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Bidirectional longitudinal associations of omega-3 polyunsaturated fatty acid plasma levels with depressive disorders

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ABSTRACT

Background: Temporality of the association of low omega-3 polyunsaturated fatty acid (n-3 PUFA) plasma levels with depression remains questionable. To determine the underlying nature of these associations, this study examined the bidirectional longitudinal associations of n-3 PUFA plasma levels with (presence, onset and course of) depressive disorders and symptoms.

Methods: Baseline (n = 2912, 28.6% with current depressive disorder) and 6-year follow-up data (n = 1966, 13.0% with current depressive disorder) of the Netherlands Study of Depression and Anxiety (NESDA) were used. Depression diagnoses and symptoms were based on psychiatric interviews and self-report questionnaires. N-3 PUFA levels (ratio of total fatty acids (mmol%)), were assessed using nuclear magnetic resonance.

Results: Using two waves of data, n-3 PUFA levels were lower among depressed persons, as compared to healthy controls (Beta = −0.047, SE = 0.011, p < .001). Nevertheless, baseline n-3 PUFA levels were not consistently associated with subsequent change in depressive symptoms, onset or remission of depressive disorders over 6 years. Furthermore, the difference in n-3 PUFA levels detected at baseline between depressed and non-depressed participants tended to dissipate over 6 years (depression-by-time estimate: p = .011). Finally, subjects depressed both at baseline and at 6-year follow up had consistently lower n-3 PUFA levels over the entire follow-up as compared to those who had never been depressed. Change in depressive disorders across waves was not consistently accompanied by change in n-3 PUFA levels over time.

Limitations: No data on intermediate time points and EPA levels were available.

Conclusions: Despite significant cross-sectional associations between n-3 PUFA plasma levels and depressive disorders and severity, this 6-year longitudinal study could not confirm an uni- or bidirectional association over time. The association between depression and n-3 PUFA plasma levels is unlikely to be causal.

1. Introduction

Low n-3 PUFA plasma levels have been found in patients with a depressive disorder in several cross-sectional studies (Lin et al., 2010; Smith et al., 2011; Wani et al., 2015). N-3 PUFAs can be mainly found in fatty fish, some other seafood, and some nuts and seeds (James et al., 2000; Simopoulos, 1999). The main three types of n-3 PUFA are α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). ALA is seen as a dietary precursor as it can be converted into EPA and DHA by enzymes called elongases (adding an extra hydrocarbon group) and desaturases (adding an extra double bond). The cross-sectional studies however do not give us insight into the temporality or causality of the association, which is important because that could help us interpret findings of n-3 PUFA supplementation RCTs and help us designing future effective interventions for depression treatment.

There are several potential mechanisms for the link between n-3 PUFAs and depression. One potential mechanism is that higher n-3 PUFAs levels directly impact on depression, by e.g. reducing depressive symptoms, or reducing the risk of onset or course of depression. This may operate through the presence of n-3 PUFAs in the brain influencing the regulation of cognitive processes, mood and affect involved in depression by their influence on phospholipid membrane permeability, rigidity and fluidity of brain cells (Van Meer et al., 2008) and therefore

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indirectly on membrane-bound receptor functioning, ion channel transport, signal transduction, membrane potential, and receptor sensitivity (McNamara and Carlson, 2006; Su, 2009). Other possible underlying mechanisms explaining the PUFA-depression link might be the effect of PUFAs on dysregulation of biological stress systems, such as the immune-inflammatory system, the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, although these biological stress systems may also be a common underlying factor determining both PUFAs and depression (Chang et al., 2018; Thesing et al., 2018b).

These explanations are the rationale behind n-3 PUFA supplementation studies. Reviews of randomized controlled trials (RCTs) supplementing n-3 PUFAs to depressed patients show that some studies do find a small to modest beneficial effect on depressive symptoms (Grosso et al., 2014; Messamore et al., 2017; Mocking et al., 2018; Sarris et al., 2016), while others do not find this, or only found small effect sizes for e.g. EPA supplements (Appleton et al., 2015, 2010; 2008; Asher et al., 2017; Bloch and Hannestad, 2012; Deacon et al., 2017). Hence the clinical relevance of such an effect is questionable. Over the years, a high probability of publication bias in n-3 PUFA supplementation RCTs has been suggested by some (Appleton et al., 2015; Bloch and Hannestad, 2012), but questioned by others (Lin et al., 2012; Martins et al., 2012). Also the relationship of n-3 PUFA biomarkers pre- and post-treatment with PUFA supplements and treatment response has shown to be inconsistent over several studies (van der Burg et al., 2019). One systematic review of four observational longitudinal studies found inconclusive evidence for n-3 PUFA intake affecting onset of depressive disorders or depressive symptoms (Sanhueza et al., 2013), while three subsequent reviews from other authors do support the hypothesis that n-3 PUFA intake and a higher quality of diet (higher fish intake) are associated with lower risk of depression (Grosso et al., 2016; Molendijk et al., 2018; Yang et al., 2018). When blood levels instead of intake were examined, no relationship between n-3 PUFA blood levels and subsequent depression symptoms or risk was evident (Astorg et al., 2009; Persons et al., 2014). In an observational study, Berger et al. (2017) found the first prospective evidence that a higher blood level of n-6 compared to n-3 PUFA is associated with an increased incidence of a mood disorder, although in a small and highly specific sample with individuals at ultra-high risk for psychosis (N = 69) (Berger et al., 2017). To date, no observational study has investigated whether n-3 PUFA levels or intake predict chronicity in depressed persons. This is important as the role of n-3 PUFA in the development of depressive disorders may be different from the role of n-3 PUFA in the progression or chronicity of depressive disorders.

