Oxidative stress and antioxidant parameters in patients with major depressive disorder compared to healthy controls before and after antidepressant treatment: results from a meta-analysis.

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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 qual- ity of life (Bijl and Ravelli, 2000) as well as on somatic health. Sufferers are at higher risk of diseases that are usu- ally 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 accel- erated 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 produc- tion 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 oth- ers — 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 dif- ferent oxidative stress markers suggests oxidative stress is increased and antioxidant defences are decreased in depres- sion (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 actu- ally 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 represen- tation 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 stud- ied in somatic disease and are the subject of an increasing number of recent publications on depression: 8-hydroxy-2^{7}- 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 deriva- tive of deoxyguanosine and it is both the most abundant and most investigated DNA lesion. It has recognized muta- genic 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 find- ings 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 lab- oratory methods, biological specimens used for oxidative stress, or the extent to which studies took potential con- founders 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 dis- order, 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.

2. Methods

2.1. Literature search and study selection

Systematic searches of the literature were conducted in the databases PubMed, EMBASE and PsycINFO up to January 8th 2014 with search terms covering major depressive disorder, bipolar disorder and depressive symptoms combined with 8- OHdG and F2-isoprostanes respectively, taking into account a wide range of synonyms used for these markers. A full list of search terms is reported in Appendix A. No limitations in the search strategy were set. The search results were reviewed by two independent reviewers (CNB and MB) by screening title and abstract, followed by a full text review. Disagreements were settled by discussion.

Studies were eligible for inclusion if they:

(1) contained a measurement of 8-OHdG or F2-isoprostanes in any body fluid or tissue in live human adult subjects;
(2) defined major depressive disorder (MDD) or bipolar dis- order (BD) according to DSM-IV or ICD-10 criteria or assessed depressive symptoms using a validated instru- ment;
(3) reported (or were able to provide) sufficient information to calculate an effect size for the difference between levels of the oxidative stress markers in control subjects and subjects with depression.

An assessment of the references of the included studies as well as a search of their citations in the PubMed database was performed to identify any additional studies.

2.2. Data extraction and risk of bias assessment

Two authors (CNB and MB) independently extracted the study characteristics (including among others biological specimen, age and sex distribution) and results from each study using a predesigned collection form (see Appendix B). The results extracted included means, standard deviations of oxidative stress markers in patient and control groups (or alternative results sufficient to calculate an effect size) and an assessment of correction for potential confounders (age, sex, ethnicity, socio-economic status, smoking, alco- hol use, body mass index (BMI), physical activity, somatic disease and antidepressant or mood stabilizer use). Authors of studies that did not contain sufficient information (means, standard deviations or standard errors and number of sub- jects) to calculate an effect size were contacted with a request for additional data. Authors of studies who only reported results on depressive symptoms as continuous vari- ables were requested to perform additional analyses using a dichotomized classification of a depressed and control group based on the appropriate cut-off for the instrument used to assess depressive symptoms. Authors of studies whose origi- nal articles did not contain adjusted results were contacted with a request to perform additional analyses adjusting for as many of the following confounders if available: age, sex, socio-economic status or education, ethnicity, smok- ing, alcohol use, BMI; physical activity, presence of somatic disease and antidepressant or mood stabilizer use. If mul- tiple adjusted analyses had been conducted, the results

corrected for the largest number of potential confounders were included in the meta-analysis.

The quality of the studies was determined by assessing the risk of bias by two independent reviewers (CNB and MB) in three domains: selection bias, information bias and con- founding. Disagreements were settled by discussion. Risk of bias assessment in observational studies requires consider- ation of the risks specific to the subject of study. For this purpose we adapted a tool by Hayden et al. (2006) (see Appendix B). Low risk of bias was defined as a score of 4.5 or higher (on a 5 point scale).

2.3. Meta-analysis

Analyses were performed with comprehensive meta-analysis (CMA) software version 2.2.064. Effect sizes (Hedges' g) were calculated and pooled using a random effects model, as considerable heterogeneity was expected. A p-value < 0.05 was considered significant. Possible publication bias was tested by inspecting the funnel plot, by the statistical significance of the Egger's test of the intercept (Sterne and Egger, 2001) and Duval and Tweedie's (2000) trim and fill procedure.

To examine heterogeneity, the I^2-statistic was calculated. Values of 25%, 50% and 75% indicate low, moderate and high heterogeneity, respectively (Higgins et al., 2003). The 95% confidence intervals around I^2 (Ioannidis et al., 2007) were calculated using the non-central chi-squared-based approach within the heterogi module for STATA version 11.0 for Mac.

