Systematic Review

The potential role of nutritional components in improving brain function among patients with Alzheimer's disease: a meta-analysis of RCT studies

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ABSTRACT

الأهداف: لمعرفة الدور المحتمل للمكونات الغذائية في تحسين وظائف المخ بين مرضى الزهايمر.

المنهجية: كانت العلاقة بين التغذية والوظيفة الدماغية في حالات مرض الزهايمر محور 19 تجربة معشاة ذات شواهد محتملة (المضبوطة) مع عينة بحثية مشتركة من 2297 مريض. تخضع هذه المضبوطة للمراجعة المنهجية والتحليل التلوي في الورقة الحالية.

النتائج: أظهرت النتائج أن الأحماض الدهنية الثانوية المشبعة الخالية من السلسلة (SFA) والأحماض الدهنية غير المشبعة (TFA) حدثت في تركيزات أعلى في أدمغة مرضى AD أكثر من مجموعة التحكم. علاوة على ذلك، كان سبب الالتهاب العصبي هو إعادة تشكيل الغشاء الدهني كما تأثرت الوظيفة الإدراكية لمرضى مرض التصلب العصبي المتعدد بالتغيرات في التيروزين والتريبتوفان والبيورين ومسارات توكوفيرول. علاوة على ذلك، في حالات مرض الزهايمر الخفيف إلى المعتدل، حدث انخفاض في الأداء الوظيفي عن طريق إعطاء ألفا توكوفيرول لأكثر من 12 شهرًا. استهلاك Souvenaid يساعد في تخليق متشابك، مما يعزز الاتصال الوظيفي. علاوة على ذلك، فإن استهلاك فيتامينات B الفولات والكوبالامين والبيريدوكسين بجرعات من 0.8 ملغ و 0.5 ملغ و 20 ملغ يوميًا ، على التوالي، على مدى فترة عام واحد أدى إلى انخفاض مستويات هرمونات الدم الحمراء في البلازما وضمور الدماغ.

الخلاصة: تحدث SFA و TFA الخالية من السلسلة بكميات أكبر في أدمغة الأفراد المصابين بمرض الزهايمر مقارنة بأولئك الذين ليس لديهم.

Objectives: To find out the potential role of nutritional components in improving brain function among patients with Alzheimer's disease (AD).

Methods: The correlation between nutrition and cerebral function in cases of AD has been the focus of 19 prospective randomised controlled trials (RCTs) with a combined research sample of 2297 patients. These RCTs are subject to systematic review and meta-analysis in the current paper.

Results: Findings showed that chain-free secondary saturated fatty acids (SFA) and trans fatty acids (TFA) occurred in higher concentrations in AD patients' brains than in controls. Furthermore, neuroinflammation was caused by remodelling of the lipid membrane and AD patients' cognitive function was impacted by alterations in tyrosine, tryptophan, purine, and tocopherol pathway metabolomics. Moreover, in cases of mild-to-moderate AD, reduction in functionality was induced by administration of alpha-tocopherol for more than 12 months. Consumption of Souvenaid helps in synaptic synthesis, which enhances functional connectivity. Furthermore, consumption of the B vitamins folate, cobalamin and pyridoxine at dosages of 0.8 mg, 0.5 mg and 20 mg per day, respectively, over a period of one year resulted in lower plasma tHcy levels and brain atrophy.

Conclusion: Chain-free SFA and TFA occur in greater amounts in the brains of individuals with AD than in those without AD.

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Life expectancy has recently increased enormously throughout the world, owing to development in medical sciences. As a result, the ageing population has expanded quickly, causing a phenomenal rise in the prevalence of late-life cognitive diseases like AD and vascular dementia (VaD).[1-3] Besides impacting cognition in ageing individuals, causing the brain to become atrophied and disrupting learning, cognitive, reasoning and communication capabilities, such conditions are also a significant burden from a social and economic perspective.[4] Dementia occurs in 5-8% of people older than 65, 15-20% of those older than 75 and 25-50% of those older than 85 years of age.[5] Age, gender, head trauma and CVD risk factors (e.g. cardiac disease, diabetes, high blood pressure, depression, high cholesterol, sedentarism, smoking, alcohol drinking) are among the known sporadic AD risk factors that are not of genetic origin.[6-8]

The creation of medication capable of deferring AD onset by disrupting and mitigating Aβ synthesis has been the aim of a number of clinical research trials and empirical work and has attracted ample annual investment from pharmaceutical companies. Even though such medication is yet to be formulated, drugs for symptom management do exist.[9] Thus, the approach toward drug development for AD, as well as the therapeutic role of nutrition in preventing AD, need to be reconsidered.

Evidence has been produced that AD risk and progression are diminished by diet-related components like antioxidants,[10,11] vitamins,[12-14] polyphenols,[15,16] and omega-3 fatty acids.[17,18] By contrast, saturated fatty acids[19] and simple carbohydrates[20] are considered to increase likelihood of AD development.[21] The RCTs carried out in the period 2010-2018 were reviewed in this paper to investigate whether AD patients' cognitive function can be enhanced based on nutritional constituents. To this end, a meta-analysis was conducted to establish the extent to which cerebral function in AD cases was influenced by nutrition-based treatments. Furthermore, subgroup meta-analyses were also carried out to determine conformance to nutrition plans, proportion of deaths due to general causes and AD, respectively, body weight (BW), lean body mass (LBW), life expectancy, quality of life (QoL), and development of additional neurodegenerative diseases.

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Methods. The literature was searched and around 2657 relevant studies were found, of which 294 were chosen for additional inspection on the basis of scrutiny of their titles and abstracts according to the established eligibility criteria. 275 out of the 294 were not included in the review and meta-analysis, leaving a final number of 23 studies that satisfied the inclusion and exclusion criteria.

The work conducted by Sofi and colleagues[22] on prospective RCTs analysing whether nutritional components influenced cerebral function in AD cases informed the research approach adopted in the present study. Thus, a combination of free text and MeSH terms (e.g. "Alzheimer's disease", "Alzheimer's dementia", "type 2 diabetes", "nutrition", "nutrient", "medical food", "randomised, double-blind controlled trial", "randomised, controlled trial", "randomised clinical trial", "prospective") was employed to search four electronic databases (i.e. PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials) for articles written in English and published between 2010 and 2018. Furthermore, to enrich the available data, the references from the chosen studies were screened as well. The most recent article was selected in cases where more than one article on the same study was available. A hierarchical strategy involving inspection of titles and abstracts coupled with accessibility of full-text article was adopted to determine whether the articles were relevant.

