Clinical Interventions in Aging

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CLINICAL TRIAL REPORT

Calanus Oil Supplementation Does Not Further Improve Short-Term Memory or Brain-Derived Neurotrophic Factor in Older Women Who Underwent Exercise Training

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Purpose: In our study, we examined changes in short-term episodic memory and brain-derived neurotrophic factor (BDNF) in women after an exercise program alone or in combination with omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation.

Patients and Methods: Fifty-five healthy elderly women (65–80 years) were randomly split into two groups: in the first group were women attending an exercise program while taking wax esters-rich oil (Calanus) supplementation (n = 28) and in the other group were women undergoing the same exercise program while taking placebo (n = 27). The 16-week exercise program consisted of functional circuit training (twice a week) and Nordic walking lessons (once a week). Short-term episodic memory was evaluated by the Czech screening Test "Pojmenování OBrázků A jejich Vybavení" (POBAV) baseline and after the program lasting 16 weeks.

Results: Our results show that short-term memory significantly improved following the exercise program, but there was no added value in using n-3 PUFA supplements. BDNF values did not differ between baseline and follow-up in either group. However, there was a statistically significant positive relationship between relative change (%) in the POBAV test and VO_2peak in the placebo group (r = 0.49).

Conclusion: Despite the added value of n-3 PUFA supplementation not being proven, our results may strengthen the importance of physical activity in averting age-related memory decline and dementia.

Keywords: cognitive function, n-3 PUFA, physical activity, aging, circuit training, Nordic walking

Introduction

The ageing process is inevitable and often results in some degree of cognitive complication. Fortunately, despite memory problems being among the most frequent health issues reported by aging people, lifestyle interventions can help delay or offset these undesirable consequences of aging. Specifically, physical activity (PA) and exercise can positively affect cognitive function,[1–4] can help decrease the risk of dementia,[5] and can have a positive effect on memory in healthy elderly subjects.[6] The number of studies investigating the effects of exercise on cognitive health is plentiful, with aerobic exercise shown to improve memory function,[7–9] and other exercise modalities such as strength training and stretching likely playing an important role as well.[10–12] Therefore, a multifaceted approach to training, eg, using a combination of aerobic and strength training, seems to be warranted as it might be more effective in slowing cognitive and motor decline than isolated types of training alone.[13]

Although many factors likely contribute to the positive effects of exercise on cognitive function, two of the most important factors include increased blood flow to the brain (providing the necessary nutrients[14] and increased

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neurotrophic factors in response to physical activity (especially brain-derived neurotrophic factor (BDNF))).[1,15,16] BDNF is a polypeptide growth factor that is expressed in the central nervous system and is considered to be extremely important for learning and forming memories. It plays a crucial role in regulating synaptic plasticity, and it also plays a role in neurogenesis and neuronal survival.[17,18]

In addition to the effect of exercise on cognitive health and memory, diet and nutritional interventions may also positively influence these functions.[19,20]

Generally speaking, dietary habits have the potential to positively influence age-related cognitive decline,[21] with many comprehensive studies investigating the Mediterranean diet and specific nutrients including n-3 PUFA, antioxidants, and B-vitamins.[14,21–23] As for n-3 PUFA, three different types are most considered: α-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). DHA and EPA are important components of the brain's neuronal membranes, and their relevance for brain function is linked to not only brain structure build-up and maintenance, but also to brain perfusion and inflammatory processes,[24] both of which can also be influenced by exercise.[25–27] Since n-3 PUFA concentration in the brain decreases with age, supplementing the diet with n-3 PUFA may help increase or maintain cognitive function.[28] It has been suggested that ≥180 mg/d of dietary DHA is associated with approximately a 50% reduction in risk of dementia,[29] while other studies have shown that dietary fish or fish oil rich in n-3 PUFA, ie, DHA and EPA, may prevent Alzheimer's disease (AD).[30]

Although traditional supplements may serve their purpose well, new supplements may be more ecological to produce, may offer quicker absorption, or may increase bioavailability, and finally, they may show more significant health benefits. One of the new types of omega-3 supplementation is Calanus Oil extracted from planktonic *Calanus finmarchicus*, which contains n-3 PUFA in a form of fatty alcohols and wax esters. It has been demonstrated that Calanus is a highly bioavailable source of DHA and EPA fatty acids;[31] however, its effect on memory and cognitive function has not been elucidated. Additionally, as the natural concentration of EPA and DHA in salmon has decreased significantly in recent years,[24] new supplementation approaches are gaining more attention. In fact, Calanus Oil is interesting from this perspective, as it likely represents one of the largest sources of omega-3 fatty acids (FA) on the planet.

