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Influence of a 12-Month Structured Exercise Program on the Micronutrient-Cognitive Fitness-Physical Association Profiles in Mild Cognitive Impairment

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Abstract.
Background: Preventive lifestyle strategies have shown promise to slow down or prevent age-related cognitive decline. However, evidence on the reciprocal longitudinal relationships between nutrition biomarkers and cognitive and physical performance is lacking. Studying nutritional, cognitive, and physical profiles over time may help to overcome this knowledge gap.
Objective: To investigate the relationship of plasma levels of the robust nutritional- and antioxidant defense-related biomarkers carotenoids and tocopherols with both indicators of cognitive and physical performance in persons with mild cognitive impairment (MCI) participating in a structured exercise program.

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Methods: Data from 40 participants with MCI of the NeuroExercise study were analyzed. Participants had undergone a blood withdrawal for the analysis of plasma concentrations of six carotenoids, two tocopherols and retinol prior to and after one-year of structured exercise. All participants had undergone a broad spectrum of cognitive and physical performance tests.
Results: Significant associations between lipophilic micronutrients and cognitive/physical measures were observed that were previously found to play a role in cognitive and physical frailty. In particular, lutein, zeaxanthin, and lycopene are confirmed as robust, reliable, and stable indicators of nutritional defense. Importantly, these micronutrients were associated with cognitive measures prior to the physical training program and to a more prominent extent with indicators of motoric function after the physical exercise program.
Conclusion: Specific profiles of lipophilic micronutrients are associated to cognitive performance measures and, especially after a structured exercise program, to indicators of physical performance.

Keywords: Carotenoids, cognitive performance, micronutrients, mild cognitive impairment, neuropsychological tests, nutrition, physical activity

INTRODUCTION

Worldwide humanity is aging and a significant shift in the demographics is noticeable through the evolving living standards. Higher age and standards pose challenges and cognitive disorders, such as dementia, which will become an ongoing concern and major medical challenge worldwide [1]. In Italy, Japan, Wales, Germany, and the Netherlands, rising numbers of dementia cases have been observed and no disease-modifying treatment or cure for dementia has been found yet, although several attempts are ongoing and aducanumab has been formally approved as a disease-modifying treatment in the United States [2–4]. Some modifiable risk factors of dementia have already been identified in previous studies [5, 6]. Therefore, early detection of cognitive decline has become increasingly important to establish treatment approaches or lifestyle modifications as early as possible. Early stages of particular interest are age-related cognitive decline, subjective cognitive impairment (SCI), and mild cognitive impairment (MCI) due to an increased risk of the individual developing dementia [7, 8].

Among modifiable risk factors, physical inactivity shows the highest population-attributable risk (PAR) of Alzheimer's disease (AD): USA (21.0%, 95% CI 5.8–36.6), Europe (20.3%, 5.6–35.6), and the UK (21.8%, 6.1–37.7) [9]. Previous studies have shown that 6 to 12 months of exercise can maintain or improve cognition among patients with dementia or MCI [10]. Additionally, interventions focusing on physical activity, cognitive training, overall lifestyle changes, and dietary interventions receive greater attention. After two decades of research, strong evidence is available on dementia-preventive effects of B vitamins, vitamin E, and n-3 fatty acids [11], which stresses the importance of analyzing physical functions as well as a nutritional status to establish multidimensional concepts as treatment approaches [5, 12].

Oxidative stress has frequently been described as a possible pathophysiological mechanism responsible for the development of cognitive impairment [13]. As oxidative stress is not only influenced by physical activity [14], but also substantially by nutrition, it may explain the importance of multimodal/holistic lifestyle changes [15]. Oxidative stress can be measured through several biomarkers, which play a role in the defense mechanism against free radicals [16]. Previous results have shown an association between nutrition- and antioxidant defense-related biomarkers in participants with MCI in the NeuroExercise Study in Germany [17]. However, the influence of a one-year training intervention on the aforementioned biomarkers and their influence on cognitive and physical function post-intervention has not been investigated yet. Therefore, this work aimed to determine the reciprocal relationships between nutrition biomarkers, cognitive performance, and physical performance in persons with MCI that underwent a structured exercise program for one year [6].