The articles had to be RCTs published in full and written in English to be included in the review. Furthermore, participants had to be older than 60 years of age and administered nutritional intervention for more than one month during therapy, without consideration for nutritional condition (i.e. well-nourished, malnourished, malnutrition risk). A standardised method of data extraction was used to derive a number of baseline attributes from the initial articles (e.g. main author, publication date, cohort nationality, sample size, number of outcomes, follow-up interval, age at entry, gender, results), which were incorporated in the meta-analysis. Data collection was undertaken by 2 investigators, with the third author (AC) intervening in the event of lack of agreement between the 2. Conformance to nutrition plans, proportion of deaths due to general causes and AD, respectively, body weight (BW), lean body mass (LBW), life expectancy, and quality of life (QoL) constituted the targeted outcomes.

Statistical analysis. The non-parametric statistical test known as Cochran's Q statistic and intended to assess if treatments yield the same outcomes was conducted to determine how heterogeneous the results of the chosen articles were. Heterogeneity was reflected

by a *p*-value of less than 0.10, while the degree of heterogeneity was measured based on the I^2 statistic and considered to be low for 25%, moderate for 50% and high for 75%. Furthermore, the combined incidence of MI and the equivalent odds and hazards ratios were calculated. The DerSimonian-Laird random-effects framework was applied when articles were markedly heterogeneous, whereas the fixed-effects framework was applied in all other cases. Two-tailed values were reported and the statistical significance of results was indicated by a *p*-value of less than 0.05, meaning that the confidence interval (C.I.) was 95%. A strategy of leave-one-out (LOO) sensitivity analysis was used where heterogeneity was high, with articles being eliminated successively to determine how they affected the combined results. The software program Review Manager (REVMAN) 5.3 Copenhagen (The Nordic Cochrane Center, The Cochrane Collaboration, 2014) was employed to conduct every statistical test.

Results. ***Patients characteristics.*** **Figure 1** shows the study selection procedure. **Table 1** provides the baseline features associated with AD and control cases. As can be seen in this table, the 23 chosen articles were published in the period 2010-2018, comprised a combined number of 2632 AD patients and 2441 controls, and the research was conducted in the US, Germany, Italy, France, the Netherlands, the UK, Sweden, Belgium, Spain, Singapore, and Norway. Male individuals accounted for 37.1% of the overall number participants (i.e. n=1305), and the patients had an average age of 75.8 years old.

Primary outcomes. Single antioxidants. According to the values of Chi^2 (2.86, *p*=0.70) and I^2 (0%), 5 articles concluded that the RCTs did not have marked heterogeneity regarding single antioxidant usage. Furthermore, single antioxidant and control did not differ regarding coenzyme Q (CoQ) concentration (MDIFF: -0.11: 95% CI, -0.65-0.43; *p*= 0.70; I^2=0%), as revealed by the random-effects model employed (**Table 2**).

Composite antioxidants. According to the values of Chi^2 (10.10, *p*=0.80) and I^2 (90%), 2 articles concluded that the RCTs did not have marked heterogeneity regarding composite antioxidant usage. Furthermore, composite antioxidant and control did not differ regarding the MMSE score at 16 weeks (MDIFF: 0.68: 95% CI, -4.70-6.06; *p*=0.80; I^2=90%), as revealed by the random-effects model employed (**Table 2**).

Omega-3. The 3 articles that examined Omega-3 found that the trials were not greatly heterogeneous, as reflected in the values of χ^2 (0.25, *p*=0.70) and I^2 (0%). Furthermore, Omega-3 and control did not differ regarding the MMSE score between baseline and 18 weeks (MDIFF: 0.13: 95% CI, -0.52-0.77; *p*=0.70; I^2 = 0%), as revealed by the random-effects model employed (**Table 3**).

Polymeric formula. The 3 articles that examined polymeric formula usage found that the trials were not greatly heterogeneous, as reflected in the values of χ^2 (0.12, *p*=0.94) and I^2 (0%). Furthermore, the polymeric formula and control did not differ regarding the treatment intervention (MDIFF: 0.06: 95% CI, -1.39-1.50; *p*=0.94; I^2 =0%), as revealed by the random-effects model employed (**Table 3**).

Docosahexaenoic acid (DHA). The 9 articles that examined DHA usage found that the trials were not

Table 2 - Comparison of single, composite antioxidant between AD patients and control group.

Study or Sub group				Control			Weight	Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI
**Single antioxidant*								
Arlt 2012	-2.1	3.7	12	-1.6	2.5	11	4.4%	-0.50 [-3.06,2.06]
De Waal 2014	25.1	2.9	86	25.4	2.7	93	43.0%	-0.30 [-1.12,0.52]
Dysken 2014	-0.95	3.65	115	-1.39	3.6	106	31.8%	0.44 [-0.52,1.40]
Galasko 2012	-1	2.5	25	-0.9	2.5	25	15.2%	-0.10 [-1.49,1.29]
Ringman 2012	-1.89	2.6	9	-0.45	2.6	11	5.6%	-1.44 [-3.73,0.85]
Total (95% CI)			247			246	100%	-0.11 [-0.65,0.43]
***Composite antioxidant*								
Galasko 2012	-2.8	2.9	28	-0.9	2.5	25	53.1%	-1.90 [-3.35,-0.45]
Shinto 2014	-1	2.42	12	-4.6	4.64	11	46.9%	3.60 [0.54,6.66]
Total (95% CI)			40			36	100%	0.68 [-4.70,6.06]

*Heterogeneity: Tau^2=0.00; Chi^2=2.86, df=4 (*p*=0.58); I^2=0%

Test for overall effect: Z=0.39 (*p*=0.70)

**Heterogeneity: Tau^2=13.63; Chi^2=10.10, df=1 (*p*=0.001); I^2=90%

Test for overall effect: Z=0.25 (*p*=0.80)

Table 1- Key features of the articles chosen for review.

