Fatty acids in depressive and anxiety disorders

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2020

document version
Publisher's PDF, also known as Version of record

The general discussion of this thesis will start with a summary of the findings of all chapters. This will be followed by a discussion of the main findings, in which the four research questions and their corresponding answers will be answered and discussed. An overview of the methodological considerations that need to be taken into account will be given. Clinical implications and recommendations for future research will then be discussed. At last, an overall conclusion on the subject of this thesis will be given.

Summary of the main findings

Below a brief summary of our findings per chapter is given (see also Figure 1). First, in **chapter 2** we studied associations between n-3 and n-6 PUFA plasma levels with depressive and anxiety disorders and various depression and anxiety characteristics using baseline data from 2912 participants of the NESDA study. We found that lower n-3 PUFA levels were only observed in patients with a current depressive disorder, especially in the more severe group with comorbid anxiety, when compared to persons without depression or anxiety. Furthermore, in currently depressed patients, lower n-3 PUFA levels were associated with higher depression severity, while no association with anxiety severity was found. No specific or clear pattern of association was detected for n-6 PUFA levels or for other clinical characteristics of depressive and anxiety disorders. PUFA alterations were not associated with pure anxiety disorders. Our findings indicate that alterations in n-3 PUFA levels, and not in n-6 PUFA levels, were specifically associated with depressive symptoms and disorders, and not with pure anxiety.

In **chapter 3** we studied associations of n-3 PUFA plasma levels (including DHA) with several psychological vulnerabilities (i.e. personality traits and cognitive reactivity measures) in 2912 participants of the NESDA study. We showed that lower n-3 PUFA and DHA levels were associated with high levels of neuroticism and hopelessness/suicidality, and with lower levels of extraversion and conscientiousness. The strengths of these associations were rather small, but in line with those reported in research on personality and chronic diseases. Associations were overall consistent in persons with versus without current depression, and also significantly present in persons without a current depression.

In **chapter 4**, we examined associations between n-3 PUFA plasma levels (including DHA) and dysregulations in three biological stress systems in 2724 participants of the NESDA study. We concluded that there is an exposure-response relationship between on the one hand having a higher number of markers indicative of inflammation and having a higher number of markers indicative of a hyperactive HPA-axis, and on the other hand low n-3 PUFA plasma levels. This means that n-3 PUFA were inversely related to the number of markers dysregulated in each stress system. For DHA, this was only found for inflammation, and not for the HPA-axis. For the ANS markers, significantly lower n-3 PUFA levels were only found in the group with the most dysregulated markers, when compared to the other groups with less dysregulated markers. Additionally, an exposure-response relationship was found of the number of dysregulated stress systems with n-3 PUFA plasma levels, but not with DHA plasma levels, meaning that a higher number of dysregulated stress systems was associated with lower n-3 PUFA plasma levels. Results for DHA were overall in line with those for n-3 PUFA, although with slightly smaller effect sizes. At last, it was found that psychopathology or antidepressant use were unlikely to have influenced associations of biological stress markers with n-3 PUFAs and DHA levels. All in all, lower n-3 PUFA and DHA plasma levels were associated with more dysregulation in biological stress systems.

In **chapter 5**, using baseline and follow-up data up until 6-years from 2083 participants of the NESDA study, we examined whether n-3 PUFA and DHA plasma levels predicted the trajectories of depression over time and, vice-versa, whether depression predicts change in n-3 PUFA and DHA plasma levels

over time. We found no consistent evidence for either direction. First, baseline n-3 PUFA levels did not consistently predict changes in depression over a period of six years, e.g. n-3 PUFA levels were not associated with changes in depressive symptoms over time, time until onset of a new depressive episode and time until remission of a depressive disorder. Second, although baseline depressive disorder and depression severity were associated with low mean levels of n-3 PUFA and DHA across the 6 years of follow-up, having a depressive disorder and a higher depression severity at baseline were not associated with a decline in n-3 PUFA and DHA levels over time. Instead, the association of depressive disorder with n-3 PUFA and DHA levels attenuated over time. Third, changes in depressive disorder status were not consistently associated with changes in n-3 PUFA levels over time. Only remission from 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. All in all, we did not find a clear indication that baseline low PUFA levels impact on subsequent increase in depression, nor did we find that depression subsequently impacts on deterioration in PUFA levels.