METHODS

Participants

Across three European countries, a randomized controlled trial—the NeuroExercise Study—investigated the effects of exercise therapy on the progression of MCI [18, 19]. For the purpose of the present sub-study, the participants

were recruited in Germany at the German Sport University (GSU). The study was conducted in accordance with the declaration of Helsinki (1975) and approved by the research ethics committee of the GSU. The participants were recruited through newspaper advertisements as well as editorials. Participants provided informed written consent to the study procedures [17, 20]. Inclusion criteria was a score between 18 and 26 on the Montreal Cognitive Assessment (MoCA), which is a widely known and validated assessment tool with the score above reflecting MCI [21]; pretesting distinguished between amnestic and non-amnestic MCI, where educational cut-offs were applied: –2 Standard Deviation (SD) for low education (<10 years of education), –1.5 SD for the middle group (10–13 years of education), and –1 SD for the highly educated (>13 years of education). These were taken from the delayed recall portion of the age-adjusted delayed memory index of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Score of <85) as previously described [17, 18, 20, 22]. The exclusion criteria included a diagnosis of AD or any other dementia, as well as a family history of early-onset dementia; epileptic seizures in the past two years; participation in any investigational drug study, significant history of alcoholism or drug abuse within last 10 years and history of vitamin B12 deficiency or hypothyroidism [17, 18]. A complete list of in- and exclusion criteria has been published elsewhere [23].

After being deemed eligible for the study, participants underwent a baseline assessment, which included the collection of various data such as their lifestyle habits, different neuropsychological testing as well as general physical and cardiovascular testing. Afterwards, participants were randomly stratified into three different groups using a centrally controlled computer-generated randomization list: Stretching and Toning (S&T) or Aerobic Exercise (AE), which underwent 3×45 min exercise sessions per week over a time period of 12 months, or a non-exercising Control Group (CG) following standard care [18, 20]. Exercise intensity was monitored using Borg's Rating of Perceived Exertion (RPE). An RPE of at least 13 was the aim of the AE group, whereas the S&T group had a target RPE <10 [24, 25].

Study overview

Data assessment occurred before (T0) and after 12 months of exercise intervention (T12). Besides a neuropsychological test battery, quality of life measures, and a physical fitness evaluation [20], a blood drawing was also completed [6, 17, 20]. At baseline (T0), blood drawing was completed before randomizing participants into the different groups.

Cognitive function assessment

The MoCA, which has also been validated to detect MCI with high sensitivity and specificity [17, 21], was used to acquire a broad measure of cognitive function. For evaluating the speed of processing and executive functions, the Trail Making Test A and B (TMT A and B) were used [26]. These two tests were completed as a paper-and-pencil-based task [26, 27]. Letter fluency and category fluency were used to test verbal functioning [28, 29]. Moreover, the CogState Battery, which is a computer-based neuropsychological test battery, was applied. It consisted of the following tasks: Detection Task, Identification Task, One Card Learning Task (OCL), One Back Task (OBT), International Shopping List Task (ISLT), International Shopping List Recall Task (ISLT Recall) [17, 18, 30].

Physical activity assessment

Cardiorespiratory fitness was assessed using an incremental exercise test on a cycle ergometer. Estimated $\dot{V}O_2$peak (mL/kg/min), which was defined as outcome measure for cardiorespiratory fitness, was used as an outcome. The health-related quality of life for people with Dementia (DemQOL) was used to evaluate the health-related quality of life and the Longitudinal Ageing Study Amsterdam Physical Activity Questionnaire (LAPAQ) to assess physical activity in the preceding 14 days [31, 32].

