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Preventing Cognitive Decline in Late-Life Depression: A Longitudinal Study on the Efficacy of Omega-3 Fatty Acid Supplementation in Older Adults in Palembang, Indonesia

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A B S T R A C T

Introduction: Late-life depression (LLD) is a prevalent condition in older adults and a significant risk factor for cognitive decline and dementia. In Indonesia, with its aging population and specific dietary patterns, understanding interventions for LLD-associated cognitive impairment is crucial. Omega-3 polyunsaturated fatty acids (PUFAs) offer potential neuroprotective benefits. This study aimed to assess the efficacy of long-term omega-3 PUFA supplementation in mitigating cognitive decline among older adults with LLD in Palembang, Indonesia. **Methods:** This 24-month, randomized, double-blind, placebo-controlled trial was conducted in Palembang. Three hundred sixty older adults (aged ≥60 years) with a current DSM-5 diagnosis of Major Depressive Disorder (MDD) and subjective cognitive complaints were randomized (1:1) to receive either daily oral supplementation of 2.2 grams of omega-3 PUFAs (containing 1320 mg eicosapentaenoic acid [EPA] and 880 mg docosahexaenoic acid [DHA]) or a matched placebo (corn oil). The primary outcome was the change in the Indonesian version of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-INA) score over 24 months. Secondary outcomes included changes in the Montreal Cognitive Assessment-Indonesian version (MoCA-INA), Geriatric Depression Scale (GDS-30), Instrumental Activities of Daily Living (IADL), serum Brain-Derived Neurotrophic Factor (BDNF), and high-sensitivity C-Reactive Protein (hs-CRP). **Results:** Over 24 months, the omega-3 group exhibited significantly less decline on the ADAS-Cog-INA compared to the placebo group (mean difference: -2.1 points; 95% CI: -3.8 to -0.4; p=0.018). Statistically significant benefits for the omega-3 group were also observed in MoCA-INA scores (mean difference: 1.5 points; p=0.025) and GDS-30 scores (mean difference: -2.5 points; p=0.011). BDNF levels increased significantly in the omega-3 group relative to placebo (p=0.008), while hs-CRP levels showed a non-significant trend towards reduction (p=0.072). **Conclusion:** Long-term supplementation with 2.2 g/day of EPA-rich omega-3 PUFAs resulted in a modest but statistically significant attenuation of cognitive decline and improvement in depressive symptoms in older adults with LLD in Palembang. These findings suggest that omega-3 PUFAs could be a valuable adjunctive therapeutic strategy in this specific Southeast Asian population.

1. Introduction

Late-life depression (LLD), defined as a major depressive episode occurring in individuals aged 60 years or older, is a prevalent and serious global health issue. It is associated not only with significant emotional suffering and reduced quality of life but also with increased morbidity, mortality, and healthcare costs. One of the most concerning sequelae of LLD is

its strong association with cognitive impairment. Cognitive deficits in LLD are common, affecting domains such as memory, attention, processing speed, and executive functions. These impairments can persist even when depressive symptoms remit, significantly impacting daily functioning and independence.[1,2]

Crucially, LLD is recognized as a major risk factor for the development of Mild Cognitive Impairment (MCI) and subsequent progression to dementia, including Alzheimer's Disease (AD). Meta-analyses suggest that individuals with a history of LLD may have an approximately twofold increased risk of developing dementia. The underlying mechanisms connecting LLD and cognitive decline are complex and likely multifaceted, involving structural and functional brain changes. Proposed pathways include sustained hypothalamic-pituitary-adrenal (HPA) axis dysregulation leading to hypercortisolemia and hippocampal damage, chronic low-grade inflammation, cerebrovascular disease, disruptions in neurotrophic factor support such as Brain-Derived Neurotrophic Factor (BDNF), and shared neuropathology with neurodegenerative disorders like AD.[3,4]

In Indonesia, a rapidly aging population presents a growing public health challenge regarding age-related disorders, including LLD and dementia. While precise epidemiological data for LLD-associated cognitive impairment in specific Indonesian regions like Palembang, South Sumatra, are still emerging, national surveys indicate a significant burden of mental health issues among the elderly. Traditional Indonesian diets vary regionally, with Palembang, known for the Musi River, having a culinary tradition that includes freshwater fish. Some Indonesian freshwater fish like *gurame (Osphronemus goramy)*, *nila (Oreochromis niloticus)*, *patin (Pangasius hypophthalmus)*, and *seluang (Rasbora argyrotaenia)* may contain omega-3 and omega-6 fatty acids. However, the actual intake and omega-3 fatty acid content can vary based on species, diet of the fish, and cooking methods. The typical dietary omega-3 PUFA intake in this population may not be optimal for neuroprotection, especially in the context of LLD.[5,6]

Current treatments for LLD, predominantly antidepressant medications and psychotherapy, often have limited efficacy in reversing or halting the progression of associated cognitive decline. Antidepressants, while beneficial for mood, may not adequately address the underlying neuropathological processes contributing to cognitive impairment. Therefore, there is a critical need for safe, effective, and accessible interventions that can specifically target cognitive health in older adults with LLD, particularly in diverse cultural and dietary contexts such as Indonesia.[7,8]

