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SCIENTIFIC INVESTIGATIONS

Omega-3 Index and Obstructive Sleep Apnea: A Cross-Sectional Study

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Study Objectives: Erythrocyte levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Omega-3 Index) were previously found to be associated with obstructive sleep apnea (OSA) at very low levels (< 5.0%) in only one epidemiologic study. OSA has comorbidities, such as arterial hypertension, heart failure, or major depression, also associated with a low Omega-3 Index. These comorbidities can be improved by increasing intake of EPA and DHA, and thus the Omega-3 Index, preferably to its target range of 8% to 11%. Symptoms of OSA might improve by increasing the Omega-3 Index, but more research is needed.

Methods: In our sleep laboratory, 357 participants with OSA were recruited, and data from 315 participants were evaluated. Three categories of OSA (none/mild, moderate, severe) were defined based on apnea-hypopnea index. Anthropometrics and lifestyle characteristics (smoking, alcohol, fish intake, omega-3 supplementation) were recorded. Erythrocyte fatty acid compositions were assessed with the HS-Omega-3 Index methodology.

Results: The mean Omega-3 Index in all 3 categories of OSA was 5.7%, and no association with OSA was found. There were more male participants with severe OSA (79.7%, $P = .042$) than females, and participants with severe OSA had a significantly higher body mass index (32.11 ± 6.39 kg/m^2, $P = .009$) than participants with mild or moderate OSA. Lifestyle characteristics were not significantly different.

Conclusions: In contrast to our hypothesis, an Omega-3 Index of 5.7% was not associated with OSA severity. Previously, an Omega-3 Index < 5.0% was associated. Although our results suggest aiming for an Omega-3 Index > 5.7% in an intervention trial with EPA and DHA in OSA, comorbidities of OSA suggest a target range of 8% to 11%.

Keywords: epidemiology, erythrocytes, hypopnea, omega-3 fatty acids

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INTRODUCTION

Several risk factors, such as excess body weight, male sex, older age, neck circumference, predispose to obstructive sleep apnea (OSA).[1–6] Conversely, OSA is an independent risk factor for arterial hypertension, heart failure, atrial fibrillation, or stroke.[1–6] In individuals with arterial hypertension or risk for cardiac disease, the prevalence of sleep apnea is 2 to 10 times higher than in individuals without the health issues mentioned.[1–6] An adequate therapy of sleep apnea can decrease mortality and morbidity.[1–6]

One epidemiologic study found low levels of omega-3 fatty acids in erythrocytes, as assessed with the HS-Omega-3 Index methodology, to be associated with OSA in United States adults.[7] Based on this epidemiologic finding, and on the anti-inflammatory effects of omega-3 fatty acids, it has been speculated that omega-3 fatty acids might be of therapeutic value in OSA, and intervention trials have been suggested.[8]

This is further supported by many epidemiologic studies that demonstrated a correlation between low blood levels of omega-3 fatty acids and risk for hypertension, heart failure, atrial fibrillation, or stroke.[8,9] In most, but not all, intervention trials, omega-3 fatty acids reduced hypertension, complications of heart failure, or major depression.[9–14] Tolerability and safety make omega-3 fatty acids an attractive therapeutic option for OSA, but data supporting this approach are scarce.[7–9] We hypothesized that there is an association between low levels of omega-3 fatty acids in erythrocytes and OSA also in Europe.

BRIEF SUMMARY

Current Knowledge/Study Rationale: If effective, the two marine omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) would be an attractive therapeutic approach to obstructive sleep apnea (OSA), because EPA and DHA are tolerable and safe, and improve comorbidities of OSA such as hypertension, heart failure, or major depression. Rather than assessing intake, research in EPA and DHA now focuses on blood levels, preferably in erythrocytes and using a standardized analytical method (HS-Omega-3 Index).

Study Impact: Although one epidemiologic study found an association of OSA with very low levels of EPA and DHA (< 5.0%), we did not find an association at higher levels (5.7%). Our data suggest aiming for an Omega-3 Index > 5.7% in an intervention trial with EPA and DHA in OSA; comorbidities of OSA suggest a target range of 8% to 11%.

METHODS

Participants

All consecutive patients presenting to the sleep laboratory of one author (K.S.) were invited to participate in the current

Table 1—Baseline characteristics (n = 315).