N	Study/ Country/ Duration	Research design	Patients (n) / Gender (n) / Age (years)	Treatment	Key outcomes	Key results
1	Dysken et al., (2014) /USA / 4 years[23]	Double-blinded RCT with placebo control and parallel group	613/ Male=594 / 78.77 Y	1000 IU di-alpha-tocopherol acetate administered two times per day. 10 mg memantine administered two times per day, alpha-tocopherol and with memantine vs placebo	ADCS=ADL, MMSE, ADAS-cog, NPI, CAS, Dependence scale level	Brain functionality in mild-to-moderate AD cases taking an AChEI was improved by alpha-tocopherol, which helped to alleviate the burden on caregivers. No favourable clinical effects were derived from administration of memantine or memantine together with alpha-tocopherol.
2	Arlt et al., (2012) / Germany, France / -[24]	RCT	23/ Male=10; Female=13 / 70.7 Y	-	- MMSE, Toc, Asc, Lag, Rate	The overall MMSE score diminished in both groups following a period of half a year. These reduction was statistically significant from baseline to 12 months in the case of the vitamin group, but not in the case of the control group.
3	Ringman et al., (2012)/ USA / 24 wk, with an open label extension to 48 wk.[25]	Double-blind RCT with placebo control	30 / Female=19 / 73.5 Y	2 or 4 g curcumin administered two times per day in four capsules of 500 mg and placebo	ADAS-Cog, NPI, MMSE, ADCS, ADL, Ab1-40 and Ab1-42 levels in plasma, Ab1-42, T-tau, P-tau and F2 IsoPs levels in CSF	The Ab1-40 and Ab1-42 levels in plasma, the Ab1-42, T-tau, P-tau and F2 IsoPs levels in CSF, and the neuropsychological outcome measures were not markedly altered by intervention.
4	Galasko et al., (2012)/ USA/ 16 wk[26]	Double-blind RCT with placebo control	78 / Female=36 / 72.73 Y	800 IU vitamin E, 200 mg vitamin C and 600 mg alpha-lipoic acid administered thrice daily in three capsules and one capsule. 400 mg CoQ administered thrice daily in two wafers alongside placebo capsules and wafer	F2 IsoPslevel CSF, Ab-42 level, Tau level, P-tau181, MMSE, ADL	CSF biomarkers were unaffected by the antioxidants, implying that the combination had no beneficial effect on AD-related clinical or biochemical manifestation indices. The F2-isoprostane levels in CSF were markedly diminished by vitamin E, vitamin C and alpha-lipoic acid, but it was still unclear how this was clinically favourable. Intensified cognitive degeneration was observed in relation to administration of vitamin E, vitamin C and alpha-lipoic acid.
5	Faxén-Irving et al., (2013)/ Sweden/ 12 months[29]	Randomised double blind placebo-controlled study	174 / M : F=84:90 / 72.75 Y	430 mg DHA and 150 mg EPA administered in four capsules of 1 g per day or placebo in the form of 1 g corn oil, including 0.6 g linoleic acid. Every capsule was supplemented with 4 mg tocopherol.	MMSE, Plasma and CSF TTR, hs-CRP	It appeared that the plasma levels of TTR were maintained by supplementation with Omega-3. There was a direct correlation between plasma TTR and MMSE and an indirect correlation between plasma TTR and ADAS-Cog. A possible mechanism for cognitive function improvement by Omega-3 was proposed.
6	Quinn et al., (2010)/ USA /18 months[30]	Randomised double blind placebo-controlled trail	402 / Female=210 / 76 Y	1 g of algal DHA capsules administered two times a day and placebo	ADAS-cog, CDR, MMSE, ADCS-ADL, NPI, QoL, AD scale. Volumetric MRI for measuring the rate at which brain atrophied.	No outcome measure was improved by DHA supplementation. Subgroup analysis revealed that paired MRI scans did not reveal any modifications in the volume of the total brain, hippocampus or ventricles.

7	Shinto et al., (2013)/ USA / 12 months[28]	3-arm, parallel group, randomised, double blind, placebo-controlled pilot clinical trial	39 / M : F= 22:17 / 75.93 Y	Omega-3: 3 g per day of fish oil concentrated in the form of triglycerides 675 mg DHA together with 975 mg of EPA daily Omega-3 + EPA: 600 mg LA in racemic form administered as single tablet daily Placebo LA: no LA Placebo oil: soybean oil alongside 5% fish oil	F2-IsoPs, ADAS-cog, MMSE, ADL, IADL	Cognition and brain functionality were improved by Omega-3 combined with alpha-lipoic acid, but not by Omega-3 alone. The groups did not exhibit any difference regarding F2-IsoPs levels at one year. It seems that the combination demonstrates safety at the assessed concentrations.
8	Scheltens et al., (2010)/ Netherlands, Germany, UK and US / 12 wk, with possible extension of 12 wk.[39]	Double-blind, randomised, controlled, multicentre trial	161 / Male=106 / 73.7 Y	125 mL/d Fortasyn Connect: 300 mg EPA, 1200 mg DHA, 106 mg Phospholipids, 400 mg Choline, 625 mg UMP, 40 mg Vit E (alpha-TE), 80 mg Vit C, 60µg selenium, 3µg Vit B12, 1 mg Vit B6, 400 µg Folic acid.	WMS, modified ADAS- cog, ADCS-ADL, NPI, Quality of life AD, CIBIC-plus	The active and control groups did not differ in terms of cognitive, neuropsychiatric manifestations, functionality and overall performance outcome measures. Subgroup analysis on very mild AD revealed that the memory domain was considerably better in the active group than the placebo group.
9	Kamphuis et al., (2011)/ Netherlands, Germany, UK and US / 12 wk, with possible extension of 12 wk.	Secondary analyses from a double-blind, randomised, controlled, multicentre, proof-of concept trial.	161/ Male=106 / 73.7 Y	125 mL/d Fortasyn Connect: 300 mg EPA, 1200 mg DHA, 106 mg Phospholipids, 400 mg Choline, 625 mg UMP, 40 mg Vit E (alpha-TE), 80 mg Vit C, 60µg selenium, 3µg Vit B12, 1 mg Vit B6, 400 µg Folic acid.	ADCS-ADL, MMSE	By comparison to control, a notable better ADCS-ADL score at 12 weeks was recorded in a patient subgroup with low BMI at baseline in active intervention, suggesting functional performance enhancement.
10	Scheltens et al., (2012)/ Netherlands, Germany, Belgium, Spain, Italy and France / 24 Week[41]	Double-blind RCT with parallel groups and conducted across several countries (the Souvenir II study)	238 male patients, with 132 in the active group Average age: 73.8 years old	125 mL/d Fortasyn Connect: 300 mg EPA, 1200 mg DHA, 106 mg Phospholipids, 400 mg Choline, 625 mg UMP, 40 mg Vit E (alpha-TE), 80 mg Vit C, 60µg selenium, 3µg Vit B12, 1 mg Vit B6, 400 µg Folic acid.	EEG, NTB memory domain, NTB executive function domain, NTB total composite, ADAS-cog orientation task, LDST.	The active group displayed a substantial increase in the NTB memory domain. The delta band was the only frequency band that showed a marked discrepancy, according to the functional connectivity analysis. This was considered indicative of functional connectivity alteration, suggesting that the active product promoted improved synapse development in mild AD.
11	Shah et al., (2013)/ USA / 24 Week[33]	Double-blind, parallel RCT spanning a period of 24 weeks (S-Connect study)	254 female patients, with 139 in active group and 135 in control group Average age: 76.7 years old	125 mL (125 kcal) per day of Fortasyn Connect or an iso-caloric control product without Fortasyn Connect	ADAS-cog, Cognitive test battery, ADCS-ADL Scale, CDR-sob	Souvenaid supplementation to AD medication intervention resulted in cognitive degeneration in both groups, according to ADAS-cog.
12	de Waal et al.,. (2014)/ Netherlands, Germany, Belgium, Spain, Italy and France / 24 Week[27]	Double-blind, parallel RCT conducted across several countries over a period of 24 weeks (Souvenir II study)	159 male patients, with 47 in control group and 45 in active group Average age: 73.3 years old	125 mL per day of Fortasyn Connect (DHA, EPA, phospholipids, choline, UMP, vitamin B12, B6, and folate, vitamins C and E, and selenium), or an iso-caloric control product without Fortasyn Connect	EEG Phase Lag Index (PLI)	Local connectivity measurement via secondary analysis revealed that the active group displayed a marked beta band alteration at intervention finalisation, and unlike the control group, whose beta band underwent decrease, the beta band of the active group maintained stability.

