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Efficacy and acceptability of anti-inflammatory eicosapentaenoic acid for cognitive function in Alzheimer's dementia: A network *meta*-analysis of randomized, placebo-controlled trials with omega-3 fatty acids and FDA-approved pharmacotherapy

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Abbreviations: 95%Cis, 95% confidence intervals; AD, Alzheimer's dementia; ADAS-cog, Alzheimer's disease assessment scale-cognition subscale; ALA, alpha-lipoic acid; EPA/DHA ratio, eicosapentaenoic acid/docosahexaenoic acid ratio; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ExHi-n3PUFA-DHA, very high dosage (>2000 mg/day) omega-3 EPA/DHA ratio < 1; ExLong-High-Mem, very-long-term memantine high dose (<= 20mg/day); ExLong-Med-Gal, very-long-term galantamine medium dose (> 16 mg/day but <=24 mg/day); Hi-n3PUFA-EPA + ALA, ALA + high dosage (>1500 mg/day) omega-3 EPA/DHA ratio > 1; Hi-n3PUFA-EPA, high dosage (1500-2000 mg/day) omega-3 EPA/DHA ratio > 1; Long-High-Riv, long-term rivastigmine high dose (<= 12mg/day); MCI, mild cognitive impairment; Med-ExHigh-Don, medium-term donepezil very high dose (> 10mg/day); Med-ExHigh-Mem, medium-term memantine very high dose (<= 28mg/day); Med-ExHigh-Riv, medium-term rivastigmine patch very high dose 17.4mg/day (> patch 13.3mg/day); Med-High-Don, medium-term donepezil high dose (<= 10mg/day); Med-High-Gal, medium-term galantamine high dose (> 24 mg/day); Med-High-Mem + Med-High-Don, medium-term memantine high dose (<= 20mg/day) + donepezil high dose (<= 10mg/day); Med-High-Mem + Med-Low-Gal, medium-term memantine high dose (<= 20mg/day) + galantamine low dose (<= 16 mg/day); Med-High-Mem + Med-Med-Riv, medium-term memantine high dose (<= 20mg/day) + rivastigmine medium dosage (<= 6mg/day); Med-High-Mem, medium-term memantine high dose (<= 20mg/day); Med-High-Riv, medium-term rivastigmine high dose (<= 12mg/day); Med-High-RivPatch, medium-term rivastigmine patch high dose (<= patch 13.3mg/day); Med-Low-Riv, medium-term rivastigmine low dose 1-4 mg/day (<= 4mg/day); Med-Low-RivPatch, medium-term rivastigmine patch low dose (<= patch 4.6mg/day); Med-Med-Don, medium-term donepezil medium dose (<= 5mg/day); Med-Med-Gal, medium-term galantamine medium dose (> 16 mg/day but <=24 mg/day); Me-n3PUFA-pDHA, medium dosage (800-1500 mg/day) omega-3 pure DHA; MMSE, Mini-Mental State Examination; NMA, network *meta*-analysis; omega-3 PUFA, omega-3 polyunsaturated fatty acid; OR, odds ratio; Pla, Placebo/control; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBC, red blood cell; RCT, randomized controlled trial; Short-High-Don, short-term donepezil high dose (<= 10mg/day); Short-High-Gal, short-term galantamine high dose (> 24 mg/day); Short-High-Mem, short-term memantine high dose (<= 20mg/day); Short-High-Riv, short-term rivastigmine high dose 12 mg/day (<= 12mg/day); Short-Low-Gal, short-term galantamine low dose (<= 16 mg/day); Short-Med-Don, short-term donepezil medium dose (<= 5mg/day); Short-Med-Gal, short-term galantamine medium dose (> 16 mg/day but <=24 mg/day); SMD, standardized mean difference; Sou, Fortasyn Connect (souvenaid.

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ABSTRACT

Alzheimer's dementia (AD) is a major contributor to global disability, and effective therapies to modify disease progression are currently lacking. The neuro-inflammatory theory is a potential etiology underlying this neurodegenerative disease. Previous randomized, controlled trials (RCTs) have provided inconclusive results regarding efficacy of omega-3 polyunsaturated fatty acids (PUFAs) regimens, which might provide anti-inflammatory benefits in the management of AD, in improving cognitive function among participants with AD. The objective of this frequentist-model based network *meta*-analysis (NMA) was to evaluate the potential advantages of omega-3 PUFAs and currently FDA-approved medications for AD on overall cognitive function in AD individuals. The primary outcomes were: (1) changes in cognitive function, and (2) acceptability, which refers to all-cause discontinuation. Additionally, secondary outcomes included quality of life, behavioral disturbances and safety/tolerability, which was assessed through the frequency of any reported adverse event. This NMA included 52 RCTs (6 with omega-3 PUFAs and 46 with FDA-approved medications) involving 21,111 participants. The results showed that long-term high-dose (1500–2000 mg/day) of eicosapentaenoic acid (EPA)-dominant omega-3 PUFAs augmented with anti-oxidants had the highest potential for cognitive improvement among all investigated treatments [standardized mean difference = 3.00, 95% confidence intervals (95 %CIs) = 1.84–4.16]. Compared to placebo, omega-3 PUFAs had similar acceptability [odds ratio (OR) = 0.46, 95 %CIs = 0.04 to 5.87] and safety profiles (OR = 1.24, 95 %CIs = 0.66 to 2.33)o. These findings support the potential neurotherapeutic effects of high dosage EPA-dominant omega-3 PUFAs for the amelioration of cognitive decline in patients with AD. Future large-scale, long-term RCTs should focus on different dosages of EPA-dominant omega-3 PUFAs regimens on improving cognitive dysfunction in patients with AD at different levels of inflammatory status and psychopathology.

1. Introduction

The prevalence of Alzheimer's dementia (AD) is continuously increasing along with the expansion of aging populations worldwide, with rates reaching up to 32% in individuals over 85 years old (Hebert et al., 2013). In 2019, the estimated number of dementia cases globally was 57.4 million (Collaborators, 2022), with significant number of cases exhibiting biobehavioural disturbances that adversely affect the quality of life of people with AD and their caregivers (Gonzalez-Salvador et al., 2000). Several hypotheses have been proposed for the etiology of AD, including β-amyloid deposition, dysfunctional neurotransmitters, and neuro-inflammation. Pharmacologic or non-pharmacologic treatments had been developed to manage AD based on the aforementioned hypothesis.

The hypothesis of β-amyloid deposition has been a prominent area of interest in the management of AD (Lesne et al., 2006). However, pharmacological interventions targeting this hypothesis have yielded inconsistent and unsatisfactory results (Piller, 2022; Tampi et al., 2021; van Dyck et al., 2023). Regarding the neurotransmitter hypothesis, various pharmacological interventions have been developed for managing AD by modulating neurotransmitters. However, their efficacy and acceptability fall short of expectations, and unfortunately, they cannot modify the course of AD (Moore et al., 2014). There are two classes of FDA-approved medications that are recommended for AD patients, including cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) (Li et al., 2019) and glutamate antagonists (memantine) (Glinz et al., 2019). A previous network *meta*-analysis demonstrated the cognitive and behavioural benefit with pharmacological interventions (Thancharoen et al., 2019). Galantamine, rivastigmine patch, and oral rivastigmine showed modest functional or behavioral benefits compared to placebo, but had significantly higher treatment discontinuation rates than placebo. The safety profile and potential adverse effects of traditional pharmacotherapies are major concerns in AD management (Moore et al., 2014). Therefore, the development of novel neurotherapeutic agents that effective target cognitive dysfunction is an urgent unmet clinical need.

Recent research has shown growing evidence implicating the role of neuro-inflammatory theory in the pathophysiology of AD.. A mendelian randomization analysis conducted by Pagoni and colleagues found that several cytokines, including interleukin (IL)-8 and IL-2, have a causal effect on AD risk and cognitive decline (Pagoni et al., 2022). In the animal study, the increased systematic tumor necrosis factor-alpha (TNF-alpha) would contribute to cognitive dysfunction and exaggerated sickness behaviors in the mice with neurodegenerated brain (Hennessy et al., 2017). Similar evidences regarding neuroinflammatory theory could also be supported by the human studies. For example, Holmes and the colleagues noticed that the increased systemic

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inflammation and the increased serum TNF-alpha were associated with an increase in cognitive decline in AD subjects (Holmes et al., 2009). The aforementioned findings in the observational studies could be supported by the findings in other clinical studies. For example, the melatonin, which was found to have anti-oxidative effect (Reiter et al., 2016), demonstrated its potential efficacy in cognitive function in AD subjects (Tseng et al., 2022). Similarly, the high-frequency repetitive transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex had been proven to have anti-inflammatory effect in target and remote brain regions (Sasso et al., 2016), which had also been found to have beneficial effect on the cognitive function in AD subjects (Tseng et al., 2023).

Omega-3 polyunsaturated fatty acids (omega-3 PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have demonstrated multiple beneficial effects on cardiovascular/cerebrovascular (Bhatt et al., 2019; Chang et al., 2020; Chang et al., 2015; Iso et al., 2001) and neuropsychiatric diseases (Chang and Su, 2020; Satogami et al., 2019; Su et al., 2018), including AD (Knöchel et al., 2017). In addition, unlike traditional, approved pharmacological treatments, omega-3 PUFAs may have more favorable acceptability and, possibly, even efficacy (Chang et al., 2018). Omega-3 PUFAs are known to have several beneficial effects, including anti-inflammatory, anti-amyloid-β protein formation, cerebrovascular regulatory, neurogenetic, and modulatory effects upon synaptic membrane function (Borsini et al., 2017; Wigner et al., 2018; Zgórzyńska et al., 2017). Several epidemiologic studies demonstrated the association of a deficiency in omega-3 PUFAs with a higher risk of dementia. For example, total plasma omega-3 PUFAs levels were significantly lower in AD patients than in normally aging control groups (Conquer et al., 2000). Similarly, in another cognitive function study, there was a significantly positive association between mini-mental state examination (MMSE) scores and red blood cell (RBC) omega-3 PUFAs levels (Wang et al., 2008). Furthermore, another epidemiologic surveillance study demonstrated a protective effect of higher blood DHA levels against dementia or AD (Schaefer et al., 2006). In addition to its merits for cognitive function, a previous, large-scale *meta*-review demonstrated that omega-3 PUFAs had good safety profiles without definitive evidence of serious adverse effects or contraindications when combined with psychiatric medications (Firth et al., 2019).

Prior *in vivo* studies demonstrated that omega-3 PUFAs may prevent aggregation of amyloid-β proteins (Hooijmans et al., 2007; Oksman et al., 2006). However, previous pairwise *meta*-analyses (Araya-Quintanilla et al., 2020; Mazereeuw et al., 2012) provided conflicting findings about the efficacy of different omega-3 PUFAs regimens for cognitive function in participants with Alzheimer's disease. The efficacy and acceptability of omega-3 PUFAs might vary across dosages as well as different eicosapentaenoic acid/docosahexaenoic acid (EPA/DHA) ratios (Su et al., 2018), so that it would be inappropriate to merge different dosages or EPA/DHA ratios omega-3 PUFAs into one study group in *meta*-analyses. Therefore, the methodological limitation of pooling all different dosages or EPA/DHA ratios of omega-3 PUFAs into a single group might explain the conflicting findings reported by previous *meta*-analyses. Therefore, it is more appropriate to consider different dosages and EPA/DHA ratios of omega-3 PUFAs as different groups when assessing clinical effects.