Variable	OSA Severity			*P* value
	None/mild	Moderate	Severe	
Age (years), mean (SD)	60.37 (12.63)	66.14 (12.33)	61.69 (12.44)	.010
BMI (kg/m^2), mean (SD)	30.64 (6.47)	29.64 (5.75)	32.11 (6.39)	.009
Total n / male n (% male)	113/74 (65.5)	74/50 (67.6)	128/102 (79.7)	.042
Currently smoking, n (%)	28 (22.8)	10 (14.5)	20 (16.4)	.275
Fish oil supplement, n (%)				.010
Rarely	117 (95.1)	58 (82.9)	109 (89.3)	
Monthly	4 (3.2)	4 (5.7)	5 (4.1)	
Weekly	1 (0.8)	4 (5.7)	8 (6.6)	
Daily	1 (0.8)	4 (5.7)	0 (0)	
Fish meals per month, n (%)				.068
None	11 (8.9)	18 (25.7)	24 (19.7)	
Less than 1/wk	46 (37.4)	22 (31.4)	43 (35.2)	
At least 1/wk	53 (43.1)	27 (38.6)	44 (36.1)	
At least 2/wk	13 (10.6)	3 (4.3)	11 (9.0)	
Alcohol consumption, n (%)				.507
Never	14 (11.4)	5 (7.1)	11 (9.0)	
Rarely	43 (35.0)	31 (44.3)	35 (28.7)	
Monthly	9 (7.3)	3 (4.3)	11 (9.0)	
Weekly	30 (24.4)	16 (22.9)	39 (32.0)	
Daily	27 (22.0)	15 (21.4)	26 (21.3)	

OSA = obstructive sleep apnea, SD = standard deviation.

prospective cross-sectional study. No exclusion or inclusion criteria were defined. Data were evaluated in an anonymized fashion. The protocol was approved by the ethics committee of the Medical Faculty of the Ludwig Maximilians-University of Munich. The study was conducted according to good clinical practice. After written informed consent, a questionnaire was handed to the participants, including questions on sex, age, body height and weight, and lifestyle, including smoking, alcohol consumption, and omega-3 fatty acid ingestion (eg, fish) and/or supplementation.

Sleep Apnea

For this study, sleep apnea was defined by the International Classification of Sleep Disorders, Second Edition. Three categories of sleep apnea were defined according to apnea-hypopnea index (AHI): none/mild (AHI = 0–14 events/h), moderate (AHI = 15–30 events/h), and severe (AHI > 30 events/h). In addition, the Epworth Sleepiness Scale was documented. Oxygen saturation, pulse transit time, electroencephalogram, electrooculogram, electromyogram, electrocardiogram, and heart rate were also assessed, but were not part of the statistical analysis.

Laboratory Methods

For analysis of erythrocyte fatty acid composition, 2.7 mL EDTA-blood was taken, and immediately sent to Omegametrix (Martinsried, Germany). There, erythrocyte fatty acid composition was analyzed according to the HS-Omega-3 Index methodology as previously described.[15] Fatty acid methyl esters were generated from erythrocytes by acid transesterification and analyzed by gas chromatography using a GC2010 Gas Chromatograph (Shimadzu, Duisburg, Germany) equipped with a SP2560, 100-m column (Supelco, Bellefonte, Pennsylvania, United States) using hydrogen as carrier gas. Fatty acids were identified by comparison with a standard mixture of fatty acids characteristic of erythrocytes. Results are given as eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) expressed as a percentage of total identified fatty acids after response factor correction. The coefficient of variation for EPA plus DHA was 5%. Analyses were quality-controlled according to DIN ISO 15189.

Statistical Analysis

The statistical analysis, sample size estimate, and the assumptions corresponded to the only comparable study thus far.[7] Age and body mass index (BMI) were normally distributed and confirmed by a Q-Q plot. Sex, smoking, alcohol consumption, fish oil supplement use, and fish meals per month were dichotomous variables. Supplementation of fish oil, fish meals per month, and alcohol consumption were divided into 4 or 5 categories (**Table 1**). To test for a difference in participant characteristics and fatty acids across apnea severity levels, the Kruskal-Wallis test for continuous data and the chi-square test for categorical data were used.

The categorical severity of sleep apnea (none/mild, moderate, severe) was predicted using a multinomial logistic regression model with intercept and fatty acid measurements as independent variables controlling for participant characteristics. First the fatty acids were excluded and only the baseline and lifestyle characteristics were examined. Then EPA und DHA were included separately, and in combination (Omega-3 Index). A value of $P < .05$ was defined as statistically significant.

