Omega-3 Supplementation and Loneliness-Related Memory Problems: Secondary Analyses of a Randomized Controlled Trial

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Objective: Loneliness enhances risk for episodic memory declines over time. Omega-3 supplementation can improve cognitive function for people experiencing mild cognitive difficulties. Accordingly, we explored whether omega-3 supplementation would attenuate loneliness-related episodic memory problems. **Methods:** Participants (n = 138) from a parent randomized controlled trial were randomized to the placebo, 1.25 grams/d of omega-3, or 2.50 grams/d of omega-3 conditions for a 4-month period. They completed a baseline loneliness questionnaire and a battery of cognitive tests both at baseline and at the end of the randomized controlled trial. **Results:** After adjustment for baseline verbal episodic memory scores, lonelier people within the placebo condition had poorer verbal episodic memory postsupplementation, as measured by immediate ($b = -0.28$, $t(117) = -2.62$, $p = .010$) and long-delay ($b = -0.06$, $t(116) = -2.07$, $p = .040$) free recall, than their less lonely counterparts. This effect was not observed in the 1.25- and 2.50-grams/d supplementation groups (all p values > .10). The plasma omega-6:omega-3 ratio data mirrored these results. There were no loneliness-related effects of omega-3 supplementation on short-delay recall or the other cognitive tests (all p values > .32). **Conclusion:** These results suggest that omega-3 supplementation attenuates loneliness-related verbal episodic memory declines over time and support the use of exploring novel interventions for treating episodic memory problems among lonely people. **Trial Registration:** clinicaltrials.gov Identifier: NCT00385723. **Key words:** loneliness, cognition, memory, omega-3, intervention.

BMI = body mass index; **RCT** = randomized controlled trial; **CVLT** = California Verbal Learning Test; **PUFAs** = polyunsaturated fatty acids; **SD** = standard deviation.

INTRODUCTION

Loneliness, an interpersonally stressful state of perceived social isolation, enhances risk for cognitive difficulties. For example, loneliness has been linked to the development of cognitive impairment and dementia among older adults. Lonelier adults 65 years and older experienced more cognitive impairment, as assessed by the Abbreviated Mental Test, than did those who were less lonely (1). Lonelier adults 75 years and older had larger cognitive declines over 10 years than their less lonely counterparts, as measured by the Mini-Mental State Examination (2). In addition, lonelier adults who were an average of 81 years old were twice as likely to develop Alzheimer's disease during a 6-year period compared with those who were less lonely (3).

Recent research has also addressed the relationship between loneliness and specific types of cognitive function. A report from the English Longitudinal Study of Ageing demonstrated that lonelier adults who were an average of 65 years old had larger declines in verbal episodic memory, but not verbal fluency, over a 4-year period compared with those who were less lonely (4). Accordingly, it is important to understand the factors that could reduce loneliness-related cognitive difficulties over time, particularly memory problems, which lonely people experience as adults.

The current study investigated whether omega-3 supplementation could alleviate loneliness-related cognitive declines. Mechanistically, omega-3 polyunsaturated fatty acids (PUFAs), commonly found in oily fish, are essential to normal brain development and maintenance. For example, omega-3 PUFAs help prevent neuronal apoptosis (5,6). Omega-3 PUFAs also reduce inflammation (7), which could have downstream effects on cognitive function (8).

Epidemiological and observational studies of dietary intake support the link between omega-3 and cognitive function, particularly global indices of cognitive impairment; people with higher dietary intake of omega-3 had a reduced risk of new-onset dementia and less global cognitive decline over time than people with lower omega-3 intake (9–11). A large population-based study demonstrated that older adults who ate more fish had better cognitive performance, as measured by a neuropsychological test battery, than those who ate less fish (12). Adults who reported higher marine-based PUFA intake had better overall cognitive function, as reflected by a better composite score across the Kendrick Object Learning Test, the Trail Making Test (Part A), and a variety of other cognitive tests, compared with those who reported lower marine-based PUFA intake (13). Indeed, a recent meta-analysis concluded that people with high adherence to a typical Mediterranean diet, which is high in fish, had a lower risk of both mild and advanced global cognitive impairment than their less adherent counterparts (14).

Studies examining the cognitive benefits of omega-3 supplementation also support the link between omega-3 and cognition, although the effects are much less consistent. A number of randomized controlled trials (RCTs) demonstrate better cognitive function, including less global cognitive impairment and better attention, in omega-3 supplemented groups compared with placebo (15–17). In addition, healthy adults who received an omega-3 supplement were faster at both working and episodic memory tasks than those who received a placebo (18). Although some studies report null effects (e.g., (19,20)), the supplementation

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literature suffers from methodological inconsistencies such as varied supplementation doses, supplementation regimen lengths, and sample characteristics (e.g., cognitively healthy versus Alzheimer's disease patients), which could contribute to the contradictory results.