Mean number of steps per day was assessed through wearing an activity watch, which was asked to be worn on the non-dominant arm for a whole week for 24 h a day [20, 33]. The Timed Up and Go test (TUG), which displays a person's ability to go out on their own [34], as well as the 30 Seconds Chair Stand Test (CST) [35] as a proxy for endurance and lower limb strength were assessed. Bilateral Hand grip strength (left-HGL; right-HGR) was evaluated through a Jamar Digital Dynamometer, which has been shown to correlate significantly with upper limb strength [18]. The physical activity assessments have been described in detail elsewhere [6, 18].

Table 1
Group demographics

	S&T ($n = 14$)	AE ($n = 12$)	CG (N = 14)	p
Age (y)	78.9 ± 3.8	77.2 ± 4.4	76.8 ± 6.4	0.522
Sex (female)	8 (57.1%)	5 (41.7%)	5 (35.7%)	0,503
BMI	25.3 ± 2.8	25.6 ± 2.2	26.5 ± 3.9	0.556
Education, N (%)				(χ^2) 0.018
Low	1 (7.15%)	0 (0.0%)	1 (7.2%)	
Middle	12 (85.7%)	4 (33.3%)	10 (71.4%)	
High	1 (7.15%)	8 (66.6%)	3 (21.4%)	
No. of medication used	1.86 ± 1.06	1.50 ± 1.94	1.50 ± 1.35	(χ^2) 0.234
RBANS	83.07 ± 12.86	78.75 ± 13.85	78.77 ± 13.81	0.636
Moca T0 (Score 0/30)	23.4 ± 1,28	23.08 ± 2.64	22.43 ± 2.17	0.442

S&T, stretching and toning group; AE, aerobic exercise group; CG, control group; BMI, body mass index; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; MoCA, Montreal Cognitive Assessment.

Lipophilic antioxidant micronutrients

The lipophilic antioxidant micronutrients were measured after blood drawing in a heparinized tube, which was centrifuged immediately, plasma separated and stored frozen at –80°C until analysis. Through High Performance Liquid Chromatography (HPLC) with UV-vis detection at 450 nm, the different carotenoids—lutein, zeaxanthin, β-cryptoxanthin, lycopene, and α-and β-carotene—were analyzed according to Stahl et al. [36, 37]. To detect the quantitation of retinol (vitamin A) and α- and γ-tocopherol (vitamin E), a second UV-vis detector was set at 325 and 292 nm and connected in series. For each micronutrient, the recovery from the column accounted for 90%. For all carotenoids, the calibration curves appeared linear from 0 to 1000 nmol/L with a correlation coefficient of 0.99. The coefficient of variation of the intra- and inter-assay precision was between 5 and 15% [17].

Subgroup analysis

For this subgroup analysis, 40 complete datasets (pre and post-test) were obtained. The smaller sample size compared to the main study was due to missing data [6], particularly on lipophilic antioxidant micronutrients. As participation in micronutrient assessment was voluntary and not part of the original proposal of the NeuroExercise project, some participants decided against the additional blood drawing.

Statistical analysis

IBM SPSS Statistics 26[ā] was utilized to analyze the data with α set at 0.05. After verifying normality using Shapiro Wilk, a repeated measures of variance analysis (ANOVA) was carried out with the within-subjects factor time (pre- and post-test) and the between-subjects factor group (S&T, AE, CG). Variables pertaining of cognitive function (CogState Battery, MoCA, TMT A+B, verbal fluency), physical fitness assessment (VO2peak, Grip Strength, LAPAQ, Steps per day, TUG, CST), quality of life (DemQOL) and lipophilic antioxidant micronutrients (lutein, zeaxanthin, cryptoxanthin, lycopene, α-carotene, β-carotene, α-tocopherol, γ-tocopherol, retinol) were compared using the aforementioned analysis. In case of significant interaction effects of time*group Bonferroni corrected *post-hoc* pairwise comparisons were conducted.

Furthermore, Pearson's correlation was used to assess correlations between lipophilic antioxidant micronutrients and the other aforementioned parameters at post-tests [17].

One way ANOVA analyses were used to test differences in demographics between the three groups. Data are presented as means ± standard deviation.

