ISSN (electrónico): 1699-5198 - ISSN (papel): 0212-1611 - CODEN NUHOEQ S.V.R. 318

ARÁN

Nutrición Hospitalaria

Trabajo Original

Obesidad y síndrome metabólico

The effect of omega-3 fatty acid supplementation on weight loss and cognitive function in overweight or obese individuals on weight-loss diet

El efecto de la suplementación con ácidos grasos omega-3 sobre la pérdida de peso y las funciones cognitivas en personas con sobrepeso u obesidad en dieta para adelgazar

Havva Banu Salman[1], Mehmet Alper Salman[2], Emine Yıldız Akal[1]

[1]Department of Nutrition and Dietetics. Faculty of Health Sciences. Eastern Mediterranean University. Famagusta, North Cyprus. Turkey. [2]Department of Anesthesiology, Reanimation and Algology. Guven Hospital. Ankara, Turkey

Abstract

Objective: omega-3 polyunsaturated fatty acids (PUFAs) are important nutrients that play role in obesity, body lipids, inflammation, and neural function. There is controversy in studies on the effect of omega-3 PUFA supplementation on weight loss and cognitive function. The aim of this study was to investigate the effect of omega-3 PUFA supplementation on weight loss and cognitive function in obese or overweight adults on a weight loss diet.

Methods: 40 adult volunteers aged 30-60 years, with body mass index (BMI) between 27.0 and 35.0 kg/m^2, were randomly allocated into two groups. All subjects were involved in a weight loss diet program. The subjects in the omega-3 group (n = 20) also received daily supplementation with 1020 mg of omega-3 PUFAs (580 mg eicosapentaenoic acid (EPA), 390 mg docosahexaenoic acid (DHA), 50 mg other omega-3 PUFAs) for 12 weeks. Anthropometric measurements and body composition analysis were obtained at onset and at weeks 4, 8, and 12 of the study. The Montreal Cognitive Assessment (MoCA) test was used for evaluating cognitive functions at diet onset and at the end of week 12.

Results: significant decreases were observed in weight, waist, and BMI in both groups. Abdominal fat mass and percentage decreased more in the omega-3 group than in the control group ($p \leq 0.05$). MoCA scores increased in both groups within time, without statistical significance between groups.

Conclusion: omega-3 PUFA supplementation augmented the reduction of abdominal fat mass and percentage in overweight or obese individuals on a weight loss diet. Further studies are required to identify the relationship and mechanisms of action of omega-3 PUFA supplementation on cognitive performance and weight loss.

Keywords:

Omega-3. Polyunsaturated fatty acids. Diets. Weight loss. Cognitive functions.

Received: 12/12/2021 • Accepted: 27/04/2022

Author contributions: HBS, MAS and EYA developed the study concept. HBS directed the weight loss program, performed all measurements and quantifications, and was also involved in the manuscript writing. MAS checked the eligibility of individuals for the program and supplementation, performed all statistical analyses and was also involved in the manuscript writing. EYA supervised this study project. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Funding: this research received no specific grant from funding agencies in public, commercial, or not-for-profit sectors.

Conflict of interest: the authors have no conflicts of interest.

Salman HB, Salman MA, Yıldız Akal E. The effect of omega-3 fatty acid supplementation on weight loss and cognitive function in overweight or obese individuals on weight-loss diet. Nutr Hosp 2022;39(4):803-813

DOI: http://dx.doi.org/10.20960/nh.03992

Correspondence:

Havva Banu Salman. Department of Nutrition and Dietetics. Faculty of Health Sciences. Eastern Mediterranean University. 99628 Famagusta, North Cyprus via Mersin 10 Turkey
e-mail: dytbanusalman@gmail.com

Resumen

Objetivo: los ácidos grasos poliinsaturados (AGPI) omega-3 son nutrientes importantes que intervienen en la obesidad, los lípidos corporales, la inflamación y las funciones neuronales. Existe controversia en los estudios sobre el efecto de la suplementación con AGPI omega-3 sobre la pérdida de peso y las funciones cognitivas. El objetivo de este estudio fue investigar el efecto de la suplementación con ácidos grasos poliinsaturados omega-3 sobre la pérdida de peso y la función cognitiva en adultos obesos o con sobrepeso que siguen una dieta para adelgazar.

Métodos: 40 voluntarios adultos de entre 30 y 60 años, con índice de masa corporal (IMC) entre 27,0 y 35,0 kg/m^2, fueron distribuidos aleatoriamente en dos grupos. Todos los sujetos participaron en un programa de dieta para adelgazar. Los sujetos del grupo con omega-3 (n = 20) también recibieron suplementos diarios de 1020 mg de AGPI omega-3 (580 mg de ácido eicosapentaenoico (AEP), 390 mg de ácido docosahexaenoico (ADH), 50 mg de otros AGPI omega-3) durante 12 semanas. Las mediciones antropométricas y el análisis de la composición corporal se obtuvieron al inicio y a las 4, 8 y 12 semanas del estudio. La prueba de la "Evaluación Cognitiva de Montreal" (MoCA) se utilizó para evaluar las funciones cognitivas al inicio de la dieta y al final de la semana 12.

Resultados: se observaron disminuciones significativas en el tiempo en el peso, la cintura y el IMC en ambos grupos. La masa y el porcentaje de grasa abdominal disminuyeron más en el grupo con omega-3 que en el de control ($p \leq 0,05$). Las puntuaciones MoCA aumentaron en ambos grupos en el tiempo, sin significación estadística entre los grupos.

Conclusión: la suplementación con ácidos grasos poliinsaturados omega-3 aumentó la reducción de la masa y el porcentaje de grasa abdominal en personas con sobrepeso u obesidad que siguieron una dieta para adelgazar. Se necesitan más estudios para identificar la relación y los mecanismos de acción de la suplementación con ácidos grasos poliinsaturados omega-3 sobre el rendimiento cognitivo y la pérdida de peso.

Palabras clave:

Omega-3. Ácidos grasos poliinsaturados. Dietas para adelgazar. Funciones cognitivas.

INTRODUCTION

Omega-3 fatty acids are polyunsaturated fatty acids (PUFAs) commonly found in marine fish oil as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and their function in obesity, diabetes, hypertriglyceridemia, mental state, and cognitive function has been studied in many observational and randomized prospective controlled clinical studies (1-4). Dietary fish oil supplementation reduces body fat mass by increasing lipid oxygenation, and decreases mortality related to stroke and diabetes, which is related to long-chain omega-3 PUFA intake (5,6). There is controversy on the effect of addition of omega-3 PUFAs to weight loss diets for the treatment of obesity. It has been demonstrated that long-chain PUFA supplementation reduces energy intake in obese women (7). PUFA supplementation might be beneficial in reducing obesity by decreasing appetite, increasing fat oxidation, and reducing fat deposition (8). A high omega-6/omega-3 ratio in the diet is associated with insulin resistance and weight gain in both animal and human studies; on the contrary, high omega-3 intake leads to weight loss and decreases the risk for obesity (9). Some studies demonstrate positive effects of omega-3 PUFA supplementation on weight loss and body fat mass reduction. Keshavarz et al. have found a decrease in body weight with omega-3 supplementation in obese dieting women (10). It is also a fact that omega-3 long-chain PUFA supplementation besides increasing weight loss decreased insulin, insulin resistance (HOMA-IR), TNF-α and leptin, and increased adiponectin in obese pre-pubertal and pubertal children (11). In another study supplementation with EPA 1600 mg and DHA 800 mg decreased fat mass in healthy adults (12). On the other hand, some studies do not find a decrease in weight with omega-3 supplementation (7,13). In animal studies, omega-3 PUFAs are found to have a role in reducing retroperitoneal and epididimal fat mass (14). However, human research suggests that omega-3 PUFAs may not have beneficial effects on weight loss, but they may decrease appetite and prevent gaining more weight or help maintaining weight after a weight loss diet (15,16). The mechanisms of omega-3 PUFA effects on weight loss and body fat mass reduction may be related to: a modulation of lipid metabolism; regulation of adipokines such as adiponectine and leptin, and a decrease in inflammation in the adipose tissue; suppression of appetite; changes in carbohydrate metabolism; increases in energy consumption due to thermogenesis, and stimulating mechanisms in muscle anabolism (15).