The other temporal mechanism explaining the association between depression and n-3 PUFAs, is depressive disorders impacting on (change in) n-3 PUFA blood levels over time. Theories suggest that having a current depressive disorder may result in a different fatty acid metabolism, for example via the biological stress systems described above, or via an unhealthy lifestyle (e.g. a poor dietary pattern) more common in depressed patients, that adversely affect n-3 PUFA levels (Mocking et al., 2018; Thesing et al., 2018b). This association has not previously been studied in a longitudinal setting.

In sum, no longitudinal observational study to date thoroughly investigated the bidirectional relationship of the association of n-3 PUFA blood levels with depression. The current study examines the bidirectional longitudinal association between n-3 PUFA levels and depression. Firstly, this study examines whether n-3 PUFA and DHA levels at baseline are predictive of changes in depression (i.e. change in depression severity, onset and remission) over 6 years. Secondly, this study examines whether baseline depression (e.g. symptoms and disorder) is predictive of subsequent 6-year changes in n-3 PUFA and DHA levels. Finally, because the results of the analyses performed to examine the abovementioned aims may be affected by an association between change in depression with change in n-3 PUFA levels, our third aim was to examine whether change in depression over 6-years parallels change in n-3 PUFA and DHA levels over 6-years.

2. Methods

2.1. Study sample

Between 2004 and 2007, 2981 participants aged between 18 and 65 years were recruited from the Dutch general population (19%), primary health care (54%) and specialized mental health care (27%) to participate in the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal observational cohort study (Penninx et al., 2008). The research protocol was approved by ethics committees of participating universities. All respondents provided written informed consent. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Exclusion criteria were a poor comprehension of the Dutch language and having a primary clinically overt diagnosis of another (e.g. psychotic, obsessive–compulsive, bipolar or severe addiction) disorder. Participants attended in-depth (psychiatric) interviews and measurements at baseline (n = 2981) and after 2, 4, and 6 years (n = 2256). At baseline and at 6-year follow-up, participants provided blood samples in which n-3 PUFAs were assessed (n = 2912, and n = 2005 respectively, with 1966 participants having blood measurements at both time points). A total of 2083 participants constituted the largest sample size, which consisted of those with baseline and 6-year follow-up data on depression severity and baseline blood sampling, as they could contribute to change in depression severity analyses (aim 1).

2.2. Measurements

2.2.1. N-3 PUFA assessment

EDTA plasma samples were collected at baseline and after 6 years, after an overnight fast, and stored at −85 °C for later assessment. Further information on n-3 PUFA assessment can be found in the supplemental method (supplement 1).

2.2.2. Diagnosis, severity and symptoms of depressive disorder

At all assessments, diagnoses of depressive disorder (major depressive disorder or dysthymia) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were ascertained using the Composite International Diagnostic Interview (CIDI, versions 2.1) (Wittchen, 1994), administered by trained research staff, to derive a diagnosis of depressive disorder at baseline, 2-, 4- and 6-year follow-up (in the preceding month) and since the last interview (since baseline, 2- or 4-year follow-up). At every assessment, the severity of depressive symptoms was assessed using the 30-item self-report Inventory of Depressive Symptomatology questionnaire (IDS-SR_{30}, range 0–84), higher scores indicating higher severity (Rush et al., 1996). The IDS-SR_{30} had a good internal consistency at baseline and 6-year follow-up (Cronbach's alpha's: 0.94 and 0.98). The Life Chart Interview (LCI), a calendar method used to determine life events to refresh memory, was assessed at all time points and assessed during which months two core depressive symptoms (sad/depressive feelings or loss of interest) were present (Lyketsos et al., 1994).

2.3. Covariates

Covariates were selected based on previous literature and were assessed at baseline and 6-year follow-up. Sociodemographic covariates comprise age, gender, and education (years). Blood sampling covariates were fasting status at time of blood withdrawal (yes/no), blood sample collection area (Amsterdam, Leiden, or Groningen), and metabolic shipment wave at baseline (1 or 2). Lifestyle variables included were smoking (never/current/former), alcohol (number of glasses per week), and physical activity. Physical activity was measured using the total Metabolic Equivalent of Task (MET) score derived from the International Physical Activity Questionnaire (IPAQ, minutes/week) (Craig et al., 2003). Somatic health variables were body mass index

(BMI, weight(kg)/length(m)^2), diabetes (yes/no), heart disease (yes/no), number of other chronic somatic disorders, use of lipid-modifying drugs (i.e. statins, yes/no), and use of n-3 PUFA supplements (yes/no). Medication and supplement use were derived from drug container inspection (Würtz et al., 2016). As antidepressant use was found to be only weakly related to lower n-3 PUFA levels in earlier analyses (Thesing et al., 2018c) it was chosen not to adjust our analyses for antidepressant use.