RESULTS

Baseline demographics, as well as physical and neuropsychological characteristics, are displayed in Table 1. Education years differed significantly between the groups, as higher educated participants were in the AE group ($p = 0.018$). No further differences were found at baseline. The laboratory values of the lipophilic micronutrients, as well as the physical and cognitive data, can be found in the supplementary materials (Supplementary Table 1).

Table 2
Significant correlations between lipophilic micronutrients and physical measures after the one-year

Correlation	Group	*r*	*p*
Quality of life measurement: Lutein/ DemQOL	CG	0.716	0.004
Lutein/ Steps per day	AE	0.747	0.013
Lutein/ CST	S&T	0.727	0.003
Lutein/ CST	EG	0.424	0.044
Lutein/ HGL	EG	–0.406	0.049
Zeaxanthin/ LAPAQ	S&T	–0.555	0.039
Zeaxanthin/ LAPAQ	EG	–0.464	0.026
Zeaxanthin/ CST	S&T	0.766	0.001
Zeaxanthin/ CST	EG	0.418	0.047
Zeaxanthin/ HGR	EG	–0.417	0.043
Zeaxanthin/ HGL	EG	–0.427	0.038
β-Cryptoxanthin/ HGR	EG	–0.405	0.050
β-Cryptoxanthin/ HGL	S&T	–0.560	0.037
β-Cryptoxanthin/ HGL	EG	–0.459	0.024
Lycopene/ VO2peak	EG	0.421	0.036
Lycopene/ DemQOL	AE	–0.624	0.040
Lycopene/ DemQOL	EG	–0.412	0.041
Lycopene/ CST	EG	0.428	0.041
α-Carotene/ DemQOL	CG	0.671	0.009
β-Carotene/ DemQOL	AE	–0.605	0.049
β-Carotene/ DemQOL	CG	0.585	0.028
β-Carotene/ CST	S&T	0.667	0.009
α-Tocopherol/ HGL	EG	–0.423	0.040

S&T, stretching and toning group; AE, aerobic exercise group; CG, control group; EG, exercise group; DemQOL, health-related quality of life for people with Dementia; LAPAQ, Longitudinal Ageing Study Amsterdam Physical Activity Questionnaire; CST, 30 Seconds Chair Stand; HGR, Hand Grip Strength Right; HGL, Hand Grip Strength Left.

Repeated measures ANOVA

Repeated measures ANOVA revealed a significant interaction effect for time*group for the variables $\dot{V}O_2$peak ($F_{2,36} = 7.641$; $p = 0.002$) and DemQOL ($F_{2,36} = 6.505$; $p = 0.004$). *Post-hoc* pairwise comparisons showed that both the AE ($p = 0.317$) and S&T ($p = 0.061$) tended to increase in $\dot{V}O_2$peak between pre and post-test, whereas a significant decrease in fitness was observed for the CG ($p = 0.002$). The S&T further improved their quality of life significantly ($p < 0.001$), whereas this was not found for AE ($p = 0.936$) and CG ($p = 0.539$) after applying Bonferroni corrected *post-hoc* tests. Apart from $\dot{V}O_2$peak and quality of life, repeated measures ANOVA did not reveal further significant changes.

Lipophilic micronutrients and functional abilities

As displayed in Table 2, several significant associations were found between the micronutrients measured and the indicators of functional abilities after one-year of exercise. Interestingly, no association was found between the CG's micronutrients level and the functional abilities. In the cumulative analysis of participants undergoing the NeuroExercise training program (S&T+AE), which are described as the Exercise Group (EG), significant associations were found between physical performance readouts and lutein with CST (EG) ($p = 0.044$) and HGL (EG) ($p = 0.049$), zeaxanthin and LAPAQ (EG) ($p = 0.026$), as well as with CST (EG) ($p = 0.047$), HGR (EG) ($p = 0.043$) and HGL (EG) ($p = 0.038$); between β-cryptoxanthin and HGR (EG) ($p = 0.050$) and HGL (EG) ($p = 0.024$), lycopene and CST (EG) ($p = 0.041$) and α-tocopherol and HGL (EG) ($p = 0.040$) (Table 2).

