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# Erythrocyte fatty acid profiles and plasma homocysteine, folate and vitamin B<sub>6</sub> and B<sub>12</sub> in recurrent depression: Implications for co-morbidity with cardiovascular disease

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## ABSTRACT

Oxidative stress induced interactions between fatty acid (FA) and one-carbon metabolism may be involved in co-occurrence of major depressive disorder (MDD) and cardiovascular disease (CVD), which have been scarcely studied together. In 137 recurrent MDD-patients vs. 73 age- and sex-matched healthy controls, we simultaneously measured key components of one-carbon metabolism in plasma (homocysteine, folate, vitamins B<sub>6</sub> and B<sub>12</sub>), and of FA-metabolism in red blood cell membranes [main polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA) and structural FA-indices (chain length, unsaturation, peroxidation)]. Results show significant positive associations of folate with EPA, DHA, and the peroxidation index, which were similar in patients and controls. After correction for confounders, these associations were lost except for EPA. Associations between B-vitamins and FA-parameters were non-significant, but also similar in patients and controls. Homocysteine and DHA were significantly less negatively associated in patients than in controls. In conclusion, these data indicate similarities but also differences in associations between parameters of one-carbon and FA-metabolism in recurrent MDD patients vs. controls, which may reflect differences in handling of oxidative stress. Further research should test the consequences of these differences, particularly the premature development of CVD in MDD.

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## 1. Introduction

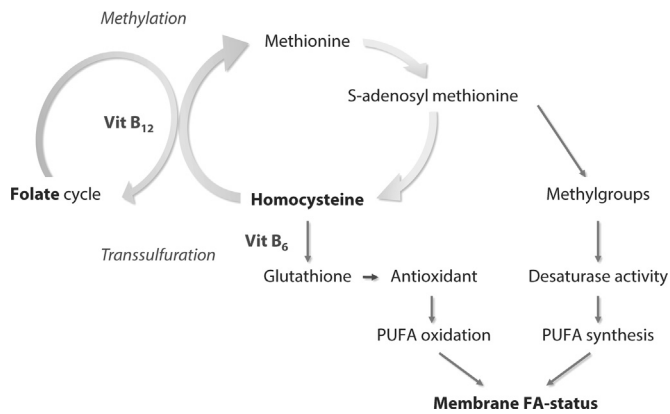
Persons with CVD have a 2.4 fold increased risk for MDD, while persons with MDD are at increased risk to develop CVD (McIntyre et al., 2009; Goldbacher et al., 2009; Kahl et al., 2012). Although the mechanisms that link both diseases are still unclear, there is increasing evidence for a fundamental role of oxidative stress (Ng et al., 2008; Roberts and Sind, 2009; Schiavone et al., 2012, Assies et al., 2014), which might be a common denominator of MDD and

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CVD through its influence on the shared biochemistry of fatty acid (FA) and one-carbon metabolisms. Thereby oxidative stress may modulate signaling and functioning of cell types particularly relevant to the pathogenesis of both CVD and MDD such as neurons, endothelial cells, immune cells and platelets (Severus et al., 2001; Assies et al., 2014).

Regarding FA-metabolism, FAs have important structural and functional (patho)physiological roles in both the nervous and cardiovascular system (Piomelli et al., 2007; McNamara, 2009). Structurally, FAs are key components of (neuronal and vascular) cell membranes (Piomelli et al., 2007). Unsaturation and chain length of membrane FAs determine membrane fluidity, which in turn influences functioning of membrane bound proteins, e.g. neurotransmitter receptors and cardiac ion channels. Moreover,



**Fig. 1.** Biological interplay between one-carbon and fatty acid metabolism. *Abbreviations:* Vit, vitamin; PUFA, polyunsaturated fatty acid. The one-carbon metabolism is closely linked to fatty acid metabolism in various ways. First, through the one-carbon-cycle, methyl groups from folate are delivered via S-adenosyl methionine to influence desaturase activity which is essential for PUFA synthesis. Second, using vitamin B<sub>6</sub>, homocysteine can be converted to glutathione, which is a major antioxidant and thereby can prevent PUFA oxidation.

oxidative stress susceptibility is determined by FA-peroxidizability, which has also been found to be lower in MDD-patients (Hulbert et al., 2007; Mocking et al., 2012a). Functionally, FAs [particularly polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA)] and their (non)enzymatic peroxidation products are increasingly shown to be fundamentally involved in regulation of oxidative stress, inflammation, and brain cytoarchitecture maintenance (Mocking et al., 2012a; Terlecky et al., 2012; Baek and Park, 2013; McNamara, 2013). Interestingly, MDD and CVD have each been consistently associated with corresponding alterations in FA-metabolism: both MDD and CVD patients have lower omega-3 (n-3) long chain PUFAs (especially EPA, C20:5n-3 and DHA, C22:6n-3) and (n-3):(n-6) PUFA ratios in plasma and erythrocytes (Assies et al., 2010; Lin et al., 2010; Mozzafarian and Wu, 2011; Assies et al., 2014).

