Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2014: 130: 163–180

DOI: 10.1111/acps.12265

Review

Effects of oxidative stress on fatty acid- and one-carbon-metabolism in psychiatric and cardiovascular disease comorbidity

Assies J, Mocking RJT, Lok A, Ruhé HG, Pouwer F, Schene AH. Effects of oxidative stress on fatty acid and one-carbon metabolism in psychiatric and cardiovascular disease comorbidity.

Objective: Cardiovascular disease (CVD) is the leading cause of death in severe psychiatric disorders (depression, schizophrenia). Here, we provide evidence of how the effects of oxidative stress on fatty acid (FA) and one-carbon (1-C) cycle metabolism, which may initially represent adaptive responses, might underlie comorbidity between CVD and psychiatric disorders.
Method: We conducted a literature search and integrated data in a narrative review.
Results: Oxidative stress, mainly generated in mitochondria, is implicated in both psychiatric and cardiovascular pathophysiology. Oxidative stress affects the intrinsically linked FA and 1-C cycle metabolism: FAs decrease in chain length and unsaturation (particularly omega-3 polyunsaturated FAs), and lipid peroxidation products increase; the 1-C cycle shifts from the methylation to transsulfuration pathway (lower folate and higher homocysteine and antioxidant glutathione). Interestingly, corresponding alterations were reported in psychiatric disorders and CVD. Potential mechanisms through which FA and 1-C cycle metabolism may be involved in brain (neurocognition, mood regulation) and cardiovascular system functioning (inflammation, thrombosis) include membrane peroxidizability and fluidity, eicosanoid synthesis, neuroprotection and epigenetics.
Conclusion: While oxidative-stress-induced alterations in FA and 1-C metabolism may initially enhance oxidative stress resistance, persisting chronically, they may cause damage possibly underlying (co-occurrence of) psychiatric disorders and CVD. This might have implications for research into diagnosis and (preventive) treatment of (CVD in) psychiatric patients.

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Key words: cardiovascular disease; fatty acids; homocysteine; oxidative stress; psychiatry

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Accepted for publication February 20, 2014

Summations

- Oxidative stress and its effects on fatty acid and 1-carbon cycle metabolism may underlie co-occurrence of cardiovascular and psychiatric disorders.
- During oxidative stress, fatty acids shorten in chain length and decrease in unsaturation and peroxidation, while the 1-carbon cycle shifts from the methylation to the transsulfuration pathway.
- While these changes initially may enhance oxidative stress resistance, persisting chronically, they may cause damage.

Please see editorial comment to this paper by M.J. McCarthy in this issue, Acta Psychiatr Scand 2014;**130**:161–162.

Considerations

- Interpreting fatty acid and 1-carbon metabolism changes as an adaptive response may partly explain disappointing results of supplementation of fatty acid and/or 1-carbon cycle components, for example B-vitamins, folate and antioxidants.
- The oxidative-stress-induced pattern of fatty acid and 1-carbon metabolism changes does not seem to be specific to cardiovascular or psychiatric disorders, but is also found in other oxidative-stress-related diseases and during ageing.
- A central role of oxidative stress in the link between psychiatric and cardiovascular disease stresses the need for monitoring of signs of oxidative stress (e.g. waist circumference) in psychiatric patients and treatment aimed at preventing oxidative stress development (e.g. diet, exercise, cognitive therapy).

Introduction

Relevance

Cardiovascular disease (CVD), including coronary heart disease, stroke and peripheral arterial disease, is the most frequent cause of excess mortality in patients with severe psychiatric disorders, such as schizophrenia, bipolar disorder and major depressive disorder (MDD) (1, 2). These patients have a doubled risk of dying from CVD, especially at an earlier age (1). Traditionally, the focus has been on schizophrenia, but CVD is of equal concern for patients with bipolar disorder or MDD (1–8). For example, MDD raises CVD risk 2.4 times (41% of MDD patients are at increased risk) (9), also prospectively (10).

On top of great personal suffering, CVD comorbidity in psychiatry causes substantial excess societal costs. Patients with high CVD risk have a more complex presentation of their psychiatric disorders, greater burden of disease, less favourable response to treatment and an adverse course and outcome (1, 2). Moreover, for example in bipolar disorder, CVD treatment accounts for 70% of total treatment costs (11). Therefore, improved understanding of CVD pathogenesis in psychiatric disorders is warranted.

However, pathophysiological mechanisms underlying the mutual association between psychiatric disorders and CVD are complex and still largely unknown. A better understanding of these mechanisms could i) provide directions for researchers investigating treatment and prevention options and ii) increase awareness among healthcare professionals for CVD risk in psychiatric patients, particularly general practitioners and psychiatrists, thereby iii) ensure early diagnosis and treatment.

Hypotheses and outline

In this review, we provide data indicating that oxidative stress underlies both psychiatric disorders and CVD (Part iii). In Part iv, we review the evidence that fatty acid (FA) metabolism mediates the manifestations of oxidative stress. Subsequently, we summarize FA metabolism alterations in psychiatric disorders and CVD. In Part v, we discuss how oxidative stress induces interrelated alterations in the methionine or 1-C cycle and FA metabolism and thereby may play an integrative role in oxidative-stress-associated pathophysiology of psychiatric disorders and CVD. In Part vi, we interpret studies that simultaneously assessed these biological alterations (oxidative stress, FA metabolism and 1-C cycle). By integrating these pathophysiological mechanisms (oxidative stress, FA and 1-C metabolism), a common pattern of specific biological alterations seems to emerge. Finally, we argue that this pattern may initially represent an adaptive process (Part vii).

Aims of the study

Hereby, we aim at shedding critical new light on the role of oxidative stress in i) the comorbidity of psychiatric disorders and CVD, ii) biochemical alterations observed in psychiatric patients vs. healthy controls and iii) results of intervention studies (e.g. supplementation, nutritional, psychological and physical exercise therapy) in this population.

Material and methods

We conducted a literature search in MEDLINE, EMBASE and PSYCINFO databases, which we complemented with review articles and cross-references.

We used search terms around oxidative stress, FA metabolism and the 1-C cycle, in combination with terms covering psychiatric disorders and CVD. It is beyond the scope of this review to address all relevant clinical studies addressing the role of oxidative stress, FAs and the 1-C cycle in CVD and psychiatry. Instead, we focussed on i) large-scale studies, reviews and/or meta-analyses addressing oxidative stress, FA metabolism or the 1-C cycle in CVD and/or psychiatric disorders; ii) specific studies combining clinical psychiatric and CVD characteristics with more detailed measurement of oxidative stress, FA metabolism or the 1-C cycle; and iii) studies simultaneously assessing oxidative stress, FA metabolism and/or the 1-C cycle in cardiovascular or psychiatric patients.