2.4. Statistical analysis

Sample characteristics of the total sample at baseline and 6-year follow-up were calculated. N-3 PUFA and DHA levels were $\log_e$ transformed to normalize their positively skewed distributions. Linear and Cox regression analyses were conducted using IBM SPSS statistics software, version 25 (IBM Corp., Armonk, NY, USA). The R packages "geepack" and "emmeans" were used to run Generalized Estimating Equations (GEE) analyses and to obtain estimated means of n-3 PUFA and DHA levels to make a visual representation of the results (R Foundation for Statistical Computing, Vienna, Austria, 2016. URL https://www.R-project.org/). The significance level was set at 0.05. Table S1 contains an overview of our aims and used sample sizes.

2.4.1. Baseline n-3 PUFA levels and subsequent depression

For our first aim, three analyses were performed for relating baseline n-3 PUFA levels to subsequent change in depressive symptoms, onset of new depressive episode and remission of depression. First, linear regression analyses were used to examine the associations between baseline n-3 PUFA and DHA levels and change in depressive symptom severity (IDS score) from baseline till 6-year follow-up in the full sample with longitudinal data (aim 1.1, n = 2083). These analyses were adjusted for baseline depression severity, as required in models estimating change scores.

Second, Cox regression analyses were used to examine the association between baseline n-3 PUFA and DHA levels and time to onset of a new depressive episode in participants without a current depressive disorder at baseline (aim 1.2, n = 1922). Onset of new depressive episode was based on the CIDI and LCI. If a participant fulfilled the criteria of a depressive disorder diagnosis during any of the follow-up periods, the LCI data was used to define the time to first depressive episode during any of the follow-up periods with at least minimal burden. Minimal burden was defined as a score of 2 or higher on a 4 point rating scale ranging from "no trouble at all" (0) to "very much troubled" (4). A new depressive episode could mean a first episode (in healthy controls) or a recurrent episode (in remitted patients). Participants who did not develop a new episode were censored at the six-year measurement (when the participant had data on all time points) or at the last available follow-up measurement (when a participant dropped out of the study).

Third, Cox regression analyses were used to examine the association between baseline n-3 PUFA and DHA levels and time to remission of depressive disorder in participants with a current depressive disorder at baseline (aim 1.3, N = 722). Using LCI data, remission was defined as a 3-month period without depressive symptoms or no depression burden. Participants who did not reach remission were censored at the six-year measurement (when the participants had data on all time points) or at the last available follow-up measurement (when a participant dropped out of the study). For both analyses, the assumption of proportional hazards was met. All analyses were adjusted for all baseline covariates, and analyses for change in depression severity were additionally adjusted for baseline depression severity.

2.4.2. Baseline depressive disorder and subsequent change in PUFA levels

For our second aim, GEE analyses were performed to examine whether current depressive disorder at baseline (versus those without a current depressed disorder at baseline) was predictive of change in n-3 PUFA and DHA levels over time (aim 2.1, n = 1966). Time (0 (baseline) and 1 (6-year follow-up)) and a time-by-baseline depression interaction term were added to the model. The latter indicated whether baseline depressive disorder was significantly associated with *change* in n-3 PUFA or DHA levels over time. These analyses were repeated with depression severity at baseline as the independent variable (aim 2.1, n = 1950). Analyses were adjusted for all covariates at baseline and at 6-year follow-up.

2.4.3. Change in depressive disorder and change in PUFA levels

For our third aim, four course groups were created based on depressive disorder status in the past month at baseline and in the past month at 6-year follow-up: 1) stable non-depressed group (no current depressive disorder at baseline or 6-year follow-up, n = 1349), 2) recovered from depression group (current depressive disorder only at baseline, n = 361), 3) new onset of depression group (current depressive disorder only at 6-year follow-up, 104), and 4) stable depressed group (current depressive disorder at both baseline and 6-year follow-up, n = 152). GEE analyses (aim 3, n = 1966) were used to examine the association of the four groups with n-3 PUFA and DHA levels over time. Time (0/1) and group-by-time interaction terms were added to the model. Baseline and 6-year follow-up n-3 PUFA levels of all groups were compared with those of the stable non-depressed group. Bar charts were made for visual representation of the results.

3. Results

3.1. Sample characteristics

The included 2912 participants at baseline had a mean age of 41.9 years (SD = 13.0, range 18–65) and 66.4% was female (Table 1). Mean n-3 PUFA and DHA levels were 3.4 (Standard deviation (SD) = 0.9) and 1.2 (SD = 0.4) mmol% at baseline, and 3.6 (SD = 0.8) and 0.9 (SD = 0.3) mmol% at 6-year follow-up. Drop-outs after 6-years (n = 725) did not differ on average in sex and age from included participants, but had a lower education and more often a depressive disorder at baseline (data available on request).