Based on the aforementioned points, we hypothesized that multimodal exercise combined with n-3 PUFA supplementation may be a better strategy for influencing cognitive function such as short-term episodic memory than exercise training alone. To address this notion, we performed 16-week holistic exercise training program with adding Calanus Oil supplementation containing n-3 PUFA and compared it to the same exercise program without the supplementation. We further tested whether a possible mechanism of memory improvement could be related to BDNF levels.

Materials and Methods

Study Design

This randomized-controlled trial is part of a larger clinical study named EXODYA (Effect of Exercise training and Omega-3 fatty acids on metabolic health and Dysfunction of Adipose tissue in the elderly; research project nr. AZV 16–29182A; NCT number: NCT03386461). Other publications from this project independently focused on specific aspects such as serum and adipose tissue lipidome, inflammation of adipose tissue, physical fitness and central cardiodynamic function. Although the study design and participants were the same in these papers, the present paper specifically focuses on changes of short-term episodic memory and BDNF plasma levels. The study was conducted as a double-blinded trial. Neither the subjects nor the investigators who came into personal contact with the subjects were informed about who was taking supplementation and who was taking placebo.

Participants

Fifty-five healthy non-obese women (70.9±3.9 yr) were recruited mainly through advertisements in local organizations that provide services for the local elderly community. As women comprise majority of such services participants and because we intended to achieve a maximal homogeneity of the sample, we chose women only. To be included, women must have been between 60 and 80 years old, and generally healthy. They were excluded if they presented any health concerns (cancer, liver, or kidney disorders, diabetes, untreated thyroid diseases), were taking medication (long-term use

of corticosteroids, beta-blockers, antirheumatic agents), and had other lifestyle factors that could have affected the study's results (weight loss of more than 3 kg during 3 months prior to the study, smoking, use of n-3 PUFA supplements before the study).

Participants were randomly divided into either an exercise and Calanus supplementation group (Cal-EX) or exercise and placebo supplementation group (Pla-EX). Two subjects dropped-out from the study during the 16-week intervention due to health issues (not connected with the exercise program itself), and one subject was excluded because of missing data in the memory test. Thus, the final analyses included 27 participants in the Cal-EX group and 25 participants in the Pla-EX group, all of whom displayed normal levels of cognitive and sensory function at baseline. The study design is visualized in the consort diagram (Figure 1).

General Procedures

For the duration of the study, all participants were encouraged to maintain their typical activities of daily living, dietary habits, sleep schedule, and the like. All evaluation methods, measures, and sample collections were performed at week 0 (baseline) and week 16 (follow-up, ie, after the intervention) on an outpatient basis. During the 16-week period, all women participated in the exercise program. In addition, the Cal-EX group was provided with omega-3 and wax esters rich supplementation (5 capsules/day of Calanus oil, Calanus a.s. Norway) while Pla-EX was supplemented by placebo (5 capsules/day of sunflower oil, Calanus a.s., Norway). Thus, the daily dosage of n-3 PUFA in the Cal-EX group was approximately 105 mg of docosahexaenoic acid (DHA) and 125 mg eicosapentaenoic acid (EPA). The dose of supplementation was chosen to achieve sufficient daily dose of EPA and DHA,[29] good adherence of the subjects to taking the pills, and a tolerance to gelatine digestion (gelatine is the major component of soft pills containing Calanus oil or placebo).