When a minimum of three samples per subgroup was available, analyses were performed categorized by: type of depression (MDD, BD, depressive symptoms above the ques- tionnaire cut-off level), laboratory method for measuring oxidative stress (chromatography [coupled to either mass- spectrometry or electrochemical detection] vs. immuno- assay), biological specimen used (urine, blood[product] or other), low or high risk of bias score, and adjusted versus unadjusted results. Studies that accounted for at least age, sex and one life-style variable (either by matching, restric- tion, adjustment or testing for baseline group differences) were defined as corrected for confounding.

3. Results

3.1. Search results, study characteristics and risk of bias scoring

3.1.1. 8-OHdG

After removal of duplicates, 79 records were assessed based on title and abstract. The full-text of 39 of these records was retrieved for further assessment. Of these studies 6 did not report sufficient information in the original articles to calculate an effect size and none was provided by authors on request (Irie et al., 2001, 2002, 2003; Maes et al., 2009;

Iida et al., 2011; Ceylan et al., 2013). In 2 studies both 8- OHdG and depression were measured but the association between the two was not the focus of study and therefore not analyzed (Wu et al., 2009; Ceprnja et al., 2011), nor was this data provided on request. In total 10 studies met all criteria for inclusion; 4 studies on depressive symptoms (Kupper et al., 2009; Wei et al., 2009a,b; Yi et al., 2012), 2 studies on MDD (Irie et al., 2005; Forlenza and Miller, 2006), 3 studies on BD (Ceylan et al., 2012; Soeiro-de-Souza et al., 2013; Huzayyin et al., 2014) and 1 study with both MDD and BD patients (Jorgensen et al., 2013) (Fig. 1). Two of the included studies (Yi et al., 2012; Jorgensen et al., 2013) provided additional data on request.

The 10 studies (Irie et al., 2005; Forlenza and Miller, 2006; Kupper et al., 2009; Wei et al., 2009a,b; Yi et al., 2012; Ceylan et al., 2012; Soeiro-de-Souza et al., 2013; Jorgensen et al., 2013; Huzayyin et al., 2014) included a total of 579 subjects with depression (332 with depressive symptoms [scoring above the cut-off of the instrument used], 141 with MDD, 106 with BD) and 729 controls. All included studies were published between 2005 and 2014. The studies include samples from the general population (N = 2), psychiatric in- and outpatient clinics (N = 4), hospital oncology (N = 2) and heart failure departments (N = 1) and 1 unreported source (Table 1). Risk of bias was scored as low in 3 studies and high in 7 studies (Appendix C).

3.1.2. F2-isoprostanes

After removal of duplicates, 221 records were assessed based on title and abstract. The full-text of 30 of these records was retrieved for further assessment. Of these stud- ies 1 did not report sufficient information in the original article to calculate an effect size and none was provided by authors on request (Freund-Levi et al., 2011). In one study both F2-isoprostanes and depression were measured but the association between the two was not the focus of study and therefore not analyzed nor provided on request (Janicki- Deverts et al., 2009). The samples of Rawdin et al. (2013) and Wolkowitz et al. (2011a) overlap, leaving 8 original sam- ples eligible for inclusion, 3 on depressive symptoms (Chung et al., 2009; Segal et al., 2012; Milaneschi et al., 2013) and 5 on MDD (Fig. 1). Six of the included studies provided additional data upon request (Chung et al., 2009, 2013; Yager et al., 2010; Wolkowitz et al., 2011a; Segal et al., 2012; Milaneschi et al., 2013).

The 8 studies (Dimopoulos et al., 2008; Chung et al., 2009, 2013; Yager et al., 2010; Wolkowitz et al., 2011a; Segal et al., 2012; Pomara et al., 2012; Milaneschi et al., 2013) include a total of 293 subjects with depression (144 subjects with depressive symptoms, 149 with MDD) and 2178 controls. All included studies were published between 2008 and 2013. The studies include samples of adults from the general population (N = 2), elderly adults form the general population (N = 3), psychiatric outpatients (N = 1), systemic lupus erythematosus (SLE) patients (N = 1) and fibromyalgia patients (N = 1) (Table 2). Risk of bias was scored as low in 3 studies and high in 5 studies (Appendix C).

3.2. *Meta-analyses*

3.2.1. *8-OHdG*

The overall effect size (Hedges' g) including all 10 studies on 8-OHdG in the meta-analysis was 0.31 (95% CI 0.06, 0.56), I^2 = 75% (95% CI 58—86%) indicating 8-OHdG is significantly increased in depression (Fig. 2a and Table 3). Egger's test for publication bias was not significant (p = 0.69). The effect size adjusted for publication bias by Duval and Tweedie's trim and fill procedure (two trimmed studies) increased marginally to 0.37 (95% CI 0.13, 0.61) indicating no or lit- tle effects of publication bias (see Appendix D for funnel plot).

