe the revisions have significantly strengthened the paper and we look forward to your final decision.