The study was approved by the Ethical Committee of the University Hospital Kralovske Vinohrady in Prague (EK-VP /17l0l20l5). Before the start of the study, all participants signed an informed consent confirming that their participation

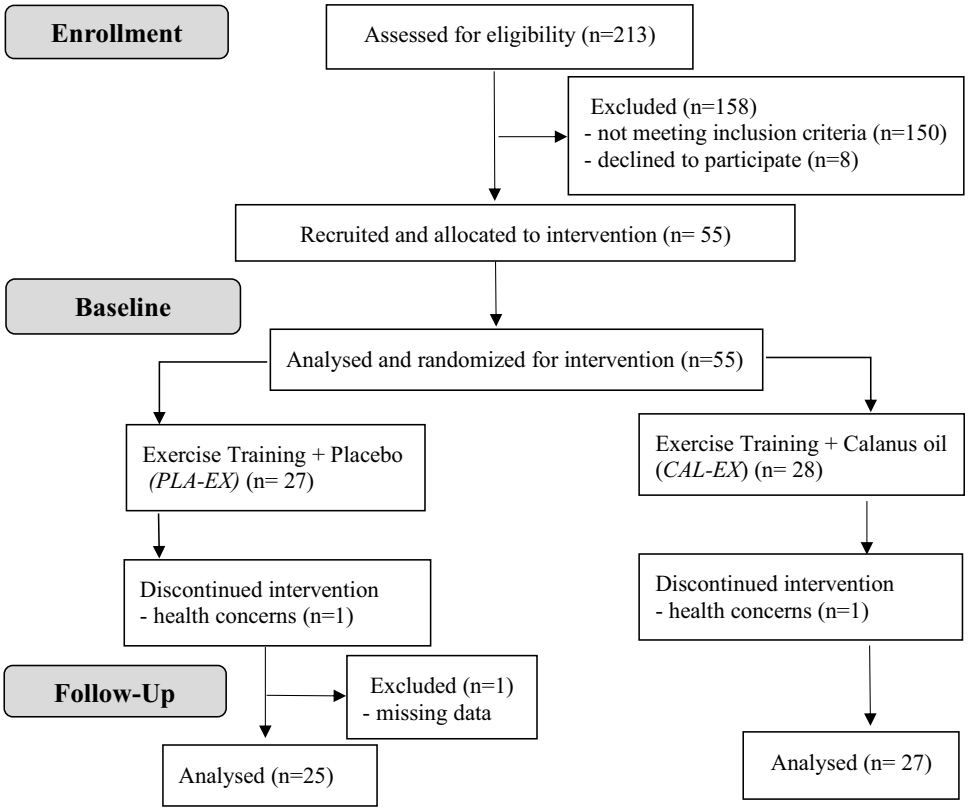

Figure 1 Consort diagram of the study design.

was voluntary; all data was anonymized. The participants received financial reward for being enrolled in the study (approximately 1/6 of the reward after baseline measurements and the remaining 5/6 after the final measurements).

Measurements

Memory

Memory was tested using the Czech screening tool named "Test Pojmenování OBrázků A jejich Vybavení" (POBAV) which is a test that is used to detect cognitive disorders.[32] The POBAV stands for an abbreviation of Czech title which means in English "Picture naming and their recall". This test has high sensitivity and specificity[32,33] and consists of two parts. First, the subjects are shown 20 pictures and are asked to name each picture using just one word for each picture, write the names down, and remember the actual names they used for the pictures. After that, they turn the paper over and are immediately asked to recall and write down as many words as they can remember, in any order. The limit for the second part (recalling and writing down the names for each picture) is either 1 minute or until the participants spontaneously give-up, with a maximum time of 2 minutes.[33] In our study, we used the second option – a maximum time limit of 2 minutes.

Each part of the test (assigning a name for each picture and recalling those names) evaluates different cognitive functions. The purpose of the test is to examine the following multiple cognitive functions: the written language, long-term semantic memory, and short-term visual episodic memory. Naming quality (written language and long-term semantic memory) is assessed with the number of errors as the sum of erroneously named and unnamed pictures. Conversely, recall is assessed by the number of correctly recalled picture names without confabulations and without repetitions. The score of the test is thus difference between the second and the first part of the test (ie, correctly recalled picture names minus naming errors). The number of naming errors or correctly recalled picture names in normal elderly adults is independent of age, education, and gender.[32]

As the subjects were free from cognitive impairment, we did not evaluate written language or the long-term semantic memory, but we instead focused mainly on evaluating short-term visual memory, ie, the number of correctly recalled particular words describing the pictures without confabulations and without repetition.

