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Short communication

Omega-3 index, cardiorespiratory fitness, and cognitive function in mid-age and older adults

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ABSTRACT

Higher levels of omega-3 fatty acids in red blood cell membranes (omega-3 index or O3I) and cardiorespiratory fitness (CRF) are each associated with reduced cognitive impairment, but little research has examined the relationship between O3I and cognitive function while accounting for CRF. We analyzed cross-sectional data from 5,464 healthy men and women aged 55–85 years who had preventive medical examinations between 2009 and 2023. Primary exposures included O3I (<4.0%, 4.0–7.9%, or ≥ 8.0%) and age- and sex-based CRF quintile (1 = low, 2–3 = moderate, 4–5 = high). Cognitive impairment was defined as a Montreal Cognitive Assessment score of ≤ 25. We used Poisson regression to estimate relative risks (RR) of cognitive impairment, controlling for covariates. O3I < 4% was associated with increased cognitive impairment relative to ≥ 8.0% (RR, 1.21; 95% CI, 1.01–1.44) in a partially adjusted model. This association did not remain statistically significant in the fully adjusted model which included CRF. Low versus high CRF was associated with cognitive impairment (RR, 1.28; 95% CI, 1.07–1.53), independent of O3I and clinical biomarkers. The interaction between CRF and O3I was not significant ($P = 0.8$). In joint association analysis, risk of cognitive impairment was elevated with lower omega-3 index or CRF or both. Additional research is needed to fully understand the association between O3I and cognitive function at varying CRF levels.

1. Introduction

Approximately two-thirds of Americans will experience some degree of cognitive impairment in their lifetime (Hale et al., 2020) and it is expected to increase from 12.2 million in 2020 to 21.6 million in 2060 (Rajan et al., 2021). The etiology of cognitive impairment is multifactorial and at least partly genetic (James and Bennett, 2019). Because no highly effective treatments for cognitive impairment currently exist, researchers have sought to identify modifiable risk factors (Serrano-Pozo and Growdon, 2019). Physical activity, education level, intellectual activities, social activities, and a Mediterranean diet may reduce risk; whereas hypertension, diabetes, obesity, and smoking may increase risk (Serrano-Pozo and Growdon, 2019). Omega-3 polyunsaturated fatty acids from nuts, seeds, fish, and certain oils comprise one component of the Mediterranean diet that may have a protective effect (Roman et al., 2019).

Omega-3 (n-3) fatty acids are polyunsaturated fatty acids (PUFAs) that cannot be synthesized in the human body and therefore are categorized as essential fatty acids (EFA). From α-linolenic acid (ALA:18:3n-3) the body can synthesize the long chain PUFAs (LCPUFAs) eicosapentaenoic acid (EPA:20:5n-3) and docosahexaenoic acid (DHA:22:6n-3), which play key roles in regulating body homeostasis and are used to synthesize anti-inflammatory eicosanoids (locally acting bioactive signaling lipids) (Saini and Keum, 2018). A large proportion of lipids in the human brain are composed of the omega-3 LCPUFAs (Bigornia et al., 2018), and these fatty acids may facilitate glucose uptake in the brain as well as neurotransmission and neuronal function (Luchtman and Song, 2013). EPA in particular may have neuroprotective properties through regulation of oxidative and anti-inflammatory processes (Cunnane et al., 2009).

In a 2022 review (Wood et al., 2022), increased consumption of n-3 PUFAs was consistently associated with reduced risk of cognitive impairment and Alzheimer's disease. However, it is challenging to determine whether the relationship between dietary factors and

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cognitive impairment is causal because of confounding by cardiovascular risk factors and physical activity (Cremonini et al., 2019) as well as error in assessment of dietary intake. The omega-3 index (O3I) is the percentage of fatty acids in red blood cell membranes that are composed of EPA and DHA, and serves as a measure of omega-3 status that does not rely on dietary recall (Harris and von Schacky, 2004). The O3I has been inversely associated with coronary heart disease mortality (Harris et al., 2017), and type 2 diabetes (Ma et al., 2021) in a dose–response manner.

Evidence also suggests that O3I is associated with greater hippocampal volume (Satizabal et al., 2022; Pottala et al., 2014; Chen et al., 2020) and reduced decline in cognitive function7 (Rouch et al., 2022; Cook et al., 2019; Tan et al., 2012), However, few studies have adjusted for physical activity, (Tan et al., 2012) and none have accounted for cardiorespiratory fitness (CRF), an objective physiological indicator of habitual physical activity (Pentikäinen et al., 2019; Shuval et al., 2022). We have previously shown that CRF is strongly associated with reduced cognitive impairment (Farrell et al., 2018). Our objective was to examine the independent and joint associations between O3I and CRF with cognitive impairment in older adults.