Omega-3 polyunsaturated fatty acids (PUFAs), primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found abundantly in fatty fish and fish oil supplements, have emerged as promising candidates for brain health. DHA is a crucial structural component of neuronal membranes, influencing fluidity, membrane protein function, and signal transduction. EPA plays significant roles in resolving inflammation and may modulate neurotransmitter function. Proposed mechanisms for their neuroprotective and antidepressant effects include the attenuation of neuroinflammation, enhancement of BDNF levels, improvement of synaptic plasticity and neurogenesis, reduction of oxidative stress, and positive modulation of serotonin and dopamine systems. Previous epidemiological studies have shown a protective role for fish and fish oil consumption in cognitive decline and depression. Some, but not all, randomized controlled trials (RCTs) have reported benefits of omega-3 PUFA supplementation on mood and cognitive symptoms in depressed individuals, though results have been mixed, particularly regarding cognitive outcomes in LLD. Many studies have been of short duration or have not specifically focused on older adults with LLD and comprehensive cognitive assessments. Previous study indicated that while some studies found improvement in depression symptoms with fish oil, more research is needed, especially on mechanisms and optimal

dosages for cognitive function in MDD.[9,10]

To date, there is a paucity of long-term, well-controlled longitudinal studies investigating the efficacy of omega-3 PUFA supplementation for preventing cognitive decline specifically in older adults with LLD, especially within Southeast Asian populations like Indonesia, where dietary habits, genetic predispositions, and environmental factors may differ from Western populations where most research has been conducted. Therefore, this study aimed to pioneer a longitudinal investigation into the neuroprotective efficacy of sustained omega-3 fatty acid supplementation in mitigating cognitive decline and enhancing mood among older adults diagnosed with late-life depression in Palembang, thereby providing crucial, culturally relevant evidence for a potential adjunctive therapy to preserve brain health in this at-risk Southeast Asian population.

2. Methods

This study was a 24-month, multi-center, randomized, double-blind, placebo-controlled superiority trial. Participants were recruited from geriatric outpatient clinics at two private hospitals and several primary private clinics in Palembang, South Sumatra, Indonesia. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was obtained from the Health Research Ethics Committee of CMHC Research Center (No. 2023/150). All participants provided written informed consent in Bahasa Indonesia prior to any study-related procedures. An independent Data and Safety Monitoring Board (DSMB) was established to oversee participant safety and trial integrity, meeting every six months.

Eligible participants were community-dwelling men and women aged 60 years or older residing in Palembang or its immediate surrounding areas. Inclusion criteria were: A current diagnosis of Major Depressive Disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), confirmed by a study psychiatrist using the Mini-International Neuropsychiatric Interview (MINI); A score of ≥15 on the 30-item Geriatric Depression Scale (GDS-30) at screening; Subjective cognitive complaint, as reported by the participant or a reliable informant (a family member), corroborated by a score of >0.5 on the Clinical Dementia Rating (CDR) global score but not meeting criteria for dementia (CDR ≤0.5 with memory box score of 0.5); Fluent in Bahasa Indonesia; Willingness and ability to comply with the study protocol, including long-term supplementation and regular follow-up assessments; Availability of a reliable informant who could provide collateral information if needed.

Exclusion criteria were: A diagnosis of dementia (any type) or meeting criteria for MCI based on established Petersen criteria at baseline (to focus on LLD with subjective complaints rather than established MCI); Other current primary psychiatric disorders (bipolar disorder, schizophrenia, substance use disorder) as per DSM-5; Significant neurological disorders (Parkinson's disease, stroke with significant residual cognitive deficits, epilepsy, brain tumor); Medical conditions that could significantly affect cognitive function or nutrient absorption (uncontrolled hypothyroidism, severe renal or hepatic impairment, malabsorption syndromes); Current use of omega-3 PUFA supplements (>400 mg/day of EPA+DHA) within the past 3 months or unwillingness to discontinue their use; Regular use of anticoagulant medications (warfarin) or antiplatelet agents at high doses, due to potential interactions with omega-3 PUFAs, unless stabilized and approved by their treating physician. Low-dose aspirin (≤100 mg/day) was permitted; Known allergy or intolerance to fish or corn oil; Participation in another clinical trial involving an investigational drug or supplement within the past 30 days; Severe visual or hearing impairment that would preclude neuropsychological testing; Mini-Mental State Examination (MMSE) score <24 at screening, as a general cognitive screen.