3.2. Baseline n-3 PUFA levels and subsequent depression

In the largest sample, including both depressed and non-depressed participants at baseline (n = 2083), linear regression analyses with and without adjustment for covariates, showed that n-3 PUFA or DHA levels at baseline were not associated with change in severity of depression over 6 years (Table 2, fully adjusted model: Beta = 0.140, standard error (SE) = 0.222, p = .53; Beta = 0.179, SE = 0.216, p = .41).

In non-depressed participants at baseline (n = 1922), Cox regression analyses without adjustment for covariates showed that a higher baseline n-3 PUFA level was significantly associated with a lower risk on the onset a new depressive episode (Table 2, hazard ratio (HR) = 0.90, 95% Confidence Interval(CI) = 0.83-0.97, p = .010). However, after adjustment for covariates, neither higher baseline n-3 PUFA level (HR = 0.95, 95%CI = 0.87–1.05, p = .31) nor higher baseline DHA level (HR = 0.99, 95%CI = 0.91–1.08, p = .79) were significantly associated with a lower risk on the onset of a new depressive episode. The covariate most contributory to the loss in significance was age, as older age has shown to be a predictor of chronicity (Schaakxs et al., 2018): adjusting the model for age reduced the effect size of the association between n-3 PUFA levels and risk of developing a new depressive episode by 23.9%, which was no longer statistically significant (p = .31)."

In depressed patients at baseline (N = 722), Cox regression analyses with or without adjustment for covariates showed no significant association between n-3 PUFA or DHA levels at baseline and time to remission of depressive disorder (Table 2, with adjustment for covariates: for n-3 PUFA: HR = 0.99, 95%CI = 0.91–1.08, p = .81; for DHA:

Table 1
Characteristics of the study sample at baseline and 6-year follow-up.

	Baseline (N = 2912)	6-year follow-up (N = 1966)
Socio-demographics		
Age (years), mean (SD)	41.9 (13.0)	48.3 (13.0)
Female, %	66.4	65.8
Education (years), mean (SD)	12.2 (3.3)	12.9 (3.3)
Sampling variables		
Fasting status		
Yes, %	95.4	88.7
No or no answer, %	4.6	11.3
Blood sample collection area		
Amsterdam, %	40.8	37.4
Leiden, %	30.5	31.5
Groningen, %	28.7	31.5
Metabolic shipment		
First, %	54.5	N.A.
Second, %	45.5	
Lifestyle and somatic health		
Smoking status		
Current, %	38.7	24.2
Former, %	33.6	41.0
Never, %	27.8	34.7
Number of glasses of alcohol per week, median (IQR)	3.7 (8.5)	7.4 (5.8)
Total MET-minutes per week, median (IQR)	3075 (3411)	3296 (3522)
BMI kg/m^2, median (IQR)	24.7 (6.0)	25.7 (5.9)
Number of chronic somatic diseases, median (IQR)	1.0 (1.0)	0.0 (1.0)
Diabetes mellitus, yes %	4.0	5.7
Heart disease, yes %	8.4	8.5
Use of statins, yes %	6.8	10.4
Use of omega-3 supplements, yes %	4.0	4.4
Polyunsaturated fatty acids		
DHA (mmol%), mean (SD)	1.2 (0.4)	0.9 (0.3)
n-3 PUFA (mmol%), mean (SD)	3.4 (0.9)	3.6 (0.8)
Clinical characteristics of depression		
Current depressive disorder, %	28.6	13.0
IDS-SR$_{30}$ total score, mean (SD)	21.4 (14.1)	15.1 (11.9)
Antidepressant use		
No, %	75.2	80.1
TCA, %	2.7	3.0
SSRI, %	16.9	11.7
Other antidepressants, %	5.3	5.2
Onset of new depressive episode between baseline and 6-year follow-up, yes (%)[1]		33.1
Remission from depressive disorder between baseline and 6-year follow-up, yes (%)[2]		80.2
Depressive disorder groups (at baseline and 6-year follow-up, 1 month recency)		
No current depression at both time points group, %		68.6
Current depression only at baseline, %		18.4
Current depression only at 6-year follow-up, %		5.3
Current depression at both time points, %		7.7

Note. SD: Standard deviation. IQR: Interquartile Range. MET: Metabolic Equivalent of Task. BMI: Body Mass Index. N-3: omega-3. IDS-SR$_{30}$: Inventory of Depressive Symptomatology – Self report 30 items. TCA: Tricyclic Antidepressant. SSRI: Selective Serotonin Reuptake Inhibitor. N.A.: Not Applicable. MDD: Major Depressive Disorder. [1] Of a subsample of 1922 participants without baseline depression. [2] Of a subsample of 722 participants with baseline depression.

HR = 1.04, 95%CI = 0.95–1.13, p = .42).