2. Materials and methods

We analyzed cross-sectional data from The Cooper Center Longitudinal Study (CCLS), which includes measures of health behaviors, CRF, clinical biomarkers, and health outcomes of individuals who have received preventive medical examinations at the Cooper Clinic in Dallas, TX, USA (Farrell et al., 2020; DeFina et al., 2015). The Cooper Institute's Institutional Review Board reviews and annually approves all procedures related to this study. Participants considered for inclusion were 6,708 men and women aged 55–85 years who presented for a medical examination (2009–2023), provided informed written consent to be included in the CCLS, and had complete information for the primary study variables. Participants with a personal history of myocardial infarction (n = 76), stroke (n = 60), diabetes (n = 274), and cancer (n = 834) were excluded, yielding 5,464 apparently healthy participants in the analytic sample.

Height and body weight were assessed via a stadiometer and a standard scale, (Shuval et al., 2015) seated resting blood pressure (BP) and fasting venous blood were obtained at the Cooper Clinic following established protocols (Barlow et al., 2016). To estimate CRF, participants completed a maximal treadmill exercise test using a modified-Balke protocol, as described elsewhere (Willis et al., 2011). Duration of the treadmill test strongly correlates with measured maximal oxygen uptake in men ($r = 0.92$) and women ($r = 0.94$) (Pollock et al., 1976; Pollock et al., 1982). We estimated VO_{2max} in mL/kg/min from the final speed and grade of the modified-Balke treadmill test using the equation VO_{2max} = (speed in meters/min × 0.1) + (speed in meters/min × 1.8 × %grade expressed as a decimal) + 3.5 (American College of Sports Medicine, 2013). We then converted VO_{2max} to metabolic equivalents (METs) using 1 MET = 3.5 mL O_2 uptake·kg^{-1} body weight·min^{-1} (Farrell et al., 2020). In accordance with a standardized CCLS approach, (Farrell et al., 2020; LaMonte et al., 2005) we categorized CRF into age- and sex-specific quintiles and then grouped into the following three categories: 1) quintile 1, low fitness; 2) quintiles 2 and 3, moderate fitness; and 3) quintiles 4 and 5, high fitness.

Blood samples were collected after a 10–12 h fast and analyzed for omega-3 content by OmegaQuant Analytics, LLC (Sioux Falls, SD). After isolation of the erythrocytes by centrifugation, the cells were analyzed for fatty acid composition. O3I was categorized as < 4.0%, 4.0–7.9%, or ≥ 8.0%, in accordance with previous research demonstrating the appropriateness of these cut-points as predictors of CHD mortality risk (Harris et al., 2017).

The outcome measure was cognitive function, as measured by the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). This 10-minute paper and pencil test was administered by a trained technician and scored on a scale of 0–30 points. The MoCA assesses various cognitive domains including attention, concentration, memory, language, calculation, and orientation. Scores ≤ 25 indicate impaired cognitive function (Gafni et al., 2022). The reported specificity of the MoCA is 87% whereas sensitivity is 90% for mild cognitive impairment and 100% for mild Alzheimer's disease (Nasreddine et al., 2005).

2.1. Statistical analysis

Descriptive statistics were calculated for each participant characteristic for the overall sample and by O3I category. We used Jonckheere-Terpstra statistics to test for trends across ordered O3I categories. We used Poisson regression with robust error variance to estimate relative risks of cognitive impairment (Zou, 2004). The first model was unadjusted, and subsequent models were sequentially adjusted for covariates. We also examined the joint association of O3I and CRF with cognitive impairment, adjusted for covariates. Finally, another model included the categorical O3I × CRF interaction adjusted for covariates.

3. Results

The sample was predominantly White (93.7%), male (70.6%), and college-educated (80.9%). The mean age was 60.4 (SD = 5.6) years. Only 6.6% were current smokers. Other sample characteristics appear in the Supplemental Table. Among participants with an O3I of < 4.0%, 28.5% were cognitively impaired, as compared to 21.5% of those with an O3I of ≥ 8.0%. In model 1 (unadjusted), O3I < 4.0% was associated with a 33% increased likelihood of cognitive impairment (RR, 1.33; 95% CI, 1.12–1.61) compared to the reference group of O3I ≥ 8.0 % (Table 1). Following adjustment for age, sex, education, smoking status, and BMI (model 2), the association remained significant (RR, 1.21; 95% CI, 1.01–1.44). In the adjusted models that included either CRF (model 3) or clinical LDL, glucose, and systolic blood pressure (model 4), O3I was no longer a significant predictor. In model 3, low CRF was associated with cognitive impairment in comparison to high CRF (RR, 1.31; 95% CI, 1.09–1.56) and further adjustment for LDL, glucose, and systolic blood pressure did not meaningfully change the estimates (model 5). In joint association analysis (Table 2), at the highest level of CRF, we found no differences in cognitive impairment across O3I levels. At both the low and moderate levels of CRF, only those with O3I < 8% had significantly increased likelihood of cognitive impairment when compared to those with both high CRF and high O3I. However, the interaction between CRF and O3I was not statistically significant ($p = 0.809$).