Both clinical concepts (CVD and psychiatric disorders) in our hypotheses and consequently search strategy cover wide areas. CVD includes, for example, stroke, coronary heart disease, type 2 diabetes mellitus and hypertension, while psychiatric disorders include MDD, schizophrenia and bipolar disorder. Because our hypotheses concern general and broad relations between psychiatric disorders and CVD risk, which do not seem to be specific to a particular psychiatric disorder or CVD entity, we chose not to limit our search strategy. However, as a result, many different forms of psychiatric disorders and CVD (risk factors) may be covered in this review. For CVD, examples of risk factors are insulin resistance, (visceral) obesity, dyslipidaemia, hypertension, subclinical inflammation and thrombosis, as encompassed by the debated concept 'metabolic syndrome' (12–14). To improve clarity and readability, we collectively addressed all these separate risk factors as CVD risk factors, where possible. In addition, we combined evidence regarding several psychiatric disorders. When a subdivision should be made, we addressed this in the text, for example, in the section Specificity.

We limited our search to articles published before May 2013 (without early date constraints). We focussed on recent articles, although we included older publications where warranted. We first excluded articles based on title and abstract (when available). Subsequently, at least two of us independently evaluated selected manuscripts. Finally, we integrated relevant data in a narrative review.

Results

Oxidative stress as shared underlying mechanism

Oxidative stress: the concept. Oxidative stress affects metabolism, signalling and functioning of cell types particularly relevant to pathogenesis of CVD and psychiatric disorders, such as neurons, endothelial cells, immune cells and platelets (15, 16). So, what is oxidative stress, and how does it originate?

Living with oxygen (O_2), that is, breathing, causes lifelong stress. Mitochondria use oxygen for energy production, thereby generating reactive oxygen species (ROS) as potentially toxic byproducts, also called free radicals. This makes mitochondria the major source of ROS (17). At low levels, ROS are essential for adequate functioning of multiple physiological systems, including intracellular messaging, apoptosis and immunity. However, at high levels, ROS may cause cellular impairment by altering DNA, proteins and lipids (18, 19).

Therefore, to handle ROS levels inherent in living in an oxygen-rich environment, organisms have multiple layers of antioxidant defence at their disposal, consisting of i) damage removal, repair or replacement systems; ii) antioxidant enzymes such as superoxide dismutases, catalases and glutathione peroxidases; and iii) dietary (e.g. vitamins A, C and E and polyphenols) and endogenous antioxidants (e.g. glutathione), which all inactivate ROS (18, 20). Despite this efficient defence, some oxidative damage is inherent in aerobic life. This is believed to underlie ageing and affect human lifespan.

In conclusion, organisms must continuously confront and control both ROS and antioxidants. This balance – often referred to as redox potential – is tightly regulated and specific to each biological site. Interference with this balance may be deleterious. So, oxidative stress can be defined as a 'disturbance in the pro-oxidant/antioxidant balance in favour of the former, leading to potential damage' (18, 20).

Causes of oxidative stress. Several studies indicate that changes in oxidative stress are largely attributable to dietary factors and physical activity levels. Various modern lifestyle factors greatly increase mitochondrial ROS production, for example i) high saturated FA and sugar intake and ii) physical inactivity. In addition, iii) smoking, alcohol and lack of fresh fruits and vegetables (antioxidants) also intensify oxidative stress (13). Seemingly contradictory, on the short term, physical activity increases oxidative stress. However, in the long term, exercise-induced oxidative stress promotes biogenesis, maintenance and clearance of dysfunctional mitochondria, thereby diminishing ROS production (21, 22). In addition, this exercise-induced oxidative stress improves endogenous antioxidant defence capacity. Thereby, regular

physical activity results in a net decrease in oxidative stress (23). Importantly, because mitochondria are the main source of ROS production, inherited and/or acquired mitochondrial dysfunction will strongly enhance oxidative stress (17). Being the source, mitochondrial membranes are subject to ROS exposure themselves; oxidative damage to these membranes may even further intensify ROS production, potentially creating a vicious cycle. Of note, brain cells also produce ROS during metabolism of important neurotransmitters in mood and psychosis (e.g. serotonin, noradrenalin and dopamine) by monoaminooxidase A and B, located on the mitochondrial membrane (16, 24).

Last but not least, psychological stress – severe life stress in particular – induces a variety of morphological and neurochemical modifications; among them oxidative stress is invariably observed (16).

Oxidative stress in CVD and psychiatric disorders. *Oxidative stress in CVD.* Considerable data indicate that ROS and oxidative stress are important features of CVD (25). A meta-analysis supported an inverse association between antioxidant enzymes (superoxide dismutase, glutathione peroxidase and catalase) and CVD (26). In addition, several studies implicate oxidative stress in CVD pathogenesis, including development of atherosclerosis and type 2 diabetes mellitus (27, 28). Increased oxidative stress was also associated with CVD risk factors in subjects that did not develop CVD yet (27), suggesting that oxidative stress may be an early causative factor in CVD pathology rather than a late consequence.

Indeed, elevated oxidative stress precedes insulin resistance, the first manifestation of CVD risk. Increased oxidative stress is probably the causal pathway that links, for example, excess caloric intake to insulin resistance (28). Furthermore, increased mitochondrial ROS production is the common feature of many different models of insulin resistance, including chronic treatment with insulin, corticosteroids, proinflammatory cytokines or lipids (29). This may suggest that insulin resistance – as a response to oxidative stress – could have an adaptive function: by decreasing glucose uptake, insulin resistance limits excess energy supply and thereby diminishes mitochondrial ROS production (28–30).

Oxidative stress in psychiatric disorders. Although it accounts for only 2% of total body mass, the brain consumes 20% of body energy (16). Besides high oxygen utilization, two more reasons make the brain most vulnerable to oxidative damage: first, its modest antioxidant defences and second, its highly oxidizable substrate, that is, lipids comprise 60–65% of brain dry weight (see 'Discussion'). This may explain the basic role of oxidative stress in psychiatric disorders and how it may function as a common pathogenetic mechanism. Evidence, although still inconsistent at some points (31), is available for increased ROS concentrations and depletion of antioxidant defences (e.g. glutathione) in MDD, schizophrenia and bipolar depression (32–37). Notably, reductions in plasma antioxidant capacity are seen in patients with chronic disease as well as early in the course of schizophrenia. In addition, evidence for genetic/acquired impaired mitochondrial function in psychiatric disorders is also growing (24, 24, 38, 39).

Two sides of the same coin. In sum, increased oxidative stress may be intrinsically involved in the shared disposition for both psychiatric disorders and CVD.

This excessive ROS production is caused by cumulative effects of not only i) genetic factors, for example a mitochondrial dysfunction, ii) severe psychological stress and iii) environmental factors, that is, an intensified form of the aforementioned modern lifestyle (excessive food intake, physical inactivity, smoking), but also, for example, malnutrition, alcohol consumption and infectious diseases. This may suggest that psychiatric disorders and CVD represent two sides of the same coin: increased oxidative stress. Then, how does oxidative stress affect the brain and cardiovascular system resulting in psychiatric disorders and CVD? In the next paragraphs, we propose that FA peroxidation may provide the explanation of how oxidative stress effects are mediated in the brain and cardiovascular system.