Emerging evidence from the omega-3 literature suggests that supplementation improves cognitive function for people experiencing mild cognitive problems. For instance, a recent meta-analysis of 10 RCTs concluded that immediate verbal recall, attention, and processing speed were better among people receiving an omega-3 supplement compared with placebo, but only for people experiencing mild cognitive impairment (21). No supplementation effects were found for cognitively healthy participants or people with Alzheimer's disease. Similarly, among healthy older adults with age-related cognitive decline, those in the omega-3 supplementation group had better visuospatial and immediate and delayed verbal memory compared with their counterparts in the placebo condition; there was no effect of supplementation on executive function or working memory (17). In addition, a recent RCT demonstrated that among adults with mild cognitive impairment, those who received an omega-3 supplement had improved working memory, immediate visual episodic memory, and delayed verbal episodic memory compared with those who received a placebo (22).

The present study is a secondary analysis of an RCT assessing the anti-inflammatory effects of omega-3 supplementation (7) (ClinicalTrials.gov identifier: NCT00385723). The consort diagram and other RCT-related documents are available in the primary report. This study explored the impact of loneliness and omega-3 supplementation on secondary outcomes in our RCT: verbal episodic memory, working memory, executive function, and verbal fluency/processing speed.

Taken together, prior research suggests that lonely adults may develop memory difficulties over time and omega-3 intake could lessen these risks. However, the existing literature linking loneliness, omega-3 supplementation, and cognitive function is in its infancy and many questions remain unanswered. Accordingly, exploratory questions and analyses are needed to begin joining these diverse literatures. The clearest preliminary hypothesis derived from prior research was that lonelier participants would have poorer verbal episodic memory than less lonely participants, and that omega-3 supplementation would attenuate these effects. We also explored the effects of loneliness and omega-3 supplementation on working memory, executive function, and verbal fluency/processing speed.

METHODS

Participant Demographics

The parent RCT participants were 138 healthy, overweight, and sedentary adults (7). The sample was primarily white (79%) and female (67%), and their average age was 51.04 (standard deviation [SD] = 7.75) years (range, 40–85 years). Additional sample characteristics are listed in Table 1 and Table S1 (Supplemental Digital Content, http://links.lww.com/PSYMED/A157).

Participant Selection

Participants were recruited through advertisements and media announcements. Individuals were ineligible if they had a convulsive, autoimmune, or inflammatory disease, or if they had dementia, Parkinson's disease, multiple sclerosis, diabetes, chronic obstructive pulmonary disease, symptomatic ischemic heart disease, liver/kidney failure, gastroesophageal reflux disease, excessively high triglycerides or low-density lipoprotein cholesterol, a body mass index (BMI) less than 22.5 kg/m^2 or more than 40 kg/m^2, or a history of cancer (except basal or squamous cell skin carcinomas) or stroke. People were also excluded if they engaged in more than 3 hours of vigorous physical exercise per week; were taking medications for depression, anxiety, cholesterol, or cardiovascular problems; or were pregnant, nursing, vegetarians, or alcoholics/drug abusers. Furthermore, individuals were ineligible if they routinely took fish oil or flaxseed supplements or ate more than two portions of oily fish per week. As part of the screening process, individuals received a 7-day supply of placebo pills (single blind). To ensure an adherent sample, those who had taken less than 80% of the pills at the end of the week were excluded from the study before randomization. The Ohio State University Institutional Review Board approved the project; all participants provided written informed consent before participation.

Procedure

Participants completed a variety of self-report questionnaires and a battery of neuropsychological tests at the beginning of the RCT, which served as baseline measures. At the end of the first visit, participants were randomized to the placebo, 1.25 (grams/d) omega-3, or 2.50 grams/d omega-3 supplementation groups by a laboratory manager who did not have participant contact. Participants took their supplements for a 4-month period and returned unused pills at the end of each month (7). After 4 months of supplementation, participants returned to the laboratory and completed the battery of neuropsychological tests for a second time. Data collection for the parent RCT began in September 2006 and ended in February 2011.

Primary Measures

Loneliness was measured with the 20-item University of California Los Angeles loneliness scale (version 3), which assessed perceptions of social isolation and loneliness (23). Example items include "How often do you feel that you lack companionship?" and "How often do you feel close to people?" (reversed). The scale is highly reliable, demonstrates construct and convergent validity, and is one of the most commonly used loneliness measures (23). Potential scores range from 20 to 80, and higher numbers indicate greater loneliness (α = .936). Participants completed the loneliness measure 4 weeks after supplementation began (i.e., 12 weeks before trial completion); all other baseline measures, except the Social Network Index Interview, were administered before supplementation began. We used this measure as a baseline assessment because there were no loneliness differences across groups (see Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A157), demonstrating that omega-3 supplementation did not affect loneliness scores. Loneliness is also relatively stable over time; the University of California Los Angeles scale has a 0.73 test-retest reliability at both 2-month and 1-year intervals (24).

Participants completed a battery of neuropsychological tests; a detailed description can be found in the Supplemental Digital Content, http://links.lww.com/PSYMED/A157. Indices of immediate free recall, short-delay free recall, and long-delay free recall from the California Verbal Learning Test, Second Edition (CVLT-II) measured verbal episodic memory (25,26). Three tests from the Wechsler Memory Scale–Third Edition assessed working memory (27); the Digit Span and Letter-Number Sequencing tasks measured verbal working memory, whereas the Spatial Span task measured visuospatial working memory. The Trail Making task was used to measure executive function (28). The Controlled Oral Word Association Task assessed verbal fluency and processing speed (29).