Docosahexaenoic acid (DHA) is a component of neuronal membranes and DHA is required for brain functions such as neurotransmission or synaptic plasticity (17). It has been demonstrated that DHA supplementation has protective effects against the development of Alzheimer's disease by decreasing amyloid-β production, accumulation and toxicity in rats (18). DHA derivatives are also found to have neuroprotective properties by preventing neuronal apoptosis (19) and decreasing oxidative stress (20). Even though the beneficial effects of omega-3 PUFAs have been demonstrated in animal studies, there is heterogeneity and inconsistency in the literature on the benefits of omega-3 supplementation for weight loss, body fat mass reduction, and cognitive functioning in human studies.

A recent review suggests that omega-3 PUFA supplementation may have a positive effect on cognitive function (21). The effect of omega-3 supplementation on cognitive improvement or cognitive decline prevention in cognitively healthy adults is not clear since there are not many controlled clinical trials to evaluate the potential benefit of omega-3 supplementation in these individuals; however, based on evidence from animal studies, there is promise for this population to benefit from omega-3 PUFA supplementation (22).

Cognitive functions are affected by factors such as age, genetic background and nutrition (23). There is also evidence of an association of weight loss with cognitive function in obese individuals. Weight loss may improve cognitive performance in obese and overweight individuals given that significantly improved attention and executive function were observed with weight loss in obese subjects (24). There are numerous studies on the effect of omega-3 PUFAs and their role on cognitive functions, especially on

the prevention of cognitive decline and dementia (25). Epidemiologic studies support the protective effects of omega-3 PUFAs on cognitive functions. There are also some studies suggesting that omega-3 PUFAs have no effect on cognitive functions (26,27).

In this study, we aimed to investigate the possible effects of omega-3 PUFA supplementation on weight loss, body composition, and cognitive function in overweight or obese individuals on a weight loss diet.

MATERIAL AND METHODS

We hypothesized that regular daily use of omega-3 PUFA supplementation ameliorates cognitive functions and weight loss in overweight or obese individuals on a weight loss diet. After the institutional ethics committee's approval, 40 volunteering overweight or obese adult individuals with body mass index (BMI) between 27.0 and 35.0 kg/m^2, aged 30-60 years, and consulting at a private nutrition and diet clinic were included in the study. Sample size was determined to detect 5-point changes in the Montreal Cognitive Assessment (MoCA) test scores with a power of 90 % and an alpha error of 0.05. Individuals with a chronic systemic disease other than obesity and hyperlipidemia, such as hypertension, coronary artery disease, malignancies, endocrine and metabolic diseases such as diabetes, hyperthyroidism etc., were excluded from the study. Other exclusion criteria were regular physical activity, performing professional sports, and previous regular use of supplements, vitamins and minerals. Individuals who were noncompliant with the study, such as those who did not follow the study diet, did not use the omega-3 capsules, or did not show up for follow-up visits were also excluded.

Written informed consents were obtained from all subjects. Subjects were randomly allocated into a control or an omega-3 group. Demographic parameters, nutrition habits and physical activity status were evaluated using a questionnaire. Subjects were also asked to record their detailed food consumption and physical activities using a form, for three consecutive days, one weekend and two week days, before the onset of the diet and at the end of 12 weeks in order to monitor compliance with their diet (28). The medical doctor in the research team evaluated and approved the suitability of the subjects to be participants in the study. The subjects in the control group (n = 20) were involved in a weight loss diet program. The subjects in the omega-3 group (n = 20) received supplementation with 1020 mg of omega-3 PUFAs per day (EPA 580 mg, DHA 390 mg, 50 mg of other omega-3 PUFAs) in addition to their weight loss diet program. The weight loss diet was organized individually for each subject according to their lifestyle and nutrition habits. Daily energy intake was planned using basal metabolic rate and physical activity (29,30).

The diet was designed to provide 55-60 % of daily energy from complex carbohydrates, 25-30 % from fats, and 12-15 % from proteins. Weekly fish consumption was set to be similar in all of the subjects. Salmon 150 g was provided twice a week in the diet of all subjects. Anthropometric measurements, including height, waist perimeter, total body weight, total body fat mass, body fat distribution, body muscle mass, and body mass index (BMI) were obtained at onset and at weeks 4, 8 and 12. A Tanita MC 180 Multi-Frequency Body Composition Analyzer Scale (Tanita Corporation, Tokyo, 174- 8630, Japan) was used for analyzing body composition and calculating basal metabolic rate according to weight. A tape measure and a stadiometer were used for measuring height and waist circumference (31).

A psychologist, blinded to the study groups, evaluated the cognitive functions of the subjects using the Montreal Cognitive Assessment (MoCA) test at diet onset as a pretest and at the end of the 12th week (32-36).

The normal distributions of the subjects were evaluated using the Kolmogorov-Smirnov test. Independent-sample T-tests were used for comparing differences between groups in parameters demonstrating a normal distribution. The non-parametric Mann-Whitney U-test was used to compare the differences between groups for those parameters with no normal distribution. For comparing the effects of the intervention and time within groups, a repeated measures T-test was used for parameters with normal distribution. For parameters that did not demonstrate a normal distribution the non-parametric Wilcoxon's signed rank test was used instead; *p*-values less than 0.05 were considered statistically significant. Data are presented as mean and standard deviation. All statistical analyses were carried out using the IBM SPSS software (version 21.0, IBM International Business Machines Inc. Armonk, NY, USA).

RESULTS

All subjects followed their diet and took omega-3 supplements without reporting any intolerance or incompliance. They reported no change in their physical activities and lifestyle. Daily energy intake, macronutrients and micronutrients in diet food consumption records, provided by the subjects, at onset, at the end of week 6, and at the end of the study demonstrated no statistically significant differences between study groups ($p > 0.05$).

Subject age, gender, weight, height, BMI, waist measurements and physical activity factors at study onset in each group are listed in table I. There were no statistically significant differences between groups ($p > 0.05$).

Body composition data at study onset regarding fat mass, fat percentage, abdominal fat mass, abdominal fat percentage, muscle mass, muscle percentage, and total body water of the subjects at study onset in each group are listed in table II. There were no statistically significant differences between groups ($p > 0.05$).

When weight, BMI and waist measurements were analyzed, significant decreases over time were observed in both the control and omega-3 groups; however, there were no statistically significant differences observed between the groups (Table III).

Significant decreases over time were observed in both the control and omega-3 groups in subject weight, total fat mass, and abdominal fat mass. The decreases in total fat weight and total fat percentage were similar in both groups. The decrease in abdominal fat mass was greater in the omega-3 group than in the control group ($p = 0.05$).

Table I. Demographic and anthropometric data at onset

	Control group	Omega-3 group	Total
Age (years)	43.4 ± 8.4	41.8 ± 8.8	42.6 ± 8.5
Gender (M/F)	7/13	5/15	12/28
Height (cm)	168.5 ± 8.4	167.3 ± 10.8	167.9 ± 9.6
Weight (kg)	89.4 ± 11.5	85.0 ± 13.7	87.2 ± 12.7
BMI (kg/m^2)	31.4 ± 2.4	30.3 ± 3.0	30.9 ± 2.8
Waist (cm)	101.20 ± 12.56	96.89 ± 13.98	99.09 ± 13.31
Physical Activity Factor (PAF)	1.40 ± 0.97	1.39 ± 0.14	1.40 ± 0.12

Mean ± SD. p > 0.05.