Fatty acids and their oxidation products as potential mediators

Fatty acids: general aspects. FAs are main components of the phospholipid bilayer, which forms the membrane of all cells and subcellular organelles (e.g. mitochondria). The 2 FA residues bound to the glycerol backbone in phospholipids determine important membrane characteristics (40) (Fig. 1). First, we provide an overview of characteristics of different FA subclasses. Then we show how these FAs influence membrane characteristics important in pathophysiology of psychiatric disorders and CVD, particularly membrane susceptibility to oxidative stress.

Fatty acids: nomenclature, synthesis and metabolism. FAs consist of hydrocarbon (CH_x) chains of

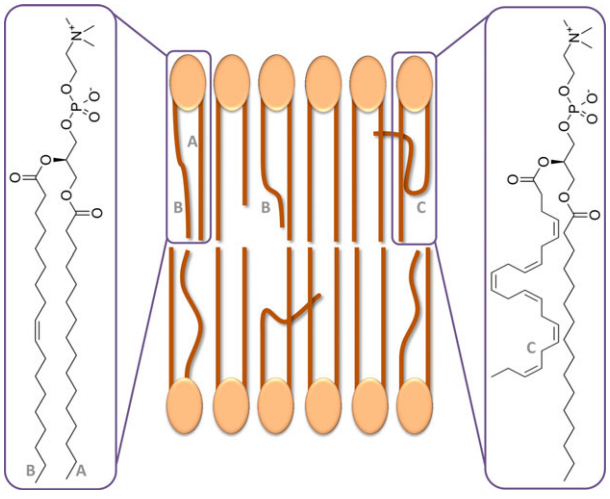

Fig. 1. Fatty acids in membrane phospholipid bilayer. (A) Saturated fatty acid; (B) monounsaturated fatty acid; (C) polyunsaturated fatty acid.

varying length, containing no saturated FAs (SFAs), one monounsaturated FAs (MUFAs) or multiple double bonds [polyunsaturated FAs (PUFAs)].

The major PUFAs belong to the omega (ω or n) ω-3, -6 and -9 series. Omega-3 and ω-6 FAs are called essential FAs, because man is incapable of *de novo* synthesis. Dietary precursors alpha-linolenic acid (ALA; C18:3ω-3) and linolenic acid (LA; C18:2ω-6) can be enzymatically converted into long-chain PUFAs by elongases and desaturases (Fig. 2; 40–43). However, because of limited conversion capacity, direct consumption of longer-chain ω-3 and ω-6 FAs, for example C20:4ω-6, arachidonic acid (AA), and C20:5ω-3, eicosapentaenoic acid (EPA), and C22:6ω-3, docosahexaenoic acid (DHA), from fatty fish, remains important. There is competition between elongases and desaturases for ω-3 and ω-6 FAs, so dietary ω-3/ω-6 balance influences synthesis. A ratio of ω-3/ω-6 of ~1 : 4 is thought to be evolutionarily optimal, but has risen to at least 1 : 15 because of the above-mentioned modern lifestyle (44).

Plasma FA concentrations are thought to reflect dietary intake, while longer-term impact is better reflected in erythrocyte (membrane), liver and adipose tissue. However, it becomes increasingly clear that FA profiles are also substantially regulated by endogenous FA metabolism (44). The relationship between intake and incorporation into peripheral tissues is nonlinear and influenced by genetic factors, age, gender and oxidative stress generated by lifestyle (stress, smoking, alcohol, physical inactivity; 44).

Fatty acids: structural role. FA length and saturation influence phospholipid membrane permeability, rigidity and fluidity. Double bonds cause curvatures in FAs, resulting in less compact arrangement in the membrane. DHA with its six double bonds therefore mainly determines increased membrane fluidity. SFAs on the contrary, by their compact arrangement, lead to 'stiffer', less fluid membranes (Fig. 1). This is important because cell membrane fluidity influences membrane-bound receptor functioning, thereby signal transduction, ion transport, mem-

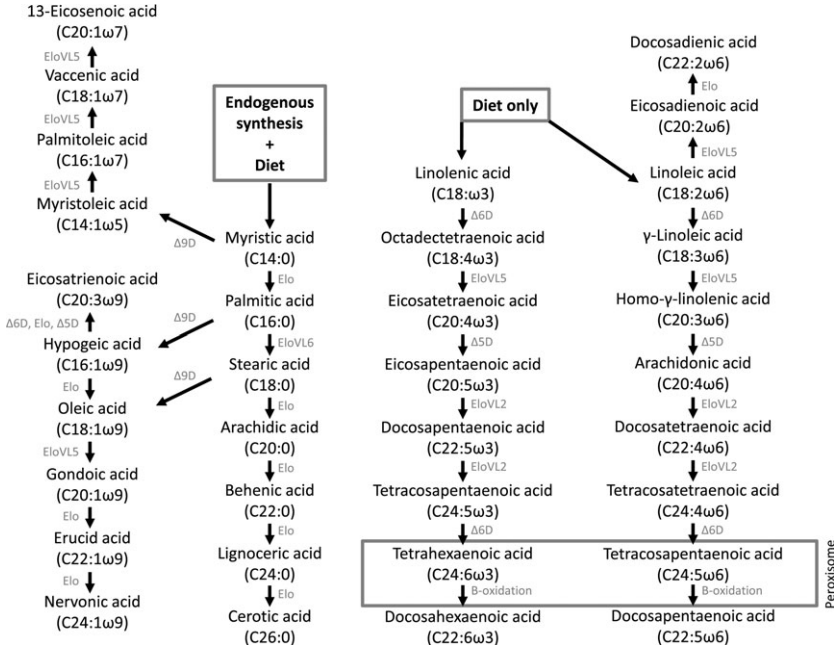

Fig. 2. Pathways of fatty acid metabolism.

brane potential and receptor sensitivity (45). This way, the principal PUFAs in the brain – DHA, EPA and AA – are thought to be involved in regulation of cognitive processes, mood and affect (46). Thus far, clinical research mainly focussed on ω-3 and ω-6 PUFAs. However, SFAs and MUFAs have their own distinct roles. For example, nervonic acid (C24:1ω-9) is a major constituent of nerve's myelin sheaths. Finally, FAs are also essential components of sphingolipids and ceramides, important structural membrane components (47).

Fatty acids: functional roles. Regarding their functional role, associations of FAs with various pathophysiological processes involved in psychiatric disorders and/or CVD have been reported. For example, FAs regulate sympathetic activity (48, 49) and are associated with endocannabinoid signalling (50, 51) and hypothalamic–pituitary–adrenal (HPA) axis activity (52). In addition, DHA increases brain-derived neurotrophic factor (BDNF; 53), which could explain ω-3 PUFA's reported neuroprotective effects (54–56). Besides these pathways, in the cardiovascular system, FAs have additional effects on triglyceride production, heart rate, myocardial efficiency, blood pressure, vascular resistance, endothelial dysfunction and thrombosis (57). Finally, FAs, as components of the aforementioned sphingolipids and ceramides, mediate responses of these signalling molecules to, for example, oxidative stress (58).

