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Letter to the Editor

Oxidation over omega-3: Reinterpreting the paradoxical link between fish oil supplements and accelerated cognitive decline

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ABSTRACT

Liao et al. (2026) recently reported an association between omega-3 supplementation and accelerated cognitive decline, mediated by FDG-PET hypometabolism. While clinically provocative, this observational finding warrants cautious interpretation. This Letter critiques four methodological limitations: (1) exposure misclassification, as ADNI's binary supplement variable ignores oxidation state and formulation (pharmacy grade vs. oxidized OTC fish oil); (2) residual confounding, since propensity score matching cannot adjust for subtle preclinical worry or lifestyle factors driving supplement initiation; (3) mechanistic overreach, as FDG hypometabolism reflects composite metabolic/inflammatory processes, not isolated synaptic dysfunction; and (4) context dependency, where effects likely hinge on baseline omega-3 status and individual oxidative load. We propose actionable refinements: biomarker-anchored dose modeling (serum EPA+DHA), negative-control sensitivity analyses, partial volume-corrected FDG mediation, and CSF synaptic marker integration. Rather than a universal "harm" signal, this paradoxical association should be framed as hypothesis generating, urging personalized prevention strategies over blanket clinical warnings.To the Editor:

Liao et al. [1] use ADNI to argue that omega-3 supplementation associates with *accelerated* cognitive decline and that FDG-PET hypometabolism mediates ~19–41% of the effect. As clinicians/researchers working at the interface of neurology, endocrinometabolic pathways, and molecular biomarkers, we find the *alert* valuable—but the causal claim and the mechanistic leap require stronger safeguards before changing practice messaging.

1) Self-reported "supplementation" remains an unmeasured-dose exposure.

ADNI records supplement use as a **yes/start-visit** variable, not confirmed dose, brand, oxidation state, or EPA/DHA formulation [1]. This makes the exposure **binary and time-varying- only in a coarse sense**. In observational neuroprevention, this is not a detail: effect direction can flip depending on whether users take *pharmacy-grade oxidized-minimal* vs *OTC fish oil with high peroxide loads* [2], and the literature also shows oxidation-quality problems are common in retail products [2]. The authors' mediation pathway could therefore be picking up **oxidized-lipid neurotoxicity** rather than a clean "omega-3 synaptic effect."

Actionable fix (can be done without new recruitment): convert exposure to a **biomarker-anchored- dose** whenever possible—e.g., use ADNI serum/plasma EPA+DHA (wt% or μg/mL) as the primary predictor in a sensitivity model; rerun LMM/mediation with continuous % EPA+DHA instead of binary yes/no. At minimum, stratify by *statin* use and *CVD burden* (both reshape omega-3 pharmacokinetics and cognitive trajectories and are classic unmeasured confounders in supplement studies).

2) Propensity score matching cannot erase "healthy-user" residual confounding here.

PSM balanced age, sex, APOE ε4, and diagnosis [1]; however, the variables most likely to drive supplement initiation—subtle preclinical worry, family history of AD, depressive/anxiety symptoms, physical activity, dietary pattern, and social engagement—are either missing or too crude in ADNI. Their reverse causality- check (pre-initiation slopes) is necessary but underpowered to exclude slow-burn- selection: wide CIs and short pre-periods make a null result easy to obtain even when small baseline divergence exists.

Actionable fix: run a **negative control- outcome** sensitivity (e.g., bone density or non-AD- lab markers available in subsets) to probe residual "health-seeking-" confounding; and report **E-values** for the LMM interaction βs so editors/readers can see how strong an unmeasured confounder would need to be to nullify the effect.

3) FDG SUVR mediation does not equal "synaptic dysfunction" without synaptic biomarkers.

The authors equate FDG hypometabolism with synaptic impairment [1]. However-, FDGPET integrates **energy metabolism, astrocytic lactate shuttling, and microglial activation**; it is *consistent with* synaptic/neuronal stress but not specific [3]. Moreover, classic ADNI ROI approaches (meta-ROI SUVR normalized to reference regions) are robust for group trends but remain sensitive to **partial-volume and reference region- choices**, especially when cortical atrophy co-varies with metabolism. Treating FDG as a clean mediator without (i) partialvolume-corrected- (PVC) SUVR, or (ii) CSF synaptic/axonal markers (neurogranin, NfL), risks reifying a composite signal as a mechanistic proof.

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Actionable fix: rerun the mediation using **PVC-FDG** if the ADNI pipeline supports it; add CSF **p-tau217/t-tau and NfL** as sensitivity mediators to separate the "AD proteinopathy track" from "neuronal injury track"; and explicitly label the pathway as *cerebral metabolic mediation* rather than *synaptic causation*.

4) Dose/quality interaction is the hypothesis that actually advances prevention.

Instead of "omega-3 may harm," the field needs to know *when* it helps and *when* it hurts. The strongest candidate moderator is **product oxidation + individual oxidative load** [2], followed by **baseline endogenous omega-3 status** (benefit tends to emerge when status is low) [4]. ADNI's binary exposure cannot test this alone, which is why the current result should be framed as **hypothesis-generating-**, not a reversal of guidelines.

Use of AI statement

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Dong'e Huang: Investigation, Writing – review & editing. **Munan Lin:** Data curation, Project administration. **Junqing Dong:** Conceptualization, Methodology, 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.

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