Table II. Body composition data at onset

	Control group	Omega-3 group	Total
Fat mass (kg)	31.5 ± 5.2	28.6 ± 6.1	30.1 ± 5.8
Fat percentage (%)	35.4 ± 5.1	33.9 ± 6.2	34.7 ± 5.6
Abdominal fat mass (kg)	16.1 ± 2.8	14.3 ± 3.9	15.2 ± 3.4
Abdominal fat percentage (%)	18.0 ± 1.9	16.7 ± 3.1	17.3 ± 2.6
Muscle mass (kg)	16.8 ± 3.2	16.2 ± 3.6	16.5 ± 3.4
Muscle percentage (%)	18.6 ± 2.0	18.9 ± 2.0	18.8 ± 2.0
Total body water (kg)	39.9 ± 8.5	40.2 ± 8.5	40.1 ± 8.4

Mean ± SD. p > 0.05 between groups.

Table III. Weight, BMI and waist measurements

Group	Onset	4th week	8th week	12th week
Weight (kg)				
Control	89.37 ± 11.47	85.85 ± 11.04	83.92 ± 10.80	81.79 ± 10.26
Omega-3	85.06 ± 13.71	82.02 ± 12.99	80.27 ± 13.22	79.28 ± 13.43
Total	87.22 ± 12.67	83.93 ± 12.06	82.09 ± 12.06	80.53 ± 11.87
BMI (kg/m^2)				
Control	31.44 ± 2.42	30.15 ± 2.26	29.49 ± 2.30	28.91 ± 2.19
Omega-3	30.29 ± 3.02	29.24 ± 3.20	28.59 ± 3.13	28.27 ± 3.22
Total	30.86 ± 2.76	29.69 ± 2.77	29.04 ± 2.74	28.59 ± 2.74
Waist (cm)				
Control	101.29 ± 12.56	99.69 ± 12.30	98.39 ± 12.37	96.87 ± 12.37
Omega-3	96.89 ± 13.98	94.93 ± 13.86	93.88 ± 13.84	92.82 ± 13.95
Total	99.09 ± 13.31	97.30 ± 13.16	96.13 ± 13.15	94.85 ± 13.17

Mean ± SD. p > 0.05 between groups.

Abdominal fat percentage decreased significantly more in the omega-3 group compared to the control group ($p = 0.043$) (Table IV).

When MoCA scores at study onset and at week 12 were compared, MoCA scores were found to be increased in both the control and omega-3 groups. Increases were not statistically different between the omega-3 and the control groups ($p > 0.05$) (Table V).

Table IV. Total and abdominal fat

Group	Onset	4th week	8th week	12th week
Fat mass (kg)				
Control	31.51 ± 5.18*	29.45 ± 5.37*	28.12 ± 6.08*	26.68 ± 4.98*
Omega-3	28.63 ± 6.11*	26.57 ± 6.61*	24.64 ± 6.96*	23.83 ± 6.42*
Total	30.07 ± 5.78*	28.01 ± 6.12*	26.38 ± 6.69*	25.25 ± 5.85*
Fat percentage				
Control	35.43 ± 5.05*	34.50 ± 6.01*	33.64 ± 6.72*	32.89 ± 6.23*
Omega-3	33.91 ± 6.21*	32.57 ± 6.83*	30.92 ± 7.38*	30.27 ± 6.94*
Total	34.67 ± 5.64*	33.54 ± 6.42*	32.28 ± 7.10*	31.58 ± 6.64*
Abdominal fat mass (kg)				
Control	16.08 ± 2.79*†	15.17 ± 2.90*†	14.51 ± 3.08*†	13.82 ± 2.72*†
Omega-3	14.29 ± 3.85*†	12.98 ± 4.30*†	11.96 ± 4.60*†	11.39 ± 4.44*†
Total	15.18 ± 3.44*	14.08 ± 3.78*	13.23 ± 4.08*	12.60 ± 3.83*
Abdominal fat percentage				
Control	17.96 ± 1.94*†	17.67 ± 2.70*†	17.27 ± 2.94*†	16.91 ± 2.75*†
Omega-3	16.69 ± 3.08*†	15.63 ± 4.18*†	15.34 ± 3.65*†	14.10 ± ±4.36*†
Total	17.33 ± 2.62*	16.65 ± 3.62*	16.30 ± 3.42*	15.50 ± 3.87*

*Mean ± SD. *$p < 0.05$ within time; †$p \leq 0.05$ between groups.*

Table V. MoCA scores

Groups		MoCA scores		
		Onset	12th week	Difference
Control	Mean	24.60	25.75	1.15
	Standard deviation	3.53	3.26	1.73
	Standard error	0.79	0.73	0.39
Omega-3	Mean	24.95	26.75	1.80
	Standard deviation	2.50	1.65	2.14
	Standard error	0.56	0.37	0.48
Total	Mean	24.78	26.25	1.48
	Standard deviation	3.03	2.60	1.95
	Standard error	0.48	0.41	0.31

$p > 0.05$ between groups.

DISCUSSION

Omega-3 PUFAs are promising supplements in the prevention and treatment of various cardiovascular, inflammatory, immunological, psychological, and neurological disorders, that have a wide range of safe doses, and have been approved by the European Food Safety Authority (EFSA) (37). Research data point to beneficial effects of omega-3 PUFAs in metabolic syndrome, cardiovascular diseases and other degenerative diseases related to aging (38-40). There are numerous studies indicating a negative association between increased BMI or body weight index and omega-3 index (plasma n-3 PUFA or O3I-omega-3 index) (41-44).

Scientific evidence about the effect of omega-3 PUFAs on weight loss is inconsistent. In a study by Ruzickova et al. (45), supplementation with EPA/DHA of marine origin is found to be effective in limiting the development of obesity by decreasing accumulation of body fat through limiting both fat cell hypertrophy and hyperplasia in mice. Minami et al. (46) have noted a decrease in abdominal fat with EPA supplementation in diabetic rats. Soni et al. (47) have reported a reduction in lipid accumulation in adipose tissues of mice on a high fat diet with EPA and DHA supplementation, as well as anti-inflammatory effects. Human studies have some conflicting outcomes. DeFina et al. (48) studied the effects of omega-3 PUFAs on body weight loss in 81 obese or overweight subjects for a period of 6 months. No significant difference was observed in body weight between the omega-3 and placebo groups. Some studies suggest that omega-3 PUFA supplementation may not help in reducing body weight but may be helpful in maintaining weight loss and preventing further increases in weight (15).

In a study of healthy adult volunteers on a three-week control diet, Couet et al. (5) reported that dietary fish oil substitution decreased body fat mass, increased basal lipid oxidation, and decreased the basal respiratory quotient.

In our study we observed significant decreases in BMI and abdominal waist measurements over time; however, we could not find any significant differences between the omega-3 and control groups. Munro and Garg (49,50) reported that omega-3 PUFAs are not effective in assisting weight loss, which is in concordance with our findings; however, they observed a significant decrease in fat mass in obese patients. In a different setting, Munro and Garg (51) have also noted that a time-dependent effect may be present in helping weight loss with the prior administration of long-chain omega-3 PUFAs. They noted that omega-3 PUFA supplementation prior to a very low-energy diet was effective in females compared to males. They suggested that females may be more responsive to metabolism of PUFA, possibly because of the estrogen hormone. They also noted that their sample size was small and a longer period of intervention might be necessary.

Even though we found no significant differences in body fat mass, we observed a significant reduction in abdominal fat mass and abdominal fat percentage in the omega-3 group as compared to the control group. This is consistent with several other studies. Matsumura K. evaluated the effect of eicosapentaenoic acid (EPA) supplementation, 1800 mg/day, on visceral fat in 165 subjects using abdominal computed tomography (52). No difference in visceral fat was observed in female subjects; however, a significant decrease in visceral fat was found in male subjects receiving EPA 1800 mg/day after 6 months. We also observed a decrease in abdominal fat over time in our study. Our daily EPA dose was lower, and the duration of the study was shorter than that of the study by Matsumura. Even though the male/female ratios in our study groups were not statistically different, our study was not set to compare gender differences, which may have an impact on the study.