A network *meta*-analysis (NMA) of existing RCTs does not only compares the efficacy or tolerability of treatments with placebo but also enables estimating the comparative efficacy and understanding the relative merits of multiple interventions (Davies et al., 2018), while also maximizing statistical power that cannot be achieved with traditional pairwise *meta*-analyses (Higgins and Welton, 2015; Naci et al., 2020). Therefore, the methodological merits of an NMA is better suited to study dosage-ratio dependent regimens, such as are relevant for omega-3 PUFAs (Tseng et al., 2022). The aim of this NMA was to compare the relative efficacy and acceptability of different dosages and of EPA/DHA ratios of omega-3 PUFAs regimens to elucidate the potential role of FDA-approved medications and omega-3 PUFAs in improving cognitive function or ameliorating cognitive decline in AD patients.

2. Materials and methods

2.1. General study guidelines

This NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Table S1) (Page et al., 2021) and the AMSTAR 2 appraisal tool (Shea et al., 2017). The current study complies with the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB: B-109–29) and has been registered in PROSPERO (CRD42022336051).

2.2. Search strategy and selection criteria

In the current NMA, we conducted a systematic review using ClinicalKey, Cochrane CENTRAL, Embase, ProQuest, PubMed, ScienceDirect, and Web of Science databases from database inception to May 28th, 2022. Furthermore, to search for unpublished studies, we conducted additional searches on ClinicalTrials.gov (Table S2). During the literature search, we intended to find and extract data from RCTs of (a) omega-3 PUFAs regimens or (b) oral medications with FDA-approval for cognition in AD. The aforementioned FDA-approved medications included donepezil, galantamine, rivastigmine, memantine, and Namzaric. In order to reduce the potential bias, we intended only to include RCTs with placebo or active controls, excluding studies using a waiting-list control. No language restriction was used. Additionally, manual searches were performed for potentially eligible articles selected from the reference lists of review articles, clinical guidelines, and pairwise *meta*-analyses (Araya-Quintanilla et al., 2020; Birks and Harvey, 2018; Cui et al., 2019; Dou et al., 2018; Glinz et al., 2019; Kishi et al., 2017; Koola et al., 2018; Li et al., 2019; McCleery and Sharpley, 2020; McShane et al., 2019; Sumsuzzman et al., 2021; Thancharoen et al., 2019; Urrestarazu and Iriarte, 2016; Wang et al., 2017; Watanabe et al., 2019; Wood et al., 2022; Zhang et al., 2016).

2.3. Inclusion and exclusion criteria

The PICO (population, intervention, comparison, outcome) setting of the current *meta*-analysis included: (1) P: patients diagnosed with AD; (2) I: omega-3 PUFAs regimens, donepezil, galantamine, rivastigmine, memantine, or Namzaric; (3) C: placebo-control or active-control; and (4) O: change in cognitive function, using a standardized assessment battery. Included were only peer-reviewed publications.

Exclusion criteria were: (1) not a clinical trial, (2) not an RCT, (3) not including only patients with AD, excluding also patients with minimal cognitive impairment, (4) not reporting *meta*-analyzable data of efficacy for cognition, and (5) not related to omega-3 PUFAs, donepezil, galantamine, rivastigmine, memantine, or namzaric. In cases of duplicated data usage (different articles based on the same sample sources), we included only the article with the largest sample size.

2.4. Data extraction

Two authors independently screened the studies and extracted the data. In cases of discrepancy, the corresponding author was consulted. If data were missing from published reports, corresponding authors or co-authors were contacted to obtain additional data.

2.5. Node definition

Because omega-3 PUFAs exert different efficacy according to dosage and EPA/DHA ratio (Su et al., 2018), we categorized the omega-3 PUFAs into "low-dosage (<800 mg/day)," "medium-dosage (800–1500 mg/day)," and "high-dosage (1500–2000 mg/day)", and "very high-dosage (>2000 mg/day)" groups, and "pure EPA", "EPA/DHA < 1", "EPA/DHA

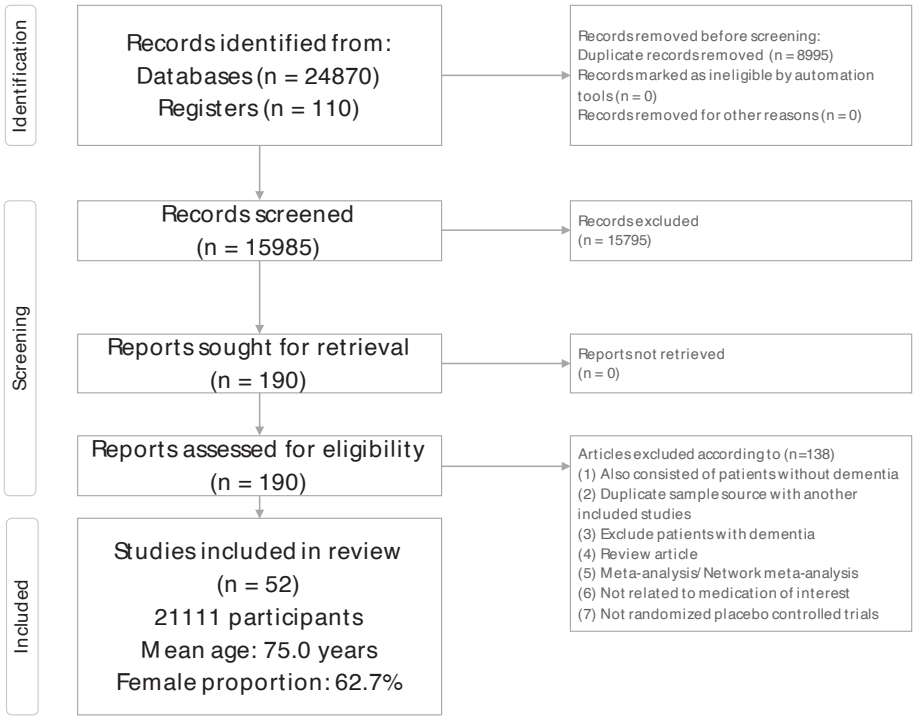

Fig. 1. Flowchart of the current network *meta*-analysis.

> 1", and "pure DHA" groups, instead of merging all omega-3 PUFAs into one group (Table S3). Also, because different dosages of individual dementia-managing medications may exert different efficacy on cognition in AD (Dou et al., 2018; Tseng et al., 2022), we also sub-grouped the individual dementia-managing medications according to their dosages. The detailed subgrouping of individual regimens is depicted in Table S3 based on the dosage subgroup proposed by Dou et al. (2018) (Dou et al., 2018) and by our previous NMA (Tseng et al., 2022) Further, in previous reports (Atri et al., 2008; Tseng et al., 2022), different efficacy of dementia-managing medications for improving cognition was found regarding different stratifications of treatment duration. Therefore, we categorized treatment arms according to different treatment durations defined in previous reports, i.e., "short term (<6 months)," "medium term (6 months - <1 year)," "long term (1 year to < 2 years)," and "very long-term (≥2 years)" (Atri et al., 2008; Tseng et al., 2022).

2.6. Outcomes

2.6.1. Primary outcomes

The primary outcomes were: (a) changes in cognitive function after treatment in patients with AD. and (b) acceptability defined as all-cause discontinuation. If studies assessed cognitive changes with different measurements, we chose the mini-mental status examination (MMSE) as the preferred measure because the MMSE: [a] has an approximately linear relationships with quality of life scores (association between Assessment of Quality of Life scale and MMSE scores: $r = 0.30$, $p < 0.0001$) (Wlodarczyk et al., 2004); [b] is widely used and accepted to serve as a surrogate measure of other time-consuming methods of staging dementia, such as the Clinical Dementia Rating (CDR) (Perneczky et al., 2006); [c] is significant for determining the time to clinically meaningful decline during longitudinal follow-up (Doody et al., 2001) and can serve as an index of disease progression and sequence of cognitive decline in patients with AD (Henneges et al., 2016); and [d] is suitable to evaluate AD patients across a wide range of severity, whereas the Alzheimer's Disease Assessment Scale-cognition subscale (ADAS-cog) is only suitable for patients with MMSE scores of ≥ 14 according to previous research (Mohs et al., 1997). If any of the potentially eligible RCTs did not provide MMSE measurements, we extracted the other cognition measurement as the primary outcome data in our NMA. In addition, all-cause discontinuation was defined as the percentage of patients dropping out for any reason before study completion.

2.6.2. Secondary outcomes and safety profile

Secondary outcomes were quality of life and behavioral disturbances. Safety/tolerability was assessed using the frequency of any adverse events reported in an intention-to-treat analysis.

2.7. Cochrane risk-of-bias tool and GRADE ratings

Two independent authors evaluated the risk of bias (interrater reliability = 0.87) for each domain according to the Cochrane risk-of-bias tool (Higgins and Green, 2009). We followed GRADE ratings recommendation in BMJ (Brignardello-Petersen et al., 2020) for quality assessment.

2.8. Statistical analysis

For continuous variables, we estimated the effect size using the standardized mean difference (SMD) with 95% confidence intervals (95 %CIs). For categorical variables, we used the odds ratio (OR) and 95% CIs and applied a 0.5-zero-cell correction during the *meta*-analysis. However, if zeroes were present in both the intervention and control arms of a study, we did not apply this correction procedure because of the risk of increasing the bias; instead, these studies were excluded from our analysis (Brockhaus et al., 2014; Cheng et al., 2016). We used the frequentist model of NMA to compare the effect size of studies with similar interventions. All comparisons were performed using a two-tailed *t*-test, and $p < 0.05$ was considered statistically significant. Heterogeneity among the included studies was evaluated using the tau value, which is the estimated standard deviation of the effect across the included studies.