13	Remington et al., (2015)/ USA / 36 months, following open label extension to 9 months[32]	A double-blind, multi site, phase II study	106 / Not reported / 77.8 Y	Nutraceutical formulation (NF) comprising 400 mg folic acid, 6 mg B12, 30 IU alpha-tocopherol, 400 mg SAM, 600 mg NAC and 500 mg ALCAR Placebo	DRS-2, CLOX-1, 12-item NPI, ADCS-ADL	The NF group showed improved cognitive outcome measures at three months, while the placebo group showed cognitive degeneration. The functional performance and neuropsychiatric symptoms of the two groups were largely similar.
14	Fonteh et al., (2014)/ USA / - [35]	RCT	139 / Female=83 / 77.2 Y	CSF collection, total protein, $A\beta_{42}$, and tau measures. CSF and fatty acid were respectively fractionated and extracted.	-	The AD group had markedly lower CSF $A\beta_{1-42}$ and markedly higher total CSF tau protein than the CH group, but in other respects, the groups did not differ.
15	Martín et al., (2010)/ Spain /-[38]	RCT	30 / Male=15, Female=15 / 65.9 Y	-	Unlike normal brains, AD brains showed abnormal lipid profiles in the lipid rafts, with especially low levels of n-3 long chain polyunsaturated fatty acids (LCPUFA, primarily 22:6n-3, docosahexaenoic acid) and monoenes (primarily 18:1n-9, oleic acid), coupled with diminished unsaturation and peroxidability indices.	Correlation analyses of all lipid variables showed that most bivariate relationships were similar between groups C > 60 and C <60. Only slight differences were detected for some lipid classes such PE (r=-0.862, p<0.005), sultatides (r = -0.863, p<0.005), and cerebrosides (r=-0.877, p<0.005), that were negatively correlated to SM in C<60 but not in C>60 groups. Similarly, CHO was negatively correlated to PE in C < 60 group (r=-0.693, p<0.05) but not in C > 60 group. The analyses revealed positive significant correlations for PC, PS, and PI versus DHA (r=0.593, p<0.01; r=0.714, p<0.001 and r=0.703, p<0.005 for PC, PS and PI, respectively)
16	Igarashi et al., (2011)/ USA/- [37]	RCT	19 / Not reported / 70.35 Y	The features of this progressive neurodegenerative disease include brain accumulation of senile (neuritic) plaques defined by amyloid-, neurofibrillary tangles, loss of synapses, neuroinflammation and excessive expression of arachidonic acid (AA, 20:4n-6)	-	The AD and control groups showed no marked differences regarding the mean levels of total brain lipids, phospholipids, cholesterol and triglycerides. Among the assessed phospholipids, only choline plasmalogen differed, with a considerable 73% reduction. The two groups displayed the same levels of fatty acid in total phospholipid.
17	Fraser et al., (2010)/ UK/ - [36]	RCT	123 / Female=68, Male=46 / 79.2 Y	Examination of fatty acid methyl esters and the content of fatty acids in the cerebral cortex	-	AD patients displayed marked decrease in stearic acid (18:0) in the frontal and temporal cortex and arachidonic acid (20:4n-6) in the temporal cortex, alongside elevated levels of oleic acid in the frontal and temporal cortex (18:1n-9) and palmitic acid (16:0) in the parietal cortex. Although AD patients exhibited greater fluctuation in DHA level compared to the control group, the mean values were largely similar. APOE genotype, age, sex or post-mortem delay had no influence on the content of fatty acid. Differentiating changes secondary to AD from changes contributing to the disease process calls for additional investigations.