Participants were tested using two versions (A and B) of the POBAV test in a counter-balanced order, ie, for some of the subjects, test A was applied at baseline and test B at follow-up, and vice versa.

Brain-Derived Neurotrophic Factor (BDNF)

Serum BDNF was measured baseline and at follow-up. The blood sample collection was performed at least 48 hours after the last exercise session and physical performance testing, after an overnight (10–12 h) fast, drinking water ad libitum. The serum concentration of BDNF was determined using xMAP technology (MILLIPLEX MAP Human Myokine Magnetic Bead Panel; Merck-Millipore, US) on the MagPIX instrument.

Physical Performance Evaluation

Physical performance was evaluated by maximal-graded exercise test on a lower body cycle ergometer (Ergoselect 200, Ergoline, Germany) baseline and at follow up. Before the procedure, all aspects of the exercise test were explained to the participants and basic anthropometric parameters were acquired. Body height was measured using a SECA 213 portable stadiometer, body mass was measured using a SECA 876 digital flat floor scale. After that, the ergometer seat height and handle distance were adjusted to fit each subject, who then became familiarized with the ergometer and the procedures. The exercise stress test began with submaximal exercise at 0.5 Watts per kilogram of body weight ($W.kg^{-1}$), which lasted 4 min. After the first 4 min, the load increment of the stress test (ramp protocol) was linear, beginning at a load of 20 W (low intensity) with an increase of 15–30 W per minute. The aim of the protocol was to achieve the expected peak load (ie, maximal intensity) within 4 to 8 min. The participants had to maintain 70–90 revolutions per minute throughout the test, and they were being asked to try to the limits of their abilities. An individual peak effort was identified (and the test stopped) when the respiratory exchange ratio (RER) exceeded 1.06 and the person was not able to continue pedaling at 70–90 revolutions per minute. None of the participants experienced any cardiorespiratory difficulties or any other

medical complications during or after the test. Oxygen consumption was measured using a breath-by-breath gas exchange analyzer Power Cube-Ergo (Ganshorn Medizine Electronic GmbH, Niederlauer, Germany).

Exercise Intervention

The exercise intervention lasted 16 weeks and included three group training sessions per week: one session of aerobic exercise (outdoor Nordic walking) and two sessions of indoor circuit training with low resistance. Each session lasted approximately 1 hour and was led by an accredited exercise trainer. For the first two weeks, the acclimatization period mainly focused on developing good posture, coordination, breathing, and flexibility while acquiring the exercise skills necessary for the remaining 14 weeks. This was done to increase exercise adherence and provide individualized attention when necessary (in order to ensure correct posture and exercise technique for the upcoming 14 weeks of training). After that, the normal circuit training and Nordic walking classes were conducted. For the sake of brevity, a detailed description of exercise intensity and contents of the lessons are published elsewhere.[34] Individual exercise adherence (percentage of attended lessons from all 46 lessons planned) was high; it ranged from 74% to 100% (mean 96.3%).

Statistical Analysis

Means and standard deviations (SD) were calculated for each continual variable. Because of the small sample sizes, we used non-parametric statistics methods.[35,36] We used Wilcoxon Signed Rank test to compare within group difference, and Mann–Whitney *U*-test to compare between groups differences. Level of significance was set as $\alpha = 0.05$ for both statistical tools. Then, we calculated Cohen's d to estimate the effect-size in the main variables. After that, Spearman Rank Correlation was used to estimate relationship between the percentage changes of VO_2peak and percentage changes in the POBAV test for both study groups together and separately. Additionally, we used a generalized linear model to estimate relationships between the BDNF post-pre mean difference and initial cognitive and physical performance levels, and BDNF blood level. Results were considered statistically significant if $p < 0.05$. All the statistics were carried out in IBM SPSS Statistics 24.