Table 2—Fatty acids (as % total fatty acids) by OSA severity (n = 315).

	OSA Severity									
Fatty Acid	**None/mild (n = 123)**	**IQR**		**Moderate (n = 70)**	**IQR**		**Severe (n = 122)**	**IQR**		***P* value**
C14:0	0.240	0.17	0.32	0.255	0.18	0.41	0.245	0.18	0.34	.300
C16:0	23.130	22.30	24.50	23.025	22.10	24.00	22.805	21.70	23.90	.130
C16:1n7t	0.110	0.08	0.14	0.120	0.09	0.15	0.100	0.08	0.14	.130
C16:1n7	0.360	0.26	0.51	0.385	0.27	0.50	0.375	0.26	0.53	.880
C18:0	17.410	16.80	18.30	16.840	16.20	17.70	17.425	16.70	18.10	.008
C18:1t	0.340	0.27	0.43	0.405	0.30	0.48	0.330	0.25	0.43	.030
C18:1n9	15.300	14.10	16.70	15.675	14.70	16.90	15.430	14.70	16.40	.280
C18:2n6tt	0.050	0.02	0.10	0.070	0.02	0.11	0.060	0.02	0.11	.380
C18:2n6ct	0.040	0.02	0.07	0.030	0.02	0.05	0.020	0.01	0.06	.052
C18:2n6tc	0.100	0.08	0.14	0.110	0.08	0.14	0.100	0.07	0.12	.060
C18:2n6	10.450	9.50	11.70	10.815	9.70	11.80	10.340	9.40	11.50	.130
C20:0	0.150	0.13	0.17	0.150	0.12	0.17	0.150	0.13	0.17	.700
C18:3n6	0.080	0.06	0.11	0.080	0.06	0.10	0.080	0.06	0.10	.820
C20:1n9	0.230	0.20	0.26	0.220	0.21	0.25	0.230	0.21	0.26	.730
C18:3n3	0.130	0.10	0.18	0.140	0.11	0.18	0.140	0.10	0.17	.560
C20:2n6	0.210	0.18	0.24	0.200	0.18	0.23	0.200	0.18	0.23	.530
C22:0	0.250	0.20	0.32	0.260	0.20	0.32	0.250	0.20	0.32	.880
C20:3n6	1.750	1.50	2.00	1.675	1.50	2.00	1.690	1.50	1.90	.440
C20:4n6	15.520	14.10	16.70	15.405	14.10	16.70	15.800	14.30	16.80	.530
C24:0	0.790	0.68	0.91	0.785	0.64	0.91	0.810	0.64	0.97	.400
C20:5n3	0.840	0.62	1.10	0.880	0.75	1.10	0.855	0.65	1.10	.550
C24:1n9	0.860	0.76	0.97	0.815	0.67	1.00	0.910	0.71	1.05	.290
C22:4n6	2.970	2.50	3.30	2.770	2.50	3.20	3.025	2.60	3.50	.110
C22:5n6	0.590	0.45	0.73	0.545	0.43	0.66	0.585	0.48	0.70	.260
C22:5n3	2.430	2.10	2.80	2.580	2.10	2.80	2.540	2.20	2.80	.490
C22:6n3	4.870	4.00	5.70	4.785	4.10	5.50	4.795	4.10	5.60	.890
Omega-3 Index	5.720	4.80	6.80	5.705	4.80	6.60	5.720	4.70	6.70	.980

IQR = interquartile range, OSA = obstructive sleep apnea.

Analyses were performed using R package Version 3.2 (R Foundation for Statistical Computing, Vienna, Austria) except the multinomial logistic regression, which was calculated with NOMREG function in IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp, Armonk, New York, United States).

RESULTS

A total of 357 patients provided informed consent. We had to exclude 37 datasets because of incomplete questionnaires and 5 data sets because of implausibility. A total of 315 datasets were analyzed.

Baseline characteristics are reported in **Table 1**. Participants had a mean age of 62.73 years (28–92 years) and 226 (71.7%) were men and 89 (28.3%) were women. Participants with moderate OSA were older (66.14 ± 12.33 years, $P = .009$) than participants with mild (60.37 ± 12.63 years) or severe OSA (61.69 ± 12.44 years). Average BMI was 30.8 ± 6.2 kg/m^2, and there was a significant difference of BMI across the OSA severity levels. Participants with severe OSA showed a higher BMI (32.1 ± 6.4 kg/m^2, $P = .01$) than participants with mild or moderate OSA (**Table 1**).