We used mixed comparison with generalized linear mixed models to make direct and indirect comparisons (Tu, 2014). To compare multiple treatment arms, we combined the direct and indirect evidence from the

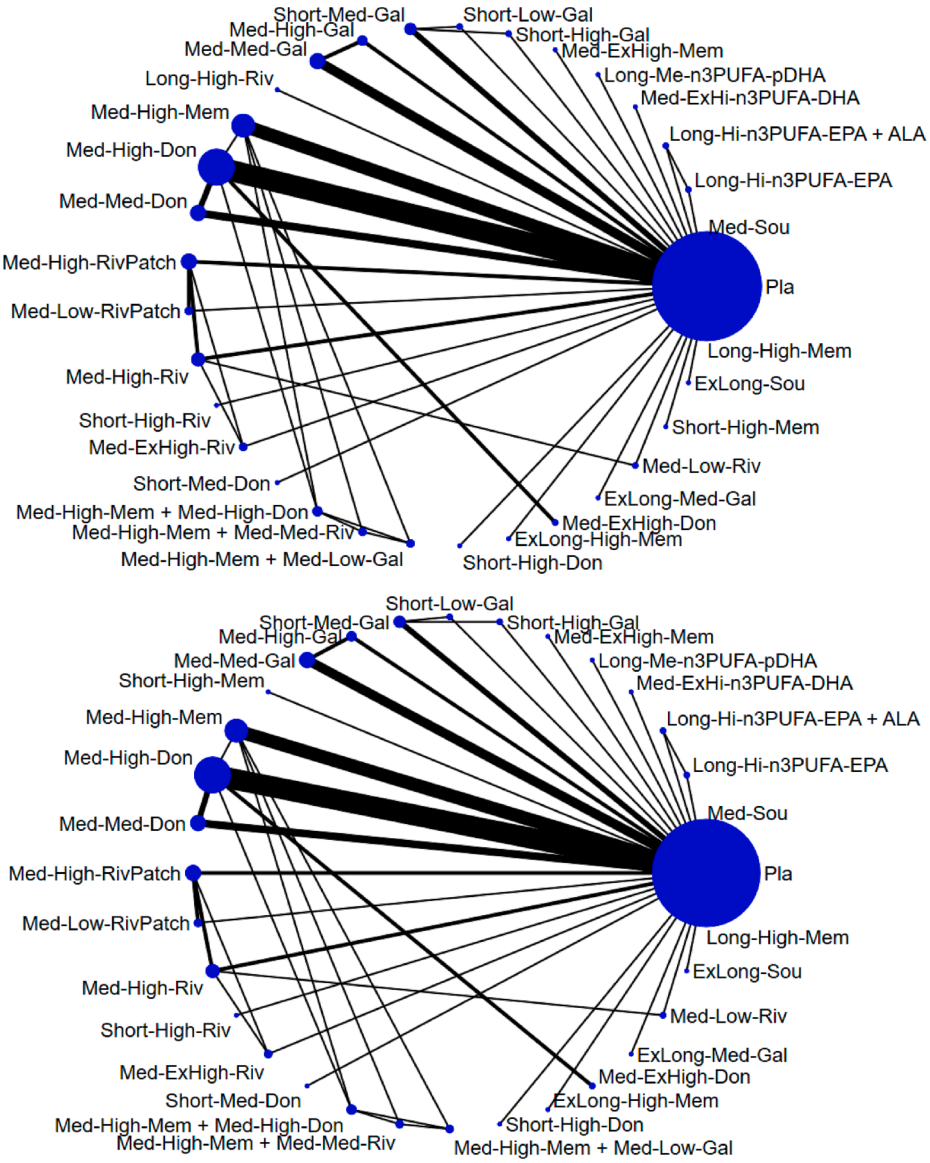

Fig. 2. The network structure of (A) changes in cognitive function and (B) acceptability in aspect of drop-out rate.

included studies (Lu and Ades, 2004). STATA version 16.0 (StataCorp Statistics/Data Analysis, StataCorp LLC, College Station, TX, USA) was used in our NMA with the *mvmeta* command (White, 2015). The restricted maximum likelihood method was used to evaluate the between-study variances (Kontopantelis et al., 2013). The surface under the cumulative ranking curve (SUCRA) (Salanti et al., 2011) was applied calculate the relative ranking probabilities of the treatment effects of all of the treatments for the target outcomes.

We evaluated the potential inconsistencies using the loop-specific approach, node-splitting method, and design-by-treatment model (Higgins et al., 2014). We used comparison-adjusted funnel plots and Egger's regression to evaluate the potentially small study effects in the order of efficacy of individual treatments (Chaimani et al., 2013). Finally, in order to reduce the potential bias of open-label treatments, we conducted a sensitivity subgroup analysis focusing only on placebo-controlled trials.

3. Results

Altogether, 190 articles were considered for full-text review (Fig. 1) and 138 were excluded for noted reasons (Table S4). Finally, 52 articles were included in the quantitative *meta*-analysis (Table S5). Fig. 2 depicts the entire network structure of the treatment arms.

3.1. Characteristics of included studies

Altogether, 21,111 participants were included in the current synthesis. The mean age of the participants was 75.0 (range = 65.2–85.7) years old), and the mean female proportion was 62.7% (range = 3.0%-84.5%). The mean treatment duration was 36.5 weeks (range = 6–208 weeks). The baseline characteristics of the included study participants are summarized in Table S5.

3.2. Primary outcome: (1) change in cognition

Compared to controls, long-term high-dosage (1500–2000 mg/day) EPA/DHA ratio > 1 omega-3 PUFAs augmented with alpha-lipoic acid (Hi-n3PUFA-EPA + ALA) (SMD = 3.00, 95 %CIs = 1.84 to 4.16), long-term rivastigmine high dose (<= 12 mg/day) (Long-High-Riv) (SMD = 1.51, 95 %CIs = 0.65 to 2.38), short-term rivastigmine high dose 12 mg/day (<= 12 mg/day) (Short-High-Riv) (SMD = 0.77, 95 %CIs = 0.03 to 1.51), medium-term memantine high dose (<= 20 mg/day) +

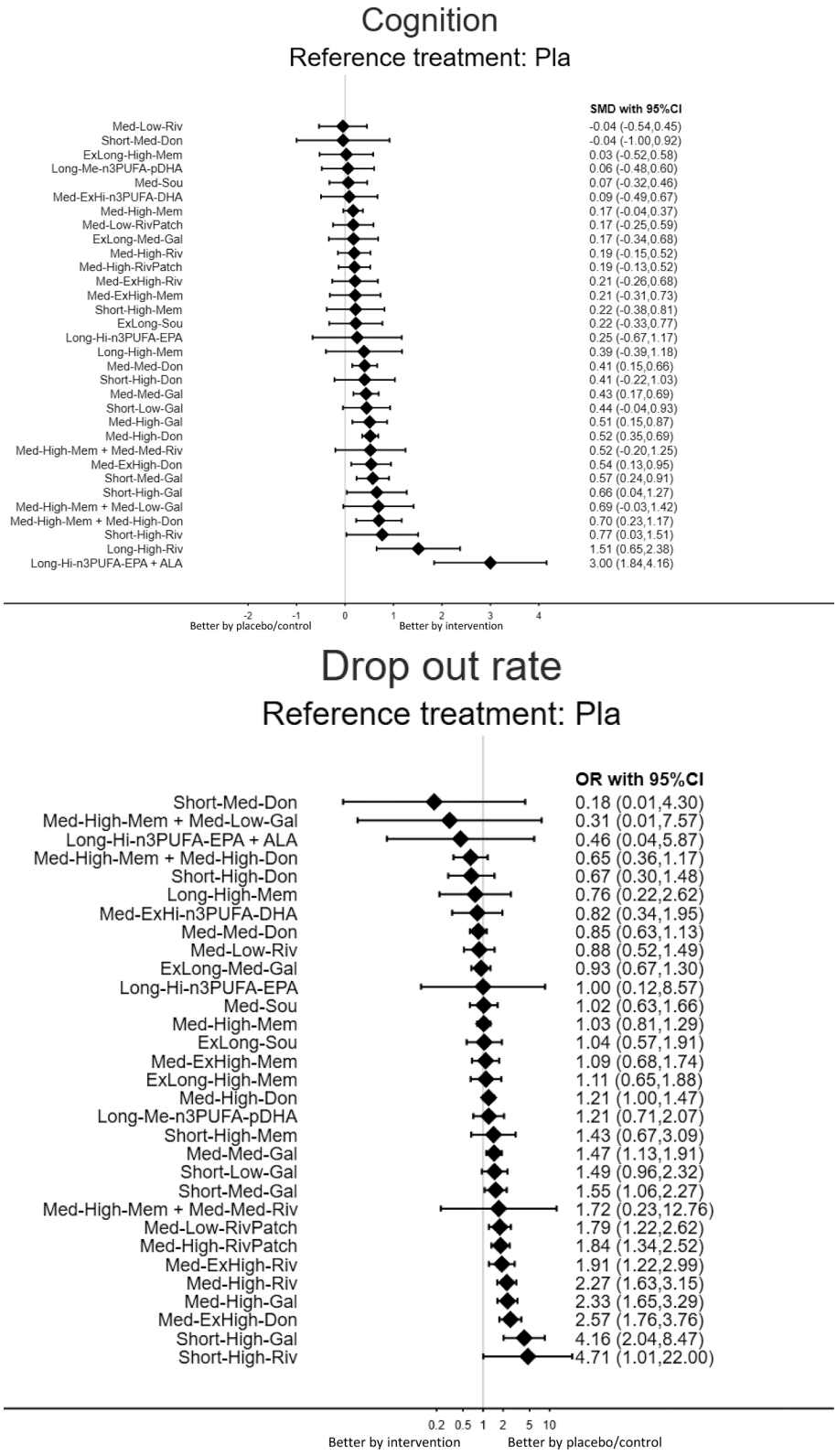

Fig. 3. Forest plot of (A) changes in cognitive function and (B) acceptability in aspect of drop-out rate.

donepezil high dose (<= 10 mg/day) (Med-High-Mem + Med-High-Don) (SMD = 0.70, 95 %CIs = 0.23 to 1.17), short-term galantamine high dose (>24 mg/day) (Short-High-Gal) (SMD = 0.66, 95 %CIs = 0.04 to 1.27), short-term galantamine medium dose (>16 mg/day but <=24 mg/day) (Short-Med-Gal) (SMD = 0.57, 95 %CIs = 0.24 to 0.91), medium-term donepezil very high dose (>10 mg/day) (Med-ExHigh-Don) (SMD = 0.54, 95 %CIs = 0.13 to 0.95), medium-term donepezil high dose (<= 10 mg/day) (Med-High-Don) (SMD = 0.52, 95 %CIs = 0.35 to 0.69), medium-term galantamine high dose (>24 mg/day) (Med-High-Gal) (SMD = 0.51, 95 %CIs = 0.15 to 0.87), medium-term galantamine medium dose (>16 mg/day but <=24 mg/day) (Med-Med-Gal) (SMD = 0.43, 95 %CIs = 0.17 to 0.69), and medium-term donepezil

Table 1A

League table of the primary outcome (1) improvement of cognition.

