



The association of omega-3 fatty acid levels with personality and cognitive reactivity

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ABSTRACT

Objective: Low omega (n)-3 polyunsaturated fatty acid (PUFA) levels have been found in patients with various major psychiatric disorders. This study aims to identify whether psychological vulnerabilities (personality and cognitive reactivity) underlying these psychiatric conditions are also associated with n-3 PUFA blood levels.

Methods: Data was used from 2912 subjects (mean age 41.9 years, 66.4% female) from the Netherlands Study of Depression and Anxiety (NESDA). Five personality dimensions (NEO Five Factor Inventory) and cognitive reactivity measures (Leiden Index of Depression Sensitivity-Revised and Anxiety Sensitivity Index) were assessed. Plasma n-3 PUFA and docosahexaenoic acid (DHA) levels (as ratios against total fatty acids; mmol%) were assessed using a nuclear magnetic resonance platform.

Results: Low n-3 PUFA and DHA levels were associated with high neuroticism (Standardized beta (Beta) = -0.045, 95% Confidence Interval (CI) = -0.079 to -0.010, $p = 0.011$; Beta = -0.058, 95%CI = -0.093 to -0.022, $p = 0.001$), low extraversion (Beta = 0.065, 95%CI = 0.031 to 0.099, $p < 0.001$; Beta = 0.074, 95%CI = 0.039 to 0.109, $p < 0.001$) and low conscientiousness (Beta = 0.060, 95%CI = 0.027 to 0.093, $p < 0.001$; Beta = 0.074, 95%CI = 0.039 to 0.108, $p < 0.001$). Low n-3 PUFA and DHA levels were related to high hopelessness/suicidality (Beta = -0.059, 95%CI = -0.096 to -0.023, $p = 0.001$; Beta = -0.078, 95%CI = -0.116 to -0.041, $p < 0.001$), but not with other cognitive reactivity measures. Directions of associations were generally consistent in subjects with and without a current depressive disorder.

Conclusion: Low n-3 PUFA and DHA levels are associated with personality (high neuroticism, low extraversion and low conscientiousness) and cognitive reactivity (high hopelessness/suicidality). Effect sizes were rather small, but in line with previous research on personality and chronic diseases. Future research should examine which lifestyle and/or biological pathways underlie these associations.

1. Introduction

Low omega-3 polyunsaturated fatty acid (n-3 PUFA) levels, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) blood levels (constituents of n-3 PUFA), have been associated with several major psychiatric disorders, for example mood disorders (unipolar and bipolar disorders), schizophrenia, attention deficit hyperactivity disorder (ADHD), impulse control disorders (including aggression), and a higher suicide risk [1–7]. Many psychiatric disorders have a heterogeneous etiology and are overlapping in symptoms [8–11]. Therefore, some research has shifted toward examining whether PUFA blood levels might be associated with more general dimensional constructs or endophenotypic traits underlying these disorders [12–15], further referred to as psychological vulnerabilities.

One of these psychological vulnerabilities may be personality traits,

with its widely used dimensions of neuroticism, extraversion, openness, agreeableness and conscientiousness [8,16,17]. In particular high neuroticism, but also low extraversion and to a lesser extent low openness, agreeableness and conscientiousness have been associated with increased risk of psychiatric disorders such as depressive and anxiety disorders and substance abuse [18–20]. Interestingly, low levels of n-3 PUFAs have also shown to be significantly associated with high neuroticism [12,13] and low extraversion [14], low openness [14] low agreeableness [12,14,15], and low conscientiousness [15], although one study found no significant associations [21]. However, the studies that do find significant associations had small sample sizes (ranging from 27 till 279) and some included only mentally healthy participants or a specific patient group (e.g. patients with bipolar disorder or paedophiles) [14,15].

Cognitive reactivity is another psychological vulnerability that

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might be associated with PUFA blood levels. Cognitive reactivity has been described as the more specific, cognitive manifestation of personality traits [22–25] and is the ease at which negative thinking patterns are reactivated through minor triggers [22,26]. It is usually divided into hopelessness/suicidality, acceptance/coping, aggression, control/perfectionism, risk aversion/harm avoidance, rumination and anxiety sensitivity [26]. Cognitive reactivity has been associated with the development, maintenance, and recurrence of depression [23–25,27–34]. Of these cognitive reactivity measures, only the associations between aggression and DHA and EPA have been studied, for which negative associations were found [35–37], for example in depressed patients [38].

Several mechanisms may be responsible for the association between n-3 PUFA and psychological vulnerabilities. N-3 PUFAs are known to have a positive effect on brain functioning: the anti-inflammatory property of N-3 PUFAs may mitigate an overactive immune system associated with mood disorders [39]. Furthermore, an increase in dietary DHA has been related to an increase in cortical serotonin and dopamine, which have been implicated in the etiology of several mental disorders [39,40]. Fatty acids may play a role in neural membrane fluidity and receptor binding [40–42] as, for instance, DHA can affect neurological function by modulating neurotransmission, neurogenesis, and myelination [43]. Therefore, they may indirectly impact on cognitive functioning, which is associated with personality [44]. Both low-grade inflammation, a neurotransmitter imbalance, and the resulting lower serotonin levels [38–43] have shown to be associated with cognitive reactivity [37,45–48]. However, n-3 PUFA levels could also be affected by personality and cognitive reactivity, as some personality traits and cognitive reactivity measures have been associated with dietary choices, including the frequency of fish intake, which is rich in n-3 PUFAs [49–56].