Sex also showed a significant difference across the OSA severity levels. Participants with severe OSA were significantly more frequently males (79.7%, $P = .042$) than participants with mild or moderate OSA. Most of the participants used fish oil supplements only rarely. There was a significant difference on fish oil supplement usage across the OSA severity levels, fewer supplements were used by participants with none/mild OSA. In an exploratory manner, we repeated our analysis restricted to participants rarely using fish oil supplements (**Table 1**), and found identical results as compared to the overall group (not shown). Frequency of smoking and fish or alcohol consumption was not significantly different between the groups (**Table 1**).

The results of fatty acid measurements according to the sleep apnea severity categories are shown in **Table 2**. Neither the Omega-3 Index, nor EPA nor DHA were different among groups. In the absence of a pertinent hypothesis, and in the absence of a quantitative relation, we consider the significant differences for fatty acids C18:0 and C18:1t a chance finding.

In **Table 3**, odds ratios from the multinomial logistic regression model are reported. As expected, a higher BMI and male sex was more frequent in the severe OSA group.

Table 3—Odds ratios from the polychotomous logistic regression model.

Variable	Overall *P* Value	Severe Versus None/Mild	Severe Versus Moderate	Moderate Versus None/Mild
Age	.013	0.98 (0.95 to 1.00)	1.03 (1.00 to 1.05)	1.05 (1.01 to 1.08)
Log(BMI) (kg/m^2)	.002	0.09 (0.02 to 0.46)	0.065 (0.009 to 0.443)	0.73 (0.10 to 5.06)
Male	.014	0.34 (0.16 to 0.71)	0.52 (0.23 to 1.17)	1.53 (0.68 to 3.45)
Currently smoking	.432	1.59 (0.76 to 3.33)	1.06 (0.43 to 2.62)	0.67 (2.8 to 1.62)
Fish oil supplement	.035			
Fish meals	.413			
Alcohol consumption	.373			
C20:5n3	.261	1.41 (0.59 to 3.42)	0.47 (0.18 to 1.18)	0.66 (0.24 to 1.84)
C22:6n3	.129	1.05 (0.79 to 1.39)	0.77 (0.56 to 1.05)	0.73 (0.53 to 1.01)
Omega-3 Index	.129	0.99 (0.79 to 1.25)	0.79 (0.61 to 1.02)	0.78 (0.60 to 1.03)

Value are presented as odds ratios (95% confidence intervals). BMI = body mass index.

DISCUSSION

In contrast to our hypothesis, we did not detect a significant association of erythrocyte omega-3 fatty acids with severity of OSA in our cross-sectional study. Superficially, our results are in contrast with the only comparable study that did find a significant association of severity of OSA with DHA levels and the Omega-3 Index.[7]

However, we observed a mean Omega-3 Index of 5.7% in all three categories of severity of OSA, with EPA slightly higher than 0.8% and DHA among 4.8% (**Table 2**). Levels of omega-3 fatty acids were much lower in all 3 categories of OSA in the study that did find a significant association.[7] Based on 8 patient characteristics, and the level of DHA in erythrocytes, Ladesich et al. proposed to predict a probability of having severe OSA.[7] Accordingly, and according to the levels of DHA we found in our population, the probability of severe OSA would be associated with a risk of approximately 18% in males and approximately 6% in females.[7] Taken together, we suggest that, at an Omega-3 Index of 5.7, the role of EPA and DHA in OSA is small, if it exists.

In all 3 categories of OSA studied, our study participants were older but less heavy than the population previously studied, whereas sex was comparably distributed.[7] Only 39.0% of our participants were in the OSA severity category none/mild, compared to 65.1% of the previously studied population. Clearly, we could not replicate the study population studied by Ladesich et al. However, because the risk for OSA increases with age and with BMI, a systematic difference between our population and the population of Ladesich et al. does not appear to explain the differences in findings.[7]

Largely based on the epidemiologic study already cited,[7] and on their anti-inflammatory properties, omega-3 fatty acids have been suggested as a therapeutic approach in OSA.[9] Clearly, in order to substantiate this suggestion, a controlled intervention trial testing the effects of omega-3 fatty acids in patients with OSA is required. As mentioned, we think that at an Omega-3 Index of 5.7%, the role of EPA and DHA in OSA is small. Nevertheless, for a trial, we suggest a target higher than 5.7%. At a target range between 8% and 11%, life expectancy is maximal, and risks for the comorbidities mentioned in the next paragraphs are minimal.[9,15] This trial design has been discussed in more detail for cardiovascular disease elsewhere.[9,15]