3.3. Baseline depressive disorder and subsequent change in PUFA levels

Adjusted GEE models (n = 1966) including the main effects of baseline depressive disorder and time showed that overall n-3 PUFA levels increased (main effect time: Beta = 0.038, SE = 0.006, p < .001) and DHA levels decreased (main effect time: Beta = −0.277, SE = 0.009, p < .001) over time. The main effects for depressive disorders at baseline indicated that participants with depressive disorders at baseline had significantly lower overall (baseline and 6-year follow-up) n-3 PUFA and DHA levels (main effects depression: Beta = −0.047, SE = 0.011, p < .001; Beta = −0.062, SE = 0.016, p < .001, respectively) as compared to participants without depressive disorders. When extending the model with a depressive disorder-by-time interaction term, interaction terms were positive and significant for both n-3 PUFA and DHA (depression-by-time: Beta = 0.031, SE = 0.012, p = .011; Beta = 0.035, SE = 0.018, p = .049) indicating that differences in PUFA levels between depressed and non-depressed subjects attenuated over time. Unadjusted analyses gave overall comparable results.

In adjusted GEE models (n = 1950) with baseline depression *severity*, time and a severity-by-time interaction, the interaction terms were non-significant for both n-3 PUFA and DHA (severity-by-time: Beta = 0.009, SE = 0.006, p = .13; Beta = 0.007, SE = 0.008, p = .36), indicating no difference in change in n-3 PUFA and DHA levels over time in those with higher depression severity. The main effects indicated that higher depression severity was associated with consistently lower n-3 PUFA and DHA (severity main effects: Beta = −0.018, SE = 0.005, p < .001; Beta = −0.024, SE = 0.007, p < .001) levels over time (Table 3). Unadjusted analyses gave overall comparable results.

3.4. Change in depressive disorder and change in PUFA levels

GEE analyses (main effects only model, see Table S3) including only the main effects for change in depression and for time, showed that the main effects for the two groups starting with depression at baseline, namely the recovered group (n-3 PUFA: Beta = −0.047, SE = 0.012, p < .001; DHA: Beta = −0.059, SE = 0.017, p < .001) and the stable depressed group (Beta = −0.047, SE = 0.018, p = .008; Beta = −0.061, SE = 0.026, p = .017) were significant. This means that on average across the 6 years of follow-up, n-3 PUFA and DHA levels were significantly lower in the recovered group and the stable depressed group, as compared to the stable non-depressed group (see Fig. 1 panel A and B).

When adding group-by-time interaction terms to this model, as compared to the stable non-depressed group, a steeper increase in n-3 PUFA and a less steep decline in DHA levels was found for the recovered (group-by-time interaction term for n-3 PUFA: Beta = 0.048, SE = 0.014, p < .001; DHA: Beta = 0.048, SE = 0.020, p = .017) and the new onset group (group-by-time interaction term for n-3 PUFA: Beta = 0.063, SE = 0.025, p = .011; DHA: Beta = 0.095, SE = 0.036, p = .008).

As a result, at 6-year follow-up, as compared to the stable non-depressed group, the stable depressed group still had significantly lower n-3 PUFA levels (main effect group: Beta = −0.043, SE = 0.021, p = .041), and the new onset of depression group had significantly *higher* DHA levels (main effect group: Beta = .077, SE = 0.033, p = .022, Fig. 1 panel A and B).

Unadjusted analyses gave overall comparable results. Of the new onset group, only a small percentage (3.4% at baseline and 7.8% at 6-year follow-up) used n-3 PUFA supplements, which makes this not a plausible explanation for the higher levels.

4. Discussion

This study confirmed significant cross-sectional associations between n-3 PUFA plasma levels and the presence and severity of depressive disorders across two waves. Nevertheless, the present large-scale longitudinal cohort study found no consistent evidence for an uni- or bidirectional longitudinal association of n-3 PUFA and DHA levels with depression. First, baseline n-3 PUFA levels did not consistently

Table 2
The association between baseline N-3 PUFA and DHA levels (mmol%) and change in depression severity over time, time to onset of new depressive episode and time to remission of depressive disorder, using either linear regression analyses or Cox regression analyses.

	Total sample (n = 2083)			Participants without current depression at baseline (n = 1922)			Patients with current depressive disorder at baseline (n = 722)		
	Change in severity of depression[2]			Time to onset of new depressive episode[3]			Time to remission of depressive disorder[3]		
	Beta	SE	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Baseline n-3 PUFA (mmol%)[1]									
Crude analyses	.329	.200	.101	0.89	0.83–0.97	.010	0.98	0.91–1.06	.53
Adjusted analyses	.140	.222	.53	0.95	0.87–1.05	.31	0.99	0.91–1.08	.81
Baseline DHA (mmol%)[1]									
Crude analyses	.327	.200	.103	0.96	0.89–1.04	.34	1.02	0.94–1.10	.70
Adjusted analyses	.179	.216	.41	0.99	0.91–1.08	.79	1.04	0.95–1.13	.42

Note. Change in severity of depression was assed using the 30-item self-report Inventory of Depressive Symptomatology questionnaire. Time to onset of new depressive episode and time to remission of depressive disorder were assessed using the Composite International Diagnostic Interview and the Life Chart Interview. Adjusted analyses are adjusted for baseline age, gender, education, fasting status, blood sample collection area, metabolic shipment, smoking, alcohol, physical activity, body mass index, heart disease, diabetes mellitus, number of other chronic somatic disorders, use of statins and use of omega-3 supplements. [1] n-3 PUFA and DHA levels are $\log_n$ transformed and standardized. [2] Linear regression analyses, additionally adjusted for baseline depression severity. [3] Cox regression analyses. SE: Standard Error. HR: Hazard Ratio. 95%CI: 95% confidence interval of HR. n-3 PUFA: omega-3 polyunsaturated fatty acids. DHA: docosahexaenoic acid.