18	Astarita et al.,. (2010)/ USA, Italy / - [34]	RCT	54 / Male=30; Female=24 / -	Docosahexaenoic acid levels in brain between AD and control	AD patients displayed dysfunctional docosahexaenoic acid biosynthesis in the liver due to suboptimal activity of the D-bifunctional protein, so that lower levels of this fatty acid with neuroprotection properties reached the brain.	Controls and AD patients differed significantly in every area, but the levels of eicosapentaenoic acid and docosapentaenoic acid were the same.
19	Kaddurah-Daouk et al., (2011)/ USA, Singapore / -[40]	RCT	30 / Male=8 /81 Y	Comparison of AD and control groups regarding neuropathology staging, levels of metabolites measured in ng/mL and selected metabolite ratios	AD patients displayed changes in tyrosine, tryptophan, purine, and tocopherol pathways, as revealed by regression models, correlations, Wilcoxon rank-sum tests and t tests applied to samples of postmortem ventricular cerebrospinal fluid from 15 AD patients and 15 non-demented patients with autopsy-confirmed diagnoses. Confirming earlier studies, decreases in norepinephrine and associated metabolites were noted as well.	The mean (SD) levels and ratios of metabolites in the AD and non-demented groups were determined. AD patients had markedly lover norepinephrine levels. There were correlations between metabolites and Braak (tangle) and CERAD (plaque) stages of nominal significance.
20	Douaud et al., (2013)/ UK / 2 years[42]	RCT	156 / Female=96 Male=60 / 76.5 Y	Baseline plasma levels, Baseline cognitive scores Between AD and control	According to the optimal Bayesian network, the plasma levels of vitamin B12 and folate were altered by the intervention, with solely B12 seeming to contribute to changes in tHcy levels, which in turn led to GM atrophy modification, leading to CDR-SOB alteration.	As indicated by regression analyses, GM loss was closely correlated with aggravation of CDR-SOB and MMSE scores, with particular bilateral accentuation in the amygdalohippocampal complex and entorhinal cortex. Unlike the placebo group, the group given B vitamins exhibited marked atrophy improvement in posterior areas of the brain, such as the bilateral hippocampus and parahippocampal gyrus, retrosplenial precuneus, lingual and fusiform gyrus, and the cerebellum.

21	Jager et al., (2012)/ UK, Norway / 2 years (43)	RCT	223 / Female=143 / 76.7 Y	Biochemical manifestations of the intervention The impact of the intervention on cognitive degeneration and on clinical outcomes	A longitudinal technique employing data from five time points and based on logistic regression with Generalised Linear Mixed Model (GLMM; binomial errors, logit link) was applied for examination of the HVLT-delayed recall (DR) score. The practice effects were diminished up to three months on the basis of the HVLT-DR score at three months as a starting point.	Compared to placebo, the group given B vitamins exhibited 30% lower mean plasma total homocysteine and stabilisation of executive function (CLOX). B vitamins were especially beneficial to patients with baseline homocysteine higher than the average of 11.3 mmol/L in terms of general cognition (MMSE), episodic memory (Hopkins Verbal Learning Test-delayed recall), and semantic memory (category fluency). B vitamins yielded clinical benefits for patients in the upper quartile of baseline homocysteine according to the global CDRS.
22	Kwok et al., (2011)/ Hong Kong / - [44]	RCT	140 / Female=89 / 78.15 Y	Comparison of supplementation and placebo in terms of plasma tHCY and serum vitamin B and folate at baseline and a year and a half	Mixed effect models that considered data at every follo-up time point and adjusted for baseline age, sex and diabetes revealed that the construction domain of MDRS at 24 months was the sole outcome variable that differed significantly between the groups	At a year and a half, plasma tHCY decreased by 33% compared to baseline in the intervention group, while it increased by 12% in the placebo group. The levels of vitamin B and folate in serum rose considerably in the supplement group, without any less-than-normal concentrations.
23	Smith et al., (2010)/ UK, Norway / -[45]	RCT	168 / Female=102 / 76.6 Y	Compliance, biological reaction to supplementation, factors related to atrophy rate in the placebo group, with atrophy rate being the key outcome	Serial volumetric MRI scans were the basis for evaluation of the alteration in the atrophy rate of the entire brain as the key outcome measure	The brain atrophied at a rate of 0.76% (95% CI, 0.63-0.90) and 1.08% (0.94-1.22) in the active and placebo groups, respectively. A correlation existed between response to intervention and homocysteine levels at baseline, with patients in the active group with .13 mmol/L homocysteine exhibiting 53% lower atrophy rate. Lower final cognitive test scores were correlated with a higher atrophy rate. Severe negative events did not differ between groups as per treatment category.

Table 3 - Comparison of Omega 3, Polymeric formula and Docosahexaenoic Acid between AD patients and control group.

Study or Sub group	Omega 3			Control			Weight	Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI
Faxen-Irving 2013	-0.8	2.78	89	-0.8	2.68	85	62.7%	0.00 [-0.81,0.81]
Quinn 2010	-3.7	5.82	238	-4.04	5.29	164	34.3%	0.34 [-0.76,1.44]
Shinto 2014	-4.3	4.31	11	-4.6	4.64	11	2.9%	0.30 [-3.44,4.04]
Total (95% CI)			338			260	100%	0.13 [-0.52,0.77]
Heterogeneity: Tau^2=0.00; Chi^2=0.25, df=2 (p=0.88); I^2=0%								
Test for overall effect: Z=0.38 (p=0.70)								
Study or Sub group	**Polymeric formula**			**Control**			**Weight**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Random, 95% CI**
Kamphuis 2011	1.2	10.6	101	0.7	11.15	99	23.0%	0.50 [-2.52,3.52]
Remington 2015	1.4	109.7	48	-0.9	111.4	34	0.1%	2.30 [-46.33,50.93]
Shah 2013	-3.74	9.76	228	-3.66	8.03	223	76.9%	-0.08 [-1.73,1.57]
Total (95% CI)			377			356	100%	0.06 [-1.39,1.50]
Heterogeneity: Tau^2=0.00; Chi^2=0.12, df=2 (p=0.94); I^2=0%								
Test for overall effect: Z=0.08 (p=0.94)								
Study or Sub group	**DHA**			**Control**			**Weight**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Random, 95% CI**
Astarita 2010	102.99	40.66	36	123.61	24.07	17	0.2%	-21.32 [-38.85,-3.79]
Fontech 2014	15.3	2.2	29	16.8	3.3	69	17.1%	-1.50 [-2.62,-0.38]
Fraser 2010	14.51	2.42	86	14.98	1.53	55	22.1%	-0.47 [-1.12,0.18]
Igarashi 2011	6.626	1.038	10	7.244	1.903	9	0.0%	-618.00 [-2017.86,781.86]
Martin 2010	4.91	1.74	10	6.87	1.07	10	15.5%	-1.96 [-3.23,-0.69]
Quinn 2010	3.18	1.21	238	3.13	0.96	164	25.6%	0.05 [-0.16,0.26]
Schektens 2012	6.5	0	114	3	0	119		Not estimable
Shah 2013	6.3	0	239	2.5	0	232		Not estimable
Shinto 2014	5.1	1.3	13	4.4	1	13	19.5%	0.70 [-0.19,1.59]
Total (95% CI)			775			688	100%	-0.56 [-1.34,0.23]
Heterogeneity: Tau^2=0.61; Chi^2=26.77, df=6 (p=0.0002); I^2=78%								
Test for overall effect: Z=1.39 (p=0.16)								

greatly heterogeneous, as reflected in the values of χ^2 (26.77, p=0.16) and I^2 (78%). Furthermore, the AD and control cases did not differ regarding the DHA usage (MDIFF: -0.56: 95% CI, -1.34-0.23; p=0.16; I^2 =78%), as revealed by the random-effects model employed (**Table 3**).