As in all epidemiologic studies, causality is impossible to establish. Of note, the number of individuals with severe OSA was higher in our study (n = 128, **Table 1**) than in the study by Ladesich et al. (n = 52), and the number of individuals with none/mild OSA was lower in our study (n = 113, **Table 1**) than in the study by Ladesich et al. (n = 228).[7] Therefore, if OSA would decrease levels of omega-3 in erythrocytes, we would have expected lower levels of omega-3 fatty acids in more severe OSA than in mild OSA, as we would have expected lower levels in our study than in the study by Ladesich et al.[7] Therefore, we do not think that OSA lowers the Omega-3 Index. As in all epidemiologic studies, reverse causality, meaning that affected individuals use omega-3 fatty acids to alleviate OSA, is also impossible to exclude. Currently, the use of omega-3 fatty acids in OSA is not common knowledge, nor is it mentioned in any guidelines.[1–6] In participants of our study who did not use a fish oil supplement, findings were identical to the overall group (Results, **Table 1**). Also, the percentages of individuals supplementing omega-3 fatty acids were minimal, and fish consumption was average for this age group in Germany,[16,17] and both were evenly distributed among the tertiles of severity of OSA. In the case of reverse causality, we would have expected a larger use of fish or fish oil supplements in the group with more severe OSA. Taken together, we found no evidence supporting reverse causality or evidence supporting the idea that OSA would lower levels of omega-3 fatty acids.

OSA is characterized by a number of comorbidities. We already mentioned hypertension, heart failure, atrial fibrillation, or stroke.[1–6] Others are systemic and vascular inflammation with endothelial dysfunction, major depression, and cognitive impairment.[18–23] All these comorbidities have been found to be associated with a low Omega-3 Index.[9–12,21,22,24] Importantly, some, but not all, meta-analyses and results from individual trials provide evidence for the positive effects of omega-3 fatty acids in hypertension, heart failure, inflammation, endothelial dysfunction, major depression, and cognitive impairment.[9,11–14,25] Only an intervention trial testing the effect of increasing the Omega-3 Index in patients with OSA will be able to dissect whether a low Omega-3 Index is causal to OSA, or merely a reflection of the comorbidities mentioned (ie, a confounder).

On a broader picture, there is evidence that quality of sleep depends on the levels of omega-3 fatty acids in erythrocytes or intake of omega-3 fatty acids.[26–28] This observatory evidence is supported by some evidence from intervention trials.[29,30] Currently, we are investigating the effects of increasing the Omega-3 Index on sleep patterns.

Levels of fatty acids C18:0 and C18:1t were significantly different across groups of OSA (**Table 2**). This finding was unexpected, and not based on a hypothesis. Because we measured a total of 26 fatty acids, this finding might be due to chance. We suggest confirming our finding in a hypothesis-driven study before more research is initiated.

Strengths and Limitations

Our cross-sectional study is only the second epidemiologic study on omega-3 in OSA, and longitudinal studies are needed to further substantiate a relation between levels of omega-3 fatty acids and risk for OSA. The population we studied was not entirely comparable to the population studied by Ladesich et al.[7] However, we studied consecutive and unselected patients, and therefore think that we studied a typical German population affected by OSA. Although their anti-inflammatory action has been suggested to mediate a potential therapeutic effect of omega-3 in OSA,[8] more detailed studies are needed to pinpoint potential mechanisms. Because of its design, our study cannot establish causality or describe any mechanisms.

In conclusion, in a cross-sectional study, we found no association between erythrocyte EPA and DHA and severity of OSA at a mean Omega-3 Index of 5.7%. Because a previous study found an association between severity of OSA and lower levels of the Omega-3 Index, aiming for an Omega-3 Index > 5.7% in an intervention trial might be suggested. However, because risk for comorbidities of OSA, such as hypertension, heart failure, or major depression is minimal with an Omega-3 Index in a target range between 8% and 11%, we consider the latter target preferable.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
DHA, docosahexaenoic acid
DIN, Deutsches Institut für Normung
EDTA, ethylenediaminetetraacetic acid
EPA, eicosapentaenoic acid
ISO, International Organization for Standardization
NOMREG, multinomial logistic regression
OSA, obstructive sleep apnea
SPSS, Statistical Package of the Social Sciences

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