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Omega-3 and omega-6 fatty acid levels in depressive and anxiety disorders

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ABSTRACT

Background: Blood levels of polyunsaturated fatty acids (PUFAs) have been associated to current depression. However, it is unclear whether this association extends to remitted depression and to anxiety disorders. This study examined the relationship of PUFAs with the presence and clinical characteristics of depressive and anxiety disorders.

Methods: Cross-sectional data was used from the Netherlands Study of Depression and Anxiety, including persons with current pure depressive disorder (n = 304), current pure anxiety disorder (n = 548), current comorbid depressive and anxiety disorder (n = 529), remitted depressive/anxiety disorder(s) (n = 897), and healthy controls (n = 634). Clinical characteristics included severity, subtypes, age of onset, duration of depression and anxiety and antidepressant use. Absolute values of omega-3 (N-3) and omega-6 (N-6) PUFAs and relative measures (as ratio of total Fatty Acids: the N-3:FA and N-6:FA ratio) in plasma were assessed using a nuclear magnetic resonance platform.

Results: Compared to controls, current comorbid depressive and anxiety disorder patients had lower N-3 PUFA levels (Cohen's d = 0.09, p = 0.012), and lower N-3:FA ratios (p = 0.002, Cohen's d = 0.11) as did current pure depressive disorder patients (Cohen's d = 0.13, p = 0.021), whereas N-6 PUFA levels were not different. No differences in PUFA levels were found between remitted patients and controls. Within patients, lower N-3 PUFA levels were only associated with higher depression severity (Beta = −0.42, p = 0.023), whereas for N-6 PUFA levels and other clinical characteristics no clear association was observed. PUFA alterations were not associated with pure anxiety.

Conclusion: It can be concluded that patients with a current depressive episode (especially the more severe cases with comorbid anxiety) have circulating N-3 PUFA levels lower than those in remission and healthy controls. No relationship was detected for N-6 PUFA levels.

1. Introduction

The impact of polyunsaturated fatty acids (PUFAs) on health are well described. Omega-3 (N-3) PUFAs consist of e.g. α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and can be mainly found in fatty fish, some other seafood, and some nuts and seeds (James et al., 2000; Simopoulos, 1999). Some randomized controlled trials have shown that intake of N-3 PUFAs ameliorate or even prevent physical illnesses such as inflammatory (Giudetti and Cagnazzo, 2012; Simopoulos, 2002) and cardiovascular diseases (La Rovere and Christensen, 2015; Simopoulos, 1999), while others have not (Hoogeveen et al., 2014; Kromhout et al., 2010). Omega-6 (N-6) PUFAs consist of e.g. linoleic and arachidonic acid which are for example found in plant and vegetable seeds and oils, as found in margarines and many processed foods (James et al., 2000; Simopoulos, 1999). High N-6 PUFA intake has been associated with chronic inflammatory diseases, cardiovascular diseases, obesity, rheumatoid arthritis, and Alzheimer's disease (Patterson et al., 2012). Low levels of N-3 and high levels of N-6 PUFAs have also been associated with neuropsychiatric disorders like depression and anxiety (Hibbeln and Salem, 1995).

Several potential biochemical mechanisms could explain the association between PUFAs and depression (Smith et al., 2011). The anti-inflammatory property of N-3 PUFAs may mitigate the overactive immune system associated with depression (Young and Conquer, 2005). Furthermore, a decrease in dietary DHA was related to a decrease in cortical serotonin and dopamine (Young and Conquer, 2005), and these neurotransmitters have been implicated in the etiology of depression

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(Smith et al., 2011; Young and Conquer, 2005). Fatty acids are implicated as regulators of gene transcription within the central nervous system (Alessandri et al., 2004; Smith et al., 2011) and may play a role in neural membrane fluidity and receptor binding (Owen et al., 2008; Smith et al., 2011; Stahl et al., 2008). For instance, DHA can affect neurological function by modulating neurotransmission, neurogenesis, myelination and more (Weiser et al., 2016).

Reviews and meta-analyses of observational studies have shown significantly lower N-3 PUFA blood levels in depressed individuals as compared to non-depressed individuals (Lin et al., 2010; Smith et al., 2011; Wani et al., 2015). However, most meta-analyses and reviews had small sample sizes (ranging from 10 to 118 depressed patients in individual studies (Lin et al., 2010)) and depression assessments between studies were diverse, from self-report questionnaires and clinical interviews to antidepressant prescriptions (Smith et al., 2011). There have been some small-scaled observational studies that found that higher n-3 PUFA blood levels were associated with lower depression severity (Adams et al., 1996; Edwards, 1998; Liu et al., 2013), especially those taking antidepressants (Féart et al., 2008), while no association with duration of depression has been found (Peet et al., 1998). Less is known about the role of clinical characteristics such as age of onset and recency of symptoms as these have never been studied in observational studies. Examining the difference in N-3 PUFA levels between current and remitted patients may help to clarify whether the association with for example N-3 PUFA is “state”-dependent (only present during an active episode and reversible after remission), or whether N-3 PUFA alterations may represent a constant underlying “trait” of depression. Although the relationship between N-6 PUFAs and depression have received much less attention, some found higher levels related to higher severity of depressive symptoms (Smith et al., 2011).