Long-Hi-n3PUFA-EPA + ALA																	***2.75 (1.74,3.76)**														***3.00 (1.95,4.05)**
***1.49 (0.04,2.93)**	Long-High-Riv																														***1.51 (0.81,2.22)**
***2.30 (1.05,3.55)**	0.81 (-0.17,1.80)	Med-High-Mem + Med-High-Don		-0.18 (-0.77,0.41)			***0.37 (0.15,0.59)**			-0.02 (-0.61,0.58)																	0.15 (-0.44,0.74)						
***2.23 (0.86,3.61)**	0.74 (-0.39,1.88)	-0.07 (-0.94,0.81)	Short-High-Riv																												***0.77 (0.23,1.31)**
***2.31 (0.94,3.68)**	0.82 (-0.30,1.95)	0.01 (-0.70,0.72)	0.08 (-0.96,1.11)	Med-High-Mem + Med-Low-Gal						0.17 (-0.43,0.76)																0.33 (-0.26,0.93)						
***2.34 (1.03,3.66)**	0.86 (-0.20,1.92)	0.04 (-0.73,0.82)	0.11 (-0.85,1.08)	0.03 (-0.92,0.99)	Short-High-Gal	0.09 (-0.33,0.50)																									***0.65 (0.19,1.11)**
***2.43 (1.22,3.63)**	***0.94 (0.01,1.87)**	0.13 (-0.45,0.70)	0.20 (-0.62,1.01)	0.12 (-0.68,0.92)	0.08 (-0.53,0.69)	Short-Med-Gal						0.13 (-0.04,0.31)																			***0.58 (0.43,0.73)**
***2.48 (1.31,3.65)**	***0.99 (0.11,1.87)**	0.18 (-0.28,0.63)	0.25 (-0.51,1.01)	0.17 (-0.56,0.90)	0.14 (-0.51,0.78)	0.05 (-0.32,0.43)	Med-High-Don		-0.04 (-0.14,0.07)				0.36 (-0.01,0.74)													-0.07 (-0.38,0.23)						***0.58 (0.31,0.85)**
***2.49 (1.28,3.71)**	***1.00 (0.07,1.94)**	0.19 (-0.40,0.78)	0.26 (-0.56,1.08)	0.18 (-0.63,0.99)	0.15 (-0.57,0.86)	0.06 (-0.43,0.56)	0.01 (-0.38,0.41)	Med-High-Gal			0.03 (-0.12,0.18)																			***0.56 (0.41,0.71)**
***2.46 (1.23,3.69)**	***0.97 (0.02,1.93)**	0.16 (-0.43,0.75)	0.23 (-0.61,1.08)	0.15 (-0.67,0.97)	0.12 (-0.63,0.86)	0.03 (-0.49,0.56)	-0.02 (-0.39,0.36)	-0.03 (-0.58,0.52)	Med-ExHigh-Don																						
***2.48 (1.11,3.84)**	0.99 (-0.14,2.11)	0.18 (-0.54,0.89)	0.24 (-0.79,1.28)	0.17 (-0.61,0.94)	0.13 (-0.82,1.08)	0.05 (-0.75,0.85)	-0.00 (-0.73,0.72)	-0.02 (-0.82,0.79)	0.01 (-0.80,0.83)	Med-High-Mem + Med-Med-Riv																0.17 (-0.43,0.76)						
***2.57 (1.38,3.76)**	***1.08 (0.18,1.98)**	0.27 (-0.27,0.80)	0.34 (-0.45,1.12)	0.26 (-0.51,1.03)	0.22 (-0.45,0.89)	0.14 (-0.28,0.57)	0.09 (-0.22,0.40)	0.08 (-0.28,0.44)	0.11 (-0.38,0.59)	0.09 (-0.68,0.86)	Med-Med-Gal																			***0.47 (0.34,0.60)**
***2.56 (1.30,3.81)**	***1.07 (0.08,2.06)**	0.26 (-0.42,0.93)	0.32 (-0.56,1.21)	0.25 (-0.63,1.12)	0.21 (-0.54,0.96)	0.13 (-0.36,0.62)	0.08 (-0.44,0.59)	0.06 (-0.54,0.67)	0.09 (-0.54,0.73)	0.08 (-0.79,0.95)	-0.01 (-0.56,0.54)	Short-Low-Gal																		***0.45 (0.28,0.62)**
***2.60 (1.41,3.78)**	***1.11 (0.21,2.01)**	0.29 (-0.22,0.81)	0.36 (-0.42,1.15)	0.29 (-0.48,1.05)	0.25 (-0.42,0.92)	0.17 (-0.25,0.59)	0.12 (-0.15,0.38)	0.10 (-0.34,0.55)	0.13 (-0.33,0.59)	0.12 (-0.64,0.88)	0.03 (-0.34,0.40)	0.04 (-0.51,0.59)	Med-Med-Don																	***0.60 (0.23,0.97)**
***2.59 (1.28,3.91)**	***1.11 (0.04,2.17)**	0.29 (-0.49,1.08)	0.36 (-0.60,1.33)	0.28 (-0.67,1.24)	0.25 (-0.63,1.13)	0.17 (-0.54,0.88)	0.12 (-0.53,0.76)	0.10 (-0.62,0.82)	0.13 (-0.61,0.88)	0.12 (-0.84,1.07)	0.03 (-0.65,0.70)	0.04 (-0.75,0.83)	-0.00 (-0.68,0.67)	Short-High-Don																***0.41 (0.03,0.78)**
***2.61 (1.21,4.01)**	1.12 (-0.05,2.29)	0.31 (-0.61,1.22)	0.38 (-0.70,1.46)	0.30 (-0.77,1.37)	0.26 (-0.74,1.26)	0.18 (-0.67,1.04)	0.13 (-0.67,0.93)	0.12 (-0.75,0.98)	0.15 (-0.74,1.03)	0.13 (-0.94,1.20)	0.04 (-0.79,0.87)	0.05 (-0.87,0.98)	0.01 (-0.81,0.84)	0.01 (-0.99,1.02)	Long-High-Mem														0.39 (-0.21,1.00)
***2.75 (1.62,3.88)**	***1.26 (0.00,2.52)**	0.45 (-0.58,1.48)	0.52 (-0.66,1.70)	0.44 (-0.73,1.61)	0.41 (-0.70,1.51)	0.32 (-0.66,1.30)	0.27 (-0.66,1.21)	0.26 (-0.73,1.25)	0.29 (-0.72,1.30)	0.27 (-0.90,1.44)	0.18 (-0.77,1.14)	0.19 (-0.85,1.24)	0.16 (-0.80,1.11)	0.16 (-0.96,1.27)	0.14 (-1.07,1.35)	Long-Hi-n3PUFA-EPA														0.25 (-0.52,1.02)
***2.78 (1.49,4.06)**	***1.29 (0.27,2.31)**	0.48 (-0.24,1.20)	0.55 (-0.37,1.47)	0.47 (-0.44,1.38)	0.43 (-0.39,1.26)	0.35 (-0.29,0.99)	0.30 (-0.28,0.87)	0.29 (-0.37,0.94)	0.32 (-0.37,1.00)	0.30 (-0.61,1.21)	0.21 (-0.40,0.82)	0.22 (-0.51,0.96)	0.18 (-0.42,0.79)	0.18 (-0.65,1.01)	0.17 (-0.79,1.13)	0.03 (-1.04,1.10)	ExLong-Sou													***0.22 (0.00,0.45)**
***2.78 (1.48,4.09)**	***1.29 (0.25,2.34)**	0.48 (-0.28,1.24)	0.55 (-0.40,1.50)	0.47 (-0.47,1.41)	0.44 (-0.42,1.30)	0.36 (-0.33,1.04)	0.30 (-0.32,0.92)	0.29 (-0.41,0.99)	0.32 (-0.40,1.04)	0.31 (-0.63,1.24)	0.22 (-0.44,0.87)	0.23 (-0.54,1.00)	0.19 (-0.46,0.84)	0.19 (-0.68,1.05)	0.17 (-0.81,1.16)	0.03 (-1.06,1.13)	0.00 (-0.81,0.81)	Short-High-Mem												0.22 (-0.10,0.54)
***2.79 (1.54,4.04)**	***1.31 (0.32,2.29)**	0.49 (-0.17,1.16)	0.56 (-0.31,1.44)	0.48 (-0.38,1.35)	0.45 (-0.33,1.23)	0.37 (-0.21,0.94)	0.31 (-0.19,0.81)	0.30 (-0.29,0.89)	0.33 (-0.29,0.95)	0.32 (-0.55,1.18)	0.23 (-0.31,0.76)	0.24 (-0.44,0.91)	0.20 (-0.34,0.73)	0.20 (-0.58,0.98)	0.18 (-0.73,1.10)	0.04 (-0.99,1.08)	0.02 (-0.71,0.74)	0.01 (-0.75,0.77)	Med-ExHigh-Riv		-0.06 (-0.22,0.10)	0.03 (-0.13,0.19)								***0.27 (0.11,0.43)**
***2.79 (1.52,4.06)**	***1.30 (0.29,2.31)**	0.49 (-0.21,1.19)	0.56 (-0.35,1.46)	0.48 (-0.41,1.37)	0.44 (-0.37,1.26)	0.36 (-0.26,0.98)	0.31 (-0.24,0.86)	0.30 (-0.34,0.93)	0.33 (-0.34,0.99)	0.21 (-0.58,1.21)	0.22 (-0.36,0.81)	0.23 (-0.48,0.95)	0.19 (-0.39,0.78)	0.19 (-0.62,1.01)	0.18 (-0.76,1.12)	0.04 (-1.02,1.10)	0.01 (-0.75,0.77)	0.01 (-0.79,0.80)	-0.00 (-0.71,0.70)	Med-ExHigh-Mem									***0.21 (0.06,0.36)**
***2.81 (1.60,4.01)**	***1.32 (0.40,2.24)**	0.51 (-0.07,1.08)	0.57 (-0.23,1.38)	0.50 (-0.30,1.29)	0.46 (-0.24,1.16)	0.38 (-0.09,0.85)	0.33 (-0.04,0.69)	0.31 (-0.17,0.80)	0.34 (-0.18,0.87)	0.33 (-0.46,1.12)	0.24 (-0.18,0.66)	0.25 (-0.34,0.84)	0.21 (-0.21,0.63)	0.21 (-0.49,0.92)	0.20 (-0.65,1.05)	0.06 (-0.92,1.03)	0.03 (-0.61,0.67)	0.02 (-0.66,0.70)	0.01 (-0.46,0.48)	0.02 (-0.60,0.63)	Med-High-RivPatch	0.07 (-0.06,0.19)		-0.02 (-0.26,0.21)						0.22 (-0.00,0.44)
***2.81 (1.60,4.02)**	***1.32 (0.40,2.25)**	0.51 (-0.07,1.09)	