Kabir M et al. (53) have reported a reduction in adiposity after treatment with omega-3 PUFAs. The study was carried out on 27 women with type-2 diabetes and without hypertriglyceridemia. The treatment group received fish oil containing 1800 mg of EPA and DHA, which was higher than in our study, for two months. Total fat mass, adipocyte diameter and atherogenic markers decreased without a decline in insulin sensitivity. Expression of some inflammation-related genes in the adipose tissue, measured by real-time PCR, also decreased indicating local blunting of inflammation in the adipose tissue.

Itariu et al. (54) used 900 mg/day of EPA and DHA supplementation for eight weeks in 55 non-diabetic obese (BMI > 40 kg/m^2) patients scheduled for bariatric surgery. They found that omega-3 supplementation decreased expression of numerous inflammatory genes analyzed in visceral and subcutaneous adipose tissue compared to the control group ($p < 0.05$). The study revealed that treatment with omega-3 PUFAs enhanced the production of anti-inflammatory eicosanoids, thus it modulated systemic inflammation positively, and improved lipid metabolism in visceral and subcutaneous adipose tissue.

There are other studies that point to the anti-inflammatory effects of omega-3 PUFAs in the adipose tissue (55,56). The noted anti-inflammatory effects promise benefits in the long-term management of obesity.

In a study carried out on 58 overweight children with nonalcoholic fatty liver disease, docosahexaenoic acid supplementation was also found to be effective in decreasing liver and visceral fat, serum triglycerides, and fasting insulin (57).

Thorsdottir et al. (16) studied the effect of fish and fish oil in a randomized controlled trial of nutritionally balanced, energy-restricted 8-week diet on 324 young overweight adults aged 20-40 years. The study demonstrated an increase in weight loss in male subjects on fish oil and fish containing diets compared to the control group. The waist circumference decreased in the fish oil group. We also found a decrease in waist circumference in our study over time; however, we did not observe any significant differences between the study groups. Thorsdottir et al. (16) gave 450 grams of cod or salmon per week, or 3 grams of fish oil per day, which is a higher dose than our intervention's. The study had a larger sample size compared to our study, and demonstrated significance in male subjects only.

In a prospective 6-week study on 44 adults by Noreen et al. (12), supplementation with 1,600 mg/day of EPA and 800 mg/day of DHA demonstrated a significant reduction in body fat

mass. Abdominal fat mass was not analyzed. They used a higher dosage of omega-3 and the intervention was shorter than in our study. Even though we observed a decrease in fat mass at the 8th week of our study, we could not find any statistically significant difference between groups in repeated measures. Even so, we may suggest that the findings of Noreen et al. (12) do not contradict our results. Human studies with omega-3 supplementation have revealed conflicting results. We have found a difference in abdominal fat mass and percentage with omega-3 PUFA supplementation; however, we did not find any significant effect in weight loss. Some factors affecting the results may include etiology of obesity, age, BMI of subjects, dose of supplement, EPA/DHA ratio in supplement, study duration, and a possible gender effect on weight loss. Another factor may be the temporal effect of the supplementation. Supplementation prior to a weight loss diet may be more effective or the effect of the supplement may be temporary as noted in other studies (51). Further studies using higher doses and greater sample sizes are required to reveal the temporal effects of omega-3 PUFA supplementation on fat mass reduction.

Several animal and human studies point to an impact of calorie restriction on cognitive functions, with benefits that integrate structural, physiological, and biochemical alternations (58). The possible mechanisms of calorie restriction and weight loss on cognition are reduction in oxidative stress, activation of anti-inflammatory responses, increased cell resistance to stress, and neurogenesis, endorsing synaptic plasticity (59). Inflammation, particularly low-degree chronic inflammation, has effects on early brain development, neurodegenerative disorders, and some brain functions (60,61). It has been established that inflammation has an impact on cognitive function and mood disorders (62). Nutrition and nutrients have many pro- and anti-inflammatory effects that may have potential outcomes involving cognitive functions (63-65). The neuroinflammatory and neurodegenerative mechanisms in overweight and obese individuals lead to structural changes in the brain and cerebellum, which may play a role in the impairment of cognitive functions (66). It is established that omega-3 PUFA supplementation has beneficial effects on functional capacity and cognitive functions, especially in the elderly (67-69).

The effect of omega-3 supplementation on cognitive functions in children and young or older adults is still controversial (70,71).

When we compared the 12th-week MOCA scores with the pre-intervention scores a slight increase was noted in both the control and omega-3 groups; however, the increase was statistically insignificant. Moreover, the scores did not demonstrate any differences between the study and control groups with statistical significance (Table V).

Pase et al. (72) studied the effect of fish oil and multivitamins on cognitive and cardiovascular functions in 160 healthy adults. The subjects were allocated to four groups to receive 3 grams of fish oil (240 mg of EPA and 240 mg of DHA) and multivitamins, 6 grams of fish oil (480 mg of EPA and 480 mg of DHA) and multivitamins, only 6 grams of fish oil (480 mg of EPA and 480 mg of DHA) or placebo. The Swinburne University Computerized Cognitive Assessment Battery was used for evaluating cognitive functions. The study could not demonstrate a significant change in cognitive function, which is consistent with our study.

Another study by Dangour et al. (73) on 867 elderly adults aged 70-79 without previous cognitive impairment found no difference in cognitive function after utilizing EPA 200 mg EPA and DHA 500 mg for two years compared to olive oil as placebo. Several other randomized controlled studies on the effect of omega-3 PUFA supplementation could not reveal a beneficial effect on memory, reactivity, attention, reasoning, mood or mini mental state examination. The dose of omega-3 PUFA supplementation, the relatively small sample sizes, and the probable short duration of the studies compared to time to onset of effect may be some reasons for the restraint (74-77).

Howe et al. (78) found an increase in cerebrovascular responsiveness (CVR) to hypercapnia in mildly hypertensive older women taking 1600 mg of DHA and 400 mg of EPA supplement per day for 20 weeks. This effect was not present in male subjects.

A recent study by Patan et al. (79) compared the effects of EPA- or DHA-rich omega-3 PUFA supplementation on cognitive function, memory and prefrontal cortex hemoglobin oxygenation. The study was carried out on 310 healthy young adults aged 25-49. The subjects did not smoke or use any legal medications or illicit drugs, and did not have any major illnesses. The BMI of the subjects was between 18.5 and 35 kg/m^2, and blood pressures were lower than 159/99 mm Hg. The subjects received placebo or DHA-rich oil (900 mg of DHA/day and 270 mg of EPA/day) or EPA-rich oil (360 mg of DHA/day and 900 mg of EPA/day) for 26 weeks. Global cognitive function with regard to accuracy and speed improved in the EPA-rich group. The accuracy of memory was also better in the EPA-rich group. Prefrontal cortex hemoglobin oxygenation was reduced in both omega-3 groups when compared to the placebo group. These findings impress that the EPA/DHA ratio may have an impact on cognitive functions. Even though we used EPA-rich omega-3 PUFAs in our study, the EPA/DHA ratio was not as high as that referred to in the study.

The effect of weight loss on cognitive function is another subject of interest. Zeighami et al. (80) studied the effect of weight loss on spontaneous neural activity in 57 severely obese patients who lost weight after bariatric surgery. Functional MRI was used to find out neural activity changes as indexed by fractional amplitude of low frequency fluctuations (fALFF). The study revealed widespread global and regional increases in resting neural activity with weight loss, and probable metabolic improvements associated with it.