Fatty acids: (non-)enzymatic oxidation. Importantly, FAs' effects may drastically change under influence of oxidation. Phospholipid membrane FAs form a major target of enzymatic and non-enzymatic oxidation, resulting in production of lipid peroxidation products (LPOs). Their double bonds make PUFAs particularly susceptible to oxidation (59).

Regarding enzymatic lipid peroxidation, enzymes (e.g. cyclooxygenases, lipoxygenases) produce eicosanoids such as prostaglandins, leukotrienes and thromboxanes. These eicosanoids regulate inflammation and coagulation: in general, those derived from ω-6 PUFAs (e.g. AA) enhance, whereas ω-3 PUFA-derived (e.g. EPA) eicosanoids suppress these processes. In addition, DHA-derived oxidation products such as docosanoids (e.g. resolvins and neuroprotectins) have neuroprotective effects (60, 61; Fig. 3).

Non-enzymatic oxidation is caused by ROS attack of PUFAs and produces manifold potentially harmful LPOs, such as malondialdehyde (general LPO measure), 8-isoprostane (LPO generated by AA peroxidation), and hydroxynonenals (ω-6 PUFA-derived LPOs) and hydroxyhexenals (ω-3 PUFA-derived LPOs). Types of LPOs produced by ROS depend on the FAs in the phospholipid bilayer, with each FA precursing a specific LPO. These different LPOs regulate immune response, antioxidant compounds and enzymes (60–62).

Taken together, data indicate that depending on their composition and concentration, FAs give rise to specific peroxidation products, which acquire novel biological activities not possessed by their unoxidized precursors, potentially important for (patho)physiology of psychiatric disorders and CVD.

FA alterations in CVD and psychiatric disorders: clinical studies. Here, we aim at providing evidence for a specific pattern of FA alterations shared between psychiatric and CVD patients, by focussing on i) reviews and/or meta-analyses addressing FA alterations in CVD and/or psychiatric disorders, ii) studies combining CVD criteria with measurement of a wider FA spectrum, that is, SFA, MUFA, ω-3, ω-6 and ω-9 FAs, with or without activity estimates of desaturases and elongases, and iii) case–control studies including CVD criteria and LPO measurement.

FA alterations in CVD. *FA: prospective studies in CVD.* A 20-year follow-up study demonstrated that high Δ9-, Δ6- and low Δ5-desaturase activity predicted CVD risk, as well as CVD mortality

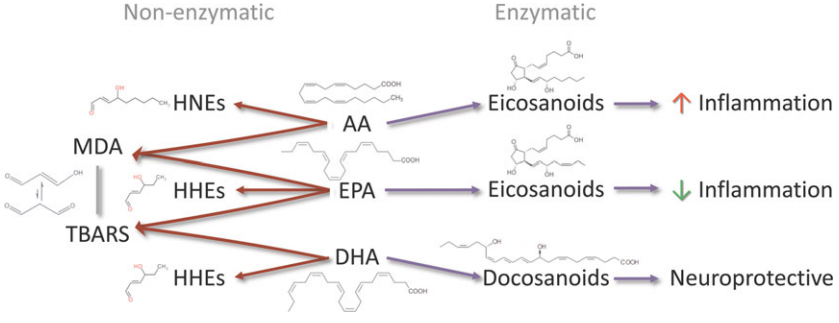

Fig. 3. (Non-)enzymatic lipid peroxidation products of AA, EPA and DHA.

(63). In 379 men (30–49 years old), SFAs were positively associated with 10-year CVD risk, even after adjustment for lifestyle (64). A prospective 7-year follow-up study involving 2724 subjects yielded comparable results. Erythrocyte 16:1ω-7, 18:3ω-3 and Δ9- and Δ6-desaturase activities were directly related to CVD risk, whereas Δ5-desaturase was inversely associated. Dietary FAs showed only modest to low correlations with erythrocyte FAs and were not significantly associated with CVD risk (65). In a recent prospective study (N = 2424), SFAs with an even chain length were found to be positively and ω-6 PUFA inversely related to subsequent CVD risk (66).

FA: cross-sectional studies in CVD. Cross-sectional analyses (N = 2980) showed associations between CVD risk and erythrocyte PUFAs, particularly LA and higher ω-6 unsaturated FAs (C18:3ω-6 and C20:3ω-6) (67). In a study of 210 men, increased SFAs, Δ9- and Δ6-desaturase- and decreased Δ5-desaturase activities were all associated with CVD risk (68). Likewise, in another study (N = 929), total PUFAs, ω-3 PUFAs and ω-3/ω-6 ratio were significantly lower in subjects with increased CVD risk. Plasma ω-3 PUFAs were inversely associated with CVD risk. In addition, high plasma total FAs increased CVD risk three times (69).

In Tunisian subjects (N = 1975) with increased CVD risk, SFAs, MUFAs and Δ9-desaturase activity were increased and positively associated with CVD risk factors, but main PUFAs (LA, DHA, AA) and Δ5-desaturase activity were decreased. In addition, CVD risk was inversely associated with PUFA concentrations (70).

LPO-CVD. With regard to LPOs, 528 obese individuals from the Framingham Offspring Study demonstrated that CVD risk was associated with increasing concentrations of the LPO 8-isoprostane, suggesting that lipid peroxidation is indeed associated with CVD risk (71). In another study, 8-isoprostane increased as CVD risk increased, with the correlation with visceral fat being stronger than with any other variable (72).

Studies in psychiatric disorders. MDD/BP-FA. Importantly, comparable FA alterations are seen in patients with psychiatric disorders. In a 14-study meta-analysis, EPA, DHA and total ω-3 PUFAs were lower in MDD patients than in controls (73). In a cross-sectional analysis of 40 medication-free patients with MDD (N = 20) and bipolar disorder (N = 20), erythrocyte DHA was i) significantly lower relative to controls, ii) inversely correlated with indices of Δ9-desaturase activity and iii) associated with elevations in 18:1ω-9 and Δ6-desaturase activity (74).

In a case–control study of 137 patients with recurrent MDD, concentrations of most SFAs and MUFAs and additionally erythrocyte PUFAs, all with >20C chain length, were significantly lower than in controls. In contrast, most shorter-chain (≤18C) SFAs and MUFAs were significantly higher in patients. Estimated activities of several elongases in patients' plasma were significantly altered, whereas Δ9-desaturase activity for C14:0 and C18:0 was significantly higher (75).