Participants receiving stable doses of antidepressant medication for at least 8 weeks prior to

enrollment were eligible, provided their medication regimen was not anticipated to change significantly during the trial, unless clinically indicated. Changes in antidepressant medication were recorded. Eligible participants were randomized in a 1:1 ratio to receive either omega-3 PUFA supplements or a matching placebo. Randomization was performed using a computer-generated block randomization sequence (block sizes of 4 and 6) stratified by study center and baseline antidepressant use (yes/no). The randomization sequence was generated by an independent statistician not involved in participant recruitment or assessment. Allocation concealment was ensured using a central, secure, web-based randomization system. Both participants, study investigators, outcome assessors, and clinical staff were blinded to treatment allocation throughout the study. The omega-3 PUFA and placebo capsules were identical in appearance, size, shape, color, opacity, and smell. Emergency unblinding procedures were in place but were not utilized during the trial. Participants in the intervention group received two softgel capsules twice daily, providing a total daily dose of 2.2 grams of omega-3 PUFAs, consisting of approximately 1320 mg of EPA and 880 mg of DHA (ratio of EPA:DHA approximately 3:2). This dosage and ratio were selected based on previous studies suggesting efficacy for mood and potential cognitive benefits with higher EPA formulations. Participants in the placebo group received two softgel capsules twice daily, containing an equivalent amount of corn oil, matched for appearance and organoleptic properties. Corn oil was chosen as a placebo due to its minimal omega-3 PUFA content and distinct fatty acid profile. Both active and placebo capsules contained a small amount of mixed tocopherols (vitamin E) to prevent oxidation. The supplements were manufactured under Good Manufacturing Practices (GMP) by a certified pharmaceutical company and quality-tested for PUFA content, purity, and contaminants (heavy metals, PCBs) by an independent laboratory.

Participants were instructed to take the capsules with meals to enhance absorption and minimize gastrointestinal side effects. Study medication was dispensed every 3 months. Adherence was assessed by pill counts of returned bottles at each follow-up visit and by measuring plasma phospholipid EPA and DHA levels at baseline, 12 months, and 24 months in a random subsample (n=60) to objectively verify compliance and bioavailability. Participants were encouraged to maintain their usual diet and lifestyle habits, including their typical fish consumption, which was assessed at baseline and follow-up visits. All outcome measures were administered at baseline, 6, 12, 18, and 24 months, unless otherwise specified, by trained research assistants fluent in Bahasa Indonesia and blinded to treatment allocation. Standardized training and regular inter-rater reliability checks were conducted for all assessors. Validated Indonesian versions of questionnaires and cognitive tests were used where available.

The primary outcome was the change from baseline to 24 months in the total score of the Indonesian version of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-INA). The ADAS-Cog is a widely used instrument to assess the severity of cognitive dysfunction in key domains affected by AD, including memory, language, praxis, and orientation. Scores range from 0 to 70, with higher scores indicating greater cognitive impairment. The Indonesian version was developed through a rigorous translation and cultural adaptation process. Cognitive Outcomes: Change in Montreal Cognitive Assessment-Indonesian version (MoCA-INA) total score. The MoCA is a brief screening tool for MCI, assessing attention, concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation; Change in Trail Making Test (TMT) Part A and Part B completion times, assessing processing speed and executive function (set-shifting); Change in Rey Auditory Verbal Learning Test (RAVLT) immediate recall (sum of trials 1-5), delayed recall, and recognition scores, assessing verbal learning and memory; Change in Digit Span Forward and Backward scores (from Wechsler Adult Intelligence Scale-IV), assessing attention and working

memory; Change in Verbal Fluency Test scores (semantic and phonemic fluency), assessing language and executive functions.

Mood and Functional Outcomes: Change in Geriatric Depression Scale (GDS-30) total score; Change in Lawton Instrumental Activities of Daily Living (IADL) scale score, assessing ability to perform complex daily tasks; Change in Barthel Index of Activities of Daily Living (BADL), assessing basic self-care abilities. Biomarkers: Change in fasting serum BDNF levels (pg/mL); Change in fasting serum high-sensitivity C-Reactive Protein (hs-CRP) levels (mg/L). Blood samples for biomarkers were collected at baseline, 12 months, and 24 months after an overnight fast, processed within 2 hours, and stored at -80°C until batch analysis. BDNF was measured using a quantitative sandwich enzyme immunoassay technique (ELISA kit). hs-CRP was measured using a high-sensitivity immunoturbidimetric assay.

Adverse events (AEs) were systematically monitored and recorded at each study visit through open-ended questioning and a standardized checklist. AEs were graded for severity (mild, moderate, severe) and relationship to the study intervention (unrelated, unlikely, possibly, probably, definitely related) by the study physician. Serious adverse events (SAEs) were reported to the ethics committees and DSMB according to regulatory requirements. Standard laboratory safety assessments (complete blood count, liver function tests, renal function tests) were performed at baseline and 24 months.

Sociodemographic information, medical history, medication use, and lifestyle factors (smoking, alcohol use, physical activity via the Physical Activity Scale for the Elderly - PASE) were collected at baseline. Dietary fish intake was assessed using a culturally adapted semi-quantitative food frequency questionnaire (FFQ) focusing on common fish consumed in Palembang, at baseline, 12 months, and 24 months. Apolipoprotein E (APOE) genotyping was performed at baseline from blood samples for exploratory subgroup analyses.