Ancillary Measures

We included a variety of ancillary measures to account for potential confounding factors; a detailed description can be found in the Supplemental Digital Content, http://links.lww.com/PSYMED/A157. The Center for Epidemiological Studies Depression scale was used to assess depressive symptoms (30). The Pittsburgh Sleep Quality Index measured sleep quality over the past month (31). Activity levels were determined by the Community Healthy Activities Model Program for Seniors questionnaire (32). To assess social integration versus

TABLE 1. Baseline Demographic Characteristics

Characteristic	Category	Full Sample ($n = 138$)	Placebo ($n = 46$)	1.25 grams/d ($n = 46$)	2.50 grams/d ($n = 46$)	p
Race	White	109 (79.0)	33 (71.7)	39 (84.8)	37 (80.4)	.449
	Black	22 (15.9)	9 (19.6)	5 (10.9)	8 (17.4)	
	Other	7 (5.1)	4 (8.7)	2 (4.3)	1 (2.2)	
Marital Status	Single	19 (13.8)	11 (23.9)	4 (8.7)	4 (8.7)	.021
	Married/Domestic partner	95 (68.8)	24 (52.2)	38 (82.6)	33 (71.7)	
	Separated/divorced/ widowed	24 (17.4)	11 (23.9)	4 (8.7)	9 (19.6)	
Sex	Male	45 (32.6)	10 (21.7)	18 (39.1)	17 (37.0)	.153
	Female	93 (67.4)	36 (78.3)	28 (60.9)	29 (63.0)	
Years of education, M (SD)	N/A	16.70 (2.82)	17.04 (2.97)	16.46 (2.27)	16.59 (3.16)	.580
Age, M (SD), y	N/A	51.04 (7.75)	51.11 (8.59)	51.07 (8.03)	50.96 (6.68)	.995

Data are shown as n (%) unless otherwise indicated.
N/A = not applicable; M = mean; SD =standard deviation.
The p value refers to the test of between group differences, which were tested with unadjusted models.

isolation, participants completed the Social Network Index Interview (33). Participants also answered questions about their weekly average alcohol consumption, current medication use, and a variety of demographic characteristics.

Omega-3 Supplementation

Participants were randomized to the placebo, 1.25 grams/d of omega-3, or 2.50 grams/d of omega-3 groups after their baseline visit. Because of the nature of the parent trial, the fish oil supplements contained a 7:1 ratio of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA); EPA has stronger anti-inflammatory effects than DHA (34). The placebo pills included palm, olive, soy, canola, and cocoa butter oils that approximated the saturated/monounsaturated/polyunsaturated ratio consumed by US adults. OmegaBrite (Waltham, MA) supplied both the omega-3 PUFA and the matching placebo pills; all supplements were coated with a fuchsia coloring. OmegaBrite added a mild fish flavor to the placebo to help disguise any differences between the omega-3 PUFAs and the placebo; we told participants about the fish flavoring to promote blindness. Further information about the supplements' fatty acid composition is available elsewhere (7).

Plasma Omega-6 and Omega-3 Assays

To quantify plasma levels of omega-6 and omega-3 PUFAs, we analyzed the fatty acid composition of both the presupplementation and postsupplementation blood samples. Lipids were extracted from plasma using chloroform/methanol (2:1, v/v) with 0.2 vol. 0.88% KCl (35). Fatty acid methyl esters of the fractions were prepared by incubating the fractions with tetramethylguanidine at 100°C (36) and analyzed by gas chromatography (Shimadzu, Columbia, MD) using a 30-meter Omegawax 320 (Supelco-Sigma) capillary column. The helium flow rate was 30 ml/min, and oven temperature ramped beginning at 175°C and held for 4 minutes then increased to 220°C at a rate of 3°C/min, as previously described (37). Retention times were compared to authentic standards for fatty acid methyl esters (Supelco-Sigma [St Louis, MO] and Matreya, Inc [Pleasant Gap, PA]). We report on fatty acids that were greater than 0.01% of peaks detected; these included myristate (14:0), palmitate (16:0), palmitoleate (16:1n7), stearate (18:0), oleate (18:1n9), vaccenate (18:1n7), linoleate (18:2n6), γ-linolenate (18:3n6), α-linolenate (18:3n3), stearidonate (18:4n3), catoleate (20:1n9), eicosadienoate (20:2n6), dihomo-γ-linolenate (20:3n6), arachidonate (20:4n6), eicosapentaenoate (20:5n3), adrenate (22:4n6), docosapentaenoate (22:5n3), and docosahexaenoate (22:6n3). For calculating the omega-6:omega-3 ratio, all identified omega-6 and omega-3 fatty acids were used.

We measured both types of PUFAs to calculate a plasma omega-6:omega-3 ratio. Omega-6 fatty acids, like arachidonic acid, increase the production of proinflammatory cytokines, whereas omega-3 fatty acids, such as EPA, are associated with lower levels of inflammation. In line with these properties, those who have lower omega-6:omega-3 ratios have better mental and physical health than do those with higher omega-6:omega-3 ratios (38,39). A lower omega-6:omega-3 ratio would also be consistent with omega-3 supplementation, which elevates omega-3 fatty acid levels.