In an 8-year follow-up population study, no consistent prospective association of depression risk with any serum FA was found, in particular not with EPA, DPA and DHA (76). Unfortunately, results of long-term prospective studies including FA spectrum, LPOs and CVD risk factors in MDD patients are currently lacking.

MDD/BP-LPO. Increased lipid peroxidation was shown in MDD patients as expressed by a significant increase in the LPO-marker MDA. Moreover, a very significant increase in LPOs was observed in recurrent MDD patients as compared to the first-episode group (35). In both bipolar and MDD patients, the LPO MDA was significantly increased compared with controls (32). In 54 MDD patients, serum LPO was significantly higher compared with healthy controls (34). Furthermore, elevated serum LPOs were found in different phases of bipolar disorder and schizophrenia compared with controls (33).

Interestingly, recently, FAs, LPOs and the prime CVD risk factor insulin resistance were combined in 47 MDD patients and controls. In patients, increased concentrations of palmitoleic acid (C16:1ω-7) and total MUFAs, together with a decreased ω-6 PUFAs, were found, with increases in SFAs. Moreover, Δ6-desaturase activity was significantly increased. Concomitantly, MDD patients had higher plasma triglycerides, LPO and insulin resistance. Importantly, FA composition of MDD patients revealed changes similar to those usually observed in patients with insulin resistance without comorbid depression (77). Moreover, recently, a relationship was found between white matter integrity and lipid peroxidation in bipolar disorder (36).

Schizophrenia FA. Recently, a systematic review and meta-analysis were performed for docosapentaenoic acid (DPA, C22:5ω-3), DHA, LA and AA in patients with schizophrenia (78). Combining 642 patients (169 antipsychotic-naïve) and 574 controls

provided substantial evidence that decreased DPA, DHA and AA are associated with the schizophrenia syndrome, apart from possible influences of antipsychotic medication. Given result heterogeneity, conclusions should be interpreted cautiously.

Schizophrenia LPO. For reports regarding lipid peroxidation in schizophrenia, we first refer to excellent recent reviews (37, 79, 80). Findings include increased LPOs (including MDA, 8-iso-prostane and hydroxynonenals). In a case–control study, plasma MDA was higher and red blood cell SOD and catalase significantly lower in schizophrenic patients and their unaffected siblings (81). In addition, an inverse relationship was found between LPOs and erythrocyte DHA and AA in antipsychotic-naïve patients (82).

Comparable pattern of FA alterations in CVD and psychiatric disorders

After reviewing the above literature, an oxidative-stress-associated pattern of alterations in FA and LPOs seems to emerge, characterized by i) increased SFAs and MUFAs, decreased long-chain PUFAs and ω-3/ω-6 ratios, increased Δ6- and Δ9-desaturase activities and decreased Δ5-desaturase activity, together with ii) increases in LPOs, in patients with CVD or psychiatric disorders (MDD, schizophrenia, bipolar disorder). Therefore, also in view of the above-described oxidative-stress-induced structural and functional effects on FA metabolism, FAs together with their (non-) enzymatic peroxidation products may underlie (part of) the clinical overlap between CVD risk factors and psychiatric disorders. However, what mechanisms can explain these effects of oxidative stress on FA metabolism? In the subsequent part of this review, we propose that the methionine–homocysteine or 1-C(arbon) cycle may play an integrating role in translating the effects of oxidative stress on FA metabolism.

The 1-C cycle as integrator

General aspects

Here, we will review studies indicating that the 1-C cycle acts as an integrator, because it regulates both oxidative stress and methylation. In the 1-C cycle, the amino acid homocysteine is a key intermediate (83). First, in the transsulfuration pathway, homocysteine can be catabolized to the most important intracellular antioxidant glutathione, with vitamin B_6 as cofactor (84). Second, in the transmethylation pathway, homocysteine can be transformed to S-adenosylmethionine, with vitamin B_{12} and folate as cofactors. S-adenosylmethionine is a universal donor of methyl groups, which are used for FA and phospholipid production, but also in epigenetic regulation of DNA transcription (83, 85; Fig. 4).

The 1-C cycle and oxidative stress

Oxidative stress interfaces with the 1-C cycle. Accumulating evidence shows that oxidative stress increases the key 1-C cycle intermediate homocysteine, while decreasing folate (86). This may be because folate has been implicated as direct ROS scavenger and can act as antioxidant *in vivo*, being degraded/depleted in the process. Thereby, folate appears to be a major determinant of homocysteine increase (86, 87).

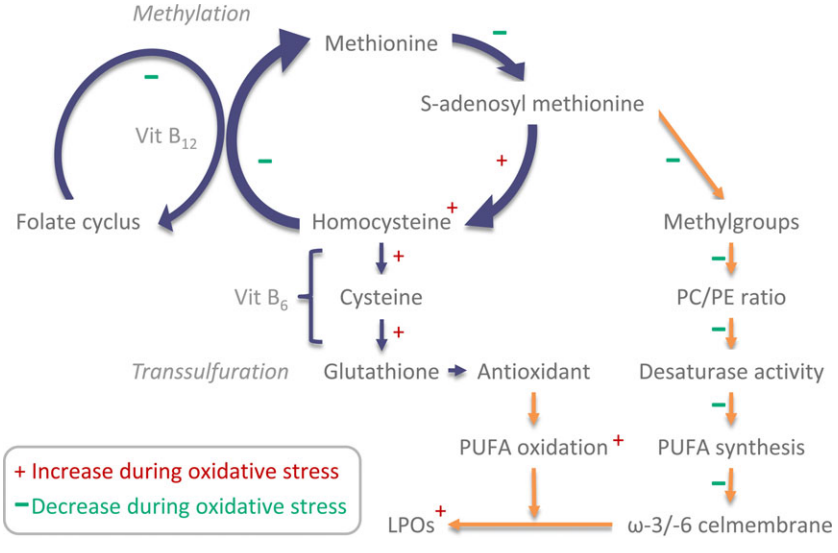

Fig. 4. Interaction between the 1-C cycle and FA metabolism and alterations during oxidative stress.

The 1-C cycle and FA metabolism

Besides this link of the 1-C cycle with oxidative stress, it is also tightly connected to FA metabolism (Fig. 4). First, methyl groups donated by S-adenosylmethionine are used for methylation of phospholipids, which are responsible for PUFA transport from liver to brain. Second, methyl group donation also regulates activity of desaturases and elongases responsible for ω-3 and ω-6 PUFA synthesis (88, 89). Third, methyl groups are also utilized in FA elongation. Importantly, finally, via DNA methylation, activity of all enzymes involved in the 1-C-cycle, FA and oxidative metabolism may be influenced (epigenetic regulation).

Changes in 1-C cycle in CVD and psychiatric disorders

1-C cycle in CVD. A 26-article meta-analysis concluded that each 5 μM homocysteine increase independently enhanced CHD risk by approximately 20% (90). In addition, meta-analysis of prospective studies showed that folate is inversely associated with CVD risk (91). Furthermore, a population study (N = 1108) observed an association between CVD risk (insulin resistance) and serum homocysteine (92).