0.58 (-0.23,1.39)	0.50 (-0.30,1.30)	0.47 (-0.24,1.17)	0.38 (-0.09,0.86)	0.33 (-0.04,0.71)	0.32 (-0.17,0.81)	0.35 (-0.18,0.88)	0.34 (-0.46,1.13)	0.24 (-0.18,0.67)	0.26 (-0.34,0.85)	0.22 (-0.21,0.64)	0.22 (-0.49,0.93)	0.20 (-0.65,1.06)	0.06 (-0.92,1.04)	0.03 (-0.61,0.68)	0.03 (-0.65,0.71)	0.02 (-0.45,0.49)	0.02 (-0.60,0.64)	0.01 (-0.33,0.34)	Med-High-Riv							***0.26 (0.05,0.46)**	***0.24 (0.11,0.37)**
***2.83 (1.56,4.09)**	***1.34 (0.34,2.34)**	0.53 (-0.17,1.22)	0.59 (-0.30,1.49)	0.52 (-0.37,1.40)	0.48 (-0.32,1.28)	0.40 (-0.21,1.01)	0.35 (-0.19,0.88)	0.33 (-0.29,0.96)	0.36 (-0.29,1.02)	0.35 (-0.54,1.24)	0.26 (-0.31,0.83)	0.27 (-0.44,0.98)	0.23 (-0.34,0.80)	0.23 (-0.57,1.04)	0.22 (-0.72,1.15)	0.08 (-0.98,1.13)	0.05 (-0.70,0.80)	0.04 (-0.74,0.83)	0.03 (-0.66,0.73)	0.04 (-0.69,0.77)	0.02 (-0.58,0.63)	0.01 (-0.60,0.62)	ExLong-Med-Gal							***0.17 (0.08,0.27)**
***2.83 (1.60,4.06)**	***1.34 (0.38,2.30)**	0.53 (-0.10,1.16)	0.60 (-0.25,1.45)	0.52 (-0.32,1.36)	0.48 (-0.26,1.23)	0.40 (-0.13,0.94)	0.35 (-0.10,0.80)	0.34 (-0.21,0.89)	0.37 (-0.22,0.95)	0.35 (-0.48,1.19)	0.26 (-0.23,0.75)	0.27 (-0.37,0.92)	0.23 (-0.26,0.72)	0.23 (-0.52,0.99)	0.22 (-0.67,1.11)	0.08 (-0.93,1.09)	0.05 (-0.64,0.74)	0.05 (-0.68,0.77)	0.04 (-0.53,0.60)	0.04 (-0.63,0.71)	0.02 (-0.33,0.38)	0.02 (-0.44,0.48)	0.00 (-0.66,0.66)	Med-Low-RivPatch							0.00 (-0.18,0.18)
***2.83 (1.66,4.01)**	***1.35 (0.46,2.23)**	***0.53 (0.06,1.01)**	0.60 (-0.16,1.37)	0.52 (-0.19,1.24)	0.49 (-0.16,1.14)	*0.41 (0.02,0.80)	***0.35 (0.11,0.60)**	0.34 (-0.07,0.76)	0.37 (-0.08,0.82)	0.36 (-0.35,1.07)	0.27 (-0.06,0.60)	0.28 (-0.25,0.81)	0.24 (-0.08,0.56)	0.24 (-0.42,0.90)	0.23 (-0.58,1.04)	0.08 (-0.86,1.03)	0.06 (-0.53,0.64)	0.05 (-0.58,0.68)	0.04 (-0.47,0.55)	0.05 (-0.52,0.61)	0.03 (-0.36,0.41)	0.02 (-0.37,0.41)	0.01 (-0.54,0.56)	0.01 (-0.46,0.47)	Med-High-Mem							0.06 (-0.03,0.15)
***2.91 (1.61,4.21)**	***1.42 (0.38,2.47)**	0.61 (-0.14,1.36)	0.68 (-0.26,1.62)	0.60 (-0.33,1.53)	0.57 (-0.28,1.42)	0.49 (-0.19,1.16)	0.43 (-0.17,1.04)	0.42 (-0.26,1.11)	0.45 (-0.26,1.16)	0.44 (-0.49,1.37)	0.35 (-0.29,0.98)	0.36 (-0.40,1.12)	0.32 (-0.32,0.95)	0.32 (-0.54,1.17)	0.30 (-0.67,1.28)	0.16 (-0.93,1.25)	0.13 (-0.67,0.94)	0.13 (-0.70,0.96)	0.12 (-0.63,0.87)	0.12 (-0.66,0.91)	0.11 (-0.56,0.77)	0.10 (-0.57,0.77)	0.09 (-0.69,0.86)	0.08 (-0.63,0.80)	0.08 (-0.54,0.69)	Med-ExHi-n3PUFA-DHA						0.09 (-0.21,0.39)
***2.94 (1.66,4.22)**	***1.45 (0.44,2.47)**	0.64 (-0.08,1.35)	0.71 (-0.21,1.62)	0.63 (-0.27,1.53)	0.60 (-0.23,1.42)	0.51 (-0.12,1.15)	0.46 (-0.10,1.02)	0.45 (-0.20,1.10)	0.48 (-0.20,1.16)	0.46 (-0.44,1.37)	0.37 (-0.23,0.97)	0.38 (-0.34,1.11)	0.34 (-0.25,0.94)	0.35 (-0.48,1.17)	0.33 (-0.62,1.28)	0.19 (-0.88,1.26)	0.16 (-0.61,0.93)	0.16 (-0.65,0.96)	0.15 (-0.57,0.86)	0.15 (-0.60,0.90)	0.13 (-0.50,0.76)	0.13 (-0.51,0.76)	0.11 (-0.63,0.86)	0.11 (-0.57,0.79)	0.11 (-0.47,0.68)	0.03 (-0.77,0.82)	Long-Me-n3PUFA-pDHA						0.06 (-0.14,0.26)
***3.04 (1.53,4.55)**	***1.55 (0.26,2.84)**	0.74 (-0.33,1.81)	0.81 (-0.40,2.02)	0.73 (-0.47,1.93)	0.70 (-0.45,1.84)	0.61 (-0.40,1.63)	0.56 (-0.41,1.53)	0.55 (-0.48,1.57)	0.58 (-0.46,1.62)	0.56 (-0.64,1.77)	0.47 (-0.52,1.47)	0.48 (-0.59,1.56)	0.45 (-0.55,1.44)	0.45 (-0.70,1.59)	0.43 (-0.81,1.67)	0.29 (-1.04,1.62)	0.26 (-0.84,1.37)	0.26 (-0.87,1.39)	0.25 (-0.82,1.32)	0.25 (-0.84,1.34)	0.23 (-0.78,1.25)	0.23 (-0.79,1.25)	0.21 (-0.87,1.30)	0.21 (-0.84,1.26)	0.21 (-0.77,1.19)	0.13 (-0.99,1.25)	0.10 (-1.00,1.20)	Short-Med-Don					-0.04 (-0.86,0.78)
***2.93 (1.71,4.16)**	***1.45 (0.50,2.39)**	***0.63 (0.02,1.24)**	0.70 (-0.13,1.54)	0.62 (-0.20,1.45)	0.59 (-0.14,1.32)	0.51 (-0.01,1.02)	***0.45 (0.03,0.88)**	0.44 (-0.09,0.97)	0.47 (-0.10,1.04)	0.46 (-0.37,1.28)	0.37 (-0.10,0.84)	0.38 (-0.25,1.00)	0.34 (-0.13,0.81)	0.34 (-0.40,1.08)	0.32 (-0.55,1.20)	0.18 (-0.82,1.18)	0.16 (-0.52,0.83)	0.15 (-0.56,0.86)	0.14 (-0.47,0.75)	0.14 (-0.51,0.80)	0.13 (-0.38,0.64)	0.12 (-0.39,0.64)	0.11 (-0.54,0.75)	0.10 (-0.47,0.68)	0.10 (-0.34,0.54)	0.02 (-0.68,0.72)	-0.01 (-0.67,0.66)	-0.11 (-1.14,0.93)	Med-Sou			0.06 (-0.21,0.32)
***2.97 (1.69,4.26)**	***1.49 (0.46,2.51)**	0.67 (-0.05,1.40)	0.74 (-0.18,1.66)	0.66 (-0.25,1.57)	0.63 (-0.20,1.46)	0.55 (-0.10,1.19)	0.49 (-0.08,1.07)	0.48 (-0.18,1.14)	0.51 (-0.18,1.20)	0.50 (-0.41,1.41)	0.41 (-0.21,1.02)	0.42 (-0.32,1.15)	0.38 (-0.23,0.99)	0.38 (-0.46,1.21)	0.36 (-0.60,1.32)	0.22 (-0.85,1.30)	0.20 (-0.58,0.97)	0.19 (-0.62,1.00)	0.18 (-0.55,0.91)	0.18 (-0.58,0.94)	0.17 (-0.48,0.81)	0.16 (-0.49,0.81)	0.15 (-0.61,0.90)	0.14 (-0.55,0.84)	0.14 (-0.45,0.73)	0.06 (-0.74,0.86)	0.03 (-0.74,0.80)	-0.07 (-1.18,1.04)	0.04 (-0.64,0.72)	ExLong-High-Mem		0.03 (-0.21,0.26)
***3.04 (1.78,4.30)**	***1.56 (0.56,2.55)**	***0.74 (0.06,1.42)**	0.81 (-0.08,1.70)	0.73 (-0.14,1.61)	0.70 (-0.09,1.49)	***0.62 (0.02,1.21)**	***0.56 (0.04,1.09)**	0.55 (-0.06,1.16)	0.58 (-0.06,1.22)	0.57 (-0.31,1.44)	0.48 (-0.08,1.04)	0.49 (-0.21,1.18)	0.45 (-0.11,1.01)	0.45 (-0.35,1.25)	0.43 (-0.49,1.36)	0.29 (-0.75,1.34)	0.27 (-0.47,1.00)	0.26 (-0.51,1.04)	0.25 (-0.39,0.89)	0.25 (-0.47,0.97)	0.24 (-0.31,0.78)	0.23 (-0.26,0.73)	0.22 (-0.49,0.93)	0.21 (-0.40,0.83)	0.21 (-0.33,0.74)	0.13 (-0.63,0.90)	0.10 (-0.63,0.84)	0.00 (-1.08,1.08)	0.11 (-0.52,0.74)	0.07 (-0.67,0.81)	Med-Low-Riv	-0.02 (-0.21,0.18)
***3.00 (1.84,4.16)**	***1.51 (0.65,2.38)**	***0.70 (0.23,1.17)**	***0.77 (0.03,1.51)**	0.69 (-0.03,1.42)	***0.66 (0.04,1.27)**	***0.57 (0.24,0.91)**	***0.52 (0.35,0.69)**	***0.51 (0.15,0.87)**	***0.54 (0.13,0.95)**	0.52 (-0.20,1.25)	***0.43 (0.17,0.69)**	0.44 (-0.04,0.93)	***0.41 (0.15,0.66)**	0.41 (-0.22,1.03)	0.39 (-0.39,1.18)	0.25 (-0.67,1.17)	0.22 (-0.33,0.77)	0.22 (-0.38,0.81)	0.21 (-0.26,0.68)	0.21 (-0.31,0.73)	0.19 (-0.13,0.52)	0.19 (-0.15,0.52)	0.17 (-0.34,0.68)	0.17 (-0.25,0.59)	0.17 (-0.04,0.37)	0.09 (-0.49,0.67)	0.06 (-0.48,0.60)	-0.04 (-1.00,0.92)	0.07 (-0.32,0.46)	0.03 (-0.52,0.58)	-0.04 (-0.54,0.45)	Pla