Table 3
The association of baseline current depressive disorder (yes/no) and baseline depression severity with n-3 PUFA and DHA levels (mmol%) over time using GEE analyses (N = 1966 and 1950, respectively).

	N = 1966					
	n-3 PUFA (mmol%)			DHA (mmol%)		
	Beta	SE	p-value	Beta	SE	p-value
Baseline current depressive disorder[1]	-.047	.011	< .001	-.062	.016	< .001
Time	.038	.006	< .001	-.277	.009	< .001
Baseline current depressive disorder*Time	.031	.012	.011	.035	.018	.049
	N = 1950					
Baseline depression severity ($IDS\text{-}SR_{30}$ score)[2]	-.018	.005	< .001	-.024	.007	< .001
Time	.038	.006	< .001	-.277	.009	< .001
Baseline depression severity*Time	.009	.006	.13	.007	.008	.36

Note. SE: Standard Error of Beta. Generalized estimating equations analyses are adjusted for baseline age, gender, education, fasting status, blood sample collection area, metabolic shipment, smoking, alcohol, physical activity, body mass index, heart disease, diabetes mellitus, number of other chronic somatic disorders, use of statins and use of omega-3 supplements. [1]Reference group: no baseline current depressive disorder. [2] Baseline depression severity scores are standardized. $IDS\text{-}SR_{30}$: 30-item self-report Inventory of Depressive Symptomatology questionnaire.

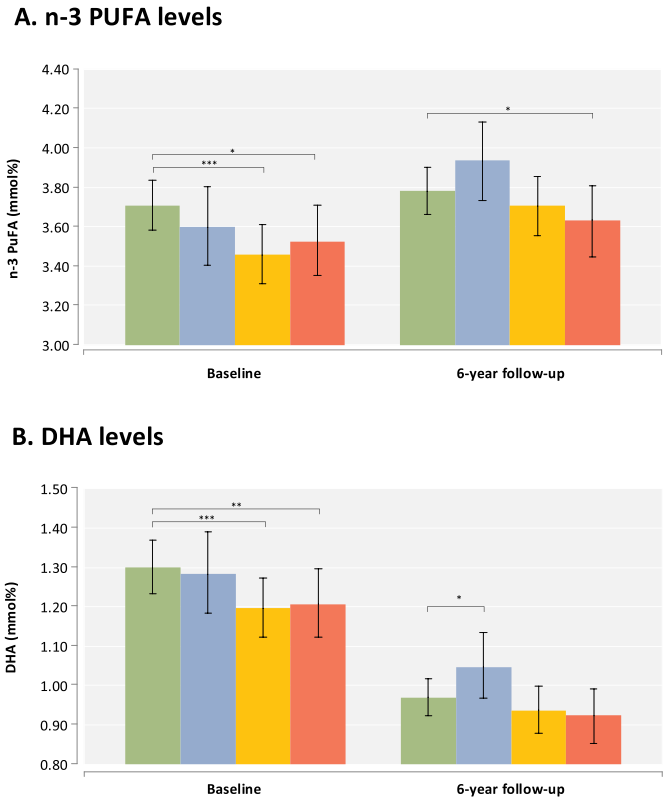

Fig. 1. The fully adjusted association of having a current depressive disorder at baseline and/or 6-year follow-up (1 month recency) with A) n-3 PUFA and B) DHA levels (mmol%) at baseline and at 6-year follow-up (n = 1966).
Note. Error bars indicate standard errors. Significance level of comparisons between the stable non-depressed group and the other groups are: * < 0.05, ** < 0.01 or *** < 001.

predict change in depression over time. Second, although baseline depressive disorder and severity were associated with low averaged n-3 PUFA and DHA levels across the 6 years of follow-up, higher depression severity was not associated with a decline in n-3 PUFA and DHA levels over time. Third, only remission of depression was associated with increasing n-3 PUFA levels over time, but not with increasing DHA levels. In addition, contrary to our expectations, increased n-3 PUFA levels were also seen for those who developed depression over time.

Our first aim was to examine whether n-3 PUFA and DHA levels at baseline were predictive of changes in depression over six years, for which we found no evidence. This is in line with a systematic review that also found inconclusive evidence for low n-3 PUFA intake (instead of plasma levels) as a predictor for the onset of depressive disorders (Sanhueza et al., 2013), but not with three more recent reviews (Grosso et al., 2016; Molendijk et al., 2018; Yang et al., 2018). An explanation for this inconsistency may be that these last three reviews included studies on intake of n-3 PUFA instead of plasma n-3 PUFA levels, which are both influenced by different factors (Shahidi and Ambigaipalan, 2018). Some previous meta-analyses of n-3 PUFA supplementation RCTs for the treatment of depression find positive results (Grosso et al., 2016, 2014; Messamore et al., 2017; Mocking et al., 2018; Sarris et al., 2016), while others do not (Appleton et al., 2015, 2010; Asher et al., 2017; Bloch and Hannestad, 2012; Deacon et al., 2017). More recently, in the MooDFOOD study n-3 PUFA supplementation did not prevent onset of depressive episodes during 1 year (Bot et al., 2019). Reasons might be the lack of significant associations between n-3 PUFA levels

and subsequent depression outcomes or a treatment effect restricted to EPA (showing relevant anti-inflammatory properties) or only as augmentation therapy (Mocking et al., 2018). Also the patient population and study characteristics may be different in our study compared to RCTs.