4. Discussion

In the present study, low O3I was associated with cognitive impairment independent of age, sex, education, smoking, and BMI. Adjusting for either CRF or cardiovascular biomarkers attenuated the association between O3I and MoCA, rendering it non-significant. Because omega-3 PUFAs can reduce blood pressure, (Zhang et al., 2022) it is not surprising that adjusting for blood pressure reduced the magnitude of the association. CRF was an especially strong predictor of MoCA along with age, sex, and education. Compared to high CRF, low and moderate CRF were associated with 25% and 28% increased likelihood of cognitive impairment, respectively. Our joint association analysis confirmed that the combination of low O3I and low or moderate CRF was associated with cognitive impairment, but failed to clearly demonstrate an interaction between these two variables.

To our knowledge, only one other observational study has investigated the relationship between O3I and MoCA scorev. In contrast to our findings, Rouch and colleagues (Rouch et al., 2022) found no associations between O3I and several measures of cognitive function in older (aged 55–97 years) adults in the U.S. and Canada. However, among ApoE ε4 carriers, who would be at increased risk for Alzheimer's, Rouch et al. observed an association between low O3I and both tau accumulation and lower performance on the Weschler Memory Scale (WMS).

Table 1
Omega-3 index, cardiorespiratory fitness, and covariates in relation to cognitive impairment among CCLS adults, 2009–2023: Multivariable Poisson Regression[a]

	Model 1	Model 2	Model 3	Model 4	Model 5
	Relative Risk (95% CI)	Relative Risk (95% CI)	Relative Risk (95% CI)	Relative Risk (95% CI)	Relative Risk (95% CI)
Omega-3 index categories (ref. ≥ 8.0 %)					
<4.0 %	**1.33 (1.11–1.58)**	**1.21 (1.01–1.44)**	1.16 (0.97–1.39)	1.17 (0.98–1.40)	1.13 (0.95–1.36)
4.0–7.9 %	1.08 (0.95–1.23)	1.06 (0.93–1.21)	1.05 (0.93–1.20)	1.05 (0.92–1.19)	1.04 (0.91–1.18)
Age (per 10 years)	–	**1.43 (1.34–1.54)**	**1.37 (1.28–1.48)**	**1.41 (1.31–1.52)**	**1.36 (1.26–1.46)**
Female sex	–	**0.70 (0.62–0.79)**	**0.69 (0.61–0.78)**	**0.71 (0.63–0.80)**	**0.70 (0.62–0.79)**
No college degree	–	**1.67 (1.51–1.86)**	**1.63 (1.47–1.81)**	**1.65 (1.49–1.83)**	**1.61 (1.45–1.79)**
Current smoker	–	1.14 (0.96–1.35)	1.11 (0.93–1.31)	1.13 (0.95–1.34)	1.10 (0.93–1.30)
BMI	–	1.03 (1.00–1.07)	0.99 (0.96–1.03)	1.01 (0.98–1.05)	0.98 (0.94–1.02)
Cardiorespiratory fitness (vs. High)[b]					
Low	–	–	**1.31 (1.09–1.56)**	–	**1.28 (1.07–1.53)**
Moderate	–	–	**1.27 (1.13–1.41)**	–	**1.25 (1.12–1.39)**
Glucose (per 10 mg/dL)	–	–	–	1.04 (1.01–1.08)	1.03 (1.00–1.07)
LDL cholesterol (per 40 mg/dL)	–	–	–	1.05 (0.99–1.11)	1.04 (0.99–1.10)
Systolic BP (per 20 mmHg)	–	–	–	**1.12 (1.05–1.20)**	**1.12 (1.05–1.20)**

[a] Cognitive impairment is defined as MoCA score ≤ 25.
[b]High = quintiles 4 & 5, moderate = quintiles 2 & 3, low = quintile 1.
BP—blood pressure, LDL–low-density lipoprotein.

Table 2
Joint association of omega-3 index and cardiorespiratory fitness on cognitive impairment[a] among CCLS adults, 2009–2023: Multivariable Poisson regression.

	Cardiorespiratory Fitness[b]		
	Low	Moderate	High
	RR (95 %CI)	RR (95 %CI)	RR (95 %CI)
Omega-3 Index			
<4.0%	1.40 (1.02–1.93)*	1.40 (1.09–1.80)	1.21 (0.94–1.57)
4.0–7.9%	1.36 (1.07–1.74)*	1.33 (1.12–1.59)	1.02 (0.87–1.20)
≥8%	1.50 (0.88–2.56)	1.17 (0.91–1.51)	1.0 (reference)

Abbreviations: CCLS- Cooper Center Longitudinal Study.
[a] Cognitive impairment is defined as MoCA score ≤25.
[b]High = quintiles 4 & 5, moderate = quintiles 2 & 3, low = quintile 1.
Adjusted for age (per 10 years), sex, college degree, current smoking, and BMI (per 3 kg/m^2).
p for interaction (fitness × omega-3 index) = 0.809.