Results

There were no significant differences between general characteristics of the participants in the Cal-EX group and the Pla-EX group at baseline (Table 1).

The pre-post intervention changes within intervention and between groups are shown in Table 2. Both groups improved their POBAV test scores and their exercise capacity (expressed as peak oxygen consumption), but there was no difference in the post-pre mean differences between groups. BDNF values did not change within or between groups. Furthermore, according to Cohen's d, the effect size was negligible in all the variables.

In the generalized linear model, baseline values of POBAV and BDNF appeared to be a significant variable for post-pre changes in BDNF, showing that the higher the baseline value, the less improvement can be expected (Table 3).

Table 1 General Characteristics of Both Groups (Baseline)

	Cal-EX	**Pla-EX**	
	n = 27	n = 25	*p*-value
Age (years)	70.8 (3.6)	71.2 (4.0)	0.724
Height (m)	1.63 (0.1)	1.62 (0.1)	0.796
Weight (kg)	72.9 (13.1)	73.1 (9.7)	0.885
BMI ($kg \cdot m^{-2}$)	27.3 (4.1)	27.4 (4.2)	0.910

Notes: Data are presented as mean (SD); Mann–Whitney *U*-test was used to test for differences.

Abbreviations: Cal-EX, group with exercise and Calanus oil supplementation; Pla-EX, group with exercise and placebo; BMI, body mass index.

Table 2 Mean Values Baseline and Follow-Up (After 16 Weeks) and Mean Differences in the Variables

	Cal-EX (n = 27)		Pla-EX (n = 25)		Cal-EX	Pla-EX	
	Baseline	**Follow-Up**	**Baseline**	**Follow-Up**	**Dif.**	**Dif.**	**Cohen's d**
POBAV (nr)	9.8 (3.2)	12.1 (2.8)[a]	11.0 (2.1)	12.7 (2.9)[a]	2.3 (3.0)	1.6 (3.6)	0.21
VO2peak (mL·kg^{-1}·min^{-1})	19.7 (4.3)	23.1 (4.8)[a]	19.3 (3.2)	23.1 (3.3)[a]	3.4 (3.6)	3.8 (3.2)	0.12
BDNF (ng·mL^{-1})	10.4 (4.4)	10.9 (3.4)	11.1 (4.9)	11.5 (4.8)	0.5 (2.8)	0.4 (3.6)	0.03

Notes: The values are presented as mean (SD); [a]Wilcoxon Signed Rank test within intervention ($p < 0.05$); According to Mann–Whitney *U*-test, there were no differences between groups ($p < 0.05$).
Abbreviations: Cal-EX, group with exercise and Calanus oil supplementation; Pla-EX, group with exercise and placebo; POBAV, Test Pojmenování OBrázků A jejich Vybavení assessing memory (as number of recalled pictures); VO2peak, peak oxygen consumption assessing cardiorespiratory fitness; BDNF, brain-derived neurotrophic factor.

Table 3 Generalized Linear Model for the BDNF Post-Pre Changes as a Dependent Variable

		95% Wald Confidence Interval		
	B	**Lower**	**Upper**	***p*-value**
Cal-EX	−5.606	−20.886	9.673	0.472
Pla-EX	0[a]			
POBAV baseline	−3.146	−6.028	−0.264	0.032
VO_2peak baseline	0.207	−1.891	2.304	0.847
BDNF baseline	−0.368	−0.547	−0.188	<0.001

Note: [a]Set to zero because this parameter is redundant.
Abbreviations: Cal-EX, group with exercise and Calanus oil supplementation; Pla-EX, group with exercise and placebo; POBAV, Test Pojmenování OBrázků A jejich Vybavení assessing memory (as number of recalled pictures); VO2peak, peak oxygen consumption assessing cardiorespiratory fitness; BDNF, brain-derived neurotrophic factor.

Furthermore, we analysed the relationships between relative changes of the above-mentioned parameters. There was a statistically significant positive correlation between the post-pre relative change of POBAV and post-pre relative change of VO_2peak in the whole group (N = 52; r = 0.43; $p < 0.01$). However, if divided according to supplementation, the relationship remained statistically significant in the Pla-EX group only (Figure 2).