Data Analytic Strategy

In the preliminary analyses, we tested a series of models that were completely unadjusted, except for baseline cognitive function scores. In addition, a pool of potential confounds were selected a priori based on their theoretical and empirical relationships to loneliness and cognitive function. Because we were analyzing secondary data from an RCT, the primary analyses only controlled for potential confounds that were marginally or significantly different across supplementation groups at baseline. We tested for between group differences using a χ^2 test for categorical outcomes and univariate analysis of variance for continuous outcomes. The remaining potential confounds were added to the ancillary analyses to ensure that our results were independent of these additional covariates.

The primary analyses tested the clearest initial prediction derived from prior research: lonelier participants would have poorer verbal episodic memory than less lonely participants, and omega-3 supplementation would attenuate these effects. There were two ways to test for loneliness-related memory problems. First, we could establish a concurrent relationship between loneliness and verbal episodic memory at baseline. Second, we could demonstrate a prospective relationship between loneliness at baseline and changes in verbal episodic memory over time. In theory, omega-3 supplementation could alter concurrent relationships, prospective relationships, or both.

To examine concurrent relationships at baseline we conducted a linear regression using SPSS 19.0 (IBM, New York, NY) that included loneliness (entered as a continuous effect) and a set of covariates (described previously in the preliminary analyses) predicting presupplementation verbal episodic memory scores. The same data analytic strategy was used for each of the other cognitive function measures.

To test for prospective relationships over time and to examine the effects of supplementation, we conducted a linear regression that included the main effect of supplementation group, the main effect of loneliness (entered as a continuous effect), the interaction between the two, and a set of covariates (described previously in the preliminary analyses) predicting postsupplementation verbal episodic memory scores. We included baseline episodic memory scores in each analysis, which allowed us to statistically investigate residual change in episodic memory from presupplementation to postsupplementation. Accordingly, the simple slope of loneliness within the placebo group represented the prospective relationship between loneliness and changes in verbal episodic memory over time. Significant loneliness by supplementation group interactions were decomposed using two sets of contrasts. The first set examined the effect of loneliness within each supplementation group, whereas the second tested the supplementation effect for participants who were lonelier (+1 SD) versus less lonely (−1 SD). The same data analytic strategy was used for each of the other cognitive function measures.

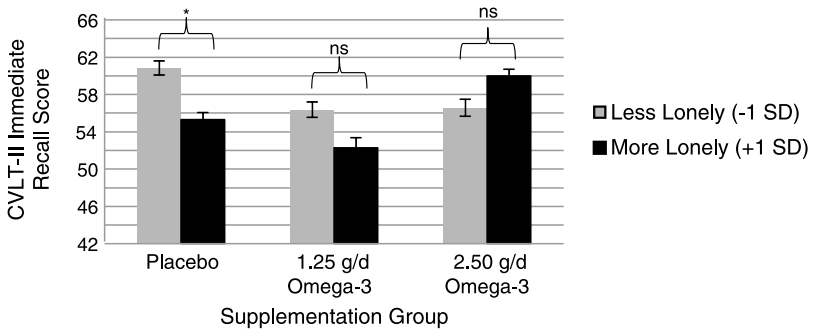

Figure 1. Loneliness by supplementation group predicting immediate free recall. Note. Higher CVLT numbers represent more words recalled, and thus better verbal episodic memory. The values depicted are the estimated marginal means at average levels of baseline immediate free recall, marital status, BMI, and activity levels. The error bars refer to the standard error of the mean. *$p \leq .05$. CVLT = California Verbal Learning Test; BMI = body mass index; ns = nonsignificant.

We conducted two sets of ancillary analyses. First, we tested whether the supplementation effects held when controlling for additional demographic, health, and psychosocial characteristics. Next, we replaced the supplementation group in our models with participants' changes in plasma levels of the omega-6:omega-3 ratio. We used this strategy because our main hypothesis argued that the effects of supplementation would differ for people who were more versus less lonely. Accordingly, one extension of this hypothesis is that the change in the omega-6:omega-3 ratio would differentially affect lonelier versus less lonely people. Furthermore, adherence to the supplementation regimen and metabolism of omega-3 can differ across people (40). The plasma analyses thus allowed us to clarify the intervention's impact by assessing actual intake/absorption of the omega-3 supplement. Accordingly, we examined whether the change in omega-6:omega-3 ratio by loneliness interaction was associated with cognitive function. We computed a change score by subtracting presupplementation from postsupplementation ratio levels. Accordingly, more negative change numbers signified a healthier change over time. Significant interactions were decomposed using two sets of contrasts. The first examined the effect of loneliness for people who had larger (+1 SD) versus smaller (−1 SD) changes in their omega-6:omega-3 ratio. The second tested the effect of the change in the omega-6:omega-3 ratio for people who were more (+1 SD) or less (−1 SD) lonely.

RESULTS

Preliminary Analyses

Sample characteristics are listed in Table 1 and Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A157. First, we tested a series of models that were completely unadjusted, except for baseline cognitive function scores (see Table S2, Supplemental Digital Content, http://links.lww.com/PSYMED/A157). There was a marginally significant loneliness by group interaction associated with immediate and long-delay free recall (F (2,121) = 2.69 [p = .072] and F (2,120) = 2.74 [p = .068]). Of the pool of potential covariates, marital status, BMI, and activity levels differed across groups at baseline (p values < .10; see Table 1 and Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A157). Because these baseline differences suggest a failure of randomization, we included these variables and baseline cognitive function scores as covariates in the primary analyses.