Since comorbidity of anxiety in depressive disorders is high, an association between anxiety and PUFAs is expected (Ross, 2009), however, much less examined. A recent study showed that participants with depression and comorbid anxiety had even lower N-3 PUFAs levels than depressed patients without comorbid anxiety(Liu et al., 2013). Lower N-3 PUFA levels have been found in social phobia (Green et al., 2006), but studies on other anxiety disorders are lacking. Others detected a linear relationship between N-3 PUFA intake and anxiety, with lower DHA intake being associated with a higher likelihood of anxiety (Jacka et al., 2012). This may indicate the possibility of additional anxiogenic impact of N-3 PUFAs deficiency.

Although numerous intervention studies with large sample sizes show that N-3 PUFA supplementation may have beneficial effects on depression (Appleton et al., 2015; Bloch and Hannestad, 2012; Grosso et al., 2014), large heterogeneity has been found in effect sizes. Some meta-analytic evidence (Appleton et al., 2010; Bloch and Hannestad, 2012), suggests a potential role of clinical depression characteristics in the efficacy of N-3 PUFA supplementation. Studies including more severe patients tend to show higher efficacy. However, others that not found this have suggested a role of depression subtypes, although they did not further speculate on which subtypes (Grosso et al., 2014).

To address the abovementioned issues, our primary aim is to examine the cross-sectional association of our primary outcomes N-3 and N-6 PUFA levels (both in absolute values and their ratio’s with total fatty acids), and our secondary outcomes DHA (both absolute and its ratio) and the N-6:N-3 PUFA ratio with remitted or current depressive and anxiety disorders, allowing us to be one of the first to examine whether there is a “trait”- or “state”-dependency of PUFA alterations and whether this is present in both disorders. It is hypothesized that N-3 measures (e.g. N-3 PUFA, N-3:FA ratio, DHA and DHA:FA ratio) will be lowest and N-6 PUFA measures (e.g. N-6 PUFA and N-6:FA) and the N-6:N-3 PUFA ratio will be highest going from persons with current depressive/anxiety disorders, to those with remitted depressive/anxiety disorders to healthy controls. In addition, our second aim is to explore whether specific clinical characteristics that often influence treatment response (severity, subtype, age of onset, duration and antidepressant use) can further differentiate patients with the largest PUFA differences, both for understanding the underlying mechanisms that link PUFA levels and psychiatric conditions, as well as for targeting the most appropriate patient group for future supplementation studies. It is hypothesized that those characteristics that indicate a worse disease course (higher severity, earlier age of onset, longer duration, use of antidepressants) are associated with unfavorable PUFA levels (lower N-3 PUFA levels and N-3:FA ratios and higher N-6 PUFA levels and N-6:FA ratios)(Driscoll et al., 2005; Henkel et al., 2006; Katon et al., 2010). We believe that our study has incremental value as to our knowledge this is one of the largest observational studies to date linking the presence and clinical characteristics of depressive as well as anxiety disorders to blood levels of PUFAs.

2. Materials and methods

2.1. Study sample

Participants were selected from the Netherlands Study of Depression and Anxiety (NESDA), a longitudinal observational cohort study (Penninx et al., 2008). Between 2004 and 2007 in total 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%). 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 clinical diagnosis of psychotic disorder, obsessive–compulsive disorder, bipolar disorder or severe addiction disorder. At baseline, participants provided blood samples (after instructions for overnight fast) and underwent a psychiatric interview. In total 69 individuals (2.3%) had no complete blood measurements and were excluded. Presence of DSM-IV diagnoses of depressive disorders (major depressive disorder or dysthymia) and anxiety disorders (social phobia, generalized anxiety disorder, panic disorder and/or agoraphobia) was ascertained using the Composite International Diagnostic Interview (CIDI, version 2.1) administered by trained researchers. For this study, we studied five groups: patients with a current (within the past month) pure depressive disorder (n = 329), pure anxiety disorder (n = 548), comorbid depressive/anxiety disorder (n = 529), remitted (lifetime but not current) depressive and/or anxiety disorder (n = 897), and healthy controls (no lifetime disorders; n = 634).

2.2. PUFA assessment

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 the lipoproteins particles. The fatty acids were assessed in EDTA plasma samples which were collected and stored at −85 °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). 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) (Soininen et al., 2015). NMR is complementary to traditional techniques such as mass spectrometry (MS) and gas-chromatography. While NMR has a lower sensitivity, it became the gold-standard method for high-throughput metabolomics, allowing a reliable quantification of a large panel of low-molecular–weight metabolites and lipid molecules in large-scale studies (Soininen et al., 2015). In Nuclear Magnetic Resonance, the total concentration of N-3 PUFA is quantified based on a spectral signal that is arising from all fatty acids containing the N-3 double bond, and therefore N-3 PUFA is not calculated as a sum of known concentrations of individual N-3 PUFAs. The DHA signal is quantified separately from a