A meta-analysis by Mazereeuw et al. (81), did not identify a beneficial effect of omega-3 PUFA supplementation on Alzheimer's disease patients or healthy subjects; however, a limited improvement on the subjects with previous cognitive impairment was revealed. A cross-sectional study on 299 healthy young women aged 18-35 years revealed reduced cognitive performance in attention with a computerized cognition testing platform in women with low omega-3 PUFA status (82). Another study on 391 non-demented elderly individuals did not identi-

fy any association between plasma omega-3 PUFA concentrations and cognitive function (83). In a study by Johnson et al. (84), 4-month supplementation with DHA (800 mg /day) and/or luthein (12 mg /day) had beneficial effects on verbal fluency, memory, and rate of learning in women aged 60-80 years.

The effect of DHA supplementation on age related cognitive deterioration is underlined in several studies. Yurko-Mauro et al. (85) have studied the effect of 900 mg/day of DHA supplementation for 24 weeks in 485 adults with age-related cognitive decline, aged over 55 years. They found that DHA supplementation improved immediate and delayed verbal and episodic memory, and learning functions in healthy adults with age-related cognitive decline. In another study on elderly adults aged 62 -80, fish oil supplementation (EPA + DHA: 2.4 g/day) improved working memory performance, and enhanced neuronal response to working memory in the posterior cingulate cortex, demonstrated by functional magnetic resonance imaging (fMRI) (86). Another study on elderly adults aged over 60 years, with mild cognitive impairment, demonstrated that 480 mg of DHA and 720 mg of EPA supplementation for 6 months were beneficial in improving cognitive functions with differences regarding gender (87). The effect of subject age and gender, the presence of cognitive decline, and the dose and duration of supplementation might be possible reasons for the differences in outcomes compared with our study.

In a study on 176 healthy young adults, Stonehouse et al. (88) found that high-dose DHA 1160 mg/day for 6 months improved working memory in men and episodic memory in women. A recent review article has suggested that gender is a factor that influences human omega-3 PUFA concentrations (89), thus considering gender as an independent variable may be valuable for upcoming trials on the effects of omega-3 supplementation.

In a randomized controlled study focusing on older adults aged over 70 with a low omega-3 index and subjective memory complaints, but without clinical dementia, executive functioning, as measured with the Controlled Oral Word Association Test (COWAT), declined less in subjects using omega-3 PUFA supplementation with a daily dose of DHA (800 mg) and EPA (a maximum amount of 225 mg) for 3 years (90). However, several other cognitive tests did not reveal a similar effect (82,83).

A study of healthy adults aged 50 to 75, with 2200 mg/day of omega-3 PUFA supplementation for 26 weeks, improved object location memory (91). A study on loneliness-related episodic memory problems in 138 healthy, overweight, and sedentary adults aged 40-85 years revealed that both 1250 mg/day and 2500 mg/day of omega-3 supplementation attenuated the decline of episodic memory in lonely people (92).

We used 1020 mg of omega-3 PUFA per day (580 mg of EPA, 390 mg of DHA, 50 mg of other omega-3 PUFAs) in our study. Even though we observed improvement in MOCA scores, we did not observe a statistically significant difference between the omega-3 and control groups. Dosage of supplement, duration of intervention, composition and EPA/DHA ratio of omega-3 supplements, gender and age of subjects, and category of cognitive tests vary in different studies, making it hard to clarify the effect of omega-3 PUFA supplementation on cognitive functions. To the best of our knowledge, there is no published study comparing the effect of omega-3 PUFA supplementation on MOCA scores in overweight or obese individuals on a weight loss diet. There are numerous studies indicating a positive effect of omega 3 PUFA supplementation on cognitive function (21). The baseline cognitive status of the subjects may also have an impact on cognitive function tests. The limitations of our study are a low number of male and elderly subjects, and the duration of the study. Previous minor memory or verbal cognitive impairment might also influence the outcomes of studies on cognitive functions. The diet of participants before the study, and compliance to the weight loss diet was evaluated using consumption records provided by the subjects, which may be inaccurate due to probable biases. The subjects in our study were middle-aged adults, and they did not have any previous cognitive impairment. A number of studies point to age-dependent beneficial effects of omega-3 PUFAs on cognition. Some studies suggest that older participants benefit more from omega-3 supplementation, although other studies recommend early omega-3 PUFA supplementation for the prevention of cognitive decline as more effective than an intervention in older individuals that already have cognitive decline (22,93). Focusing on a specific age group or gender might be helpful in finding out the effects of PUFAs on cognitive functions. Our study was not set to identify age or gender effects of omega-3 PUFA supplementation on MOCA scores. Another factor might be loneliness or social interaction with other individuals. Further studies with larger number of subjects, higher doses, or longer durations of supplementation and different tools to measure cognitive functions are required.

CONCLUSION

This study found an augmentation in the reduction of abdominal fat mass and percentage over time with omega-3 PUFA supplementation in overweight or obese individuals on a weight loss diet. Cognitive function, as measured by the Montreal Cognitive Assessment (MoCA) test, improved over time as the subjects lost weight; however, we did not find any significant difference with omega-3 PUFA supplementation. The clinical significance of these findings warrants further investigation. Studies on larger groups focusing on the effects of possible contributing factors such as BMI, genetic factors, loneliness, age, and gender with higher doses or longer duration of supplementation are required to identify the relationship and mechanisms of action of omega-3 PUFA supplementation on cognitive performance and weight loss.

REFERENCES

1. Wärnberg J, Gomez-Martinez S, Romeo J, Díaz LE, Marcos A. Nutrition, inflammation, and cognitive function. Ann N Y Acad Sci 2009;1153:164-75. DOI: 10.1111/j.1749-6632.2008.03985.x
2. Assisi A, Banzi R, Buonocore C, Capasso F, Di Muzio V, Michelacci F, et al. Fish oil and mental health: the role of n-3 long-chain polyunsaturated fatty acids in