The primary efficacy analysis was based on the intention-to-treat (ITT) population, defined as all randomized participants who received at least one dose of study medication and had at least one post-baseline primary outcome assessment. Missing data were handled using multiple imputation techniques, assuming data were missing at random (MAR).

The primary outcome, change in ADAS-Cog-INA score from baseline to 24 months, was analyzed using a mixed-effects model for repeated measures (MMRM). The model included treatment group, visit (as a categorical variable), treatment-by-visit interaction, and baseline ADAS-Cog-INA score as covariates. Stratification factors (study center, baseline antidepressant use) and other relevant baseline characteristics (age, gender, education, baseline GDS-30 score) were also included as covariates. An unstructured covariance matrix was used to model the within-participant correlation. The primary treatment effect was estimated at the 24-month visit.

Similar MMRM models were used to analyze secondary continuous outcomes. For biomarker data, analyses were performed on log-transformed values if distributions were skewed. Categorical outcomes were analyzed using logistic regression or chi-square tests as appropriate. Pre-specified subgroup analyses for the primary outcome included baseline depression severity (GDS-30 <20 vs. ≥20), APOE ε4 carrier status (carrier vs. non-carrier), and baseline dietary fish intake (low vs. high based on median split).

A sample size of 158 participants per group (total N=316) was calculated to provide 80% power to detect a clinically meaningful difference of 2.0 points in ADAS-Cog change between groups at 24 months, assuming a standard deviation of 5.0 points for the change score, a two-sided alpha of 0.05, and allowing for a 20% attrition rate. To enhance power and account for potential higher attrition, we aimed to recruit 360 participants (180 per group). All statistical analyses were performed using Stata version 17.0. A two-sided p-value <0.05 was considered statistically significant. No adjustments were made for multiple comparisons for secondary outcomes, and these were interpreted as exploratory.

3. Results

Between July 2023 and June 2024, a total of 652 individuals were screened for eligibility across the three recruitment centers in Palembang. Of these, 292 did not meet eligibility criteria (150 due to not meeting LLD criteria, 55 had pre-existing dementia or significant neurological conditions, 42 declined participation, 25 had MMSE <24, and 20 due to other reasons). Consequently, 360 eligible participants were randomized: 180 to the omega-3 PUFA group and 180 to the placebo group. Overall, 302 (83.9%) participants completed the 24-month study (153 [85.0%] in the omega-3 group and 149 [82.8%] in the placebo group). Reasons for discontinuation were similar between groups and included withdrawal of consent (omega-3: n=10; placebo: n=12), loss to follow-up (omega-3: n=9; placebo: n=11), adverse events (omega-3: n=5; placebo: n=6), and other reasons (relocation, serious non-study related illness; omega-3: n=3; placebo: n=2).

The baseline demographic and clinical characteristics of the randomized participants were well-balanced between the two treatment groups (Table 1). The mean age of participants was 67.5 (SD 5.8) years, and 62.2% were female. The mean duration of formal education was 8.2 (SD 3.1) years. The mean GDS-30 score at baseline was 19.8 (SD 4.5), indicating moderate to severe depressive symptoms. The mean baseline ADAS-Cog-INA score was 12.5 (SD 4.1), and the mean MoCA-INA score was 22.1 (SD 2.8). Approximately 30% of participants were APOE ε4 carriers, with no significant difference between groups.

Baseline dietary fish intake, assessed by FFQ, indicated that the majority of participants consumed freshwater fish (*patin, gabus, nila*) 2-3 times per week on average, while marine fish consumption was generally lower, around once per week. There were no significant differences in estimated baseline EPA+DHA intake from diet between the groups (mean 250 mg/day, SD 120 mg/day). Approximately 45% of participants were on stable antidepressant medication at study entry, primarily selective serotonin reuptake inhibitors (SSRIs).

Adherence to study medication, assessed by pill counts, was high in both groups, with an average of 88.5% (SD 10.2%) in the omega-3 group and 89.1% (SD 9.8%) in the placebo group over the 24-month period (p=0.68) (Table 2). In the subsample (n=60) analyzed for plasma phospholipid fatty acids, the omega-3 group showed a significant increase in EPA and DHA levels from baseline to 12 months and 24 months (p<0.001 for both), while levels remained largely unchanged in the placebo group. At 24 months, mean total plasma EPA+DHA levels were 8.5 mol% (SD 1.8) in the omega-3 subgroup and 3.9 mol% (SD 1.1) in the placebo subgroup.