Pairwise (upper-right portion) and network (lower-left portion) *meta*-analysis results are presented as estimated effect sizes for the outcome of improvement of cognition in patients with Alzheimer's dementia. Interventions are reported in order of mean ranking of cognition improvement, and outcomes are expressed as standardized mean difference (SMD) (95% confidence intervals). For the pairwise *meta*-analyses, SMD of>0 indicate that the treatment specified in the row had more improvement than that specified in the column. For the network *meta*-analysis (NMA), SMD of>0 indicate that the treatment specified in the column had more improvement than that specified in the row. Bold results marked with * indicate statistical significance.

Table 1B

League table of the primary outcome (2) acceptability in aspect of drop-out rate.

Short-Med-Don										0.18 (0.01,4.25)																				
0.28 (0.01,7.01)	Med-High-Mem + Med-High-Don		3.13 (0.12,83.33)								3.14 (0.12,81.35)								***0.51 (0.31,0.84)**				0.57 (0.07,4.74)								
0.28 (0.01,7.14)	0.97 (0.36,2.63)	Short-High-Don								0.67 (0.31,1.41)																				
0.59 (0.01,51.85)	2.07 (0.09,48.65)	2.13 (0.08,56.72)	Med-High-Mem + Med-Low-Gal								1.00 (0.02,52.63)												0.18 (0.01,4.02)								
0.22 (0.01,5.15)	0.77 (0.41,1.45)	0.79 (0.34,1.84)	0.37 (0.02,9.03)	Med-Med-Don						0.94 (0.71,1.23)								***0.60 (0.38,0.97)**												
0.40 (0.01,23.16)	1.41 (0.10,19.41)	1.45 (0.10,21.06)	0.68 (0.01,40.47)	1.85 (0.14,24.08)	Long-Hi-n3PUFA-EPA + ALA					0.46 (0.04,5.79)						0.46 (0.04,5.79)														
0.22 (0.01,5.91)	0.79 (0.28,2.27)	0.81 (0.25,2.65)	0.38 (0.01,10.39)	1.03 (0.41,2.58)	0.56 (0.04,8.28)	Med-ExHi-n3PUFA-DHA				0.82 (0.36,1.87)																				
0.21 (0.01,5.13)	0.74 (0.33,1.64)	0.76 (0.29,1.98)	0.36 (0.01,9.03)	0.97 (0.53,1.77)	0.52 (0.04,7.08)	0.94 (0.34,2.59)	Med-Low-Riv			1.09 (0.65,1.84)																***0.34 (0.22,0.53)**				
0.24 (0.01,7.14)	0.85 (0.22,3.36)	0.88 (0.20,3.82)	0.41 (0.01,12.54)	1.11 (0.31,3.96)	0.60 (0.04,10.25)	1.08 (0.24,4.88)	1.15 (0.30,4.42)	Long-High-Mem		0.76 (0.23,2.55)																				
0.20 (0.01,4.70)	0.70 (0.35,1.37)	0.72 (0.30,1.70)	0.34 (0.01,8.28)	0.91 (0.59,1.41)	0.49 (0.04,6.45)	0.88 (0.35,2.23)	0.94 (0.50,1.76)	0.82 (0.23,2.94)	ExLong-Med-Gal	0.93 (0.77,1.12)																				
0.18 (0.01,4.30)	0.65 (0.36,1.17)	0.67 (0.30,1.48)	0.31 (0.01,7.57)	0.85 (0.63,1.13)	0.46 (0.04,5.87)	0.82 (0.34,1.95)	0.88 (0.52,1.49)	0.76 (0.22,2.62)	0.93 (0.67,1.30)	Pla	1.05 (0.83,1.31)	0.99 (0.64,1.52)	0.96 (0.56,1.65)	0.92 (0.63,1.34)	0.90 (0.58,1.42)	1.00 (0.12,8.42)	0.82 (0.52,1.30)	0.81 (0.64,1.02)	0.70 (0.34,1.43)	0.68 (0.46,1.01)	***0.68 (0.53,0.88)**		***0.65 (0.46,0.91)**	***0.66 (0.43,1.00)**	***0.60 (0.40,0.91)**	***0.53 (0.34,0.82)**	***0.40 (0.25,0.64)**	***0.38 (0.27,0.53)**		***0.21 (0.05,0.97)**	***0.21 (0.09,0.45)**
0.18 (0.01,4.23)	0.63 (0.34,1.18)	0.65 (0.28,1.49)	0.31 (0.01,7.40)	0.83 (0.57,1.19)	0.45 (0.03,5.79)	0.80 (0.32,1.96)	0.85 (0.48,1.52)	0.74 (0.21,2.61)	0.91 (0.61,1.36)	0.97 (0.77,1.23)	Med-High-Mem							1.35 (0.78,2.34)				0.18 (0.01,4.02)								
0.18 (0.01,4.36)	0.63 (0.30,1.36)	0.65 (0.26,1.66)	0.31 (0.01,7.67)	0.83 (0.47,1.45)	0.45 (0.03,6.00)	0.80 (0.30,2.16)	0.86 (0.42,1.75)	0.74 (0.20,2.80)	0.91 (0.51,1.63)	0.98 (0.60,1.58)	1.00 (0.59,1.71)	Med-Sou																		
0.18 (0.01,4.38)	0.62 (0.27,1.46)	0.64 (0.23,1.75)	0.30 (0.01,7.70)	0.81 (0.41,1.60)	0.44 (0.03,6.06)	0.79 (0.27,2.27)	0.84 (0.38,1.88)	0.73 (0.18,2.90)	0.89 (0.45,1.79)	0.96 (0.52,1.76)	0.98 (0.51,1.89)	0.98 (0.45,2.14)	ExLong-Sou																	
0.17 (0.01,4.08)	0.59 (0.28,1.27)	0.61 (0.24,1.54)	0.29 (0.01,7.18)	0.78 (0.45,1.35)	0.42 (0.03,5.62)	0.75 (0.28,2.02)	0.80 (0.40,1.63)	0.70 (0.19,2.62)	0.85 (0.48,1.51)	0.92 (0.57,1.46)	0.94 (0.56,1.59)	0.94 (0.48,1.84)	0.95 (0.44,2.06)	Med-ExHigh-Mem																
0.17 (0.01,4.07)	0.59 (0.26,1.30)	0.60 (0.23,1.57)	0.28 (0.01,7.16)	0.77 (0.42,1.40)	0.41 (0.03,5.61)	0.74 (0.27,2.05)	0.79 (0.38,1.68)	0.69 (0.18,2.65)	0.84 (0.45,1.57)	0.90 (0.53,1.54)	0.93 (0.52,1.65)	0.93 (0.45,1.89)	0.94 (0.42,2.11)	0.99 (0.49,2.00)	ExLong-High-Mem															
0.18 (0.00,8.35)	0.65 (0.07,6.02)	0.67 (0.07,6.60)	0.31 (0.01,14.61)	0.85 (0.10,7.40)	0.46 (0.04,5.87)	0.82 (0.08,8.32)	0.88 (0.10,8.01)	0.76 (0.06,9.08)	0.93 (0.11,8.18)	1.00 (0.12,8.57)	1.03 (0.12,8.90)	1.02 (0.11,9.25)	1.04 (0.11,9.71)	1.09 (0.12,9.84)	1.11 (0.12,10.10)	Long-Hi-n3PUFA-EPA														
0.15 (0.01,3.70)	0.53 (0.24,1.18)	0.55 (0.21,1.43)	0.26 (0.01,8.52)	0.70 (0.38,1.28)	0.38 (0.03,5.11)	0.67 (0.24,1.87)	0.72 (0.34,1.53)	0.63 (0.16,2.41)	0.77 (0.41,1.43)	0.82 (0.48,1.40)	0.84 (0.47,1.51)	0.84 (0.41,1.73)	0.86 (0.38,1.92)	0.90 (0.44,1.82)	0.91 (0.43,1.93)	0.82 (0.09,7.53)	Long-Me-n3PUFA-pDHA													
0.15 (0.01,3.58)	***0.54 (0.30,0.94)**	0.55 (0.24,1.25)	0.26 (0.01,6.24)	***0.70 (0.52,0.94)**	0.38 (0.03,4.89)	0.68 (0.28,1.65)	0.72 (0.41,1.27)	0.63 (0.18,2.20)	0.77 (0.52,1.13)	0.83 (0.68,1.00)	0.85 (0.64,1.13)	0.85 (0.50,1.42)	0.86 (0.45,1.63)	0.90 (0.54,1.50)	0.91 (0.52,1.60)	0.83 (0.10,7.14)	1.00 (0.57,1.77)	Med-High-Don									***0.47 (0.37,0.60)**		
0.13 (0.01,3.29)	0.45 (0.17,1.19)	0.47 (0.15,1.41)	0.22 (0.01,5.79)	0.59 (0.26,1.34)	0.32 (0.02,4.59)	0.57 (0.18,1.82)	0.61 (0.24,1.55)	0.53 (0.12,2.28)	0.65 (0.28,1.50)	0.70 (0.32,1.50)	0.72 (0.32,1.60)	0.71 (0.29,1.77)	0.73 (0.27,1.94)	0.76 (0.31,1.87)	0.77 (0.30,1.96)	0.70 (0.07,6.83)	0.85 (0.33,2.15)	0.84 (0.38,1.86)	Short-High-Mem										
0.12 (0.01,2.98)	***0.43 (0.21,0.91)**	0.45 (0.18,1.12)	0.21 (0.01,5.24)	***0.57 (0.33,0.96)**	0.31 (0.02,4.09)	0.55 (0.21,1.46)	0.59 (0.29,1.17)	0.51 (0.14,1.90)	0.62 (0.36,1.08)	0.67 (0.43,1.04)	0.69 (0.42,1.13)	0.69 (0.36,1.32)	0.70 (0.33,1.48)	0.73 (0.38,1.39)	0.74 (0.37,1.48)	0.67 (0.07,6.01)	0.81 (0.41,1.63)	0.81 (0.50,1.32)	0.96 (0.40,2.33)	Short-Low-Gal			0.98 (0.68,1.41)							
0.13 (0.01,2.97)	***0.44 (0.23,0.85)**	0.45 (0.20,1.06)	0.21 (0.01,5.22)	***0.58 (0.39,0.85)**	0.31 (0.02,4.06)	0.56 (0.23,1.39)	0.60 (0.33,1.08)	0.52 (0.15,1.84)	***0.63 (0.42,0.97)**	***0.68 (0.52,0.89)**	***0.70 (0.49,0.99)**	0.70 (0.40,1.21)	0.71 (0.37,1.38)	0.74 (0.43,1.27)	0.75 (0.42,1.36)	0.68 (0.08,5.94)	0.83 (0.46,1.50)	0.83 (0.60,1.14)	0.98 (0.43,2.20)	1.02 (0.61,1.70)	Med-Med-Gal							***0.69 (0.51,0.93)**			
0.11 (0.00,4.48)	0.38 (0.05,2.68)	0.39 (0.04,3.35)	0.18 (0.01,4.07)	0.49 (0.07,3.71)	0.27 (0.01,6.83)	0.48 (0.05,4.23)	0.51 (0.06,4.05)	0.44 (0.04,4.66)	0.54 (0.07,4.12)	0.58 (0.08,4.31)	0.60 (0.08,4.44)	0.60 (0.08,4.67)	0.61 (0.07,4.92)	0.63 (0.08,4.97)	0.64 (0.08,5.10)	0.58 (0.03,10.97)	0.71 (0.09,5.61)	0.70 (0.10,5.19)	0.83 (0.10,7.12)	0.87 (0.11,6.75)	0.85 (0.11,6.43)	Med-High-Mem + Med-Med-Riv								
0.12 (0.00,2.85)	***0.42 (0.21,0.85)**	0.43 (0.18,1.05)	0.20 (0.01,5.01)	***0.55 (0.34,0.89)**	0.30 (0.02,3.91)	0.53 (0.20,1.37)	0.57 (0.29,1.09)	0.49 (0.13,1.80)	0.60 (0.36,1.00)	***0.65 (0.44,0.95)**	0.66 (0.42,1.04)	0.66 (0.36,1.22)	0.67 (0.33,1.38)	0.71 (0.39,1.29)	0.71 (0.37,1.37)	0.65 (0.07,5.73)	0.79 (0.41,1.51)	0.78 (0.51,1.20)	0.93 (0.39,2.18)	0.96 (0.63,1.48)	0.95 (0.60,1.51)	1.11 (0.14,8.55)	Short-Med-Gal								***0.40 (0.21,0.77)**
0.10 (0.00,2.46)	***0.36 (0.18,0.73)**	***0.37 (0.15,0.90)**	0.18 (0.01,4.33)	***0.47 (0.29,0.77)**	0.26 (0.02,3.38)	0.46 (0.18,1.18)	***0.49 (0.27,0.90)**	0.43 (0.12,1.55)	***0.52 (0.31,0.86)**	***0.56 (0.38,0.82)**	***0.57 (0.37,0.90)**	0.57 (0.31,1.06)	0.58 (0.28,1.19)	0.61 (0.33,1.12)	0.62 (0.32,1.19)	0.56 (0.06,4.95)	0.68 (0.35,1.31)	0.68 (0.44,1.04)	0.80 (0.34,1.89)	0.83 (0.46,1.50)	0.82 (0.51,1.30)	0.96 (0.13,7.39)	0.86 (0.50,1.49)	Med-Low-RivPatch	1.03 (0.81,1.31)					
0.10 (0.00,2.38)	***0.35 (0.18,0.69)**	***0.36 (0.15,0.86)**	0.17 (0.01,4.19)	***0.46 (0.30,0.71)**	0.25 (0.02,3.26)	0.45 (0.18,1.13)	***0.48 (0.27,0.83)**	0.41 (0.12,1.49)	***0.51 (0.32,0.80)**	***0.54 (0.40,0.75)**	***0.56 (0.38,0.83)**	***0.56 (0.31,0.99)**	0.57 (0.29,1.13)	0.59 (0.34,1.05)	0.60 (0.32,1.12)	0.54 (0.06,4.78)	0.66 (0.36,1.23)	***0.66 (0.46,0.95)**	0.78 (0.34,1.79)	0.81 (0.47,1.40)	0.80 (0.53,1.21)	0.94 (0.12,7.12)	0.84 (0.51,1.38)	0.97 (0.72,1.32)	Med-High-RivPatch	1.09 (0.73,1.61)	0.94 (0.70,1.25)			
0.10 (0.00,2.32)	***0.34 (0.16,0.71)**	***0.35 (0.14,0.87)**	0.16 (0.01,4.09)	***0.44 (0.26,0.76)**	0.24 (0.02,3.20)	0.43 (0.16,1.14)	***0.46 (0.24,0.87)**	0.40 (0.11,1.49)	***0.49 (0.28,0.85)**	***0.52 (0.33,0.82)**	***0.54 (0.32,0.89)**	0.54 (0.28,1.03)	0.55 (0.26,1.16)	0.57 (0.30,1.09)	0.58 (0.29,1.16)	0.52 (0.06,4.70)	0.64 (0.32,1.27)	0.63 (0.39,1.03)	0.75 (0.31,1.82)	0.78 (0.42,1.47)	0.77 (0.46,1.29)	0.90 (0.12,7.01)	0.81 (0.45,1.46)	0.94 (0.56,1.56)	0.96 (0.62,1.48)	Med-ExHigh-Riv	0.96 (0.64,1.42)			
0.08 (0.00,1.93)	***0.29 (0.14,0.56)**	***0.29 (0.12,0.70)**	0.14 (0.01,3.39)	***0.37 (0.24,0.58)**	0.20 (0.02,2.64)	***0.36 (0.14,0.91)**	***0.39 (0.23,0.64)**	0.34 (0.09,1.21)	***0.41 (0.26,0.65)**	***0.44 (0.32,0.61)**	***0.45 (0.30,0.68)**	***0.45 (0.25,0.81)**	***0.46 (0.23,0.92)**	***0.48 (0.27,0.85)**	***0.49 (0.26,0.91)**	0.44 (0.05,3.87)	0.54 (0.29,1.00)	***0.53 (0.36,0.78)**	0.63 (0.27,1.45)	0.66 (0.38,1.14)	***0.65 (0.42,0.99)**	0.76 (0.10,5.77)	0.68 (0.41,1.13)	0.79 (0.52,1.19)	0.81 (0.59,1.11)	0.84 (0.55,1.30)	Med-High-Riv				
0.08 (0.00,1.88)	***0.28 (0.14,0.55)**	***0.29 (0.12,0.68)**	0.13 (0.01,3.31)	***0.36 (0.23,0.57)**	0.20 (0.01,2.58)	***0.35 (0.14,0.90)**	***0.38 (0.20,0.71)**	0.33 (0.09,1.18)	***0.40 (0.25,0.64)**	***0.43 (0.30,0.61)**	***0.44 (0.29,0.67)**	***0.44 (0.24,0.79)**	***0.45 (0.22,0.90)**	***0.47 (0.26,0.84)**	***0.47 (0.25,0.89)**	0.43 (0.05,3.78)	***0.52 (0.28,0.98)**	***0.52 (0.35,0.77)**	0.61 (0.27,1.43)	0.64 (0.36,1.12)	***0.63 (0.45,0.88)**	0.74 (0.10,5.64)	0.66 (0.40,1.11)	0.77 (0.46,1.29)	0.79 (0.49,1.26)	0.82 (0.47,1.44)	0.97 (0.60,1.57)	Med-High-Gal			
0.07 (0.00,1.71)	***0.25 (0.13,0.48)**	***0.26 (0.11,0.63)**	0.12 (0.00,2.99)	***0.33 (0.21,0.51)**	0.18 (0.01,2.35)	***0.32 (0.12,0.82)**	***0.34 (0.18,0.65)**	0.30 (0.08,1.08)	v0.36 (0.22,0.60)	***0.39 (0.27,0.57)**	***0.40 (0.26,0.61)**	***0.40 (0.22,0.74)**	***0.41 (0.20,0.83)**	***0.42 (0.23,0.78)**	***0.43 (0.22,0.82)**	0.39 (0.04,3.45)	***0.47 (0.25,0.91)**	***0.47 (0.34,0.65)**	0.56 (0.24,1.31)	0.58 (0.32,1.04)	***0.57 (0.36,0.91)**	0.67 (0.09,5.07)	0.60 (0.35,1.03)	0.70 (0.41,1.19)	0.71 (0.44,1.17)	0.74 (0.41,1.34)	0.88 (0.53,1.46)	0.91 (0.54,1.51)	Med-ExHigh-Don		
0.04 (0.00,1.30)	***0.14 (0.03,0.72)**	***0.14 (0.02,0.80)**	0.07 (0.00,2.29)	***0.18 (0.04,0.86)**	0.10 (0.00,1.91)	0.17 (0.03,1.02)	***0.19 (0.04,0.95)**	0.16 (0.02,1.17)	***0.20 (0.04,0.95)**	***0.21 (0.05,0.99)**	0.22 (0.05,1.03)	0.22 (0.04,1.09)	0.22 (0.04,1.16)	0.23 (0.05,1.16)	0.23 (0.05,1.20)	0.21 (0.02,2.98)	0.26 (0.05,1.31)	0.26 (0.05,1.21)	0.30 (0.05,1.70)	0.32 (0.06,1.57)	0.31 (0.07,1.49)	0.36 (0.03,4.57)	0.33 (0.07,1.60)	0.38 (0.08,1.86)	0.39 (0.08,1.88)	0.41 (0.08,2.02)	0.48 (0.10,2.33)	0.49 (0.10,2.40)	0.55 (0.11,2.66)	Short-High-Riv	
0.04 (0.00,1.12)	***0.16 (0.06,0.39)**	***0.16 (0.05,0.47)**	0.08 (0.00,1.97)	***0.20 (0.09,0.44)**	0.11 (0.01,1.56)	***0.20 (0.06,0.61)**	***0.21 (0.09,0.51)**	***0.18 (0.04,0.76)**	***0.22 (0.10,0.49)**	***0.24 (0.12,0.49)**	***0.25 (0.12,0.52)**	***0.25 (0.10,0.58)**	***0.25 (0.10,0.64)**	***0.26 (0.11,0.62)**	***0.27 (0.11,0.65)**	0.24 (0.03,2.31)	***0.29 (0.12,0.71)**	***0.29 (0.14,0.61)**	***0.34 (0.12,0.98)**	***0.36 (0.17,0.78)**	***0.35 (0.17,0.75)**	0.41 (0.05,3.47)	***0.37 (0.19,0.73)**	***0.43 (0.19,0.97)**	***0.44 (0.20,0.96)**	0.46 (0.20,1.07)	0.55 (0.25,1.20)	0.56 (0.25,1.24)	0.62 (0.28,1.39)	1.13 (0.21,6.19)	Short-High-Gal