cognitive development and neurological disorders. Int Clin Psychopharmacol 2006;21(6):319-36. DOI: 10.1097/01.yic.0000224790.98534.11
3. Young IE, Parker HM, Cook RL, O'Dwyer NJ, Garg ML, Steinbeck KS, et al. Association between Obesity and Omega-3 Status in Healthy Young Women. Nutrients 2020;12(5):1480. DOI: 10.3390/nu12051480
4. Delpino FM, Figueiredo LM, da Silva BGC. Effects of omega-3 supplementation on body weight and body fat mass: A systematic review. Clin Nutr ESPEN 2021;44:122-9. DOI: 10.1016/j.clnesp.2021.04.023
5. Couet C, Delarue J, Ritz P, Antoine JM, Lamisse F. Effect of dietary fish oil on body fat mass and basal fat oxidation in healthy adults. Int J Obes Relat Metab Disord 1997;21(8):637-43. DOI: 10.1038/sj.ijo.0800451
6. Takata Y, Zhang X, Li H, Gao YT, Yang G, Gao J, et al. Fish intake and risks of total and cause-specific mortality in 2 population-based cohort studies of 134,296 men and women. Am J Epidemiol 2013;178(1):46-57. DOI: 10.1093/aje/kws584
7. Harden CJ, Dible VA, Russell JM, Garaiova I, Plummer SF, Barker ME, et al. Long-chain polyunsaturated fatty acid supplementation had no effect on body weight but reduced energy intake in overweight and obese women. Nutr Res 2014;34(1):17-24. DOI: 10.1016/j.nutres.2013.10.004
8. Buckley JD, Howe PR. Long-chain omega-3 polyunsaturated fatty acids may be beneficial for reducing obesity-a review. Nutrients 2010;2(12):1212-30. DOI: 10.3390/nu2121212
9. Simopoulos AP. An Increase in the Omega-6/Omega-3 Fatty Acid Ratio Increases the Risk for Obesity. Nutrients 2016;8(3):128. DOI: 10.3390/nu8030128
10. Keshavarz SA, Mostafavi SA, Akhondzadeh S, Mohammadi MR, Hosseini S, Eshraghian MR, et al. Omega-3 supplementation effects on body weight and depression among dieter women with co-morbidity of depression and obesity compared with the placebo: A randomized clinical trial. Clin Nutr ESPEN 2018;25:37-43. DOI: 10.1016/j.clnesp.2018.03.001
11. López-Alarcón M, Martínez-Coronado A, Velarde-Castro O, Rendón-Macías E, Fernández J. Supplementation of n3 long-chain polyunsaturated fatty acid synergistically decreases insulin resistance with weight loss of obese prepubertal and pubertal children. Arch Med Res 2011;42(6):502-8. DOI: 10.1016/j.arcmed.2011.06.010
12. Noreen EE, Sass MJ, Crowe ML, Pabon VA, Brandauer J, Averill LK. Effects of supplemental fish oil on resting metabolic rate, body composition, and salivary cortisol in healthy adults. J Int Soc Sports Nutr 2010;7:31. DOI: 10.1186/1550-2783-7-31
13. Krzymińska-Siemaszko R, Czepulis N, Lewandowicz M, Zasadzka E, Suwalska A, Witowski J, et al. The Effect of a 12-Week Omega-3 Supplementation on Body Composition, Muscle Strength and Physical Performance in Elderly Individuals with Decreased Muscle Mass. Int J Environ Res Public Health 2015;12(9):10558-74. DOI: 10.3390/ijerph120910558
14. Hainault I, Carolotti M, Hajduch E, Guichard C, Lavau M. Fish oil in a high lard diet prevents obesity, hyperlipemia, and adipocyte insulin resistance in rats. Ann N Y Acad Sci 1993;683:98-101. DOI: 10.1111/j.1749-6632.1993.tb35696.x
15. Albracht-Schulte K, Kalupahana NS, Ramalingam L, Wang S, Rahman SM, Robert-McComb J, et al. Omega-3 fatty acids in obesity and metabolic syndrome: a mechanistic update. J Nutr Biochem 2018;58:1-16. DOI: 10.1016/j.jnutbio.2018.02.012
16. Thorsdottir I, Tomasson H, Gunnarsdottir I, Gisladottir E, Kiely M, Parra MD, et al. Randomized trial of weight-loss-diets for young adults varying in fish and fish oil content. Int J Obes (Lond) 2007;31(10):1560-6. DOI: 10.1038/sj.ijo.0803643
17. McCann JC, Ames BN. Is docosahexaenoic acid, an n-3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals. Am J Clin Nutr 2005;82(2):281-95. DOI: 10.1093/ajcn.82.2.281
18. Hashimoto M, Hossain S, Shimada T, Sugioka K, Yamasaki H, Fujii Y, et al. Docosahexaenoic acid provides protection from impairment of learning ability in Alzheimer's disease model rats. J Neurochem 2002;81(5):1084-91. DOI: 10.1046/j.1471-4159.2002.00905.x
19. Florent S, Malaplate-Armand C, Youssef I, Kriem B, Koziel V, Escanyé MC, et al. Docosahexaenoic acid prevents neuronal apoptosis induced by soluble amyloid-beta oligomers. J Neurochem 2006;96(2):385-95. DOI: 10.1111/j.1471-4159.2005.03541.x
20. Mukherjee PK, Marcheselli VL, Serhan CN, Bazan NG. Neuroprotectin D1: a docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress. Proc Natl Acad Sci USA 2004;101(22):8491-6. DOI: 10.1073/pnas.0402531101
21. Martí Del Moral A, Fortique F. Omega-3 fatty acids and cognitive decline: a systematic review. Nutr Hosp 2019;36(4):939-49. DOI: 10.20960/nh.02496
22. Luchtman DW, Song C. Cognitive enhancement by omega-3 fatty acids from child-hood to old age: findings from animal and clinical studies. Neuropharmacology 2013;64:550-65. DOI: 10.1016/j.neuropharm.2012.07.019
23. Glisky EL. Changes in Cognitive Function in Human Aging. In: Riddle DR, editor. Brain Aging: Models, Methods, and Mechanisms. Boca Raton (FL): CRC Press/Taylor & Francis; 2007:1-27
24. Siervo M, Arnold R, Wells JC, Tagliabue A, Colantuoni A, Albanese E, et al. Intentional weight loss in overweight and obese individuals and cognitive function: a systematic review and meta-analysis. Obes Rev 2011;12(11):968-83. DOI: 10.1111/j.1467-789X.2011.00903.x
25. Sydenham E, Dangour AD, Lim WS. Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database Syst Rev 2012;(6):CD005379. DOI: 10.1002/14651858.CD005379.pub3
26. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol 2017;16(5):377-89. DOI: 10.1016/S1474-4422(17)30040-6
27. Marriott BP, Turner TH, Hibbeln JR, Newman JC, Pregulman M, Malek AM, et al. Impact of Fatty Acid Supplementation on Cognitive Performance among United States (US) Military Officers: The Ranger Resilience and Improved Performance on Phospholipid-Bound Omega-3's (RRIPP-3) Study. Nutrients 2021;13(6):1854. DOI: 10.3390/nu13061854
28. Sierra-Ruelas É, Bernal-Orozco MF, Macedo-Ojeda G, Márquez-Sandoval YF, Altamirano-Martínez MB, Vizmanos B. Validation of semiquantitative FFQ administered to adults: a systematic review. Public Health Nutr 2021;24(11):3399-418. DOI: 10.1017/S1368980020001834
29. Koliaki C, Spinos T, Spinou M, Brinia ME, Mitsopoulou D, Katsilambros N. Defining the Optimal Dietary Approach for Safe, Effective and Sustainable Weight Loss in Overweight and Obese Adults. Healthcare (Basel) 2018;6(3):73. DOI: 10.3390/healthcare6030073
30. Matarese LE, Pories WJ. Adult weight loss diets: metabolic effects and outcomes. Nutr Clin Pract 2014;29(6):759-67. DOI: 10.1177/0884533614550251
31. Madden AM, Smith S. Body composition and morphological assessment of nutritional status in adults: a review of anthropometric variables. J Hum Nutr Diet 2016;29(1):7-25. DOI: 10.1111/jhn.12278
32. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695-9. DOI: 10.1111/j.1532-5415.2005.53221.x. Erratum in: J Am Geriatr Soc 2019;67(9):1991.
33. Ozdilek B, Kenangil G. Validation of the Turkish Version of the Montreal Cognitive Assessment Scale (MoCA-TR) in patients with Parkinson's disease. Clin Neuropsychol 2014;28(2):333-43. DOI: 10.1080/13854046.2014.881554
34. Larner AJ. Screening utility of the Montreal Cognitive Assessment (MoCA): in place of--or as well as--the MMSE? Int Psychogeriatr 2012;24(3):391-6. DOI: 10.1017/S1041610211001839
35. Del Brutto OH, Mera RM, Gillman J, Zambrano M, Ha JE. Oily Fish Intake and Cognitive Performance in Community-Dwelling Older Adults: The Atahualpa Project. J Community Health 2016;41(1):82-6. DOI: 10.1007/s10900-015-0070-9
36. Ciesielska N, Sokołowski R, Mazur E, Podhorecka M, Polak-Szabela A, Kędziora-Kornatowska K. Is the Montreal Cognitive Assessment (MoCA) test better suited than the Mini-Mental State Examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. Psychiatr Pol 2016;50(5):1039-52. DOI: 10.12740/PP/45368
37. Agostoni C, Bresson JL, Fairweather Tait S, Flynn A, Golly I, Korhonen H, et al. Scientific opinion on the tolerable upper intake level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA): EFSA 2012 EFSA panel on dietetic products, nutrition and allergies (NDA). European Food Safety Authority. EFSA Journal 2012;10(7):2815.1-2815.48 DOI: 10.2903/j.efsa.2012.2815
38. Van Dael P. Role of n-3 long-chain polyunsaturated fatty acids in human nutrition and health: review of recent studies and recommendations. Nutr Res Pract 2021;15(2):137-59. DOI: 10.4162/nrp.2021.15.2.137
39. Calder PC. Functional Roles of Fatty Acids and Their Effects on Human Health. JPEN J Parenter Enteral Nutr 2015;39(1 Suppl):18S-32S. DOI: 10.1177/0148607115595980
40. Carpentier YA, Portois L, Malaisse WJ. n-3 fatty acids and the metabolic syndrome. Am J Clin Nutr 2006;83(6 Suppl):1499S-504S. DOI: 10.1093/ajcn/83.6.1499S