At 24 months, participants in the omega-3 PUFA group showed significantly less cognitive decline (a smaller increase in ADAS-Cog-INA scores) compared to those in the placebo group. The mean increase in ADAS-Cog-INA score from baseline was 1.9 (SE 0.4) points in the omega-3 group and 4.0 (SE 0.4) points in the placebo group. The adjusted mean difference between groups at 24 months was -2.1 points (95% CI: -3.8 to -0.4; p=0.018) in favor of the omega-3 group; MoCA-INA: The omega-3 group showed a significantly greater improvement in MoCA-INA scores compared to the placebo group at 24 months (adjusted mean difference: 1.5 points; 95% CI: 0.2 to 2.8; p=0.025). The omega-3 group experienced a mean increase of 1.2 (SE 0.3) points, while the placebo group showed a mean decrease of -0.3 (SE 0.3) points; Trail Making Test (TMT): For TMT Part B, the omega-3 group showed a significantly smaller increase in completion time (indicating better performance) compared to the placebo group at 24 months (adjusted mean difference: -15.2 seconds; 95% CI: -29.5 to -0.9; p=0.038). No significant difference was observed for TMT Part A (p=0.115); Rey Auditory Verbal Learning Test (RAVLT): The omega-3 group demonstrated significantly better performance on delayed recall at 24 months compared to the placebo group (adjusted mean difference: 1.1 words; 95% CI: 0.1 to 2.1; p=0.030). Differences in immediate recall (sum of trials 1-5) and recognition did not reach statistical significance (p=0.082 and p=0.150, respectively); Digit

Span & Verbal Fluency: No statistically significant differences were observed between the groups for changes in Digit Span (Forward or Backward) or Verbal Fluency (semantic or phonemic) scores (all p>0.10); GDS-30**:** Participants in the omega-3 group experienced a significantly greater reduction in depressive symptoms on the GDS-30 compared to the placebo group at 24 months (adjusted mean difference: -2.5 points; 95% CI: -4.4 to -0.6; p=0.011). The mean decrease was 6.8 (SE 0.6) points in the omega-3 group and 4.3 (SE 0.6) points in the placebo group; IADL & BADL: There were no statistically significant differences between the groups in changes in Lawton IADL scores (p=0.210) or Barthel Index scores (p=0.355) over 24 months, although both groups showed slight declines in IADL scores. Serum BDNF: Fasting serum BDNF levels increased significantly in the omega-3 group from a baseline mean of 20.1 (SD 5.5) pg/mL to 25.3 (SD 6.1) pg/mL at 24 months. In contrast, BDNF levels in the placebo group remained relatively stable (baseline: 19.8 (SD 5.2) pg/mL; 24 months: 20.5 (SD 5.8) pg/mL). The adjusted mean difference in change from baseline between groups at 24 months was 4.5 pg/mL (95% CI: 1.2 to 7.8; p=0.008) in favor of the omega-3 group; Serum hs-CRP: Serum hs-CRP levels decreased in the omega-3 group from a baseline median of 2.1 (IQR 1.0-3.5) mg/L to 1.7 (IQR 0.8-2.9) mg/L at 24 months. The placebo group showed a slight increase from a median of 2.0 (IQR 0.9-3.3) mg/L to 2.2 (IQR 1.1-3.6) mg/L. While the trend favored the omega-3 group, the difference in change (analyzed on log-transformed data) did not reach statistical significance (p=0.072).

In pre-specified exploratory subgroup analyses for the primary outcome (ADAS-Cog-INA change at 24 months), there was no statistically significant interaction between treatment effect and baseline depression severity (p for interaction = 0.31), APOE ε4 carrier status (p for interaction = 0.45), or baseline dietary fish intake (p for interaction = 0.28). However, point estimates suggested a potentially larger benefit in APOE ε4 non-carriers and those with lower baseline fish intake, though these observations require cautious interpretation due to the exploratory nature and limited power of subgroup analyses.

Omega-3 PUFA supplementation was generally well-tolerated. The overall incidence of AEs was similar between the omega-3 group (65.0%) and the placebo group (62.8%) (p=0.65). The most common AEs reported were mild gastrointestinal symptoms (eructation, dyspepsia, diarrhea), which were slightly more frequent in the omega-3 group (18.3%) compared to the placebo group (12.8%) (p=0.13), but were mostly transient and did not lead to discontinuation. There were no significant differences in the incidence of other AEs, including infections, musculoskeletal complaints, or cardiovascular events.

The number of SAEs was low and comparable between groups: 8 SAEs in 6 participants in the omega-3 group and 10 SAEs in 7 participants in the placebo group. None of the SAEs were considered by the investigators or DSMB to be related to the study intervention. No clinically significant differences were observed in laboratory safety parameters between the groups at 24 months.

4. Discussion

This 24-month, randomized, double-blind, placebo-controlled trial conducted in Palembang, Indonesia, demonstrated that long-term supplementation with 2.2 g/day of EPA-rich omega-3 PUFAs resulted in a statistically significant, albeit modest, attenuation of global cognitive decline, as measured by the ADAS-Cog-INA, in older adults with late-life depression. Furthermore, the omega-3 intervention led to significant improvements in specific cognitive domains (executive function as per TMT-B, and verbal memory as per RAVLT delayed recall), a reduction in depressive symptoms (GDS-30), and an increase in serum BDNF levels compared to placebo. These findings provide important evidence for the potential role of omega-3 PUFAs as a supportive therapeutic strategy for preserving cognitive function and improving mood in this vulnerable, and previously understudied, Southeast Asian population.[11,12]

Table 1. Baseline demographic and clinical characteristics of participants.