1-C cycle in psychiatry. Involvement of the 1-C cycle in psychiatric disorders is supported by substantial evidence. For example, novel epigenetic findings demonstrate how the 1-C-derived methyl donor S-adenosylmethionine influences expression of key genes in the brain affecting memory, learning, cognition and behaviour, whose expression was found to be reduced in psychiatric patients (93–95).

In the largest sample examined to date concerning psychiatric symptomatology, a cross-sectional study of 11 757 participants, a significant positive relationship was found between elevated homocysteine and actual depressive symptoms (96). Another recent unique study in medication-naïve first-episode psychotic patients found significantly lower blood vitamin B_{12} and folate compared with matched controls. These reductions paralleled significant increases in plasma homocysteine and cortisol (97).

Similar pattern of 1-C cycle alterations in CVD and psychiatric disorders. In both psychiatric disorders and CVD, a pattern of alterations in key 1-C cycle components (homocysteine, vitamin B_{12}, folate) seems to emerge. This pattern is characterized by increased homocysteine and glutathione, together with decreased concentrations of folate, vitamin B_{12} and S-adenosylmethionine (83, 87, 88). These alterations may be interpreted as a switch from the transmethylation pathway to the transsulfuration pathway. Being linked to oxidative stress on the one hand, and FA metabolism on the other, the 1-C metabolism is well positioned to integrate the effects of oxidative stress on FA metabolism. However, is this integrating role of the 1-C cycle supported by studies simultaneously assessing these three factors?

Fatty acids and the 1-C cycle: the integrated picture

Overview. We proposed a model in which oxidative-stress-associated alterations in FA metabolism, translated by integrative changes in the 1-C cycle, explain comorbidity of psychiatric disorders and CVD. The oxidative-stress-induced shift in the 1-C cycle from the methylation to the transsulfuration pathway may limit bioavailability of methyl groups, thereby possibly leading to decreases in FA chain length and unsaturation. Following this model, it can be hypothesized that studies that simultaneously assessed these factors will observe increases in oxidative stress accompanied by associated corresponding alterations in FA metabolism (reductions in long-chain PUFAs and increases in SFAs, MUFAs and LPOs) and the 1-C cycle (increased glutathione and homocysteine and decreased folate) (Fig. 4). In this subsequent Part (vi), we will review studies that applied such a combined approach.

Oxidative stress, the 1-C cycle and FAs: integrated clinical studies. Thus far, clinical studies combining CVD risk factors, parameters of oxidative stress, the 1-C cycle, FA metabolism and (non-) enzymatic LPOs are still scarce. In healthy men, homocysteine was inversely related to plasma AA and DHA, total ω-3 PUFAs and ω-3/ω-6 PUFA ratio (98). Severus et al. (99) were the first to draw attention to the interaction between ω-3 FAs, homocysteine and the increased mortality in MDD patients. Furthermore, in an uncontrolled study in 44 MDD patients, normal plasma homocysteine coincided with a decrease in erythrocyte membrane ω-3 FA and a significant positive association between the sum of ω-6 FAs and homocysteine was found (100).

Essential FA and B-vitamin status were assessed in 61 schizophrenic patients. Patients had high erythrocyte SFAs, MUFAs and low ω-3 and ω-6 series PUFAs, together with low vitamin B_{12} and high homocysteine. Importantly, homocysteine variance proved to be best explained by folate (101). Kale et al. (97) found that reductions in

folate and vitamin B_{12} and increases in homocysteine were accompanied by significantly reduced membrane DHA.

Therefore, this handful of clinical studies on MDD integrating oxidative stress markers, FAs and the 1-C cycle indeed suggest a close interaction between FA metabolism and the 1-C cycle in handling oxidative stress.

Discussion

Summary

So far, we provided evidence that CVD and psychiatric disorders often co-occur (Part i), which may be explained by the underlying role of oxidative stress (Part iii). In Part iv, we provided evidence that FA metabolism may be an important mediator of the effects of oxidative stress on the brain and cardiovascular system. We supported this view by showing a specific corresponding pattern of oxidative-stress-associated comparable FA alterations in psychiatric disorders and CVD, consisting of shorter, less unsaturated FAs, and increases in LPOs. In Part v, we proposed that the 1-C cycle may translate the effect of oxidative stress on FA metabolism: indeed, psychiatric disorders and CVD are both associated with oxidative-stress-associated increases in homocysteine and reductions in folate. This is corroborated by studies observing associations of FA metabolism with 1-C cycle parameters in response to oxidative stress (Part vi).

While thus far these alterations are mainly considered to be harmful, here, we review data indicating that this pattern may well (partly) represent an (initially) adaptive response to increased oxidative stress.

Evidence for an adaptive potential

Apparent discrepancy between observed alterations and supplementation studies. Above reviewed alterations in FA metabolism and the 1-C cycle gave rise to clinical trials aiming at 'normalizing' these concentrations to treat and/or prevent psychiatric disorders and CVD. Increases in homocysteine are being supplemented with folate and B-vitamins, and decreases in long-chain PUFAs are being supplemented with EPA and DHA. Indeed, homocysteine falls and FA concentrations rise following supplementation. However, oxidative stress parameters do not always improve after FA supplementation (102). In addition, thus far, no clear clinical benefits could be demonstrated for ω-3 FA and/or folate and other B-vitamin supplementation in CVD or psychiatric disorders. Meta-analysis of randomized, double-blind, placebo-controlled trials in patients with a history of CVD showed insufficient evidence for a secondary preventive effect of ω-3 FA supplements against overall cardiovascular events (103–105). In addition, a recent meta-analysis of trials on ω-3 FA treatment of MDD involving 731 depressed patients suggests a small, but non-significant benefit of ω-3 FA for MDD, nearly entirely attributable to publication bias (106). A third updated review of PUFA supplementation for schizophrenia revealed persistent inconclusive results (107). Likewise, data from recent large randomized controlled trials have shown that there is no clear benefit of lowering homocysteine concentrations with folate or B-vitamins (108, 109). This lack of clinical effect of interventions aimed at lowering homocysteine supports the view that homocysteine is not an instigator, but rather an indicator of oxidative stress in CVD and psychiatric disorders (86, 87). These negative results of supplementation trials seem puzzling and in contrast to the distinct alterations in FA metabolism and the 1-C cycle in CVD and psychiatric patients. In addition, meta-analyses suggest that if any effect of FA supplementation can be noted, it is particularly for EPA (110), while it is mainly DHA, which differs between depressed patients and controls (111).

This apparent discrepancy between observational studies reporting clear alterations and supplementation studies showing inconsistent effects led us to the hypothesis that the observed alterations in FA metabolism and the 1-C cycle may (partly) consist of adaptive responses to increased oxidative stress.