Vitamin C. The 3 articles that examined vitamin C usage found that the trials were not greatly heterogeneous, as reflected in the values of χ^2 (5.90, p=0.40) and I^2 (83%). Furthermore, the AD and control cases did not differ regarding the vitamin C usage (MDIFF: -3036.54: 95% CI, -10095.76-4.022.68; p=0.40; I^2=83%), as revealed by the random-effects model employed (**Table 4**).

Vitamin E. The 4 articles that examined vitamin E usage found that the trials were not greatly heterogeneous, as reflected in the values of Chi2 (3.35, p=0.47) and I^2 (70%). Furthermore, the AD and control cases did not differ regarding the vitamin E usage (MDIFF: -27.55: 95% CI, -101.71-46.60; p=0.47; I^2=70%), as revealed by the random-effects model employed (**Table 4**).

Secondary outcomes. Plasma total homocysteine (tHcy). The 4 articles that examined the tHcy levels found that the trials were not greatly heterogeneous, as reflected in the values of χ2 (181.22, p=0.31) and I^2 (99%). Furthermore, the AD and control cases did not differ regarding the tHcy levels (MDIFF: 383.81: 95% CI, -353.62-1121.24; p=0.31; I^2=99%), as revealed by the random-effects model employed (**Table 4**).

Vitamin B12. The 4 articles that examined vitamin B12 usage found that the trials were not greatly heterogeneous, as reflected in the values of χ^2 (49.29, p=0.39) and I^2 (98%). Furthermore, the AD and control cases did not differ regarding the vitamin B12 usage (MDIFF: -2.73: 95% CI, -8.91-3.44; p=0.39; I^2=98%), as revealed by the random-effects model employed (**Table 4**).

Folate. The 4 articles that examined folate usage found that the trials were not greatly heterogeneous, as reflected in the values of χ^2 (37.20, p=0.31) and I^2

Table 4 - Comparison of Vitamin C, E, B12, Folate, Plasma total homocysteine (tHcy) between AD patients and control group

Study or Sub group	Vitamin E			Control			Weight	Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI
Dysken 2014	57.2	14.3	140	56.9	13.6	140	64.9%	0.27 [-3.01,3.55]
Kaddurahdaouk 2011	40	59	15	119	157	15	35.1%	-79.00 [-163.88,5.88]
Schektens 2010	12	0	106	14	0	106		Not estimable
Schektens 2012	44.5	0	116	32	0	119		Not estimable
Total (95% CI)			377			380	100%	-27.55 [-101.71,46.60]
Heterogeneity: Tau²=2202.80; Chi²=3.35, df=1 (*p*=0.07); I²=70%								
Test for overall effect: Z=0.73 (*p*=0.47)								
Study or Sub group	**Vitamin C**			**Control**			**Weigt**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Random, 95% CI**
Arlt 2012	20	5.3	12	21.7	5.5	11	58.5%	-1.70 [-6.12,2.72]
Kaddurahdaouk 2011	10.2	6.2	15	17.5	9.8	15	41.5%	-7311.00 [-13210.70,-1411.30]
Schektens 2012	11.5	0	116	14.5	0	119		Not estimable
Total (95% CI)			143			145	100%	-3036.54 [-10095.76,4022.68
Heterogeneity: Tau²=22182555.07; Chi²=5.90, df=1 (*p*=0.02); I²=83%								
Test for overall effect: Z=0.84 (*p*=0.40)								
Study or Sub group	**Vitamin B12**			**Control**			**Weight**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Random, 95% CI**
Douaud 2013	11.8	3.6	80	11.4	3.1	76	50.3%	0.40 [-0.65,1.45]
Jager 2012	8.7	0	110	12.4	0	113		Not estimable
Kwok 2011	9.3	2.7	61	15.2	4.8	58	49.7	-5.90 [-7.31,-4.49]
Smith 2010	8.7	0	84	12.1	0	83		Not estimable
Total (95% CI)			335			330	100%	-2.73 [-8.91,3.44]
Heterogeneity: Tau²=19.44; Chi²=49.29, df=1 (*p*<0.00001); I²=98%								
Test for overall effect: Z=0.87 (*p*=0.39)								
Study or Sub group	**Folate**			**Control**			**Weight**	**Mean Difference**
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**		**IV, Random, 95% CI**
Douaud 2013	29	18	80	29	18	76	49.4%	0.00 [-5.65, 5.65]
Jager 2012	83.8	0	110	24.7	0	113		Not estimable
Kwok 2011	43	7	61	22.3	11.8	58	50.6%	20.70 [17.19,24.21]
Smith 2010	82.1	0	84	24.9	0	83		Not estimable
Total (95% CI)			335			330	100%	10.47 [-9.81,30.76]
Study or Sub group	Plasma homocysteine			Control			Weight	Mean Difference
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI
Douaud 2013	356	167	80	347	99	76	50.2%	9.00 [-33.83,51.83]
Jager 2012	690	0	110	348	0	113		Not estimable
Kwok 2011	1090	367	61	328	158	58	49.8%	761.50 [660.66,862.34]
Smith 2010	672	0	84	366	0	83		Not estimable
Total (95% CI)			335			330	100%	383.81 [-353.62,1121.24]
Heterogeneity: Tau²=281565.80; Chi²=181.22, df=1 (*p* <0.00001); I²=99%								
Test for overall effect: Z=1.02 (P=0.31)								

(97%). Furthermore, the AD and control cases did not differ regarding folate usage (MDIFF: 10.47: 95% CI, -9.81-30.76; *p*=0.31; I²= 97%), as revealed by the random-effects model employed (**Table 4**).