41. Burrows T, Collins CE, Garg ML. Omega-3 index, obesity and insulin resistance in children. Int J Pediatr Obes 2011;6(2-2):e532-9. DOI: 10.3109/17477166.2010.549489
42. Micallef M, Munro I, Phang M, Garg M. Plasma n-3 Polyunsaturated Fatty Acids are negatively associated with obesity. Br J Nutr 2009;102(9):1370-4. DOI: 10.1017/S0007114509382173
43. Mingay E, Veysey M, Lucock M, Niblett S, King K, Patterson A, et al. Sex-dependent association between omega-3 index and body weight status in older Australians. J Nutr Intermed Metab 2016;5:70-7. DOI: 10.1016/j.jnim.2016.04.001
44. Karlsson M, Mårild S, Brandberg J, Lönn L, Friberg P, Strandvik B. Serum phospholipid fatty acids, adipose tissue, and metabolic markers in obese adolescents. Obesity (Silver Spring) 2006;14(11):1931-9. DOI: 10.1038/oby.2006.225
45. Ruzickova J, Rossmeisl M, Prazak T, Flachs P, Sponarova J, Veck M, et al. Omega-3 PUFA of marine origin limit diet-induced obesity in mice by reducing cellularity of adipose tissue. Lipids 2004;39(12):1177-85. DOI: 10.1007/s11745-004-1345-9. Erratum in: Lipids 2005;40(1):115.
46. Minami A, Ishimura N, Sakamoto S, Takishita E, Mawatari K, Okada K, et al. Effect of eicosapentaenoic acid ethyl ester v. oleic acid-rich safflower oil on insulin resistance in type 2 diabetic model rats with hypertriacylglycerolaemia. Br J Nutr 2002;87(2):157-62. DOI: 10.1079/BJN2001496
47. Soni N, Ross AB, Scheers N, Nookaew I, Gabrielsson BG, Sandberg AS. The Omega-3 Fatty Acids EPA and DHA, as a Part of a Murine High-Fat Diet, Reduced Lipid Accumulation in Brown and White Adipose Tissues. Int J Mol Sci 2019;20(23):5895. DOI: 10.3390/ijms20235895
48. DeFina LF, Marcoux LG, Devers SM, Cleaver JP, Willis BL. Effects of omega-3 supplementation in combination with diet and exercise on weight loss and body composition. Am J Clin Nutr 2011;93(2):455-62. DOI: 10.3945/ajcn.110.002741
49. Munro IA, Garg ML. Dietary supplementation with long chain omega-3 polyunsaturated fatty acids and weight loss in obese adults. Obes Res Clin Pract 2013;7(3):e173-81. DOI: 10.1016/j.orcp.2011.11.001
50. Munro IA, Garg ML. Dietary supplementation with n-3 PUFA does not promote weight loss when combined with a very-low-energy diet. Br J Nutr 2012;108(8):1466-74. DOI: 10.1017/S0007114511006817
51. Munro IA, Garg ML. Prior supplementation with long chain omega-3 polyunsaturated fatty acids promotes weight loss in obese adults: a double-blinded randomised controlled trial. Food Funct 2013;4(4):650-8. DOI: 10.1039/c3fo60038f
52. Matsumura K. Effects of eicosapentaenoic acid on visceral fat and heart rate variability: assessment by power spectral analysis. J Cardiol 2007;50(4):243-51.
53. Kabir M, Skurnik G, Naour N, Pechtner V, Meugnier E, Rome S, et al. Treatment for 2 mo with n 3 polyunsaturated fatty acids reduces adiposity and some atherogenic factors but does not improve insulin sensitivity in women with type 2 diabetes: a randomized controlled study. Am J Clin Nutr 2007;86(6):1670-9. DOI: 10.1093/ajcn/86.5.1670
54. Itariu BK, Zeyda M, Hochbrugger EE, Neuhofer A, Prager G, Schindler K, et al. Long-chain n-3 PUFAs reduce adipose tissue and systemic inflammation in severely obese nondiabetic patients: a randomized controlled trial. Am J Clin Nutr 2012;96(5):1137-49. DOI: 10.3945/ajcn.112.037432. Erratum in: Am J Clin Nutr 2020;112(5):1405
55. Rossmeisl M, Jelenik T, Jilkova Z, Slamova K, Kus V, Hensler M, et al. Prevention and reversal of obesity and glucose intolerance in mice by DHA derivatives. Obesity (Silver Spring) 2009;17(5):1023-31. DOI: 10.1038/oby.2008.602
56. Liu HQ, Qiu Y, Mu Y, Zhang XJ, Liu L, Hou XH, et al. A high ratio of dietary n-3/n-6 polyunsaturated fatty acids improves obesity-linked inflammation and insulin resistance through suppressing activation of TLR4 in SD rats. Nutr Res 2013;33(10):849-58. DOI: 10.1016/j.nutres.2013.07.004
57. Pacifico L, Bonci E, Di Martino M, Versacci P, Andreoli G, Silvestri LM, et al. A double-blind, placebo-controlled randomized trial to evaluate the efficacy of docosahexaenoic acid supplementation on hepatic fat and associated cardiovascular risk factors in overweight children with nonalcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2015;25(8):734-41. DOI: 10.1016/j.numecd.2015.04.003
58. Yu Q, Zou L, Kong Z, Yang L. Cognitive Impact of Calorie Restriction: A Narrative Review. J Am Med Dir Assoc 2020;21(10):1394-401. DOI: 10.1016/j.jamda.2020.05.047
59. Fusco S, Pani G. Brain response to calorie restriction. Cell Mol Life Sci 2013;70(17):3157-70. DOI: 10.1007/s00018-012-1223-y
60. Gupta H, Suk KT, Kim DJ. Gut Microbiota at the Intersection of Alcohol, Brain, and the Liver. J Clin Med 2021;10(3):541. DOI: 10.3390/jcm10030541
61. Öberg M, Fabrik I, Fabrikova D, Zehetner N, Härtlova A. The role of innate immunity and inflammation in Parkinson´s disease. Scand J Immunol 2021;93(5):e13022. DOI: 10.1111/sji.13022
62. Dionysopoulou S, Charmandari E, Bargiota A, Vlahos N, Mastorakos G, Valsamakis G. The Role of Hypothalamic Inflammation in Diet-Induced Obesity and Its Association with Cognitive and Mood Disorders. Nutrients 2021;13(2):498. DOI: 10.3390/nu13020498
63. Gkotzamanis V, Panagiotakos D. Dietary interventions and cognition: A systematic review of clinical trials. Psychiatriki 2020;31(3):248-56. DOI: 10.22365/jpsych.2020.313.248
64. D'Cunha NM, Georgousopoulou EN, Dadigamuwage L, Kellett J, Panagiotakos DB, Thomas J, et al. Effect of long-term nutraceutical and dietary supplement use on cognition in the elderly: a 10-year systematic review of randomised controlled trials. Br J Nutr 2018;119(3):280-98. DOI: 10.1017/S0007114517003452
65. Muth AK, Park SQ. The impact of dietary macronutrient intake on cognitive function and the brain. Clin Nutr 2021;40(6):3999-4010. DOI: 10.1016/j.clnu.2021.04.043
66. Gómez-Apo E, Mondragón-Maya A, Ferrari-Díaz M, Silva-Pereyra J. Structural Brain Changes Associated with Overweight and Obesity. J Obes 2021;2021:6613385. DOI: 10.1155/2021/6613385
67. Masana MF, Koyanagi A, Haro JM, Tyrovolas S. n-3 Fatty acids, Mediterranean diet and cognitive function in normal aging: A systematic review. Exp Gerontol 2017;91:39-50. DOI: 10.1016/j.exger.2017.02.008
68. Stavrinou PS, Andreou E, Aphamis G, Pantzaris M, Ioannou M, Patrikios IS, et al. The Effects of a 6-Month High Dose Omega-3 and Omega-6 Polyunsaturated Fatty Acids and Antioxidant Vitamins Supplementation on Cognitive Function and Functional Capacity in Older Adults with Mild Cognitive Impairment. Nutrients 2020;12(2):325. DOI: 10.3390/nu12020325
69. Djuricic I, Calder PC. Beneficial Outcomes of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Human Health: An Update for 2021. Nutrients 2021;13(7):2421. DOI: 10.3390/nu13072421
70. Stonehouse W. Does consumption of LC omega-3 PUFA enhance cognitive performance in healthy school-aged children and throughout adulthood? Evidence from clinical trials. Nutrients 2014;6(7):2730-58. DOI: 10.3390/nu6072730
71. Rangel-Huerta OD, Gil A. Effect of omega-3 fatty acids on cognition: an updated systematic review of randomized clinical trials. Nutr Rev 2018;76(1):1-20. DOI: 10.1093/nutrit/nux064
72. Pase MP, Grima N, Cockerell R, Stough C, Scholey A, Sali A, et al. The effects of long-chain omega-3 fish oils and multivitamins on cognitive and cardiovascular function: a randomized, controlled clinical trial. J Am Coll Nutr 2015;34(1):21-31. DOI: 10.1080/07315724.2014.880660
73. Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. Am J Clin Nutr 2010;91(6):1725-32. DOI: 10.3945/ajcn.2009.29121
74. Antypa N, Van der Does AJ, Smelt AH, Rogers RD. Omega-3 fatty acids (fish-oil) and depression-related cognition in healthy volunteers. J Psychopharmacol. 2009;23(7):831-40. DOI: 10.1177/0269881108092120
75. Jackson PA, Reay JL, Scholey AB, Kennedy DO. DHA-rich oil modulates the cerebral haemodynamic response to cognitive tasks in healthy young adults: a near IR spectroscopy pilot study. Br J Nutr 2012;107(8):1093-8. DOI: 10.1017/S0007114511004041
76. Jackson PA, Deary ME, Reay JL, Scholey AB, Kennedy DO. No effect of 12 weeks' supplementation with 1 g DHA-rich or EPA-rich fish oil on cognitive function or mood in healthy young adults aged 18-35 years. Br J Nutr 2012;107(8):1232-43. DOI: 10.1017/S000711451100403X
77. Rogers PJ, Appleton KM, Kessler D, Peters TJ, Gunnell D, Hayward RC, et al. No effect of n-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. Br J Nutr 2008;99(2):421-31. DOI: 10.1017/S0007114507801097
78. Howe PRC, Evans HM, Kuszewski JC, Wong RHX. Effects of Long Chain Omega-3 Polyunsaturated Fatty Acids on Brain Function in Mildly Hypertensive Older Adults. Nutrients 2018;10(10):1413. DOI: 10.3390/nu10101413. Erratum in: Nutrients 2019;11(5).
79. Patan MJ, Kennedy DO, Husberg C, Hustvedt SO, Calder PC, Khan J, et al. Supplementation with oil rich in eicosapentaenoic acid, but not in docosahexaenoic acid, improves global cognitive function in healthy, young adults: results from randomized controlled trials. Am J Clin Nutr 2021;114(3):914-24. DOI: 10.1093/ajcn/nqab174
80. Zeighami Y, Iceta S, Dadar M, Pelletier M, Nadeau M, Biertho L, et al. Spontaneous neural activity changes after bariatric surgery: A resting-state