The remaining covariates (that did not differ across groups at baseline) were then added to the ancillary analyses. Specifically, in addition to the control variables used in the primary analyses, we added age, years of education, sex, race, social integration, current depressive symptoms, sleep quality, typical number of alcoholic drinks per week, and medication use (41–45).

Primary Analyses

First, we conducted an analysis predicting verbal episodic memory, as measured by the CVLT, controlling for marital status, BMI, activity levels, and baseline CVLT scores. Although not the focus of this investigation, the links between supplementation group and cognitive function scores are reported in Table S3, Supplemental Digital Content, http://links.lww.com/PSYMED/A157. Loneliness and baseline immediate free recall were unrelated (F (1,125) = 1.76, p = .19). However, there was a significant loneliness by supplementation group interaction associated with postsupplementation immediate free recall (F (2,117) = 5.05, p = .008, R^2 = 0.04). We decomposed the interaction by first testing the effect of loneliness on immediate free recall within each supplementation group (see Fig. 1). Lonelier participants within the placebo condition had worse immediate free recall

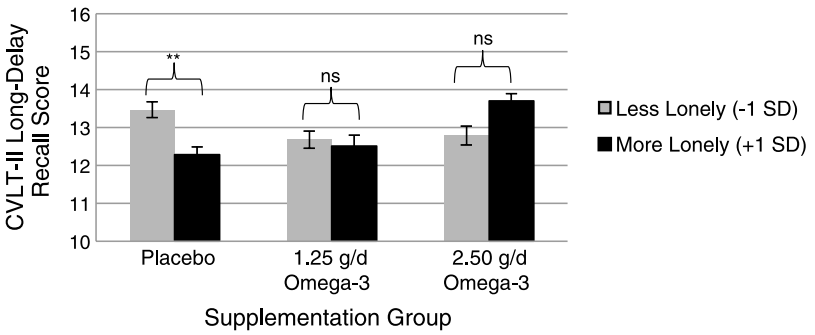

Figure 2. Loneliness by supplementation group predicting long-delay free recall. Note. Higher CVLT numbers represent more words recalled, and thus better verbal episodic memory. The values depicted are the estimated marginal means at average levels of baseline long-delay free recall scores, marital status, BMI, and activity levels. The error bars refer to the standard error of the mean. ** $p \leq .01$. CVLT = California Verbal Learning Test; BMI = body mass index; ns = nonsignificant.

than their less lonely counterparts, independent of their baseline values ($b = -0.28$, $t\,(117) = -2.62$, $p = .010$). This simple slope demonstrated that loneliness was prospectively related to immediate free recall among nonsupplemented participants. Importantly, the loneliness effect was not observed among people taking the 1.25- and 2.50-grams/d omega-3 supplements ($b = -0.20$ [$t\,(117) = -1.52$, $p = .13$] and $b = 0.17$ [$t\,(117) = 1.64$, $p = .10$], respectively.

Next, we tested the effect of supplementation for people who were more (+1 SD) or less (−1 SD) lonely (see Table S4, Supplemental Digital Content, http://links.lww.com/PSYMED/A157). There were no differences in immediate free recall for lonelier people taking the placebo versus the 1.25-grams/d omega-3 supplement ($t\,(117) = -1.17$, $p = .25$). However, lonelier participants had better immediate free recall when they were taking the 2.50-grams/d omega-3 supplement compared with the placebo ($t\,(117) = 2.33$, $p = .022$). Furthermore, lonelier participants had better immediate free recall when they were taking the 2.50-grams/d versus the 1.25-grams/d omega-3 supplement ($t\,(117) = 3.14$, $p = .002$). Contrary to expectations, less lonely participants had worse immediate free recall when they were taking the 1.25- and 2.50-grams/d omega-3 supplements compared with the placebo, although the latter effect was marginal ($t\,(117) = -2.06$ [$p = .041$] and $t\,(117) = -1.88$ [$p = .063$], respectively). There were no differences in immediate free recall for less lonely people taking the 1.25- and 2.50-grams/d omega-3 supplements ($t\,(117) = 0.09$, $p = .93$).

Loneliness and baseline short-delay free recall were unrelated ($F\,(1,125) = 1.66$, $p = .20$). In addition, the loneliness by supplementation group interaction and the simple slope of loneliness within the placebo group predicting short-delay free recall were nonsignificant ($F\,(2,117) = 0.90$ [$p = .41$, $R^2 = 0.01$] and $t\,(117) = -0.39$ [$p = .69$], respectively).

Loneliness and baseline long-delay free recall were unrelated ($F\,(1,124) = 1.24$, $p = .27$). However, there was a significant loneliness by supplementation group interaction associated with long-delay free recall ($F\,(2,116) = 3.38$, $p = .038$, $R^2 = 0.03$). First, we tested the effect of loneliness on long-delay free recall within each supplementation group (see Fig. 2). Lonelier participants within the placebo condition had worse long-delay free recall than their counterparts who felt more socially connected ($b = -0.06$, $t\,(116) = -2.07$, $p = .040$). This simple slope demonstrated that loneliness was prospectively related to long-delay free recall among nonsupplemented participants. Importantly, the loneliness effect was not observed among people taking the 1.25- and 2.5-grams/d omega-3 supplements ($b = -0.01$ [$t\,(116) = -0.23$, $p = .82$] and $b = 0.05$ [$t\,(116) = 1.58$, $p = .12$], respectively).