Discussion. *Primary outcomes.* Single antioxidants, including ascorbic acid (AA) and vitamin E, Souvenaid, vitamin E and memantine, vitamins E and C, and CoQ, were investigated in five of the reviewed articles,[23-27] none of which differed significantly (*p*=0.70) according to statistical analysis. The response of brain functionality to alpha-tocopherol, memantine and their combination was investigated by Dysken and colleagues[23] in cases of mild-to-moderate AD; findings suggested that, by

contrast to controls, the 152 participants with AD administered 2000 IU/d alpha-tocopherol for 5 years suffered moderate reduction in functionality, but administration of neither 20 mg/d memantine nor alpha-tocopherol combined with memantine had any impact on the Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) scale. Meanwhile, the biochemical and clinical impact of AA and vitamin E on 12 participants with AD was examined by Arlt and colleagues,[24] who found that cognitive function was not altered significantly by administration of 1000 mg/d AA and 400 IU/d vitamin E alongside cholinesterase inhibitor for 12 months, according to the Mini-Mental State Examination (MMSE). Nevertheless, following 4 weeks, there was an improvement in the concentration of CSF antioxidant, while following 12 months, there was a decrease in CSF lipid oxidation. In the study by Ringma and colleagues,[25] the focus was on the ability of the polyphenolic compound with antioxidant effects called curcumin C3 complex administered in 2 or 4 g/d to decrease beta-amyloid accumulation in a number of 32 participants with mild-to-moderate AD over a duration of 24 weeks. No discrepancies of note were observed in the AD Assessment Scale - Cognitive Subscale (ADAS-Cog), secondary outcomes, including the Neuropsychiatric Inventory (NPI), the ADCS-ADL scale, or Ab1-42, t-tau, p-tau181 or F2-isoprostane concentrations in CSF. Another study employed a sample of 78 patients to explore how oxidative stress, CSF biomarkers and ADCS-ADL responded to vitamin E (800 IU/d), vitamin C (500 mg/d), a-lipoic acid (ALA) (900 mg/d) and CoQ administered thrice daily for 16 weeks. The patients administered vitamins E and C and ALA showed 19% lower levels of F2-isoprostane, although AB42, tau and P-tau181 levels in CSF did not differ significantly. Nevertheless, the patients administered vitamins E and C and ALA did exhibit a more rapid decrease in the MMSE score, which is worrying from a safety perspective.[26] Electroencephalography (EEG) was employed by De Waal and colleagues[27] to determine how the beta band of the brain of 179 patients responded to the isocaloric control product Souvenaid administered in 125 ml/d for 24 weeks. Results indicated that the control group displayed a reduction in brain networks, whereas the active group displayed no alteration.

The effects of the composite antioxidants vitamin E / vitamin C / ALA and curcumin were investigated in 2 studies.[26,28] No significant differences (p=0.80) were observed in these studies. The primary outcome evaluated in both these studies was peripheral F2-isoprostane concentration. Galasko et al[26] 2012 reported a 19% decline in levels of F2-isoprostane in the E/C/ALA group, while Shinto et al[28] 2014 did not find any significant evidence. Nevertheless, one study[28] judged that administration of Omega-3 FA had a negative impact on the MMSE score, while administration of Omega-3 FA combined with ALA had a negative effect not only on the MMSE score but also on the IADL score.

The impact of Omega-3 FA and DHA on AD was investigated in three studies.[28-30] Statistical analysis revealed no significant effects of these substances (p=0.70) in any of these studies. In keeping with the results obtained by Quinn and colleagues and Shinto and colleagues,[28,30] regarding the DHA influence on the ADAS-cog score, Faxén-Irving and colleagues[29] found that the concentration of plasma transthyretin (TTR), which is related to AB plaque decrease in the brain, was increased by DHA supplementation. Therefore, degeneration of cognition and functionality in cases of mild-to-moderate AD is not markedly diminished by administration of 2 g/d DHA of algal extract origin or consumption of 765 mg/d of fish with high levels of Omega-3 FA.

Polymeric formula usage was addressed in 3 studies,[31-33] and all of them indicated that it had no substantial impact on participants with AD (p=0.94). Meanwhile, the clinical product Souvenaid was investigated by 2 studies,[31,33] which reported better tolerance of the food by AD patients. Kamphuis et al., 2011 31 reported a higher ADAS-cog score in patients with a high baseline ADAS-cog score and effects directly associated with its regular intake. Shah et al., 2013[33] do not report any significant change in ADAS-cog score upon consumption of Souvenaid for a period of 24 weeks. Ringman et al[25] designed a nutrient formula using folate, vitamin E, cobalamin, SAM, NAC, and acetyl-L-carnitine. The IADL score of participants with AD was not substantially enhanced by the nutrient formula, although the dementia rating scale was improved.

Nine studies[28,30,33-39] reported on the effect of DHA. In these studies, no significant (p=0.16) difference was reported in its use by AD patients. Both Quinn et al[28,] 2020 and Shinto et al[30] 2014 reported no significant effect of the consumption of DHA (2 gram/day) and omega-3 FA (675 mg DHA and 975 mg EPA/d) on cognitive function of either AD patients or normal subjects. According to Scheltens et al[39]consumption of Souvenaid (125 ml/day) does not statistically improve IADL score, ADAS-cog score, QoL, or Interview-Based Impression of Change coupled with Caregiver Input or

Neuropsychiatric Inventory, but did lead to markedly better activities of delayed verbal recall. Meanwhile, DHA concentration in AD patients' brains were analysed by three studies,[34,35,37] which found that AD patients had significantly less DHA than individuals without AD. By contrast, DHA was reported by Fraser and colleagues36 to be more or less the same in cases with and without AD. Fonteh et al[35] reported high levels of even chain-free SFAs and TFAs in AD patients and 37 showed varying concentrations of lipid in the brain, resulting in lipid membrane remodeling and leading to neuroinflammation in AD patients. Similarly, Astarita et al[34] showed dysfunction in the synthesis of DHA by the liver, resulting in low levels of DHA in the brains of AD patients.

The results of three studies[24,40,41] indicated that cognitive function in cases of mild-to-moderate AD was not noticeably affected by AA (p=0.40). More specifically, Arlt and colleagues[24] revealed that administration of 1000 mg/d of AA and 400 IU/d of vitamin E for 12 months did not lead to considerably better cognitive function. Meanwhile, Kaddurah-Daouk and colleagues[40] observed that participants with AD exhibited alterations in the metabolomics of the tyrosine, tryptophan, purine, and tocopherol pathways, which play a central role in normal cognitive function. Finally, Scheltens et al., 2012[41] assessed the impact of medicinal food, concluding that regular consumption of Souvenaid (125 ml/day) for 24 weeks results in better functional connectivity as a result of synaptic formation.