Regarding the one-carbon metabolism (Fig. 1), homocysteine is a key intermediate and indicator of systemic oxidative stress levels (Stanger et al., 2009; Hofmann, 2011). In the *transmethylation pathway*, homocysteine is transformed to S-adenosylmethionine – a universal donor of methyl groups – with vitamin B<sub>12</sub> and folate as co-factors. Methylgroups are essential for epigenetic regulation of DNA-transcription (McGowan et al., 2008). In the *transsulfuration pathway*, homocysteine is condensed to the principle cellular antioxidant glutathione, with vitamin B<sub>6</sub> as co-factor (Forman et al., 2009) (Fig. 1). MDD and CVD are also associated with comparable oxidative stress related alterations in one-carbon metabolism, such as high homocysteine and low folate levels (Bjelland et al., 2003; Morris et al., 2003; Bottiglieri, 2005; Kim et al., 2008; Humphrey et al., 2008; Murakami et al., 2008; Stanger et al., 2009; Wang et al., 2012; Nabi et al., 2013; Lok et al., 2014) (Fig. 1).

Of note, one-carbon- and FA-metabolism interact (Fig. 1). Biochemically, methyl groups from one-carbon metabolism are used for various steps in FA-transport and -synthesis, e.g. desaturase and elongase activity regulation. Methylgroups are also used for the synthesis of phosphatidylcholine critical for the delivery of important PUFAs from the liver to the plasma and peripheral tissues (Devlin & Green, 2009). Vice versa, FAs may influence one-carbon metabolism by e.g. effects on oxidative stress and expression of genes involved in homocysteine synthesis (Berstad et al., 2007).

Human observational research reported an inverse association of DHA but not for EPA with homocysteine and a positive association with folate, in various non-psychiatric, healthy and metabolically diseased populations (Li et al., 2006, 2007; Huang et al.,

2012; Kume et al., 2013; Huang et al., 2013). Intervention studies showed that folate administration in rats increased n-3 PUFA (EPA, DHA) in plasma and tissue lipids, but AA was unaffected (Pita and Delgado, 2000).

In humans, lowering plasma homocysteine using folate, vitamin B<sub>12</sub>, and vitamin B<sub>6</sub> had no effect on plasma n-3 long-chain PUFA (Crowe et al., 2008), while short-term vitamin B<sub>6</sub> restriction decreased plasma n-3 and n-6 PUFA concentrations and tended to increase the plasma (n-3):(n-6) PUFA ratio (Zhao et al., 2012). The other way around, n-3 PUFA supplementation induced significant decreases in plasma homocysteine, this effect was dose dependent and non-linear (Piolot et al., 2003; Zeman et al., 2006; Pooya et al., 2010; Huang et al., 2011).

Severus et al. (2001) first proposed the importance of the link between one-carbon metabolism and FA-metabolism in psychiatric disorders, but to our knowledge, only three studies have investigated this relation. The first, an uncontrolled explorative study of our group in 44 patients with (recurrent) MDD, reported a decrease in n-3 PUFAs in erythrocyte membranes and a significant positive association between the sum of n-6 PUFAs and plasma homocysteine (Assies et al., 2004). The second, a study in never-medicated patients with schizophrenia, showed that erythrocyte membrane DHA reductions paralleled significant increases in plasma homocysteine (Kale et al., 2010). The third, an intervention study of our group, showed that add-on EPA-supplementation did not affect one-carbon metabolites in diabetes mellitus patients with comorbid MDD (Mocking et al., 2012b).

We now extended our earlier pilot study to 137 recurrent MDD-patients, and additionally included 73 matched non-depressed controls. Although we already reported alterations in FA-metabolism and one-carbon metabolism in these patients compared to controls (Assies et al., 2010; Lok et al., 2014) we did not examine possible differences in nature and strength of associations of the parameters of FA- and one-carbon metabolism between patients and controls.

We hypothesized that in recurrent MDD-patients (I) homocysteine would be negatively associated with EPA, DHA, FA-chain length, -unsaturation, and -peroxidizability, (II) folate, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> would be positively associated with EPA, DHA, FA-chain length, -unsaturation, and -peroxidizability. In addition, given the above proposed altered handling of oxidative stress, we expected these relations to be more outspoken in recurrent MDD-patients.

## 2. Methods and materials

### 2.1. Study subjects

#### 2.1.1. Enrollment and diagnosis

The present study was an add-on to a randomized controlled trial investigating the effect of cognitive therapy on recurrence in patients with recurrent MDD (Bockting et al., 2005; Lok et al., 2011). At two years follow-up of the trial, we invited participating patients for this add-on study. In addition, we recruited controls through media-advertisements, matched using strata based on gender and 5-year age groups. The medical ethical committee of the Academic Medical Center of the University of Amsterdam approved the study protocol and all participants provided written informed consent.

#### 2.1.2. Inclusion criteria

Both patients and controls had to be aged 18–65. For the patients, inclusion criteria of the initial trial were: at least 2 previous MDD-episodes in the last 5 years, according to the Structured Clinical Interview for DSM-IV disorders (SCID) (First et al., 1996);

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