Subgroup analyses in the 8-OHdG studies showed signif- icantly larger effect sizes for studies that were conducted in plasma or serum vs. those in urine (p < 0.001) and stud- ies that were performed with immuno-assays vs. those with chromatography (p = 0.006). Studies with a low risk of bias showed a significantly lower effect size compared to stud- ies with a higher risk of bias (p = 0.02). Subgroup analyses by type of depression (depressive symptoms or BD vs. MDD) and results corrected and uncorrected for confounders revealed no significant differences (Table 3).

3.2.2. *F2-isoprostanes*

The overall effect size (Hedges' g) including all 8 stud- ies on F2-isoprostanes in the meta-analysis was 0.48 (95%

Table 1 *Study characteristics of the included studies on the association of 8-OHdG with major depressive disorder, bipolar disorder and depressive symptoms.*

8-OHdG	Study													
	design	description	disorder	N	N	method	specimen	analysis	Socio demo-graphics	Life-style	Somatic disease	AD\mod stabiliz-ers	correction confounding	Hedges' g (95% CI)
Forlenza and Miller (2006)	CC	General population	MDD	62	85	DSM-IV (DISH)	Serum	ELISA	+	+	+	+	+	0.47 (0.14, 0.80)
Irie et al. (2005)	CC	Psychiatric outpatients	MDD	30	60	DSM-IV	Leukocytes	HPLC/ED	–	–	–	–	–	0.76 (0.31, 1.21)
Jorgensen et al. (2013)	CC	Psychiatric department	MDD[a]	26	27	DSM-IV (MINI)	Urine	UPLC/MS	±	±	–	+	+	−0.07 (−0.81, 0.67)
	CC	Psychiatric department	MDD[b]	23	27	ICD-10 psychiatrist	Urine	UPLC/MS	±	±	+	–	+	−0.10 (−0.85, 0.65)
	CC	Psychiatric department	BD[c]	6	27	ICD-10 psychiatrist	Urine	UPLC/MS	±	±	+	–	+	−0.15 (−1.13, 0.82)
Ceylan et al. (2012)	CC	Not reported	BD	36	14	DSM-IV (SCID)	Blood nos	GC/MS	–	–	–	–	–	−0.23 (−0.83, 0.38)
Soeiro-de-Souza et al. (2013)	C	Psychiatric outpatients	BD	50	50	DSM-IV (SCID)	Plasma	ELISA	±	–	–	+	–	1.15 (0.74, 1.57)
Huzayyin et al. (2014)	CC	Specialist psychiatric clinic	BD	14	16	DSM-IV (SADS-L)	Lymph-oblasts	ELISA	±	–	–	–	–	0.17 (−0.53, 0.87)
Kupper et al. (2009)	C	Heart failure outpatients	DS	38	72	BDI ≥ 10	Serum	ELISA	–	–	–	–	–	0.14 (−0.25, 0.53)
Wei et al. (2009a)	CC	Oncology department	DS	52	30	HAM-D ≥ 20	Serum	ELISA	±	±	+	–	+	0.81 (0.35, 1.28)
Wei et al. (2009b)	CC	Oncology department	DS	63	43	HAM-D ≥ 20	Serum	ELISA	+	–	+	–	+	0.64 (0.25, 1.04)
Yi et al. (2012)														
Males	C	Municipal workers	DS	105	196	CES-D ≥ 16	Urine	HPLC/ED	±	+	–	+	+	−0.01 (−0.25—0.23)
Females	C	Municipal workers	DS	74	136	CES-D ≥ 16	Urine	HPLC/ED	±	+	+	+	+	−0.09 (−0.37, 0.19)

BD, bipolar disorder; BDI, Beck Depression Inventory; C, cohort; CC, case—control; CES-D, Centre for Epidemiological Studies Depression Scale; DISH, Depression Interview and structured Hamilton Interview; DS, depressive symptoms; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; ELISA, enzyme-linked immunosorbent assay GC/MS, gas chromatography/mass spectrometry HAMD, Hamilton Depression Rating Scale; HPLC/ED, high-performance liquid chromatography/electrochemical detector; ICD-10, International Statistical Classification of Diseases and Related Health Problems; MDD, major depressive disorder; MINI, Mini International Neuropsychiatric Interview; NOS, not otherwise specified; SADS-L, Schedule for Affective Disorders and Schizophrenia, lifetime version; SCID, structured clinical interview for DSM-IV; UPL/MS, ultra performance liquid chromatography/mass spectrometry.