Lipophilic micronutrients and its associations with cognitive performance and quality of life

Cognitive performance measures were significantly associated with lycopene and CogState Detection (EG) ($p = 0.044$) as well as with CogState Identification (EG) ($p = 0.004$). In the CG sporadic associations between α-carotene and β-carotene and DemQOL were observed (Table 2), as well as

Table 3
Significant correlations between lipophilic micronutrients and cognitive measures after the one-year intervention

Correlation	Group	*r*	*p*
Zeaxanthin/ CogState Detection	CG	–0.553	0.040
Lycopene/ Cogstate Detection	AE	–0.744	0.006
Lycopene/ Cogstate Detection	EG	–0.398	0.044
Lycopene/ Cogstate Identification	AE	–0.764	0.004
Lycopene/ Cogstate Identification	EG	–0.551	0.004
α-Carotene/OCL	CG	0.565	0.035
β-Carotene/OCL	AE	0.608	0.036
β-Carotene/OCL	CG	0.536	0.048

S&T, stretching and toning group; AE, aerobic exercise group; CG, control group; EG, exercise group; OCL, One Card Learning Task.

between zeaxanthin and CogState Detection and both α-carotene and β-carotene with OCL.

DISCUSSION

As previously shown by Gerger et al., this substudy to the NeuroExercise multi controlled study also revealed that there is a significant association between plasma levels of various lipophilic antioxidant micronutrients with both physical and cognitive performance [6, 17]. While one year of controlled exercise did not lead to significant changes in the concentrations in the individual plasma levels of the various lipophilic micronutrients, one important observation could be made at follow-up: In relationship to cognitive and motoric functions, the micronutrients were shown to associate with cognitive measures prior to the physical training program and with indicators of motoric function after the one-year physical exercise program [17]. This is in agreement with research showing that physical exercise contributes to the antioxidant defense mechanism of the body [38]. This shift in the association of micronutrients becoming predominantly indicators of physical fitness after one-year of structured exercise supports the use of robust lipophilic micronutrients as a monitoring instrument for the effect of lifestyle strategies [39]. Exercise is enforcing various stressors to the human body and, thus, increasing exposure to reactive nitrogen species (RNS) and reactive oxygen species (ROS). Oxidative balance is preserved through a multifaceted antioxidant defense system of antioxidant enzymes within the physiological bounds to decrease the chances for oxidative damage [40]. RNS and ROS function as messengers through redox-sensitive protein interaction to regulate various processes in the body such as mitochondrial biogenesis or immune response [41]. Further, exercise upregulates the endogenous antioxidant defense system [42].

The numbers of studies investigating the various associations between physical and cognitive performance with antioxidative defense systems are small but increasing [17, 38]. In order to further explore the impact nutrition has on cognitive brain function and brain health, the interdisciplinary field of 'Nutritional Cognitive Neuroscience' has recently been introduced and has already contributed to this new research area with their pathophysiological investigations and nutritional intervention studies. Especially the field of cognitive, physical, and dietary interventions has recently garnered attention in the scientific community, with our study adding to the existing body of knowledge. The focus of that attention has been on their success in showing that different stages of cognitive impairment can be influenced by physical activity and nutrition. Here, oxidative stress was defined as the influencing factor of attention [5]. Moreover, previous evidence elaborated that in age-related cognitive neurodegeneration, oxidative distress and eustress play a major role [5, 16, 43–45]. 'Oxidative distress' describes adverse elevated levels of ROS. These elevated levels, especially in combination with changes in O_2 levels, may result in molecular damage to the central nervous system due to its relative sensitivity [5, 43]. The carotenoids analyzed in the present investigation are shown to be efficient lipophilic antioxidants in the living being [46]. They function as robust biomarkers of dietary exposure occurring in different organisms, i.e., animals, plants, and microorganisms. However, it should always be considered that different variables, such as carotenoid distribution, metabolism, and bioavailability, as well as the dietary supply, depend on various host factors, including genetic makeup, age,

sex, lifestyle, and diseases [47]. As the NeuroExercise study aimed to change lifestyle habits by increasing physical activity but did not control for further host factors, this may explain the lack of statistically relevant changes in our substudy. Similar to the variation concerning the host factors, there is also a different distribution of the carotenoids in various organs in the body. Curiously, in the frontal and occipital lobes of the human brain tissue, xanthophylls account for 66–77% of the total carotenoids [48].