Pairwise (upper-right portion) and network (lower-left portion) *meta*-analysis results are presented as estimated effect sizes for the outcome of drop-out rate in patients with Alzheimer's dementia. Interventions are reported in order of mean ranking of acceptability, and outcomes are expressed as odds ratio (OR) (95% confidence intervals). For the pairwise *meta*-analyses, OR of<1 indicate that the treatment specified in the row had better acceptability than that specified in the column. For the network *meta*-analysis (NMA), OR of<1 indicate that the treatment specified in the column had better acceptability than that specified in the row. Bold results marked with * indicate statistical significance.

medium dose (<= 5 mg/day) (Med-Med-Don) (SMD = 0.41, 95 %CIs = 0.15 to 0.66) were associated with significantly better improvement in cognition (Table 1A, Fig. 2A, and Fig. 3A). According to the SUCRA, Hi-n3PUFA-EPA + ALA, Long-High-Riv were associated with the two best cognitive improvement (Table S6A).The subgroup analysis focusing on placebo-controlled RCTs revealed similar findings (Table S7A, Table S6B, Figure S1A, and Figure S2A).

3.3. Primary outcome: (2) acceptability reflected by dropout rates

Compared to controls, several FDA-approved pharmacotherapy but not the omega-PUFAs were associated with significantly higher dropout rates (Table 1B, Table S6C, Fig. 2B, and Fig. 3B).