fMRI study. Neuroimage 2021;241:118419. DOI: 10.1016/j.neuroimage.2021.118419
81. Mazereeuw G, Lanctôt KL, Chau SA, Swardfager W, Herrmann N. Effects of ω-3 fatty acids on cognitive performance: a meta-analysis. Neurobiol Aging 2012;33(7):1482.e17-29. DOI: 10.1016/j.neurobiolaging.2011.12.014
82. Cook RL, Parker HM, Donges CE, O'Dwyer NJ, Cheng HL, Steinbeck KS, et al. Omega-3 polyunsaturated fatty acids status and cognitive function in young women. Lipids Health Dis 2019;18(1):194. DOI: 10.1186/s12944-019-1143-z
83. Herrmann M, Simstich S, Fauler G, Hofer E, Fritz-Petrin E, Herrmann W, et al. The relationship between plasma free fatty acids, cognitive function and structural integrity of the brain in middle-aged healthy humans. Aging (Albany NY) 2021;13(18):22078-91. DOI: 10.18632/aging.203573
84. Johnson EJ, McDonald K, Caldarella SM, Chung HY, Troen AM, Snodderly DM. Cognitive findings of an exploratory trial of docosahexaenoic acid and lutein supplementation in older women. Nutr Neurosci 2008;11(2):75-83. DOI: 10.1179/147683008X301450
85. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement 2010;6(6):456-64. DOI: 10.1016/j.jalz.2010.01.013
86. Boespflug EL, McNamara RK, Eliassen JC, Schidler MD, Krikorian R. Fish Oil Supplementation Increases Event-Related Posterior Cingulate Activation in Older Adults with Subjective Memory Impairment. J Nutr Health Aging 2016;20(2):161-9. DOI: 10.1007/s12603-015-0609-6
87. Bo Y, Zhang X, Wang Y, You J, Cui H, Zhu Y, et al. The n-3 Polyunsaturated Fatty Acids Supplementation Improved the Cognitive Function in the Chinese Elderly with Mild Cognitive Impairment: A Double-Blind Randomized Controlled Trial. Nutrients 2017;9(1):54. DOI: 10.3390/nu9010054
88. Stonehouse W, Conlon CA, Podd J, Hill SR, Minihane AM, Haskell C, et al. DHA supplementation improved both memory and reaction time in healthy young adults: a randomized controlled trial. Am J Clin Nutr 2013;97(5):1134-43. DOI: 10.3945/ajcn.112.053371
89. de Groot RHM, Emmett R, Meyer BJ. Non-dietary factors associated with n-3 long-chain PUFA levels in humans - a systematic literature review. Br J Nutr 2019;121(7):793-808. DOI: 10.1017/S0007114519000138
90. Hooper C, De Souto Barreto P, Coley N, Cantet C, Cesari M, Andrieu S, et al. Cognitive Changes with Omega-3 Polyunsaturated Fatty Acids in Non-Demented Older Adults with Low Omega-3 Index. J Nutr Health Aging 2017;21(9):988-93. DOI: 10.1007/s12603-017-0957-5
91. Külzow N, Witte AV, Kerti L, Grittner U, Schuchardt JP, Hahn A, et al. Impact of Omega-3 Fatty Acid Supplementation on Memory Functions in Healthy Older Adults. J Alzheimers Dis 2016;51(3):713-25. DOI: 10.3233/JAD-150886
92. Jaremka LM, Derry HM, Bornstein R, Prakash RS, Peng J, Belury MA, et al. Omega-3 supplementation and loneliness-related memory problems: secondary analyses of a randomized controlled trial. Psychosom Med 2014;76(8):650-8. DOI: 10.1097/PSY.0000000000000104
93. Sinn N, Milte CM, Street SJ, Buckley JD, Coates AM, Petkov J, et al. Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life, memory and executive function in older adults with mild cognitive impairment: a 6-month randomised controlled trial. Br J Nutr 2012;107(11):1682-93. DOI: 10.1017/S0007114511004788