Another important influential construct on oxidative stress should be considered, as ROS and similar components are not only generated internally, but also influenced by external factors. The most obvious influence in daily life is air pollution with its gases, metals, organic compounds, and a diverse mixture of particulate matter [49, 50]. It is commonly known that air pollution distresses the state of health through promoting respiratory as well as cardiovascular morbidity and mortality with recent research suggesting that these effects even go as far as affecting the brain [51, 52]. Metal toxicity is a further factor, as heavy metals are generating ROS, which in consequence might lead to toxic mechanisms, like hepatotoxicity, neurotoxicity, and nephrotoxicity [53, 54]. As the stratospheric ozone is depleting, ultraviolet (UV) radiation may present another concern. Through UVA, as well as UVB radiation, research suggests an effect in adverse biological mechanisms, such as DNA and membrane damage, leading to phototoxicity, inflammation, skin aging, and malignant tumors [50]. Inflammatory pathways are also activated through an alteration in enzymes induced by pesticides affecting multiple organs [50]. As all participants in this sub-study lived in urban area of Cologne, their exposure to environmental factors was similar. Unhealthy lifestyle habits such as alcohol abuse and cigarette smoke are also defined as environmental factors [50]. However, alcohol abuse was included as an exclusion criterion of the NeuroExercise, and, thus, did most probably not affect results of our sub-study. Future research, especially with participants from different areas (i.e., urban, rural), need to take these factors into account.

In the Healthy Aging in Neighborhoods of Diversity across the Life Span study, statistical significance was found between vitamin E and verbal memory performance ($p = 0.002$), with this association largely driven by the carotenoid lycopene [55]. Another inverse association was assessed between lutein-zeaxanthin and lycopene with brain global pathology [56]. This can be observed in previous work of Polidori et al. and Dias et al., who have shown that lycopene, zeaxanthin, and lutein had a significantly lower concentration in patients with Alzheimer's disease that suffered from vascular comorbidities than in healthy subjects [57, 58]. In the present study, a significant correlation was found between the carotenoid lycopene and the CogState Detection and the CogState Identification in the Aerobic Exercise Group, as well as in the general Exercise Group. Both tests belong to the CogState Battery, with the Detection Task assessing psychomotor function and the Identification Task evaluating the attention of the individual [30]. A significant correlation between cognitive measures and endothelial function [59, 60], as well as between cognitive measures and micronutrients is well-established [5, 13, 16, 17, 48, 57, 58]. The collected data did not support this notion, as no changes in cognition were found. Nevertheless, positive correlations between both lutein and zeaxanthin levels in subjects within the S&T group and the EG and their ability to perform in the chair stand test were found. Furthermore, performance success was positively correlated with lycopene in the EG and β-carotene in the S&T group. Lutein and its isomer, zeaxanthin, accumulate in the human brain over time. They form a macular pigment by crossing the blood-retina barrier to serve as a protection against age-related eye diseases. Other studies have also observed an association between cognitive functions and optical density of the macular pigment indicating the presence of lutein and zeaxanthin in the central retina. The difference in observations may be explained by differences in methods. Where Stringham et al. observed physiological factors in the retina, which, unlike blood serum, have not been shown to at least weakly reflect lutein and zeaxanthin concentration in the central nervous system [61]. The lack of significant changes in lipophilic antioxidant micronutrients over the course of the study is potentially due to the lack of nutritional intervention in the NeuroExercise Study.