Our second aim was to examine whether depressive disorder at baseline was predictive of subsequent 6-year changes in n-3 PUFA and DHA levels. Although depressive disorder and severity were consistently associated with low n-3 PUFA and DHA levels over time (e.g. significant main effects), we did not find that those with (highest) depression were showing more decline in n-3 PUFA and DHA levels over time. Instead, we found that the baseline difference in n-3 PUFA and DHA levels between the current depressed patients and the non-depressed patients attenuated over time. No previous studies have examined this direction of the association. One explanation may be that over 6 years regression to the mean in PUFA levels has taken place. Alternatively, depression and PUFA alterations may have occurred at the same time, but the strength of such an association may have dissipated over time, meaning that this process takes some time to set back. As third variables, dysregulations in biological stress systems, an unhealthy food intake (e.g. food low in n-3 PUFAs), unhealthy lifestyle (including smoking), socio-economic status, medication/drug use or a disease status may promote alterations in PUFA levels and influence the depression development. Additionally, Appleton et al. (2007) have shown that the association between n-3 PUFA levels and depressive symptoms disappears when adjusted for a social deprivation score. However no further studies have attempted to replicate this finding and in NESDA data to compute a deprivation score was not available. Having a depression, in turn, may also be of influence on the dietary intake of PUFAs, thereby influencing n-3 PUFA blood levels over time (Mocking et al., 2018; Thesing et al., 2018c). No other studies have examined these hypotheses.

Finally, our third aim was to examine whether change in depression over 6-year parallels change in PUFA levels over 6-year. Subjects depressed both at baseline and at 6-year follow up had consistently lower n-3 PUFA levels over the entire follow-up as compared to those never depressed. Developing a depressive disorder was not associated with decreasing n-3 PUFA and DHA levels over time. Recovering from a depression was not consistently associated with increasing n-3 PUFA and DHA levels over time. Overall, change in n-3 PUFA and DHA levels over time was not consistently linked to change in depression over time, e.g. disease state. No previous studies have examined this. As analyses were adjusted for n-3 PUFA supplement use, this could not be an explanation. Of note, the recovered from depression group in this article is based on baseline and follow-up data and not only on baseline data as in our earlier publication (Thesing et al., 2018c).

The presence of a consistent cross-sectional association, together with the lack of time-lagged longitudinal relationship, may potentially suggest the presence of a third stable factor influencing both PUFA levels and the risk of depression. For instance, genetic variants have been shown to impact on PUFA levels and depression-related phenotypes (Milaneschi et al., 2019; Su et al., 2010). Interestingly, genetic variants linked to nutrient circulating levels could be leveraged in Mendelian Randomization (MR) analyses to infer the potential causal impact of the nutrient on the risk of psychiatric disorder (Carnegie et al., 2019). Using this design, a recent MR study (Milaneschi et al., 2019) showed that n-3 PUFA is unlikely to have a causal role in the development of MDD. These results are in line with the phenotypic association pattern emerging in from the present study.

Some strengths and limitations can be noted. A strength is the large sample including healthy controls, remitted and current depressed patients. Plasma rather than erythrocyte n-3 PUFA levels were used, while erythrocyte n-3 PUFA levels – mostly as part of phospholipids – are more likely to reflect longer-term dietary intake and may therefore over time be more strongly associated with depression than plasma levels. Additionally, as PUFA levels were measured in blood, they are likely to be influenced by factors such as dietary intake, next to absorption, clearance through oxidation, biosynthesis of eicosanoids and leukotrienes, and usage of PUFAs as building block in cell membranes and other structures (Shahidi and Ambigaipalan, 2018). Temporal stability of the PUFA measures was conform expectations as there were 6 years between the two measurements and as PUFA levels are highly influenced by fish intake, which is not considered to be stable over the years within countries and persons. Both PUFAs and depressive disorder status and characteristics were assessed multiple times (at baseline, 2-, 4- and 6-year follow up), which is data lacking in previous studies (Berger et al., 2017), although an association may be missed by not examining intermediate time points. Dietary intake and EPA were not measured, while especially EPA might be effective in depression treatment (Mocking et al., 2016). Remission and onset of depressive disorders were largely based on retrospective reports. However, the LCI uses a calendar method to determine life events during the follow-up periods to refresh memory, which minimizes recall bias. Drop-out of participants could have led to attrition bias, however drop-out participants only had a lower education and more often a depressive disorder at baseline, compared to included participants. We could have adjusted the analyses for antidepressant use, but as antidepressant use was found to be only weakly related to lower n-3 PUFA levels in earlier analyses (Thesing et al., 2018c) it was chosen not to.