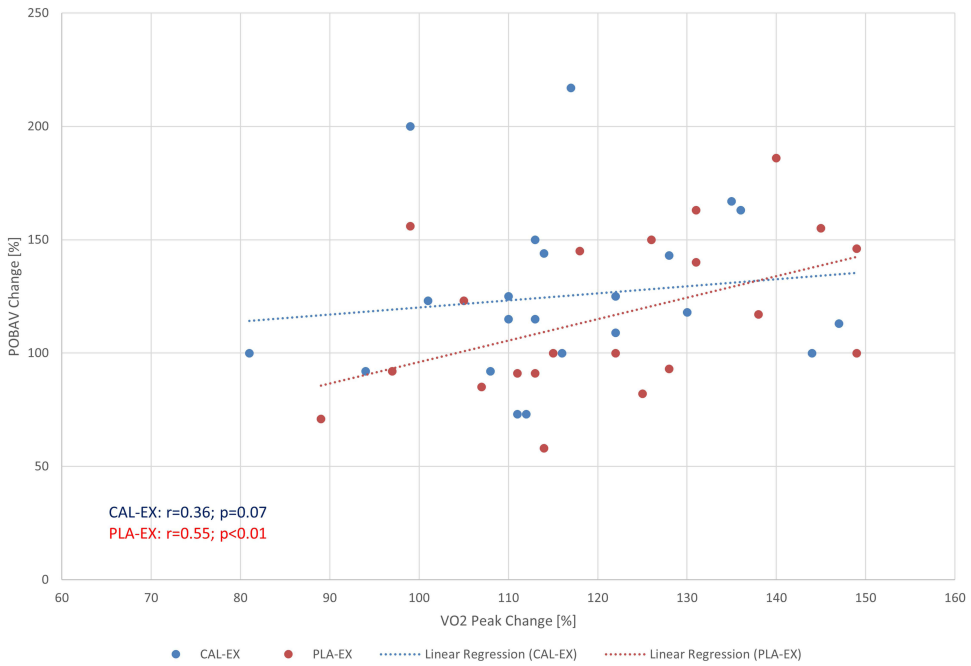

Figure 2 Relationship between the percentual difference of VO_2peak and percentual difference in the POBAV test.

Discussion

Since previous research showed that exercise in combination with n-3 PUFA supplementation has considerable benefits on health and fitness,[34,37–39] we aimed to determine whether the same would occur for cognitive function, specifically short-term episodic memory. In agreement with our hypothesis, short-term episodic memory (POBAV scores) increased after the study period, but the addition of Calanus Oil supplementation did not seem to further improve memory in our group of healthy women. Nevertheless, when changes in POBAV were expressed relative to the changes in aerobic fitness (VO_2peak), there was a moderate correlation. Although this relationship does not indicate a cause-and-effect relationship, the correlation does indicate that exercise-induced increases in aerobic fitness may enhance short-term episodic memory as that is a more likely physiological response than memory affecting aerobic fitness. Furthermore, it seems likely that BDNF levels do not play a role in the short-term memory improvement.

The short-term improvement of episodic memory in this study is in line with other studies that have shown a positive effect of physical exercise on memory,[6–9,11,12] but the lack of further improvement in memory with the addition of Calanus Oil supplementation contradicted our hypothesis. It is possible that a greater dose of n-3 PUFA could have resulted in more beneficial synergic effects,[40] but the dosage in this study was kept on the lower borderline of recommended dose to ensure subject adherence. On the other hand, even a much greater DHA dose (eg, 625 mg DHA per day) used in other studies[41,42] showed no beneficial effect on cognitive function after 16 weeks, meaning the role of omega-3 supplementation in cognitive function improvement is questionable.