It needs mentioning that other nutritional components may also impact cognitive function. A high intake of saturated fatty acids can enhance cognitive impairment, whereas a high consumption of the omega-3 group might reduce the risk of dementia [62, 63]. In addition, curcumin may have positive effects in individuals with MCI; however, no significant differences were established for individuals affected by AD either supplementing curcumin or a placebo [64]. Nevertheless, another study revealed positive effects

on chronic inflammatory processes influencing Aβ protein plaques in the brain [65]. Therefore, supplementing curcumin may present a promising treatment approach that could be implanted in multi-domain type interventions (e.g., exercise and nutritional).

Taking around 500 mg of caffeine might also have therapeutic effects when it comes to neuromodulatory and neuroprotective properties, as Aβ levels in the brain decreased in animal studies through the inhibition of synthesizing enzymes [66]. Additionally, a resveratrol intake improved different measures of cognitive performance [67], but has similarly led to negative side effects such as hyperplastic changes of kidneys and gallbladder, diarrhea, vomiting, leukocytosis, and more. A lower dose of 0.3 g/kg b.w./day for 4 weeks did not show any side effects [68, 69] and may be added to multi-domain interventions. Similarly, probiotic bacteria should be taken into account when thinking about such studies, as these contain anti-inflammatory effects on the digestive system with various benefits. They prevent pro-inflammatory components of infiltrating the bloodstream, which are possibly involved in neurological diseases [70, 71], and in the case of a dysbiosis may even get through the brain blood barrier and affect the pathogenesis of AD [72, 73]. Taken together with results from our sub-study, multidimensional treatment approaches are warranted in future studies, which assess holistic lifestyle changes that include both exercise as well as nutritional interventions.

The present study has some limitations, especially the small sample size that restricts the generalizability of the data. It is also important to note that we observed differences in educational levels between the groups at baseline but did not include these in the analysis. As the groups were randomly stratified using an independent statistician's computer-generated list, these differences occurred rather by chance. Furthermore, only two participants of the total sample had a low educational status with less than 10 years. As very low to none education is mainly known to affect dietary patterns, the difference between individuals with 10–13 years of education and those with over 13 years may be insignificant. However, the role of education needs to be further clarified in future studies using bigger sample sizes. Even though our sample size was rather small, the values observed in our study are in accordance with previous research. Furthermore, the unique study design with an exercise intervention over 12 months, as well as the extensive yet standardized data collection with robust biomarkers, and data regarding physical and cognitive performance, allows comparability to previous and future studies. The nutritional and dietary status were not controlled within this sub-study at follow-up, which may have influenced micronutrient status. However, participants stated to have not substantially changed their lifestyle behavior other than exercise. As this was similar between the control and intervention groups, we believe that dietary patterns, which were similar at baseline [17], did not differ between the various groups. Nevertheless, data needs to be interpreted cautiously given this limitation and future studies are warranted to assess and control for nutritional changes. As nutrition was not a major focus of the NeuroExercise study, this may further explain the lack of changes observed over the course of the study. Whereas physical performance increased, micronutrient profile and cognitive function did not change. However, the associations between lifestyle factors and cognition observed in the study demonstrate the importance of assessing the cause and effect of multidimensional treatment approaches, including exercise and nutrition, on cognition.

Conclusions

In this subsample of 40 participants of the NeuroExercise study, cognition and micronutrient levels did not differ between the intervention groups and the control group after 12 months of an exercise program, even though differences in fitness were observed between the groups. Nevertheless, significant correlations between the plasma levels of carotenoids and several cognitive and physical data indicate an association between these parameters. As lifestyle factors such as physical activity and nutritional habits have gained attention in regard to disease prevention, the detected associations may point towards multifactorial lifestyle changes. Combined nutritional and physical interventions may have bigger effects on cognition in persons at risk for dementia. Therefore, further studies are warranted that investigate the role of dietary intake and its influence on the plasma carotenoid levels as well as the effect on cognitive and physical performance. Therefore, multidimensional approaches should be established to deepen not only our understanding of the complex processes of the aging brain but also provide insight into potential treatment approaches. With humanity ageing worldwide and with a significant shift in the demographics, such treatment approaches would be of utter importance.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. The funders (EU JPND) 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.

SUPPLEMENTARY MATERIAL

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