Next, we tested the effect of supplementation for people who were more (+1 SD) or less (−1 SD) lonely (see Table S4, Supplemental Digital Content, http://links.lww.com/PSYMED/A157). There were no differences in long-delay free recall for lonelier people taking the placebo versus the 1.25-grams/d omega-3 supplement ($t\,(116) = 0.33$, $p = .74$). However, lonelier participants had better long-delay free recall when they were taking the 2.50-grams/d omega-3 supplement compared with the placebo ($t\,(116) = 2.59$, $p = .011$). Furthermore, lonelier participants had marginally better long-delay free recall when they were taking the 2.50-grams/d versus the 1.25-grams/d omega-3 supplement ($t\,(116) = 1.77$, $p = .079$). There were no differences between the supplementation groups for less lonely participants (all p values > .18; see Table S5, Supplemental Digital Content, http://links.lww.com/PSYMED/A157, for presupplementation to postsupplementation change scores for both immediate and long-delay free recall).

We also explored whether loneliness and the loneliness by group interaction were associated with performance on the working memory, executive function, and verbal fluency/processing speed tasks, controlling for marital status, BMI, activity levels, and baseline cognitive function scores. Loneliness and baseline working memory and executive function were unrelated (all p values > .39). Loneliness was related to baseline verbal fluency/processing speed ($b = 0.21$, $F\,(1,126) = 4.10$, $p = .045$). However, none of the loneliness by supplementation group interactions were significant (see Table S2, in Supplemental Digital Content, http://links.lww.com/PSYMED/A157), and the contrasts testing the effect of loneliness within the placebo condition (assessing residual changes in cognitive function for nonsupplemented participants) were also nonsignificant (all p values > .32). Accordingly, loneliness was concurrently and prospectively unrelated to working memory, executive function, or verbal fluency/processing speed, and the omega-3 supplement did not affect the relationship between loneliness and these cognitive domains. The one exception was a significant relationship between loneliness and baseline verbal fluency/processing speed, albeit in an unexpected direction.

Ancillary Analyses

Additional Potential Confounds

Ancillary analyses tested whether the loneliness by supplementation group interaction predicting both immediate and long-delay free recall remained when we added age, years of education, sex, race, social integration, current depressive symptoms, sleep quality, typical number of alcoholic drinks per week, and medication use to the primary models. Nonsteroidal anti-inflammatory drugs were the most common type of medication used in this sample ($n = 24$). The interactions between loneliness and supplementation group remained significant after adjusting for the above variables.

Plasma Omega-6:Omega-3 Ratio

We examined whether loneliness and the change in omega-6:omega-3 ratio were associated with cognitive function. Similar to the primary analyses, we controlled for baseline cognitive scores, marital status, activity levels, and BMI. We also controlled for baseline omega-6:omega-3 ratios to account for the influence of baseline ratio levels on subsequent changes.

The interaction between changes in the omega-6:omega-3 ratio and loneliness was significantly associated with immediate free recall ($F\,(1,118) = 4.44$, $p = .037$). First, we tested the effect of loneliness for people who had less (−1 SD) versus more (+1 SD) healthy improvements in their omega-6:omega-3 ratio. Among people who had smaller improvements in their

omega-6:omega-3 ratio, lonelier people had worse immediate free recall than did less lonely people ($b = -0.24$, t (118) = -2.31 $p = .023$). This effect was not observed for people who had larger improvements in their omega-6:omega-3 ratio; loneliness and immediate free recall were unrelated among people with larger omega-6:omega-3 improvements ($b = -0.04$, t (118) = -0.50 $p = .62$). Next, we tested the effect of the omega-6:omega-3 ratio change for people who were more (+1 SD) or less lonely (-1 SD). Among lonelier participants, healthier improvements in the omega-6:omega-3 ratio were related to marginally better immediate free recall ($b = -0.46$, t (118) = -1.67, $p = .097$). For people who were less lonely, changes in the omega-6:omega-3 ratio were unrelated to immediate free recall ($b = 0.33$, t (118) = 1.13, $p = .26$).

The loneliness by plasma omega-6:omega-3 interaction predicting short-delay free recall was nonsignificant (F (1,118) = 0.79, $p = .38$). However, the interaction between changes in the omega-6:omega-3 ratio and loneliness was marginally associated with long-delay free recall (F (1,117) = 3.11, $p = .080$). Among people who had smaller improvements in their omega-6:omega-3 ratio, loneliness and long-delay free recall were negatively associated, although this contrast was nonsignificant ($b = -0.04$, t (117) = -1.43 $p = .16$). Loneliness and long-delay free recall were unrelated among people with larger omega-6:omega-3 improvements ($b = 0.02$, t (117) = 1.04 $p = .30$). Among lonelier participants, improvements in the omega-6:omega-3 ratio were related to marginally better long-delay free recall ($b = -0.13$, t (117) = -1.68, $p = .096$). For people who were less lonely, changes in the omega-6:omega-3 ratio were unrelated to long-delay free recall ($b = 0.05$, t (117) = 0.69, $p = .49$).