5. Conclusions

We found a general pattern of low n-3 PUFA and DHA levels in those with (highest) depression. Nevertheless, we found no consistent evidence for an uni- or bidirectional longitudinal relationship, suggesting that this association is not a causal one. We did not find a clear indication that depression impacts on deterioration in PUFA levels nor did we find that baseline low PUFA levels impact on subsequent increase in depression. We did not find evidence for a direct causal relationship. There may be underlying third factors that could explain the previous cross-sectional associations found and the lack of positive results of some n-3 PUFA supplementation RCTs. More longitudinal observational and well-designed experimental studies are needed to replicate our hypothesis and findings and to examine possible underlying third factors or other options for depression treatment, in example n-3 PUFA supplementation in specific depression subtypes.

Author statement

Contributors

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Declaration of competing interest

None of the authors have any conflicts of interest.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.02.011.

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Update

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Corrigendum to "Bidirectional longitudinal associations of omega-3 polyunsaturated fatty acid plasma levels with depressive disorders" [J. Psychiatr. Res. 124 2020, 1–8]

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The authors regret that Fig. 1 is missing a legend. The authors now provide a figure including the legend. The authors would like to apologise for any inconvenience caused.

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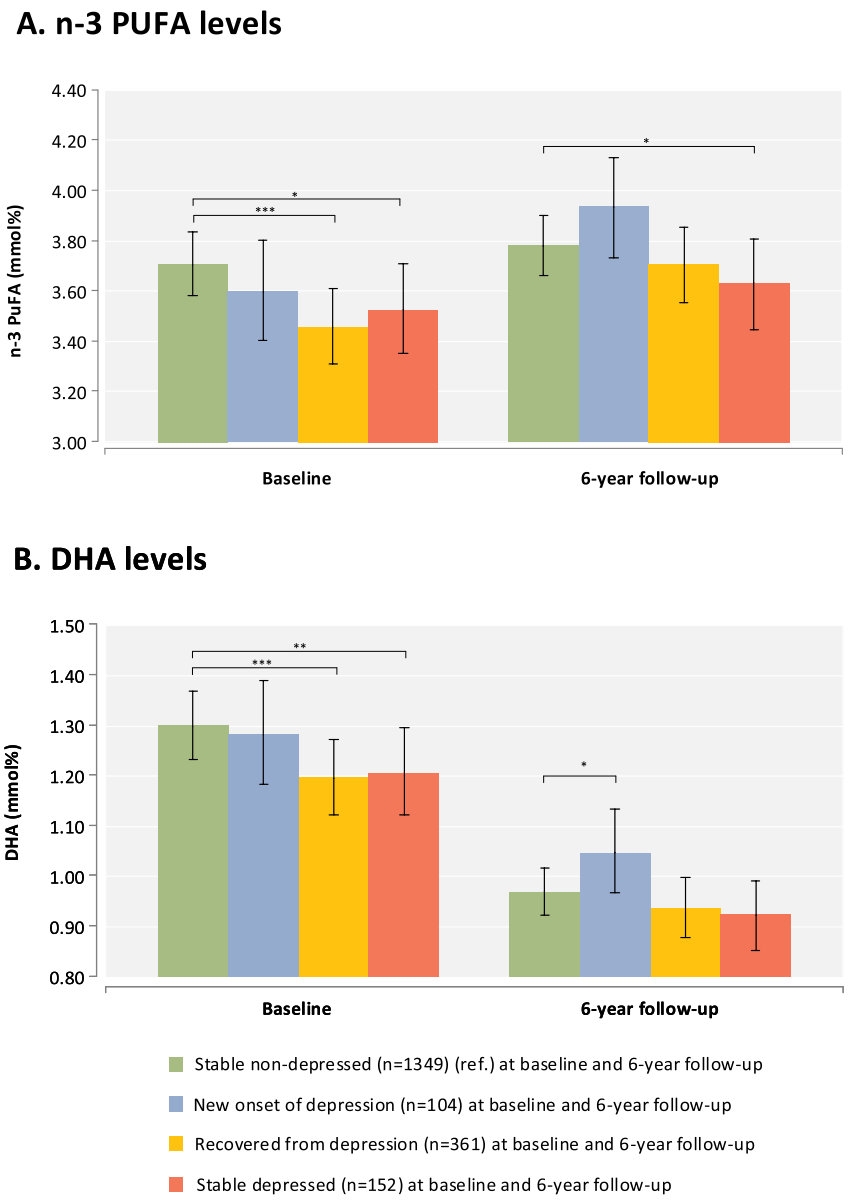
A. n-3 PUFA levels
n-3 PuFA (mmol%)
4.40
4.20
4.00
3.80
3.60
3.40
3.20
3.00
*
***
*
Baseline
6-year follow-up
B. DHA levels
DHA (mmol%)
1.50
1.40
1.30
1.20
1.10
1.00
0.90
0.80
**
***
*
Baseline
6-year follow-up
Stable non-depressed (n=1349) (ref.) at baseline and 6-year follow-up
New onset of depression (n=104) at baseline and 6-year follow-up
Recovered from depression (n=361) at baseline and 6-year follow-up
Stable depressed (n=152) at baseline and 6-year follow-up