Exercise-induced improvement of memory may be explained by adaptive changes in nervous system,[43] improvement of cardiovascular health and increased brain perfusion.[14] Interestingly, though, the improvements in short-term memory did not coincide with increase in BDNF concentration after our study. This finding is in line with study of Coelho-Júnior et al, who also observed cognitive function improvements without any positive changes in BDNF,[44] while other studies showed BDNF improvements in conjunction with improvements in physical fitness and cognitive function.[2,16] One possible rationale for these contradictory findings is the baseline cognitive characteristics of the subjects. For example, a previous study noted that increases of BDNF in response to an exercise program occurred in individuals with mild cognitive impairment,[15] whereas the subjects in our study did not have any cognitive impairments. As a result, the average baseline BDNF data of our subjects would necessitate an even greater increase in order to be significant. Nevertheless, even in our healthy population group, the improvement of cognitive function and increase of BDNF concentration is dependent on their initial baseline levels as shown by the linear model for BDNF changes presented in Table 3.

Additionally, it is important to consider that other physiological factors are in play and cannot be ignored, such as genetics and epigenetics.[45] Despite not measuring it in the present study, it is possible that our findings may relate to different BDNF genotypes, as the Val66Met polymorphism has been shown to reduce the BDNF secretion level and memory impairment.[18,43] However, it has been shown that the beneficial contribution of training on cognitive functions is independent of the BDNF genotype.[15]

In summary, although our findings do not support the beneficial effects of combining Calanus Oil supplementation with exercise training on memory, it is important to note that there is no doubt that regular physical activity is one of the most important factors known to promote health across the lifespan, including cognitive health.[46] The positive relationship between improvements in memory tests and exercise capacity suggests a dose-response relationship and further stresses the importance of exercise intensity and volume. In fact, the effects of exercise on cognitive function are even stronger in older people,[47] and lifelong activity is linked with healthier (disease-free) aging and with being physically independent.[48] For these reasons, it is important to provide elderly with exercise programs that are sustainable, evidence-based, multi-faceted, and individually tailored to personal needs, interests, and medical issues.[49]

Furthermore, an individual approach should also include counseling about proper nutrition and reasonable use of supplements according to evidence-based medicine.

Limitations

Although the present study provides noteworthy additions to the body of knowledge about the effects of exercise and n-3 PUFA on cognitive health, the study was not without limitations. For example, we did not include a non-exercising

control group because we did not believe that a do-nothing control group would have been beneficial for science or the subjects. Therefore, some may view that as a limitation, we believe that including such a group would not have added any noteworthy information in the present study.

Secondly, we used an easy screening test to evaluate short-term episodic memory instead of more well-known methods such as the Mini-Mental State Examination or MoCa test. This was done because of the test's availability, and the easy and quick administration, which did not have to involve a psychiatrist. Therefore, this testing method lends itself to a wider population, which seems to be a positive aspect in our opinion.

Finally, the Calanus oil contained a relatively low level of n-3 PUFA compared to other supplements used in similar studies focusing on the n-3 PUFA effect. However, its unique composition with a high level of wax esters could have brought new information about the effects of these compounds on cognitive function. We also acknowledge that the sample size could have been larger, but this study was based on the EXODYA clinical trial,[50] which included a given number of subjects due to the feasibility and cost of many demanding methodologies and due to ethical reasons (clinical examinations and repeated biopsies represent a significant burden for elderly participants).

Conclusion

Our study found an improvement in the short-term visual episodic memory after implementing the exercise program, without any additional effects of Calanus Oil on the memory test and exercise capacity. These effects were not associated with improvement of the BDNF concentration in the blood. Overall, our findings show the importance of regular physical activity for maintaining cognitive function in the elderly, independent of using omega-3 fatty acid supplementation. Considering the relationship, we observed between improvements in memory and aerobic fitness, it may be also suggested that greater increases in exercise capacity can lead to greater cognitive function. However, this idea should be clarified in further studies.

Data Sharing Statement

The authors intend to provide full individual data of participants without identification data, upon request. Please send your request for original data to the e-mail address of Klara Daďova, Ph.D.: dadova@ftvs.cuni.cz.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethical Committee of the University Hospital Kralovske Vinohrady in Prague (research project nr. AZV 16-29182A; NCT number: NCT03386461).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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Disclosure

This manuscript has not been previously submitted or published and is not under consideration in any other peer-reviewed media. Dr Michaela Šiklová reports non-financial support from Calanus Oil a.s., outside the submitted work. The authors declare having no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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