The impact of vitamin E administration on AD was addressed by four studies,[23,39-41] but none of them reported any marked influence (p=0.47). In terms of a-tocopherol, Kaddurah-Daouk et al., 2011[40] reported modifications in the tocopherol pathway in AD patients, which is crucial for proper cognitive function. By promoting synaptic links and enhancing the ability to undertake activities of delayed verbal recall, administration of 125 ml/d Souvenaid for 12 and 24 weeks led to better functional connectivity, according to Scheltens and colleagues.[39,41] On the other hand, no alterations were noted in the IADL score, ADAS-cog score, QoL, and Interview-Based Impression of Change coupled with Caregiver Input.

Secondary Outcomes. Four studies[42-45] reported on the levels of plasma total homocysteine. However, no significant difference (p=0.31) was identified between patients with AD and control individuals. All the studies reported on the effect of daily consumption of vitamin B (0.8 mg B9, 0.5 mg B12 and 20 mg B6) on plasma tHcy and reported that when baseline tHcy levels were above 11 µmol/L, significant effects were observed on reducing gray matter atrophy of the brain and on stable cognitive function (CLOX). Similarly, when B9 and B12 were administered at dosages of 5 and 1 mg daily, respectively, for 2 years, plasma tHcy levels were reduced.

Four studies[42-45] reported on the effect of vitamin B12 on the development of MCI into AD. Statistical analysis showed no significant evidence of an effect on this change (p=0.39). From the studies of Douaud et al[42], de Jager et al[43], and Smith et al[45] it can be seen that vitamin B12 (0.5 mg/d) administered in combination with other B vitamins significantly lowers brain atrophy in MCI patients. However, such results are evident only in patients with high baseline plasma tHcy levels (>11 µmol/L). According to Kwok et al., 2011,[44] when vitamin B12 is given at a dosage of 0.5 mg per day for 2 years in combination with folic acid, it results in a significant reduction in plasma tHcy levels. On the other hand, neuropsychological scores, including the Mattis Dementia Rating Scale (MDRS), the Neuropsychiatric Inventory and the Cornell Scale for Depression in Dementia, did not display notable modifications.

Four studies[42-45] reported on the use of folate. Statistical analysis of these studies revealed no significant evidence (p=0.31) of its effect on patients with AD. From all four studies[42,43,45] it is evident that consumption of vitamin B9 (20 mg/d) for a period over 1 year significantly reduces plasma tHcy levels and brain atrophy. Similarly, the findings of Kwok et al[44] 2011 reveal that when 5 mg of B9 was orally administered for a period of 2 years, plasma tHcy levels decreased significantly. By contrast, neuropsychological scores, including the MDRS, the Neuropsychiatric Inventory and the Cornell Scale for Depression in Dementia, did not exhibit any alterations. Additionally, as previously mentioned, the effectiveness of vitamin B9 was based on baseline plasma tHcy levels.

Limitations. Although a RCT is the best method by which to minimize bias and confusion and establish causality, conducting RCTs is not always possible. However, few published RCTs have concluded that antioxidants, B vitamins, and omega-3 PUFAs do not reduce the incidence of neurodegenerative disorders or the risk of AD. The results of these RCT studies contradict the findings of observational studies, which may be due to a number of reasons, chief among them that nutrients mainly play a preventive role rather than a protective role in the onset of AD pathogenesis. Second, variations in the dosage of nutrients between epidemiological studies and RCTs lead to poor results. Suboptimal research interval, interactions between nutrients and between drugs and nutrients, lack of consideration for social and behavioural aspects, lack of homogeneity among research populations, nutrient

concentrations, exposure duration, compliance with treatment, length of follow-up and primary outcome are all factors impacting RCTs.[46,47] Therefore, to expand the findings obtained, secondary outcomes (e.g. conformance to nutrition plan, body weight lean body mass, QoL, life expectancy, blood biomarkers) must be assessed as well (Schueren et al., 2018). Hence, null RCT results do not automatically signify that a particular nutrient is ineffective against AD; this is because previous studies have clearly demonstrated that, if they are taken at the right time and in the right concentration, the majority of nutrients can be beneficial.

In conclusion, Chain-free SFA and TFA occur in greater amounts in the brains of individuals with AD than in those without AD. Moreover, lipid membrane remodeling results in neuroinflammation in AD patients. Additionally, poor synthesis of DHA by the liver due to dysfunction results in accelerated AD disorder. Moreover, unlike controls, AD patients' cognitive function is susceptible to the impact of alterations in the tyrosine, tryptophan, purine and tocopherol pathway metabolomics. Additionally, individuals with mild-to-moderate AD exhibit reduction in brain functionality as a result of administration of alpha-tocopherol for more than 12 months. However, when vitamin E is taken in combination with AA and ALA, it results in a faster decline in MMSE score, which raises safety concerns. Souvenaid has been claimed by a number of epidemiological works to have a positive action and be well-tolerated by individuals with AD. However, in the present study, it was not possible to demonstrate that Souvenaid use improved beta band network and brain functionality. Nevertheless, Souvenaid can lead to better functional connectivity as it promotes synaptic synthesis. Additionally, the effects of this medicinal food are based on the baseline ADAS-cog score, i.e., the higher the score, the more pronounced the effect of Souvenaid. These studies also failed to demonstrate a positive relationship between consumption of Souvenaid and the IADL score. However, one study reported improved delayed verbal recall tasks. When Omega-3 FA is applied alone or in combination, it results in MMSE score decline. The levels of brain AB plaque are diminished by DHA administration, but this study has not observed DHA to enhance cognition and functionality. B vitamins, such as folate, cobalamin, or pyridoxine, consumed at 0.8 mg, 0.5 mg, and 20 mg levels each day, respectively, for a period of more than 1 year result in lower plasma tHcy levels and reduced brain atrophy. However, these effects are based on baseline plasma tHcy levels, which should be above 11 µmol/L. Contrary to such results, the neuropsychological scores used in this study (e.g. MDRS, Neuropsychiatric Inventory, Cornell Scale for Depression in Dementia) did not suggest that plasma tHcy had any influence on cognitive function (CLOX). There is a strong possibility that such nutrients exert their positive effects when a mixture of nutrients are consumed together instead of when one nutrient is consumed. Therefore, further research is necessary to determine how such nutrients act in synergy and try to determine how nutrients contribute to food and diet.

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