Characteristic	Omega-3 group (N=180)	Placebo group (N=180)	Total (N=360)	P-value
Sociodemographic data				
Age (years), Mean (SD)	67.4 (5.7)	67.6 (5.9)	67.5 (5.8)	0.78
Gender, N (%)				0.85
Female	111 (61.7%)	113 (62.8%)	224 (62.2%)	
Male	69 (38.3%)	67 (37.2%)	136 (37.8%)	
Education (years), Mean (SD)	8.1 (3.0)	8.3 (3.2)	8.2 (3.1)	0.62
Marital status, N (%)				0.91
Married	105 (58.3%)	107 (59.4%)	212 (58.9%)	
Widowed	60 (33.3%)	58 (32.2%)	118 (32.8%)	
Divorced/Separated	15 (8.3%)	15 (8.3%)	30 (8.3%)	
Living situation, N (%)				0.88
With family	155 (86.1%)	152 (84.4%)	307 (85.3%)	
Alone	25 (13.9%)	28 (15.6%)	53 (14.7%)	
Recruitment center, N (%)				0.95
Hospital X	70 (38.9%)	72 (40.0%)	142 (39.4%)	
Hospital Y	55 (30.6%)	53 (29.4%)	108 (30.0%)	
Private clinics	55 (30.6%)	55 (30.6%)	110 (30.6%)	
Clinical characteristics				
GDS-30 score, mean (SD)	19.7 (4.4)	19.9 (4.6)	19.8 (4.5)	0.71
ADAS-Cog-INA score, mean (SD)	12.4 (4.0)	12.6 (4.2)	12.5 (4.1)	0.66
MoCA-INA score, mean (SD)	22.0 (2.7)	22.2 (2.9)	22.1 (2.8)	0.59
MMSE score, mean (SD)	26.6 (1.7)	26.4 (1.9)	26.5 (1.8)	0.48
Duration of current MDE (months), Mean (SD)	10.5 (6.1)	10.8 (6.5)	10.7 (6.3)	0.69
History of prior MDE, N (%)	85 (47.2%)	89 (49.4%)	174 (48.3%)	0.72
APOE ε4 carrier, N (%)	53 (29.4%)	55 (30.6%)	108 (30.0%)	0.84
Antidepressant use at baseline, N (%)	80 (44.4%)	82 (45.6%)	162 (45.0%)	0.85
SSRI	72 (90.0% of users)	74 (90.2% of users)	146 (90.1%)	0.97
Other	8 (10.0% of users)	8 (9.8% of users)	16 (9.9%)	
Lifestyle & dietary factors				
Dietary EPA+DHA (mg/day from FFQ), Mean (SD)	248 (118)	252 (122)	250 (120)	0.79
Freshwater fish consumption (times/week), Median (IQR)	2.5 (2.0-3.0)	2.5 (2.0-3.0)	2.5 (2.0-3.0)	0.88
Marine fish consumption (times/week), Median (IQR)	1.0 (0.5-1.5)	1.0 (0.5-1.0)	1.0 (0.5-1.5)	0.75
Physical activity (PASE score), Mean (SD)	95.5 (30.2)	93.8 (31.5)	94.7 (30.8)	0.64
Smoking status, N (%)				0.92
Never smoker	130 (72.2%)	128 (71.1%)	258 (71.7%)	
Former smoker	35 (19.4%)	36 (20.0%)	71 (19.7%)	
Current smoker	15 (8.3%)	16 (8.9%)	31 (8.6%)	
Common comorbidities, N (%)				
Hypertension	75 (41.7%)	79 (43.9%)	154 (42.8%)	0.73
Diabetes mellitus type 2	38 (21.1%)	35 (19.4%)	73 (20.3%)	0.70
Dyslipidemia	62 (34.4%)	59 (32.8%)	121 (33.6%)	0.78

Notes: ADAS-Cog-INA Score: Alzheimer's Disease Assessment Scale-Cognitive Subscale (Indonesian version); GDS-30 Score: Geriatric Depression Scale (30 items); IQR: Interquartile Range; MDE: Major Depressive Episode; MMSE Score: Mini-Mental State Examination; MoCA-INA Score: Montreal Cognitive Assessment (Indonesian version); PASE: Physical Activity Scale for the Elderly.

Table 2. Adherence to study intervention and plasma phospholipid omega-3 fatty acid levels (Subsample N=60).

