



Letter to the Editor

Do methodological limitations and confounding factors explain the apparent acceleration of cognitive decline in older adults taking omega-3 fatty acid supplements?



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ABSTRACT

Not applicable

Dear Editor,

We read with interest the recent report by Liao and colleagues [1]. These findings are in direct opposition to Wei *et al.*, who on the same ADNI cohort reported that omega-3 supplementation was associated with a 64% reduced risk of Alzheimer's Disease (AD) (HR: 0.36, 95% CI: 0.18, 0.72; $P = 0.004$) [2]. In this letter, we draw attention to methodological and interpretive concerns that, in our view, were not adequately addressed in the article by Liao *et al.*, and may explain these discordant observations.

Omega-3 users and non-users were matched for age, sex composition, frequencies of APOE $\epsilon 4$ carriers, diagnosis, education, ADAS-Cog13 scores, FDG-SUVR, stroke, insomnia, depression, anxiety, and Parkinson's disease. However, what is not discussed is that for many of these characteristics there were very high numbers of missing values, (Table 1).

Of note, for insomnia 91% and 81% of omega-3 non-users and users, respectively, had missing values, which is a significant risk factor for dementia. This missing data limits the ability to match groups appropriately, and by extension this information cannot be included in modelling. Indeed, only four characteristics were included (age, sex, APOE $\epsilon 4$ status, and diagnosis), thereby limiting the potential to control for many important dementia risk factors.

Wei *et al.*, analysed 1135 participants without dementia and included in their model age, sex, education, cognitive status (MCI vs normal cognition), APOE $\epsilon 4$ status, medical history (hyperlipidemia, hypertension, diabetes, stroke history, insomnia, depression, anxiety, smoking status, coronary artery disease), alcohol intake, multivitamin, vitamin B12, and folate supplementation, anti-hypertensive drugs, and anti-diabetic drugs, and BMI [2]. Many of these are particularly important in omega-3 PUFA research, and lack of their consideration is an important factor in the inconsistent findings of clinical trials with

omega-3 fatty acids [3].

The authors address the potential for reverse causality by comparing longitudinal cognitive trajectories; however, this approach only incorporates cognitive changes, and not wider potential drivers of intake, such as cardiovascular health, depression, and anxiety, which are all risk factors for AD. Furthermore, approximately 40% of participants were APOE4 carriers, the strongest genetic risk factor for late-onset AD. This proportion is substantially higher than that observed in most population-based cohorts [4], raising concerns about representativeness. APOE4 carriers are more vulnerable to accelerated cognitive decline and metabolic dysfunction and due to the very limited range of characteristics included in the modelling, the issues of reverse causality, selection bias, and wider generalizability of the findings remain.

The categorisation of omega-3 supplementation was based on self-reported intake at a single timepoint, and provides no indication of dose, duration, compliance, or type of omega-3 fatty acid. The authors suggest that the exposure definition was validated by analysis of serum omega-3 levels. However, no information is provided about which lipid fraction was analysed nor whether the participants were fasted (as values can be highly influenced by recent dietary intake [5]), or the timing of the sampling or the number of participants included in the analysis. This all limits the confidence that can be apportioned to this categorisation.

There are also important inconsistencies in the alignment of cognitive outcomes. The correlation plots indicate that individuals receiving omega-3 supplementation exhibited extremely low MMSE scores (<10), very high ADAS-Cog scores (>60), and markedly elevated CDR scores (>15). While MMSE and ADAS-Cog values in these ranges are consistent with severe dementia, corresponding CDR scores would typically fall within a moderate stage. This discordance is clinically implausible and suggests potential issues with score scaling, data harmonization, or analytical processing. Such internal inconsistency substantially weakens

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Abbreviations: ADAS-Cog13, Alzheimer's disease assessment scale-cognitive subscale 13; APOE, apolipoprotein E; DHA, docosahexaenoic acid; FDG, fluorodeoxyglucose; MMSE, mini mental state exam; SUVR, standardized uptake value ratio.

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Table 1
Number and percentage of participants with missing demographic characteristics.

Characteristic	Omega-3 non-users (546)*	Omega-3 users (273)*
Education	371 (68%)	104 (38%)
ADAS-Cog13	227 (42%)	167 (61%)
FDG SUVR	148 (27%)	82 (30%)
Stroke	275 (50%)	217 (79%)
Parkinson	226 (41%)	166 (61%)
Insomnia	497 (91%)	222 (81%)
Anxiety	275 (50%)	217 (79%)
Depression	275 (50%)	217 (79%)

* Total number participants per group
Abbreviations: ADASCog13, Alzheimer's Disease Assessment Scale-Cognitive subscale 13; FDG, fluorodeoxyglucose; SUVR, standardized uptake value ratio.

confidence in the reported associations.

Importantly, attributing such profound cognitive decline to omega-3 supplementation alone is highly unlikely. This interpretation is further undermined by the absence of concordant changes in established biomarkers of AD pathology. Notably, the authors report no association between omega-3 supplementation and longitudinal changes in amyloid- β deposition, tau aggregation, or grey matter atrophy. Given the well-established relationship between cognitive decline and these neuropathological processes, it is difficult to reconcile severe cognitive deterioration without parallel biological progression. This discrepancy strongly suggests the presence of unaccounted confounding factors or biases.

The authors also report increased FDG hypometabolism in omega-3 supplemented participants and interpret this as evidence of synaptic injury, potentially driven by oxidative stress related to DHA peroxidation. However, this mechanistic explanation is not supported by the data presented. No measures of brain DHA levels, lipid peroxidation products, neuronal integrity, or mitochondrial function were included. In the absence of such evidence, the proposed link between DHA peroxidation and reduced glucose metabolism remains speculative. Therefore, this interpretation appears overstated and insufficiently grounded in the empirical findings of the study.

Given these widespread limitations and the highly speculative nature of the drivers of adverse effects by the authors, we consider a much more

cautious interpretation of these findings is warranted.
Sincerely,

CRedit authorship contribution statement

Simon C. Dyall: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Mélanie Plourde:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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.

References

[1] Liao ZB, Hu ZC, Zeng GH, et al. The association between omega-3 supplementation and cognitive decline in older adults. *J Prev Alzheimers Dis* 2026;13(6):100569. <https://doi.org/10.1016/j.tjpad.2026.100569>.
[2] Wei BZ, Li L, Dong CW, Tan CC, Alzheimer's Disease Neuroimaging I, Xu W. The relationship of omega-3 fatty acids with dementia and cognitive decline: evidence from prospective cohort studies of supplementation, dietary intake, and blood markers. *Am J Clin Nutr* 2023;117(6):1096–109. <https://doi.org/10.1016/j.ajcnut.2023.04.001>.
[3] Dyall SC, Plourde M. Omega-3 polyunsaturated fatty acids in neurodegenerative disorders: mixed designs = mixed results. *Prog Lipid Res* 2025;100:101356. <https://doi.org/10.1016/j.plipres.2025.101356>.
[4] Husain MA, Laurent B, Plourde M. APOE and Alzheimer's disease: from lipid transport to physiopathology and therapeutics. *Front Neurosci* 2021;15:630502. <https://doi.org/10.3389/fnins.2021.630502>.
[5] Brenna JT, Plourde M, Stark KD, Jones PJ, Lin YH. Best practices for the design, laboratory analysis, and reporting of trials involving fatty acids. *Am J Clin Nutr* 2018;108(2):211–27. <https://doi.org/10.1093/ajcn/nqy089>.

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