Taken together, there are only a few studies (of which most with a small sample size) that comprehensively investigated the relationship between n-3 PUFAs and one or more psychological vulnerabilities that may underlie several psychiatric disorders. The associations of n-3 PUFAs with some cognitive reactivity measures have not been studied at all. Most of the studies only included healthy individuals or patients with one specific psychiatric disorder and there has not been a study including all psychological vulnerabilities together in one study. Therefore, the aim of this large-scale cross-sectional study is to investigate the association all these psychological vulnerabilities with n-3 PUFAs and DHA in a large sample, including both currently healthy and currently psychiatrically ill participants. By including both currently healthy and psychiatrically ill individuals, a wide range of variation in psychological vulnerabilities was available.

2. Materials and 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 [57]. The research protocol was approved by ethics committees of participating universities. All respondents provided written informed consent. 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. For this study, baseline data was used as that is when n-3 PUFA levels were assessed. Participants provided blood samples (after instructions for overnight fast) and underwent a psychiatric interview. For this study, we excluded 69 participants (2.3%) due to missing blood samples, resulting in a sample size of 2912. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

2.2. PUFA assessment

As described before [7], the fatty acids measured are esterified fatty acids stemming from the lipoprotein particles, so these are not free fatty acids in the plasma but rather bound within cholesteryl esters, triglycerides and phospholipids inside lipoproteins particles. They were assessed in EDTA plasma samples which were stored at -80°C for later assessment. Blood samples were shipped in 2 batches (April and December 2014, further referred to as metabolic assessment wave 1 and 2, respectively). In 2015, among other metabolites, PUFA levels were quantified at 22°C using a commercially available high-throughput proton Nuclear Magnetic Resonance (NMR) metabolomics platform (Nightingale Health Ltd., Helsinki, Finland) [58]. Fatty acid metabolism is influenced by several factors, for example use of statins or estrogens [59–61]. Therefore, relative PUFA measures (as percentage of total fatty acids yielding mmol% values) have been found biologically more informative, because this reflects PUFA levels in relation to overall fatty acid levels and better accounts for the interrelationship between these two [62]. Spearman rho correlations (Table S1) show that absolute and relative measures are highly correlated. The present analyses focused primarily on relative measures. Additional results based on absolute values are presented in the supplemental materials.

2.3. Psychological vulnerabilities

Personality traits were determined by the NEO Five-Factor Inventory (NEO-FFI), a short form of the Revised NEO Personality Inventory (NEO-PI-R) [63]. The NEO-FFI is a self-report questionnaire consisting of 60 items with a five-point scale (0 through 4) assessing five personality domains (neuroticism, extraversion, openness, agreeableness, and conscientiousness) with a minimum score of 12 and a maximum total score of 60 per domain. Psychometric studies indicated good psychometric properties for the NEO-FFI, with high internal consistency, retest stability and cross-observer validity [64,65].

Cognitive reactivity was assessed by the Leiden Index of Depression Sensitivity-Revised (LEIDS-R) [26] and the Anxiety Sensitivity Index (ASI) [66]. The LEIDS-R is a self-report questionnaire consisting of 34 items with a five-point scale (0 through 4) assessing six subscales (hopelessness/suicidality, acceptance/coping, aggression, control/perfectionism, risk aversion/harm avoidance and rumination) with a minimum total score of 0 and a maximum score of 136 (with higher scores indicating a more pronounced cognitive reaction to sad mood). The LEIDS-R has been found to discriminate between never-depressed and recovered depressed patients [26,67]. Longitudinal studies support the reliability and validity of the LEIDS-R [68–71]. The ASI is a self-report questionnaire consisting of 16 items with a five-point scale (0 through 4) with higher scores indicating a more pronounced cognitive reaction to anxiety [66]. Studies have shown the ASI total score to be a reliable and valid instrument [66,72].

2.4. Covariates and effect modifiers

Sociodemographic covariates were 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 assessment wave (1/2). Lifestyle variables included were current smoking status (never/current/former), use of alcohol (number of glasses per week), and physical activity. Level of physical activity was measured using the total Metabolic Equivalent of Task (MET) score derived from the International Physical Activity Questionnaire (IPAQ) and expressed as MET-minutes per week [73]. Somatic health variables were Body Mass Index (BMI, continuous), diabetes (yes/no), heart disease (yes/no), number of other chronic somatic disorders (continuous), use of lipid-modifying drugs (i.e. statins, yes/no), and use of n-3 PUFA supplements (yes/no). Body Mass Index was calculated as the measured weight(kg)/

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