Parameter	Omega-3 Group	Placebo Group	P-value (Between Groups)
Adherence (Full Cohort, N=360)			
Mean adherence by pill count over 24 months, % (SD)	88.5 (10.2)	89.1 (9.8)	0.68
Plasma phospholipid fatty acids (Subsample, N=60)	**(n=30)**	**(n=30)**	
Eicosapentaenoic acid (EPA) (mol %)			
Baseline, mean (SD)	1.2 (0.4)	1.2 (0.5)	0.85
24 months, mean (SD)	5.0 (1.2)	1.4 (0.5)	<0.001
Change from baseline, mean (SD)	+3.8 (1.1)	+0.2 (0.3)	<0.001
P-value (Within Group Change from Baseline)	<0.001	0.15	
Docosahexaenoic acid (DHA) (mol %)			
Baseline, mean (SD)	2.5 (0.6)	2.6 (0.7)	0.70
24 months, mean (SD)	3.5 (0.9)	2.5 (0.7)	<0.001
Change from baseline, mean (SD)	+1.0 (0.7)	-0.1 (0.4)	<0.001
P-value (Within Group Change from Baseline)	<0.001	0.45	
Total EPA+DHA (mol %)			
Baseline, Mean (SD)	3.7 (0.8)	3.8 (0.9)	0.78
24 Months, mean (SD)	8.5 (1.8)	3.9 (1.1)	<0.001
Change from baseline, mean (SD)	+4.8 (1.5)	+0.1 (0.6)	<0.001
P-value (Within Group Change from Baseline)	<0.001	0.60	

Table 3. Primary and secondary efficacy outcomes at 24 months.

Outcome measure & unit	Group	Baseline mean (SD)	24-Month mean (SD)	Change from baseline mean (SE)	Adjusted mean difference (95% CI) [Omega-3 vs Placebo]	P-value
Primary cognitive outcome						
ADAS-Cog-INA score (points)	Omega-3	12.4 (4.0)	14.3 (4.3)	+1.9 (0.4)	-2.1 (-3.8 to -0.4)	0.018
	Placebo	12.6 (4.2)	16.6 (4.5)	+4.0 (0.4)		
Secondary cognitive outcomes						
MoCA-INA score (points)	Omega-3	22.0 (2.7)	23.2 (2.8)	+1.2 (0.3)	+1.5 (0.2 to 2.8)	0.025
	Placebo	22.2 (2.9)	21.9 (3.0)	-0.3 (0.3)		
TMT part B (seconds)	Omega-3	145.5 (35.2)	150.1 (38.5)	+4.6 (5.1)	-15.2 (-29.5 to -0.9)	0.038
	Placebo	143.8 (33.9)	163.6 (40.1)	+19.8 (5.5)		
TMT part A (seconds)	Omega-3	60.2 (15.1)	62.5 (16.0)	+2.3 (2.0)	-1.5 (-5.5 to 2.5)	0.115
	Placebo	59.8 (14.8)	63.6 (16.5)	+3.8 (2.1)		
RAVLT - Delayed recall (words)	Omega-3	5.2 (2.1)	5.8 (2.3)	+0.6 (0.3)	+1.1 (0.1 to 2.1)	0.030
	Placebo	5.1 (2.0)	4.6 (2.2)	-0.5 (0.3)		
RAVLT - Immediate recall (Trials 1-5 Sum) (words)	Omega-3	38.5 (7.5)	39.2 (7.8)	+0.7 (0.8)	+1.2 (-0.2 to 2.6)	0.082
	Placebo	38.1 (7.2)	37.6 (7.5)	-0.5 (0.8)		
RAVLT - Recognition (words)	Omega-3	13.5 (1.5)	13.7 (1.4)	+0.2 (0.2)	+0.3 (-0.2 to 0.8)	0.150
	Placebo	13.4 (1.6)	13.3 (1.5)	-0.1 (0.2)		
Digit Span - Total score	Omega-3	10.1 (2.5)	10.3 (2.6)	+0.2 (0.3)	+0.2 (-0.5 to 0.9)	0.582
	Placebo	10.0 (2.4)	10.0 (2.5)	0.0 (0.3)		
Verbal fluency - Total score (words)	Omega-3	28.5 (6.5)	29.0 (6.7)	+0.5 (0.7)	+0.6 (-1.0 to 2.2)	0.431
	Placebo	28.2 (6.3)	27.7 (6.6)	-0.1 (0.7)		
Secondary mood outcome						
GDS-30 score (points)	Omega-3	19.7 (4.4)	12.9 (4.0)	-6.8 (0.6)	-2.5 (-4.4 to -0.6)	0.011
	Placebo	19.9 (4.6)	15.6 (4.2)	-4.3 (0.6)		
Secondary functional outcomes						
Lawton IADL scale (points)	Omega-3	7.5 (0.8)	7.2 (1.0)	-0.3 (0.2)	+0.2 (-0.2 to 0.6)	0.210
	Placebo	7.4 (0.9)	6.9 (1.1)	-0.5 (0.2)		
Barthel index (ADL) (points)	Omega-3	98.5 (3.0)	98.0 (3.5)	-0.5 (0.5)	+0.3 (-0.8 to 1.4)	0.355
	Placebo	98.2 (3.2)	97.4 (3.8)	-0.8 (0.5)		

Notes: SD: Standard Deviation; SE: Standard Error; CI: Confidence Interval.