In **chapter 6** we examined whether fatty acid measures were predictive of time until MDD recurrence up to 8 years of follow-up in patients remitted from MDD, using data from 356 participants from the NESDA and 118 participants from the first DELTA cohort study and the DELTA-neuroimaging study. We found that time till MDD recurrence was not consistently associated with n-3 PUFA, EPA, DHA or n-6 PUFA blood levels, nor with the n-3:n-6 PUFA ratio, chain length index or unsaturation index. This means that recurrence of MDD after remission cannot be predicted by fatty acid measures.

In **chapter 7** we found that n-3 PUFA and EPA levels can be effectively increased by fish oil supplements, but that supplement induced changes in n-3 PUFA, EPA, DHA and n-6 PUFA levels over time were not associated with changes in depressive symptoms over time, and baseline PUFA levels were no effect modifiers in the effect of n-3 PUFA fish oil supplements or a food related behavioral activation therapy on depressive symptoms. This provides us with one possible explanation for the lack of prevention effect for depressive disorders found in the MooDFOOD depression prevention trial. It can be concluded that increasing n-3 PUFA, DHA and EPA levels using fish oil supplements is not a viable option to reduce depressive symptoms in persons who have sub-clinical depressive symptoms, to prevent the development of a clinical depressive disorder.

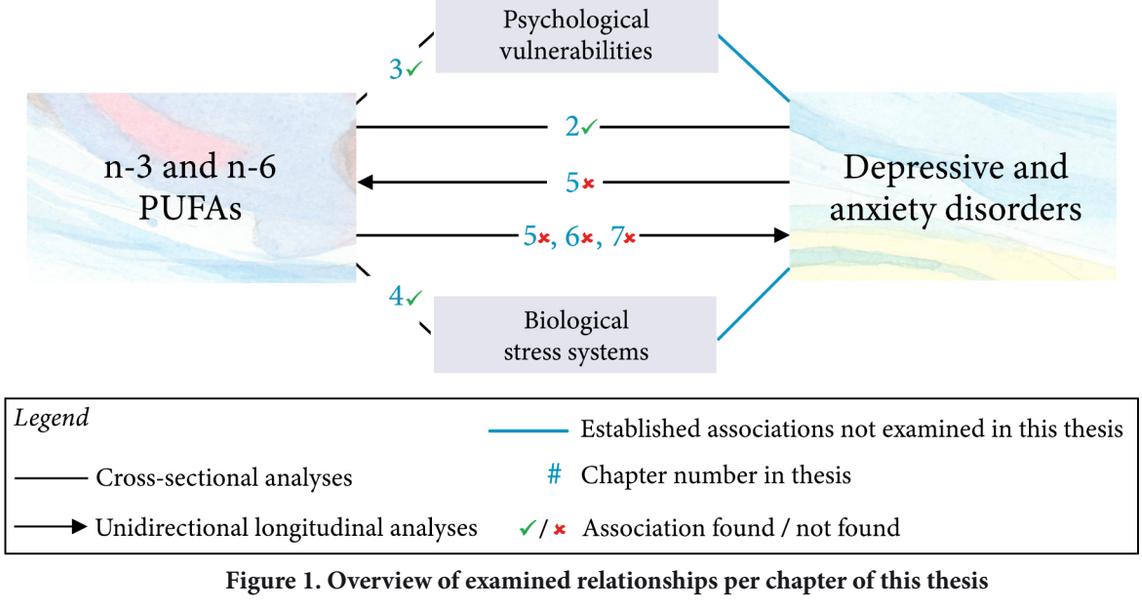

Figure 1. Overview of examined relationships per chapter of this thesis