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Letter to the Editor



Response to letter to the editor: "Reevaluating the Neuroprotective promise of dietary nitrate: Commentary on Rajendra et al. (2025)"

In response:

We thank Dr. Aphale and colleagues for their careful and constructive feedback regarding our study, "Baseline habitual dietary nitrate intake and Alzheimer's Disease related neuroimaging biomarkers in the AIBL study." We are grateful for the opportunity to respond to the methodological and interpretive observations they raise. Please find our responses to their points below:

1. Biochemical plausibility underlying differential impact of plant- vs animal nitrate.

In the manuscript we state that "the results lend some support to the hypothesis that habitual plant nitrate may improve neuroimaging markers of AD," however, we acknowledge that our study was unable to assess intermediary biomarkers such as serum NO metabolites or cerebrovascular indices within the available cohort. Our findings nevertheless build upon a robust body of literature supporting the cardiovascular benefits of plant-based nitrate via the nitric oxide pathway [1–3], with growing evidence now also supporting potential brain health benefits [4,5]. While the observed association is biologically plausible, we agree that direct validation through biochemical markers is an important direction for future research.

2. Potential non-linear dose-response relationships.

Thank you for highlighting the possibility of non-linear dose-response relationships. While splines offer flexibility, we chose tertile-based exposure classification for interpretability and to avoid added complexity in modelling interactions. We believe this simpler approach preserves clarity without compromising the detection of meaningful associations.

3. Residual confounding from overall dietary patterns or unmeasured lifestyle variables

We note, as detailed in our limitations section, that causality cannot be inferred from these observational data, nor can the influence of residual or unmeasured confounding be entirely excluded.

4. Food Frequency Questionnaire (FFQ), recall bias and misclassification.

This is a recognised methodological limitation. As discussed in the manuscript, dietary intake was assessed at baseline and may have

changed over the subsequent 126 months. Our preliminary investigations suggest general stability in dietary habits among cognitively unimpaired participants, but self-reported measures are inherently susceptible to recall bias. We attempted to mitigate this by including only those individuals who were cognitively unimpaired at dietary assessment, thus reducing bias from memory impairment. Moreover, while the estimation of nitrate intake relies on comprehensive nitrate content of food databases, the values used are best considered as estimates.

5. Potential interactions between nitrate intake and vascular comorbidities.

We agree that exploring interactions between nitrate intake and vascular comorbidities (such as hypertension or diabetes) would be of value. However, our current study was limited by the available sample size to maintain adequate statistical power for such stratified analyses. Of note, in previous work we have explored the association between nitrate intake and dementia-related mortality stratified by baseline prediabetes and diabetes status observing significant associations in both those with and without prediabetes or diabetes [5]. Such lines of inquiry are important for ongoing and future research.

Conclusion

Once again, we thank Dr. Aphale and colleagues for their engagement with our research. Their feedback underscores the challenges and opportunities in advancing our understanding of dietary nitrate and neurodegenerative disease.

Sincerely,

Catherine Bondonno, on behalf of all the co-authors.

CRediT authorship contribution statement

Catherine Bondonno: Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Catherine Bondonno 

*Edith Cowan University School of Medical and Health Sciences, Western
Australia, Australia*

E-mail address: c.bondonno@ecu.edu.au.