The observed effect size on the primary outcome, a mean difference of -2.1 points on the ADAS-Cog-INA, is comparable to or slightly larger than what has been reported for some symptomatic treatments for AD over shorter durations. While modest, this difference over a 2-year period could be clinically relevant in delaying the progression of cognitive symptoms that significantly impact daily life. The improvements seen in MoCA-INA scores further support a broader beneficial effect on cognitive function. The specific benefits in executive function and verbal memory are noteworthy, as these domains are commonly impaired in LLD and are critical for independent living. The lack of effect on some other cognitive measures, such as attention (Digit Span) and verbal fluency, might suggest a degree of domain specificity in the action of omega-3s or that the measures used were not sensitive enough to detect subtle changes in this population.[13,14]

The significant reduction in depressive symptoms in the omega-3 group is consistent with findings from several meta-analyses that support the antidepressant effects of omega-3 PUFAs, particularly those with higher EPA content, in individuals with MDD. It is plausible that the observed cognitive benefits are, in part, mediated by the improvement in depressive symptoms, as mood and cognition are closely intertwined. However, the increase in BDNF, a key neurotrophin involved in neuronal survival, synaptic plasticity, and neurogenesis, suggests a more direct neurobiological effect of omega-3s on brain health. Our finding of increased serum BDNF in the omega-3 group aligns with preclinical data and some human studies, suggesting that omega-3s may enhance neurotrophic support, thereby contributing to both antidepressant and pro-cognitive effects.[15,16]

We also observed a trend towards a reduction in hs-CRP, a marker of systemic inflammation, in the omega-3 group. Chronic low-grade inflammation is implicated in the pathophysiology of both depression and cognitive decline. Although the difference did not reach statistical significance in our study, possibly due to sample size or the relatively healthy inflammatory status of some participants at baseline, the anti-inflammatory properties of omega-3 PUFAs are well-documented and could contribute to the observed clinical benefits by mitigating neuroinflammation.[17,18]

This study is one of the few long-term RCTs of omega-3 supplementation for cognitive health in older adults with LLD, and to our knowledge, the first of its kind in an Indonesian population. The baseline dietary assessment in Palembang indicated a moderate intake of freshwater fish but relatively lower marine fish consumption, leading to an estimated average dietary EPA+DHA intake below levels generally considered optimal for significant neuroprotection (greater than 500 mg/day). This might have provided a favorable context for observing the effects of supplementation. The documented increase in plasma EPA+DHA levels in the supplemented group confirmed good adherence and bioavailability of the intervention. The study was strengthened by its randomized, double-blind, placebo-controlled design, long duration, comprehensive outcome assessments, and high retention rate.[19,20]

Several limitations should be considered when interpreting these findings. First, the study was conducted in a single city, Palembang, and while efforts were made to recruit from diverse settings, the generalizability of the findings to other regions of Indonesia or other ethnic groups with different dietary patterns and genetic backgrounds needs further investigation. Second, while the ADAS-Cog is a widely recognized tool, its sensitivity to change in populations without dementia or with milder cognitive impairment can vary. The use of a locally adapted version (ADAS-Cog-INA) is a strength, but cross-cultural validation is an ongoing process. Third, although we adjusted for baseline antidepressant use, we cannot entirely rule out interactions between the study supplement and ongoing psychotropic medications, though such changes were monitored and were similar between groups. Fourth, while we assessed dietary fish intake, quantifying precise baseline omega-3 status through red blood cell fatty acid analysis for all participants

would have been ideal for exploring interactions with baseline nutrient levels. Fifth, the lack of significant change in IADL scores might suggest that the observed cognitive benefits, while statistically significant, were not yet substantial enough to translate into major improvements in complex daily functioning over the 2-year period, or that the IADL scale was not sensitive enough. Finally, as with any study relying on self-report for adherence (pill counts) and dietary intake, some reporting bias is possible, although objective biomarker data from a subsample supported good adherence.

Despite these limitations, the findings of this study have important clinical and public health implications. Given the safety, tolerability, and relatively low cost of omega-3 PUFA supplements, they represent a potentially attractive adjunctive strategy for older adults with LLD in Palembang and similar settings, aimed at mitigating cognitive decline and improving mood. The positive results encourage further research into the optimal dosage, EPA:DHA ratio, and duration of supplementation for different populations and stages of cognitive impairment. Future studies could also explore the combination of omega-3s with other lifestyle interventions, such as physical activity or cognitive training, and investigate their effects on more direct measures of brain structure and function through neuroimaging. Understanding the role of genetic factors, such as APOE genotype, in modulating the response to omega-3s also warrants further exploration, although our exploratory subgroup analysis did not show a significant interaction.

5. Conclusion

In this 24-month randomized controlled trial in older adults with late-life depression in Palembang, Indonesia, daily supplementation with 2.2 grams of EPA-rich omega-3 polyunsaturated fatty acids resulted in a modest but statistically significant attenuation of global cognitive decline and improvements in specific cognitive domains, depressive symptoms, and serum BDNF levels compared to placebo. These findings suggest that long-term omega-3 PUFA supplementation may be a beneficial and well-tolerated adjunctive therapeutic approach for managing cognitive and affective symptoms in this vulnerable population. Further research is warranted to confirm these effects in larger and more diverse populations and to elucidate the underlying mechanisms more fully.

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