Similar to the primary analyses, the loneliness by change in omega-6:omega-3 ratio interactions associated with working memory, executive function, and verbal fluency/processing speed were nonsignificant (all p values > .12).

DISCUSSION

The current study examined whether omega-3 supplementation attenuated loneliness-related cognitive difficulties. Omega-3 supplementation had specific effects on verbal episodic memory among lonelier people, as measured by immediate and long-delay free recall. Specifically, loneliness was unrelated to immediate or long-delay free recall at baseline. However, loneliness was prospectively related to both types of recall over the course of the trial; lonelier people who were taking the placebo had worse immediate and long-delay free recall postsupplementation than their less lonely counterparts. This effect was not observed among people taking the lower- and higher-dose supplements; lonelier and less lonely adults had similar free recall scores when they were taking the 1.25- and 2.50-grams/d omega-3 supplements. In addition, lonelier participants taking the higher-dose supplement (2.50 grams/d) had better immediate and long-delay free recall than lonelier participants who were taking either the placebo or lower-dose (1.25 grams/d) supplement. Relative to placebo, the lower-dose supplement did not affect immediate or long-delay free recall for lonelier people. Interestingly, among less lonely people, those taking the lower- or higher-dose omega-3 supplement had worse immediate recall than those taking the placebo. However, this effect was not replicated with long-delay free recall; supplementation had no effect on long-delay free recall for less lonely participants.

The supplementation group effects were also consistent with the plasma omega-6:omega-3 analyses. Among lonelier participants, improvements in the plasma omega-6:omega-3 ratio were related to marginally better immediate and long-delay free recall. However, for people who were less lonely, changes in the omega-6:omega-3 ratio were unrelated to immediate and long-delay free recall. Adherence to the supplementation regimen and metabolism of omega-3 can differ across people (40). Accordingly, the plasma analyses bolster the supplementation effects by providing an objective index of intake/absorption of the omega-3 supplement. Taken together, the results of the current study demonstrated that a higher dose of omega-3 supplementation and corresponding improvements in the omega-6:omega-3 ratio affect immediate and long-delay free recall, two indices of verbal episodic memory, among lonelier people.

The current study suggests that loneliness and omega-3 supplementation have specific effects on certain types of cognitive function and not others. Corroborating the limited extant loneliness literature, the current study demonstrated loneliness-related supplementation effects on both immediate and long-delay free recall, two types of verbal episodic memory. However, there were no effects for working memory, executive function, or verbal fluency/processing speed. Even within the domain of verbal episodic memory, omega-3 supplementation had different effects on distinct types of recall; omega-3 supplementation attenuated loneliness-related difficulties with immediate and long-delay free recall, but not short-delay free recall. The CVLT short-delay recall task introduces retroactive interference; participants are asked to recall words from the original list after the presentation of a second list. Accordingly, this task is more challenging than the other two conditions; the immediate free recall data were collected soon after presentation of the first list, and the long-delay free recall data were collected after a significant delay, thus allowing any retroactive interference to dissipate. Taken together, these data suggest that the prophylaxis offered by omega-3 supplementation might be load modulated, with omega-3 supplementation helpful for slightly easier conditions of episodic memory load, but not within a more challenging condition. However, it is important to note that this is the first study examining the cognitive benefits of omega-3 supplementation for lonely people; additional research is imperative to replicate these findings using more nuanced designs of episodic memory performance and a parsimonious battery of neuropsychological assessment.

Prior research has demonstrated that lonelier people have larger verbal episodic memory declines over time than less lonely people (4). The present findings extend previous work in an important new direction by demonstrating that omega-3 supplementation altered loneliness-related verbal episodic memory changes over time. However, previous loneliness research focused on changes in cognitive function over a longer period (e.g., 4 years), whereas the current study was conducted for 4 months.

Interestingly, the residual change scores in Table S5, Supplemental Digital Content, http://links.lww.com/PSYMED/A157, suggest that less lonely people in the placebo group had improved immediate and long-delay free recall over time, possibly reflecting the effect of repeated testing over a relatively short time frame (i.e., a practice effect). On the other hand, lonelier participants' recall did not improve and may have actually worsened over time. Omega-3 supplementation eliminated the observed differences between lonelier and less lonely participants. Accordingly, an unanswered question is whether omega-3 supplementation would attenuate age-related cognitive declines among lonely people over a longer period. In this context, it is noteworthy that a recent meta-analysis concluded that omega-3 supplementation improved immediate verbal memory among people experiencing mild cognitive difficulties (21), suggesting that supplementation has the potential to help lonely people who are experiencing more substantial cognitive decline over time.

