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Is depression associated with increased oxidative stress? A systematic review and meta-analysis

Catherine N. Black[a,d,*], Mariska Bot[a,d], Peter G. Scheffer[b], Pim Cuijpers[c,d], Brenda W.J.H. Penninx[a,d]

[a] Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands
[b] Department of Clinical Chemistry, Metabolic Laboratory, VU University Medical Center, Amsterdam, The Netherlands
[c] Department of Clinical Psychology, VU University Amsterdam, The Netherlands
[d] EMGO Institute for Health and Care Research, Amsterdam, The Netherlands

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Summary
Background: It has been suggested that depressed persons have increased oxidative stress and decreased anti-oxidant defences. 8-Hydroxy-2′-deoxyguanosine (8-OHdG) and F2-isoprostanes, measures of oxidative DNA and lipid damage respectively, are among the most reliable oxidative stress markers, but studies on their association with depression show conflicting results. This meta-analysis quantifies the association between depression and these markers and explores factors that may explain inconsistencies in the results.
Methods: A systematic literature search was conducted in PubMed, EMBASE and PsycINFO. Studies assessing the association of 8-OHdG or F2-isoprostanes with elevated depressive symptoms, major depressive disorder (MDD) or bipolar disorder (BD) were pooled in two random-effect models.
Results: The pooled effect size (Hedges' g) for the association of depression with oxidative stress was 0.31 ($p = 0.01$, $I^2 = 75\%$) for 8-OHdG (10 studies, 1308 subjects) and 0.48 ($p = 0.001$, $I^2 = 73\%$) for F2-isoprostanes (8 studies, 2471 subjects), indicating that both markers are increased in depression. There was no indication of publication bias for either marker. The F2-isoprostane results did not differ by type of depression, biological specimen, laboratory method or quality, however subgroup analyses in the 8-OHdG studies showed significantly stronger associations in plasma/serum vs. urine samples ($p < 0.01$), in measurements performed with immuno-assay vs. chromatography—mass spectrometry ($p < 0.01$) and weaker associations in high quality studies vs. low ($p = 0.02$).

* Corresponding author at: Department of Psychiatry, VU University Medical Center, Postbus 74077, 1070 BB Amsterdam, The Netherlands. Tel.: +31 20 788 4597.
E-mail address: c.black@ggzingeest.nl (C.N. Black).

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Conclusion: This meta-analysis finds that oxidative stress, as measured by 8-OHdG and F2-isoprostanes, is increased in depression. Larger-scale studies are needed to extend the evidence on oxidative stress in depression, and examine the potential impact of treatment.

1. Introduction

Depression is a leading cause of morbidity worldwide (Vos et al., 2012). Depression is highly prevalent (Kessler et al., 2003) and has a profound impact on functioning and quality of life (Bijl and Ravelli, 2000) as well as on somatic health. Sufferers are at higher risk of diseases that are usually associated with increasing age such as cardiovascular disease (Nicholson et al., 2006), obesity (Luppino et al., 2010), diabetes (Mezuk et al., 2008), cancer (Chida et al., 2008), cognitive impairment (Barnes et al., 2006) and have a higher all-cause mortality rate (Cuijpers et al., 2014). It is hypothesized that increased metabolic stress and accelerated cellular ageing may be underlying pathways that contribute to this poorer physical health in individuals with depression (Wolkowitz et al., 2011b). A fast growing body of evidence suggests the involvement of a specific component of metabolic stress, oxidative stress, in the pathophysiology of depression (Maes et al., 2011).

Oxidative stress refers to the biologically damaging effects of free radicals (Valko et al., 2007). The production of free radicals, or reactive oxygen species (ROS), is a normal process in aerobic metabolism and ROS perform a number of physiological roles in cellular signalling and in the defence against pathogens. However, when present in excess, ROS cause damage to lipids, proteins and DNA, and can ultimately result in cell death. Oxidative stress is a well-recognized mechanism in ageing and disease. It has been shown to play a role in the pathophysiology of — among others — cardiovascular disease, diabetes mellitus, cancer and Alzheimer's disease (Valko et al., 2007). Additionally, there is evidence suggesting that oxidative stress may be increased in a number of psychiatric disorders, including depression (Pandya et al., 2013).

A recent meta-analysis pooling data from studies with different oxidative stress markers suggests oxidative stress is increased and antioxidant defences are decreased in depression (Palta et al., 2014). In line with these findings, increased nitric oxide (NO) and lipid peroxidation, as measured by thiobarbituric acidic reactive substance (TBARS) assay, have also been found in patients with bipolar disorder, however these patients did not differ from controls in anti-oxidant enzymes levels (Andreazza et al., 2008). Overall, these studies suggest that oxidative stress is increased in major depressive disorder and bipolar disorder.

There is a wide range of oxidative stress biomarkers and laboratory techniques available, each of which has its own strengths and limitations (Dalle-Donne et al., 2006). To date there is no consensus on the most appropriate biomarkers of oxidative stress in general and the validity of many of those in use is to still be established. ROS have a short half-life, making measurement difficult. Levels of antioxidants, vitamins or anti-oxidant enzymes are informative, but reflect only one side of redox homeostasis, leaving the question unanswered whether decreased levels are actually also indicative of increased oxidative damage. Studies show quite consistently that lipid peroxidation reflected by malondialdehyde (MDA) measured with the TBARS assay is increased in depression (Palta et al., 2014) and in bipolar disorder (Andreazza et al., 2008). However this commonly used method also has well recognized limitations: MDA is not a specific product of lipid peroxidation, and the TBARS assay itself can generate MDA, causing overestimation of levels. MDA therefore cannot be considered an optimal representation of oxidative stress in vivo (Meagher and FitzGerald, 2000; Dalle-Donne et al., 2006).

The current study focusses on two important measures of oxidative damage that have already been widely studied in somatic disease and are the subject of an increasing number of recent publications on depression: 8-hydroxy-2′-deoxyguanosine (8-OHdG) and F2-isoprostanes. The majority of the currently available literature on these markers in depression was not included, or not yet available for inclusion, in the previous meta-analyses on this subject. 8-OHdG and F2-isoprostanes reflect oxidative damage to DNA and lipids respectively. 8-OHdG is an oxidized derivative of deoxyguanosine and it is both the most abundant and most investigated DNA lesion. It has recognized mutagenic properties and has been linked to — among others — the development of cancer (Valavanidis et al., 2009). F2-isoprostanes, oxidized derivatives of arachidonic acid, have come to be considered the preferred approach to assess oxidative stress in vivo and lipid peroxidation in particular (Niki, 2014).

Several studies have found elevated levels of F2-isoprostanes (Dimopoulos et al., 2008; Yager et al., 2010; Chung et al., 2013) and 8-OHdG (Irie et al., 2005; Forlenza and Miller, 2006) in patients with depression, but these findings have not been consistent (Yi et al., 2012; Rawdin et al., 2013). Earlier studies did not systematically explore to what extent the (conflicting) findings are due to e.g. the laboratory methods, biological specimens used for oxidative stress, or the extent to which studies took potential confounders such as health and lifestyle factors into account. The present study extends the current evidence-base by systematically meta-analysing the literature on two robust markers of oxidative stress, 8-OHdG and F2-isoprostanes, and their association with depression (major depressive disorder, bipolar disorder and elevated depressive symptoms). In addition, by conducting subgroup analyses based on type of depression, biological specimen, laboratory method used to measure oxidative stress, correction for confounders and the quality of studies, this study aims to identity factors that contribute to the inconsistent findings of individual studies.