

FARI Commentary on a recent omega-3 and cognitive health report

We've been asked several times about the report from Liao et al.¹ that concluded,

“Omega-3 supplementation may be associated with accelerated cognitive decline in older adults, potentially through adverse effects on cerebral synaptic function rather than classical Alzheimer’s Disease (AD) proteinopathies. These findings challenge the prevailing view of omega-3 as uniformly beneficial and highlight the need for a cautious reassessment of its widespread use for cognitive protection.”

Our team at the Fatty Acid Research Institute (Aleix Sala-Vila, PhD in particular) has prepared a short rebuttal to provide context for this report. The biggest problem is that the conclusions of Liao et al. directly contradict another study on very similar topics done in the same cohort, and Liao et al. don't even cite this previous study (Wei et al. 2023²). Both studies were conducted in the Alzheimer’s Disease Neuroimaging Initiative (ADNI). As noted in the abstract (below) from Wei et al. long-term users of omega-3 fatty acid supplements exhibited a 64% *reduced* risk of AD (full abstract reprinted below).

Previous data have linked omega-3 fatty acids with risk of dementia. We aimed to assess the longitudinal relationships of omega-3 polyunsaturated fatty acid intake as well as blood biomarkers with risk of Alzheimer’s disease (AD), dementia, or cognitive decline. Longitudinal data were derived from 1135 participants without dementia (mean age=73 y) in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort to evaluate the associations of omega-3 fatty acid supplementation and blood biomarkers with incident AD during the 6-y follow-up. A meta-analysis of published cohort studies was further conducted to test the longitudinal relationships of dietary intake of omega-3 and its peripheral markers with all-cause dementia or cognitive decline. Causal dose–response analyses were conducted using the robust error meta-regression model. In the ADNI cohort, long-term users of omega-3 fatty acid supplements exhibited a 64% reduced risk of AD (hazard ratio: 0.36, 95% confidence interval: 0.18, 0.72; P = 0.004). After incorporating 48 longitudinal studies involving 103,651 participants, a moderate-to-high level of evidence suggested that dietary intake of omega-3 fatty acids could lower risk of all-cause dementia or cognitive decline by ~20%, especially for DHA intake (relative risk [RR]: 0.82, I² = 63.6%, P = 0.001) and for studies that were adjusted for apolipoprotein APOEε4 status (RR: 0.83, I²=65%, P=0.006). Each increment of 0.1 g/d of DHA or EPA intake was associated with an 8%~ 9.9% (P_{linear}<0.0005) lower risk of cognitive decline. Moderate-to-high levels of evidence indicated that elevated levels of plasma EPA (RR: 0.88, I² = 38.1%) and erythrocyte membrane DHA (RR: 0.94, I² = 0.4%) were associated with a lower risk of cognitive decline. Dietary intake or long-term supplementation of omega-3 fatty acids may help reduce risk of AD or cognitive decline.

Table comparing the studies

	Liao et al ¹	Wei et al ²
N	819, divided into 273 FOS users and 546 non-users, matched for age, sex, <i>APOE</i> ϵ 4 status, and diagnosis	1135
Mean Age	73	73
Yrs follow-up	5	6
Exposures	FOS use or not	FOS use or not; Plasma omega-3
Outcome	<p>Rate of change in cognitive function tests, including:</p> <p>1) MMSE – a screening test rather than a test to deeply explore cognitive performance.</p> <p>2) ADAS-Cog13 – mostly designed to assess Alzheimer-type cognitive impairment. Less sensitive in very early disease, highly functioning individuals; non-Alzheimer cognitive disorders</p> <p>3) CDR-SB – helpful for distinguishing progression to advanced stages (e.g., mild cognitive impairment, mild dementia, moderate/severe dementia), but not that useful in cognitively healthy people.</p>	<p>Incident Alzheimer’s Disease</p> <p>Also reporting a meta-analysis of 31 studies including omega-3 exposure metrics (dietary intake, plasma or RBC omega-3)</p>
Covariates in Models	Age, sex, <i>APOE</i> ϵ 4 status, and diagnosis (cognitively normal, early mild cognitive impairment, late mild cognitive impairment, significant memory concern, or Alzheimer’s disease).	Age, sex, education, clinical diagnosis [undefined], <i>APOE</i> ϵ 4 status, insomnia, depression, anxiety, hypertension, diabetes mellitus, hyperlipidemia, smoking, BMI, stroke, and coronary artery disease, alcohol intake, multivitamins, vitamin B12, folate, anti-hypertensive drugs and antidiabetic drugs.
Conclusions	“Omega-3 supplementation may be associated with accelerated cognitive decline in older adults”	“Dietary intake or long-term supplementation of omega-3 fatty acids may help reduce risk of AD or cognitive decline”

General conclusions.

1. The fact that opposite conclusions were obtained using the same dataset suggests that the statistical approach may have influenced the outcome. Substantial differences between the studies were observed regarding adjustment for baseline factors, many of which may have contributed to imbalances between groups in the Liao paper. Specifically, Liao et al. just adjusted for the 4 variables used to match users vs non-users and nothing else. Wei et al. adjusted for 16 additional variables. This alone could have explained the differences in outcomes. Not adjusting for education is an especially glaring omission.
 2. The mix of subjects with widely different baseline cognitive status – from normal to established Alzheimer’s Disease – is also a problem. The relationship between omega-3 supplementation and cognitive trajectory would clearly differ by stage of disease. Reporting non-linear associations would have been more useful.
 3. The tests used in the Liao paper are not the optimal ones. The Mini-Mental State Examination (MMSE) is primarily a screening test; the Preclinical Alzheimer Cognitive Composite (PACC) or the Free and Cued Selective Reminding Test would have been more appropriate for monitoring cognitive decline in cognitively healthy individuals. In addition, the other two tests were too focused on detecting cognitive deficits in advanced stages of disease rather than subtle changes in cognitively healthy people, who tend to score near the upper end of the scale (leaving little room to detect improvement or mild decline).
 4. Liao et al focused (however poorly) on *cognitive decline* whereas Wei et al. focused on actual *disease outcomes*. The latter are more clear-cut and clinically-relevant than the former.
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1. Liao Z-B, Hu Z-C, Zeng G-H, Chen J, Li X-P, Liu Y-H, Yao X-Q and Wang Y-R. The association between omega-3 supplementation and cognitive decline in older adults. *The journal of prevention of Alzheimer's disease*. 2026;13:100569.
 2. Wei BZ, Li L, Dong CW, Tan CC and 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;117:1096-1109.