Return to normal after combating oxidative stress. If these alterations represent adaptive responses to increased oxidative stress, one would expect that by combating oxidative stress (e.g. by weight reduction and/or physical exercise), a return to 'normal' values may be seen, that is, i) insulin resistance decreases, ii) in the 1-C cycle, homocysteine decreases and folate rises and iii) in FA metabolism, SFAs and MUFAs decrease and PUFAs increase, in parallel with a decrease in LPO. Although evidence remains scarce thus far, some indications exist (21, 112–115). If this pattern is further corroborated in well-designed randomized controlled trials, this may strengthen the view that interrelated alterations in FAs and the 1-C cycle induced by oxidative stress at least initially may represent an adaptive response.

Biochemical explanation for a potentially adaptive effect. In addition, interpreting the observed FA

alterations – that is, shorter chains and less unsaturation – as an adaptive response, may make sense from a biochemical perspective. The FA alterations – the decrease in PUFAs in particular – make cell membranes less peroxidizable. This decreased peroxidizability may make cells more resilient to oxidative stress. This could also explain why mammal species with a more peroxidation-resistant membrane live longer (59), and offspring of human nonagenarians have more peroxidation-resistant erythrocyte membranes than controls (116). In addition, rat skeletal muscle mitochondrial membranes, highly exposed to oxidative stress, have more MUFAs and less PUFAs compared with whole muscle membranes (117). This decreased membrane unsaturation may reflect selective pressure towards membranes that are more resistant to oxidative damage by ROS produced in their vicinity. The negative effect of low polyunsaturation on membrane fluidity may be counterbalanced by the higher percentage of MUFA and the known low cholesterol content of mitochondrial membranes (117).

In addition, in the 1-C cycle, oxidative stress invokes a shift towards transsulfuration and rise in glutathione production. Glutathione as the major cellular antioxidant may thereby partly adaptively combat the oxidative stress that caused its formation. Moreover, although LPOs were considered to be harmful thus far, increasing data support an adaptive/protective role of LPOs. For example, LPOs were shown to acquire novel biological activities, including stimulation of antioxidant defences and the ability to regulate immune responses (15, 16, 21, 49, 60, 61), possibly counteracting the oxidative stress that generated them (118).

In sum, results indicate that, for example, lower ω-3 PUFA and higher homocysteine concentrations do not necessarily stand for harmful deficiencies/excesses, but may initially reflect adaptive alterations in FA and 1-C cycle metabolism to optimally handle oxidative stress.

Limitations and challenges

Role of Medication. Major psychotropic drugs are associated with increased CVD risk, especially weight gain. However, importantly, evidence for the bilateral association between CVD and psychiatric disorders predates psychotropic agents. So, altered glucose metabolism and dyslipidaemia seem to be integral to psychiatric disorders. Interestingly, therapeutic response to some antipsychotics seems associated with weight gain during treatment (119). Psychotropic drugs may work through intercalation in membrane phospholipids. Fluidity of membranes rich in essential FAs, influenced by diet, could be a contributing factor to the action of psychotropics (120). In addition, some antipsychotics and antidepressants have antioxidative effects possibly owing to effects on mitochondrial respiratory chain enzymes (121).

Specificity. Noteworthily, thus far, the discussed pattern of FA alterations (LPOs included) seems not specific to CVD or any psychiatric disorder, but is also found in other oxidative-stress-related diseases such as Alzheimer's and Parkinson's disease, as well as in normal ageing (122, 123). Therefore, one could consider oxidative stress as a relatively non-specific factor having nothing to do with underlying (patho)physiology of any (psychiatric) disease. However, we propose that oxidative stress and its influence on FA and 1-C cycle metabolism lies at the basis of a wide range of (patho) physiology. This aspecificity causes problems but may also hold promises.

For instance, how could it be that the clinical picture may greatly vary, despite this proposed common underlying (patho)physiology? This may be due to a multitude of different levels of modifying factors, varying from (epi)genetic variations regulating genes of, for example, the mitochondrial respiratory chain, FA metabolism and the 1-C cycle, LPO production and their different locations (brain, cardiovascular system), together with exogenous factors such as psychological stress (39, 124–127). For instance, the stress hormone cortisol translocates to mitochondria to regulate mitochondrial gene expression (24). Moreover, disease-specific neuroanatomical patterns in mitochondrial complex 1 alterations were found in schizophrenia, bipolar disorder and major depression (38). Nevertheless, further research is needed to develop more reliable diagnostic and prognostic markers, for example, to distinguish between diseases. Giustarini et al. (18) provide directions on how to more reliably measure oxidative stress, for example at tissue level, to detect more clear and specific relations between oxidative stress and various diseases. On the other hand, this generalizability of the discussed pattern suggests that interventions aimed at reducing oxidative stress may provide opportunities to improve health outcomes in general, including mental and cardiovascular health.

Reverse causality and confounding. While the above-proposed theoretical model may provide an interesting perspective to explain CVD and psychiatric comorbidity, evidence is far from conclusive.

Most evidence is correlational, therefore limiting conclusions regarding causality. Although some prospective and/or intervention studies have been performed, and studies usually attempted to control for confounding, part of the described biological alterations may be explained by known confounders, including smoking, reduced dietary quality and lack of physical activity, which are all more common in psychiatric populations compared with the general public. On the other hand, these risk factors are all known to induce oxidative stress, which may suggest that instead of confounders, these factors represent mediating and/or moderating factors, with (e.g. bidirectional) effects on oxidative stress on their causal pathway. Hereafter, we will describe specific study designs to further test the above-proposed biological framework of oxidative-stress-induced alterations in FA and 1-C cycle metabolism.

Research implications

Oxidative stress decreasing interventions. Following the proposed framework, a successful lowering of oxidative stress would be expected to normalize FA and 1-C cycle alterations and consequently improve CVD risk and clinical outcomes. However, unfortunately, effectively lowering oxidative stress levels is not that easy, particularly in the brain (128).

Current antioxidant supplementation does not seem to be effective (18), coined as the antioxidant paradox. This can be explained because supplemented antioxidants i) do not enter the brain; ii) distort endogenous antioxidant responses and physiological oxidative stress (as noted above); and iii) not always act antioxidant *in vivo* (128–130). Alternatively, it may be more effective to prevent oxidative stress from arising in the first place. Future randomized controlled trials mutually combining add-on lifestyle interventions (e.g. diet, physical exercise) and investigation of (adjuvant) novel oxidative-stress-relieving treatments are therefore urgently needed. For example, effects on oxidative stress of N-acetylcysteine through the 1-C cycle, but also psychotherapy (21, 131–135), may be interesting topics of future investigation. In addition, it might be worthwhile to look for ways to prevent disrupted mitochondrial oxidative stress formation, that is, mitochondrial therapy (24, 136). Importantly, these studies should combine clinical outcomes with biochemical parameters, for example oxidative stress, (non-)enzymatic LPOs and the 1-C cycle, to understand underlying biological mechanisms.