Many other researchers have reported significant relationships between O3I and cognitive function. In fact, among the 14 studies reviewed by Rouch et al., (Rouch et al., 2022) only 3 had entirely null findings. (Coro et al., 2021; Dretsch et al., 2014; Erhardt et al., 2021) Most of these studies determined that O3I was related to at least some measures of cognitive function. (Rouch et al., 2022) However, they did not account for the protective effects of CRF. In perhaps the largest prospective study (N = 6,708) investigating the relationship between O3I and cognitive impairment, Amman et al. (2017) found that one standard deviation increase in O3I was associated with an 8% reduced risk of dementia among women 65 years of age and older. In one of few studies that included adjustment for physical activity, Tan et al. (2012) found that Framingham Offspring Study participants in the lowest quartile of O3I had significantly lower scores for executive function and abstract thinking as compared to the top 3 quartiles combined. In contrast to our study, most previous studies have assessed more than one cognitive outcome, which may have increased the likelihood of significant findings. However, most studies did not assess objectively measured CRF, which is not influenced by social desirability or recall bias (Rouch et al., 2022). Therefore, our study may provide a more accurate assessment of the associations between O3I, CRF, and cognitive impairment.

In contrast with the results of many observational studies, evidence from clinical trials generally has not supported a strong effect of omega-3 status on cognitive function (Alex et al., 2020). In their systematic review of 25 randomized controlled trials, Alex and colleagues (2020) concluded that omega-3 supplementation had no effect on global cognitive function and a small beneficial effect on memory in older adults without dementia. Although Wood et al. (2022) emphasized promising evidence from observational studies in their review, they acknowledged that most clinical trials failed to find a benefit of omega-3 intake for cognitive function. They suggested that this disparity may be due to differences in participant characteristics between observational and experimental studies, with the latter tending to include adults with existing cognitive impairment, but evidence has not yet demonstrated that earlier interventions yield greater benefit.

Our study has several strengths, including a large sample size and objective measures of omega-3 status and CRF. Further, we reduced the potential impact of confounding variables by adjusting for many covariates. This study also has a number of limitations. Importantly, since the study design is cross-sectional, we cannot determine whether the association between O3I and cognitive impairment is causal. Additionally, we cannot exclude the possibility of reverse causality; namely, individuals with impaired cognitive function may be less likely to consume omega-3 rich diets or to have higher levels of physical fitness. However, prospective cohort studies have consistently found CRF to be associated with reduced dementia risk over time (Lee, 2021). Changes in eating habits are common in adults with mild cognitive impairment or dementia (Lyketsos et al., 2002), but little is known about how cognitive impairment might influence intake of omega-3 fatty acids, in particular. However, in the current study we did not account for dietary intake, which has been associated with both the independent and dependent variables, due to insufficient pertinent data in the analytic sample (Shuval et al., 2015). Finally, because the study sample is predominantly White and well-educated with access to quality medical care, generalizability to more diverse samples is limited.

5. Conclusions

In summary, in the present study, O3I was associated with cognitive function independent of many variables, but not independent of CRF, which appears to be a more important predictor of cognitive function. We also did not find a significant interaction effect of O3I and CRF. Further investigation in larger, more diverse samples may yield additional insights on the association between O3I and cognitive function at varying levels of CRF.

CRediT authorship contribution statement

Kimberly N. Doughty: Writing – original draft, Conceptualization, Methodology. **Juliana Blazek:** Conceptualization, Methodology, Writing – review & editing. **David Leonard:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – review & editing. **Carolyn E. Barlow:** Conceptualization, Methodology, Data curation, Writing – review & editing. **Laura F. DeFina:** Conceptualization, Methodology, Writing – review & editing. **Omree Shuval:** Conceptualization, Methodology, Writing – review & editing. **Stephen W Farrell:** Methodology, Writing – review & editing. **Kerem Shuval:** Conceptualization, Methodology, Writing – review & editing, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. No external funding was provided for this study. The authors thank Kenneth H. Cooper, MD, MPH for establishing the Cooper Center Longitudinal Study, the Cooper Clinic physicians and staff for collecting clinical data, and The Cooper Institute for maintaining the database. Additionally, we are grateful to the CCLS participants.

Data availability

A scientific data request may be submitted to the Cooper Institute's Scientific Review Board Committee for review. The Committee meets regularly to assess the merits of all requests.

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