3.4. Secondary outcome: Change in quality of life

Compared to controls, Med-High-Mem + Med-High-Don (SMD = -0.47, 95 %CIs = -0.86 to −0.09), and Med-High-Don (SMD = -0.27, 95 %CIs = -0.45 to −0.10) were associated with significantly better post-treatment quality of life (Table S7B, Table S6D, Figure S1B, and Figure S2B).

3.5. Secondary outcome: Changes in behavioral disturbances

Compared to controls only Short-High-Mem (SMD = -0.55, 95 %CIs = -0.98 to −0.13) were associated with significantly higher improvements in behavioral disturbances (Table S7C, Table S6E, Figure S1C, and Figure S2C).

3.6. Safety profile reflected by the frequency of any adverse events reported

Compared to controls, only souvenaid (Sou) (OR = 0.77, 95 %CIs = 0.59 to 1.00) was associated with significantly lower frequency of any adverse events. The other investigated omega-3 PUFAs supplements were not associated with significantly higher drop-out than controls. Conversely, compared to controls, several FDA-approved pharmacotherapies were associated with significantly higher frequency of any adverse event (Table S7D, Table S6F, Figure S1D, and Figure S2D).

3.7. Risk of bias, publication bias, inconsistency assessment, and GRADE ratings

Overall, we found that 74.7% (272/364 items), 23.1% (84/364 items), and 2.2% (8/364 items) of the included studies had a low, unclear, and high risk of bias, respectively. Unclear reporting of the allocation procedures and blinding of the participants or research personnel were the most often encountered reasons for high risk of bias (Figure S3A-S3B). Funnel plots were generally symmetrical (Figure S4A-S4D), and Egger's test indicated no significant publication bias among the articles included in the NMA. In general, the NMA did not demonstrate inconsistencies in terms of either local inconsistencies as assessed using the loop-specific approach and node-splitting method, or global inconsistencies according to the design-by-treatment method (Table S8-S10). The GRADE evaluation results are listed in the appendix. In brief, the overall quality of the evidence of the NMA was low to medium (Table S11).

4. Discussion

To the best of our knowledge, this is the first NMA providing an overview of the potential benefits of omega-3 PUFAs and the FDA-approved medications for AD (i.e., donepezil, rivastigmine, memantine, and galantamine) for patients with AD. The most important finding of the current NMA is that different dosages and treatment durations of FDA-approved medications as well as high-dosage (1500–2000 mg/day) EPA-dominant omega-3 PUFAs improved cognition, quality of life and behavioral disturbances in AD participants. Regarding specific effect of omega-3 PUFAs *plus* ALA on specific cognitive sub-categories, no RCTs addressing its efficacy on specific cognitive sub-categories. Furthermore, the omega-3 PUFAs supplement had similar fair acceptability regarding drop-out rate and safety profiles regarding the frequency of any adverse event compared with controls. Several hypotheses support the rationale of PUFA supplementation or medications to improve cognitive function in patients with AD. The most proposed hypotheses are: (a) anti-oxidant/anti-inflammatory effects, (b) anti-amyloid-β protein formation effects, and (c) cerebrovascular protective effects.

4.1. (a) Anti-oxidant/inflammasome hypothesis

The most relevant hypothesis regarding the efficacy of omega-3 PUFAs in AD management was the anti-inflammatory properties by omega-3 PUFAs. In previous research, AD been frequently associated with increased oxidative stress, thus, treatments with antioxidative stress effects might exert beneficial effects on cognitive function (Tonnies and Trushina, 2017; Tseng et al., 2022). Cholinesterase inhibitors, such as galantamine, donepezil, and rivastigmine, play an important role for the improvement of cognitive, functional and behavioral disturbance (Li et al., 2019). In animal studies, the omega-3 PUFAs and ALA was proven to exert antioxidant and anti-inflammatory activities (Nair et al., 2020) by reducing TNF-alpha levels, which might support their protective role in ameliorating cognitive decline in AD patients. Our findings suggest that the Hi-n3PUFA-EPA + ALA arm exhibited superior efficacy compared to the Hi-n3PUFA-EPA arm (Table 1A), which may indicate an additional benefit of ALA. This potential benefit could be attributed to the fact that EPA is one of the metabolites of ALA's metabolic pathway (Takic et al., 2022). However not all RCTs have supported the anti-oxidant/anti-inflammation hypothesis. In a recent RCT (Shinto et al., 2014), the authors demonstrated significantly improved cognitive function in patients with AD. However, the oxidative stress marker (i.e. peripheral F2-isoprostane levels) was not significantly improved. This inconsistency might be due to the measurement of different oxidative stress markers in different studies (F2-isoprostane vs TNF-alpha) (Shinto et al., 2014).

EPA helps to ameliorate decreased neurogenesis in the presence of IL-1β, whereas DHA can help in neurogenesis without this precondition (Borsini et al., 2021). EPA has an anti-apoptosis effect, while DHA has a pro-apoptosis effect in the presence of IL-1β (Borsini et al., 2021). Venlafaxine and EPA both provide anti-inflammatory effects, but DHA results in pro-inflammatory effects (Horowitz et al., 2014). The therapeutic strategies targeting metabolites and enzymes of the kynurenine pathway would be relevant therapeutic interventions as they are key factors that suppress neurogenesis and enhance neuro-apoptosis (Borsini et al., 2017). Therefore, EPA and DHA could enhance neuronal differentiation by alternative mechanisms (Katakura et al., 2013).

4.2. (b) Anti-amyloid-β protein formation hypothesis

Another hypothesized mechanism is antagonism of amyloid-β protein formation (Jicha and Markesbery, 2010). Donepezil decreases the level of amyloid precursor protein, and rivastigmine has some effect in modulating the formation of the amyloid precursor protein. The cell membranes of brain tissue with sufficient omega-3 PUFAs were found to prevent amyloid-β protein formation, reduce enzymatic augmentation of γ-secretase activity, and inhibit fibrillation of toxic amyloid-β protein (Hashimoto et al., 2008). Studies in tissue cultures (Oksman et al., 2006) and transgenic mice (Green et al., 2007) all support this ameliorating effect of omega-3 PUFAs on amyloid-β protein formation.

4.3. (c) cerebrovascular protective hypothesis

In our previous *meta*-analysis, cerebrovascular-protective medications (i.e. statins) were associated with a lower risk of dementia (Chu et al., 2018). The benefits of cerebrovascular protection include ensuring a sufficient supply of nutrients, enhanced removal of toxic metabolites, and better oxygenation of neurons, which was found to be a deficit in AD patients (Jicha and Markesbery, 2010).

In sum, the above evidence provides the mechanistic underpinnings for the observed efficacy of different treatments for cognition in AD patients. This NMA indicates that rivastigmine and omega-3 PUFAs supplementation has potent therapeutic effects on the improvement of cognition. These results might support the hypothesis that omega-3 PUFAs supplementation plus other antioxidants ameliorates the cognitive decline (or improves cognitive function) in AD patients through several different pathways associated with AD-related pathophysiology. However, FDA-approved anti-AD treatments were each associated with higher frequencies of adverse events than controls, limiting their clinical utility for AD management. Therefore, the evidence from this NMA provides a sound rationale for future large-scale RCTs to investigate the potential role and optimal dosing of omega-3 PUFAs and, possibly, other treatments investigating their benefit-to-risk ratio regarding cognition in patients with AD.

4.4. Strengths and limitations:

The current NMA has several strengths. First, due to the large numbers of included RCTs and participants (52 RCTs and 21,111 participants), the current NMA provides more information and robust evidence on the potential utility of omega-e PUFAs for cognition in AD than RCTs and traditional *meta*-analyses. Second, we only included RCTs to increase the reliability and validity of the current study. In addition, we also performed subgroup analyses of placebo-controlled trials to enhance the confidence in the findings of this study. Third, to inform clinical treatment choice, we included RCTs of FDA-approved regimens in the current study, which helps clinicians make relevant comparisons of omega-3 PUFAs with traditional pharmacologic interventions.

There are several limitations in the current NMA. First, some analyses in this study were limited by reduced statistical power, including heterogeneity in the participant characteristics (e.g., comorbid diseases, concomitant medications, wide age range, lack of uniform diagnostic criteria for AD, wide variety of rating scales of secondary outcomes, and different trial durations) and the small number of trials for some treatment arms (i.e., omega-3 PUFA supplements). Second, as addressed in the methods, as the treatment duration increased, the effects on cognition between dementia-managing medications and placebos were more significant (Riemersma-van der Lek et al., 2008). Nevertheless, the relatively overall short treatment duration among the included RCTs (mean duration = 36.5 weeks, range = 6–208 weeks) limits the results of the current NMA. Third, there might be heterogeneity regarding the initial severity of cognition, anxiety, behavioral dysregulation and quality of AD patients across the different studies, which could affect the outcomes. Fourth, we only included RCTs reporting efficacy of cognition. Therefore, any RCTs reporting on side effects or acceptability only, but not on cognition would have been excluded. We choose this restriction, in order to increase the methodological homogeneity in the recruited RCTs, as all the population and research methods were selected for the same study aim. However, this selection likely reduced the final numbers of the included RCTs. Finally, although our study is strengthened by comparing different treatments within an NMA methodology, generalization of our results is still limited and dependent on the included studies and the possible comparisons between studies. Future research is warranted to assess the efficacy of omega-3 PUFAs focusing on the optimal dosage and EPA-dominant or DHA-dominant as well as treatment duration for the alleviation of cognitive decline in AD in different medical settings.

5. Conclusion

The current network *meta*-analysis (NMA) provides evidence supporting the potential efficacy of several FDA approved treatments, particularly rivastigmine and high dose EPA-dominant omega-3 PUFAs for the amelioration of cognitive decline in AD patients. Furthermore, omega-3 PUFAs supplementation had the most favorable acceptability and safety profiles among all of the investigated treatments. These findings serve as a clear indication for further investigation into the efficacy of different medication and supplementation dosages of omega-3 PUFAs for cognitive dysfunction in AD patients through future, large-scale, methodologically robust, and longer-term RCTs.

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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Data availability

Data will be made available on request.

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The Institutional Review Board of the Tri-Service General Hospital has confirmed that no ethical approval is required (TSGHIRB: B-109-29). The current study did not direct involve individual participant so that we did not have the chance to approach individual participant or explore individual participant's information. Therefore, it would be impossible to obtain Consent to Participate in the current study.

Patient and public involvement reporting:

The current study did not direct involve individual participant so that we did not have the chance to approach individual participant or explore individual participant's information. Therefore, it would be impossible to obtain Consent to Publication in the current study.

Transparency statement

All the authors affirmed that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Authors' contributions:

Bing-Syuan Zeng, Mein-Woei Suen, Ping-Tao Tseng, and Yi-Cheng Wu, who contributed equally as first authors, took the whole responsibility of literature search, screen, data extraction, analysis, and manuscript drafting.

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Ming-Kung Wu, Yow-Ling Shiue, and Kuan-Pin Su, who contributed equally as corresponding authors, take the whole responsibility of concept formation, data curation, manuscript revision, and manuscript submission.

All authors approved the final submitted version of the manuscript.

Appendix

Table 1A.
Table 1B.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.04.017.

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