Subgroups, windows of opportunity and personalized medicine. Another factor that may be of special interest to future trials may be definition of subgroups. For example, effects of folate and vitamin B_{12} on negative symptoms in schizophrenia depended on genetic variation in folate absorption (137). In genetically vulnerable groups, supplementation may have an effect, while in patients with decreased folate secondary to oxidative stress, supplementation may have no or even opposite effects. A similar idea can be noted for FA supplementation, where patients with low long-chain ω-3 PUFA concentrations resulting from genetically reduced enzymatic conversion of ALA into EPA and DHA may benefit from supplementation, while in case of adaptive low concentrations, supplementation will not be effective (138–140). An additional indication that such subgroups exist may be the observed bimodal distribution of FA concentrations in MDD and schizophrenia (141, 142).

Besides this cross-sectional classification, subgroups may also be defined longitudinally in time (staging), that is, supplementation effectiveness depends on timing. For instance, disease stage may influence supplementation effectiveness; for example, long-chain ω-3 PUFA was shown to reduce the rate of progression to first-episode psychotic disorder specifically in adolescents and young adults aged 13–25 years with subthreshold psychosis (143). This might be explained because supplementation took place early in the disease – during adolescent neurodevelopment. This period may provide a window of opportunity where it might be possible to interfere in the proposed pathophysiological cascade before the point of no return – that is, the stage in which the production of ROS damaged products starts to overwhelm ROS defence – consequently reducing the risk of potentially toxic LPO formation.

Future research aimed at disentangling these subgroups may help to find those subgroups of patients who may actually benefit from supplementation and at what time point, resulting in clearer effects in treatment trials. This will pave the way to develop personalized medicine interventions, for example specialized nutritional therapy (144).

Relation between inflammation and oxidative stress. - Over the last decade, studies consistently reported increased levels of a variety of peripheral inflammatory biomarkers in psychiatric disorders, for example MDD (145, 146). Interestingly, as briefly indicated earlier, oxidative stress and inflammation are inextricably tied processes (147). Importantly, evidence indicates that this relation may be

bidirectional: oxidative stress elicits an immune response, while immune activation may also result in oxidative stress. This chicken-or-egg question could be the topic of another review, but some points of clarification may better place this review in context. The main pathophysiological pathway proposed here is that oxidative stress induces (non) enzymatic initially adaptive alterations in, for example, membrane lipids (LPOs). Because of the above-discussed immunoregulatory effects of FAs and their peroxidation products, these alterations subsequently prime the immune system to adequately handle oxidative stress and restore the redox balance as much as possible. This would imply that MDD, as well as other psychiatric disorders and CVD, is primarily an oxidative-stress-based disorder with secondary inflammatory consequences.

However, in some cases, inflammation may be the causative factor. For example, (randomized) treatment with supraphysiological concentrations of TNFα and inflammatory disease are associated with development of psychiatric disorders. This may fit with our theoretical model, because both treatment with TNFα and inflammatory disease are known to result in elevated levels of oxidative stress, thereby making it one of the possible driving forces behind the described oxidative-stress-associated changes in FA metabolism and the 1-C cycle. However, this route appears to be only present in specific subtypes of patients (145, 148). Interestingly, in physiological concentrations, many cytokines have antioxidant properties, thereby potentially being involved in adaptive oxidative stress regulation (146, 149). In sum, disentanglement of these bidirectional relationships may be an interesting topic for future investigation.

Clinical implications

Supplementation risks. The above-provided evidence that decreases in, for example, FA concentrations do not necessarily represent shortages, and increases excesses, has important consequences for clinical treatment. True deficits should be supplemented, whereas decreases as adaptive responses could potentially be hindered or even be made harmful by supplementation, the more so, because potentially dangerous effects of FA supplementation have not been systematically studied thus far. Moreover, FAs in capsules may be prone to oxidation *in* and *ex vivo,* leading to production of biologically active, possibly harmful LPOs (150). Recent examples may be effects of DHA administration during pregnancy to prevent postnatal depression (151, 152). Another example of unintended negative effects was prevention of health-promoting effects of exercise by presumed antioxidants vitamin C and vitamin D (23).

As long as a just interpretation (adaptation vs. deficit) of FA alterations is not known, reluctance in supplementing is warranted. This contrasts the large number of people currently using diverse forms of supplementation, unsupported by solid scientific evidence (153).

As a more effective alternative, lowering oxidative stress by physical exercise, a healthy diet, reducing psychological stress (e.g. cognitive therapy and/or antidepressants) and weight loss have been proven beneficial for psychiatric symptomatology and CVD risk (3, 21, 133–135, 154–156). Therefore, these interventions should be routinely implemented in clinical care for these patients.

Monitoring CVD risk in psychiatric patients. Finally, in spite of consensus recommendations and guidelines, appropriate surveillance of anthropometric and metabolic parameters has not yet been rigorously implemented in psychiatric care (157). Obstacles to implementation need to be overcome by making CVD risk monitoring mandatory (158). The concept 'metabolic syndrome' (MetS) encompasses a cluster of CVD risk factors and may be a helpful tool for clinicians to assess CVD risk. Although there is continuing debate regarding the MetS criteria and concept, this clustering of risk factors is unequivocally linked to an increased risk for developing type 2 diabetes mellitus and CVD (12–14). Thereby, the concept MetS could guide clinicians which/when psychiatric patients should receive treatment for their increased CVD risk.

To conclude, oxidative stress elicits connected responses thought to be involved in the bilateral association between psychiatric disorder and CVD. In this review, we focussed on two main and interrelated factors that may be involved in handling of oxidative stress: FA metabolism and the 1-C cycle. An oxidative-stress-related pattern seems to emerge with FA-metabolism increases in SFAs and MUFAs and decreased PUFAs together with increased (non-)enzymatic LPOs. The 1-C cycle shifts away from the methylation pathway and production of methyl groups needed for PUFA production, neurotransmitters and DNA methylation, to the transsulfuration pathway resulting in synthesis of the major intracellular antioxidant glutathione.

We propose that these alterations primarily represent an adaptive response. This is corroborated by the fact that combating oxidative stress (particularly by physical exercise) may result in reversal of the alterations. However, although initially

reversible and protective, the alterations may turn irreversible, irreparable and harmful. Combining clinical and biochemical criteria in randomized controlled trials aimed at combating oxidative stress in specifically selected patients may help in this distinction and consequently improve diagnosis of and (preventive) treatment for (CVD in) psychiatric disorders.

Acknowledgements

The authors would like to gratefully acknowledge the Academic Medical Center, University of Amsterdam and the Fatty Acids in Diabetes, Depression and Schizophrenia (FADDS) Study group for their support. Dr. H.G. Ruhé was supported by a NWO/ZonMW VENI-Grant #016.126.059.

Declaration of interest

All authors report no biomedical financial interests or potential conflicts of interest over the last 2 years, in general and also not specifically in relation to the present study. All funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

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