Demographic characteristics, mental and physical health, and health behaviors may contribute to the link between loneliness and cognitive function. For instance, lonelier people have poorer sleep quality than less lonely people (44,46); poor sleep quality enhances risk for cognitive problems (43). In addition, lonelier people experience more concurrent depression and larger increases in depressive symptoms from 1 year to the next than their counterparts who feel more socially connected (47–49). Depression enhances risk for cognitive problems (42). The current study used stringent selection criteria that excluded people with major medical comorbidities. In addition, the primary and ancillary analyses demonstrated that the results were unchanged after accounting for BMI, activity levels, age, years of education, sex, race, current depressive symptoms, sleep quality, typical number of alcoholic drinks per week, and medication use. The present study also demonstrated that the effects of loneliness and omega-3 supplementation were unconnected to participants' level of social integration and marital status, which index the number of social relationships a person has rather than the perceived quality of those relationships. Taken together, the current data suggest that omega-3 supplementation reduces loneliness-related episodic memory problems independent of participants' number of social contacts, demographic characteristics, health, and health behaviors.

Additional research is needed to delineate the pathways linking loneliness and omega-3 supplementation to memory. There are a number of plausible mechanisms. For example, it is possible that supplementation was linked to better episodic memory among lonely people (compared with placebo) because it reduced feeling of loneliness, thereby improving cognitive function. However, loneliness is relatively stable over time, with test-retest reliabilities around 0.73 for both 2-month and 1-year intervals (24), and loneliness is difficult to change through interventions (50). The omega-3 and cognitive function literatures suggest two physiological possibilities that may partially explain the relationships evident in the current study: inflammation and neural function. Elevated inflammation is linked to cognitive problems (8), and omega-3 supplementation reduces inflammation (7). However, exploratory analyses reported in the Supplemental Digital Content, http://links.lww.com/PSYMED/A157, suggest that inflammation did not drive the current results. Omega-3 PUFAs are essential to neuronal health. For example, omega-3 PUFAs (particularly EPA and DHA) promote glucose uptake and the production of ketones in the brain, the brain's primary and secondary sources of energy, respectively (51). Omega-3 PUFAs also help prevent neuronal apoptosis and have been implicated in a number of other components of brain function (5,6). Consistent with this finding, people who consumed more omega-3 PUFAs had greater gray matter volume in the corticolimbic structures, including the right hippocampus, than did people who consumed less omega-3 PUFAs (52). Accordingly, omega-3 supplementation may be beneficial for lonelier people because of its effects on neural function and maintenance. Previous research has linked loneliness and verbal episodic memory problems (4); understanding the mechanisms driving lonely peoples' memory declines should also lend insight into the factors that may underlie the current study's supplementation effects. Exploration of potential mechanisms linking loneliness to memory problems and how omega-3 supplementation attenuates these effects provides one important direction for future research.

The current sample was primarily white and female and was relatively homogeneous in terms of overall health and health behaviors, one limitation of the current study. Accordingly, additional research should test the relationships among loneliness, omega-3 supplementation, and cognitive function in more diverse samples, particularly in terms of race and sex, before using any interventions in real-world settings. Marital status, one indicator of social isolation, differed across supplementation groups at baseline, another limitation. However, marital status was included as a covariate in the primary analyses, demonstrating that the loneliness effects were independent of marital status. Loneliness was measured 4 weeks into the RCT, one design limitation. However, supplementation groups did not differ significantly in their loneliness scores, demonstrating that the initial 4 weeks of supplementation did not affect loneliness. In addition, loneliness is relatively stable over time (24).

The omega-3 supplement was a higher dose than recommended by the American Heart Association, but was still below the amount the Food and Drug Administration "generally recognized as safe" (7). This is notable because the benefits of omega-3 supplementation among lonelier participants were only seen within the higher-dose condition. In the current study, the benefits of higher-dose supplementation on loneliness-related episodic memory difficulties were seen after a relatively short time (4 months). Further research should investigate whether lonely individuals benefit to a greater degree when supplemented for a longer period and with different doses of omega-3 PUFAs.

Clinical Implications

Primary care physicians, nurses, and mental health practitioners may encounter people experiencing memory problems on a regular basis. Previous research has demonstrated that loneliness is a risk factor for verbal episodic memory declines among adults and general cognitive impairment among the elderly (4).

Accordingly, medical staff could benefit from assessing loneliness among people who report cognitive difficulties. Furthermore, interventions that decrease loneliness should reduce memory problems. However, a recent review concluded that most loneliness interventions are ineffective and the most promising intervention is cognitive behavioral therapy (50), a time- and resource-intensive treatment. The current results suggest that omega-3 supplementation may attenuate loneliness-related episodic memory problems (perhaps without affecting the actual experience of loneliness) and thus offer insight into novel interventions, although additional research is needed before any interventions are used in a real-world setting.

CONCLUSIONS

In sum, prior research has demonstrated that lonelier people have worse verbal episodic memory over time than less lonely people. The current study demonstrated that omega-3 supplementation, particularly a higher-dose supplement (i.e., 2.50 grams/d), attenuated loneliness-related episodic memory problems. Specifically, lonelier participants taking the placebo had poorer verbal episodic memory than their less lonely counterparts, independent of their baseline episodic memory scores. This effect was not observed among participants taking an omega-3 supplement. Furthermore, lonelier participants taking the higher-dose supplement had better verbal episodic memory than lonelier participants taking the placebo. The effects of supplementation were specific to the verbal episodic memory domain. These data suggest novel new directions for loneliness and omega-3 research and support the exploration of omega-3 interventions for treating episodic memory problems among lonely people.

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