[a] *Subsample of patients in Jorgensen et al. (2013) described in the article as M-DEP (moderately depressed) patients.*

[b] *Subsample of patients in Jorgensen et al. (2013) described in the article as S-DEP (severely depressed patients unipolar only).*

[c] *Subsample of patients in Jorgensen et al. (2013) described in the article as S-DEP (severely depressed, bipolar only).*

[d] *Socio-demographics include age, sex, socio-economic status (income, education or other), ethnicity. Lifestyle: smoking, alcohol, BMI, physical activity. Somatic disease: presence of (chronic) disease (cardiovascular, infectious, auto-immune or malignancy) that may influence oxidative stress levels. Antidepressant/mood stabilizers: current use. +, confounders is accounted for; –, confounder is not accounted for; ±, some, but not all of the confounders in the category have been accounted for. Studies are defined as corrected (+) if the have accounted for age, sex and at least on life-style variable.*

Table 2 *Study characteristics of the included studies on the association between F2-isoprostanes and major depressive disorder and depressive symptoms.*

F2-isops	Study design	Sample description	Depressive disorder	Patients N	Controls N	Diagnostic method	Biological specimen	F2-isoprostane analysis	Confounders[a]				Overall correction confounding	Effect size Hedges' g (95% CI)
									Socio demographics	Life-style	Somatic disease	AD \mood stabilizers		
Chung et al. (2013)	CC	General population	MDD	18	36	DSM-IV (SCID)	Urine	GC/MS	±	±	+	+	+	1.12 (0.53, 1.72)
Dimopoulos et al. (2008)	CC	General population >60 years	MDD	33	33	DSM-IV psychiatrist	Plasma	ELISA	±	±	+	+	+	1.11 (0.60, 1.63)
Pomara et al. (2012)	CC	General population >60 years	MDD	28	19	DSM-IV (SCID)	CFS	ELISA	±	±	−	−	+	0.88 (0.28, 1.48)
Yager et al. (2010)	CC	General popluation	MDD	57	74	DSM-IV (DISH)	Serum	ELISA	+	+	+	+	+	0.45 (0.10, 0.80)
Wolkowitz et al. (2011a)	CC	Psychiatric outpatients	MDD	13	14	DSM-IV (SCID)	Plasma	GC/MS	+	+	+	+	+	−0.16 (−0.89, 0.58)
Chung et al. (2009)	CC	Fibromyalgia patients	DS	28	20	CES-D ≥ 16	Urine	GC/MS	−	−	+	−	−	0.37 (−0.20, 0.94)
Milaneschi et al. (2013)														
Males	C	General	DS	31	996	GDS ≥ 5	Urine	RIA	+	+	+	−	+	0.30 (−0.06, 0.66)
Females	C	population 70—79 years	DS	52	896	and/or AD use	Urine	RIA	+	+	+	−	+	−0.02 (−0.30, 0.26)
Segal et al. (2012)	CC	SLE patients	DS	33	90	CES-D ≥ 16	Plasma	GC/MS	±	±	−	−	+	0.38 (−0.02, 0.78)

AD, antidepressant; C, cohort; CC, case—control; CES-D, Centre for Epidemiological Studies Depression Scale; CFS, cerebrospinal fluid; DISH, Depression Interview and structured Hamilton Interview; DS, depressive symptoms; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders IV; ELISA, enzyme-linked immunosorbent assay; GC/MS, gas chromatography/mass spectrometry; GDS, geriatric depression scale; HAMD, Hamilton Depression Rating Scale; ICD-10, International Statistical Classification of Diseases and Related Health Problems; MDD, major depressive disorder; RIA, radio immuno assay; SCID, structured clinical interview for DSM-IV; SLE, systemic lupus erythematosus.[a] Socio-demographics include age, sex, socio-economic status (income, education or other), ethnicity. Lifestyle: smoking, alcohol, BMI, physical activity. Somatic disease: presence

Table 3 *Results of meta-analyses on the association of 8-OHdG and F2-isoprostanes with depressive symptoms, major depressive disorder and bipolar disorder.*

8-OHdG		N studies	Hedges' g	95% CI	p	I^2	95% CI
All studies (depressive symptoms, MDD, BD)		10	0.31	0.06, 0.56	0.01	75%	58—86%
Egger's test for publication bias[a]		10			0.69		
Subgroup analyses		N samples	Hedges' g	95% CI	p[f]	I^2	95% CI
Depression[b]	Depressive symptoms	4	0.27	−0.06, 0.60	0.67	78%	48—91%
	MDD	3	0.37	0.01, 0.74	Reference	48%	0—83%
	BD	4	0.28	−0.48, 1.05	0.83	83%	55—93%
Biological specimen[c]	Urine	2	−0.05	−0.22, 0.12		0%	0—79%
	Plasma/serum	6	0.52	0.18, 0.87	<0.01	75%	43—89%
Laboratory method	Chromatography	4	0.05	−0.20, 0.31		50%	0—79%
	Immunoassay	6	0.58	−0.28, 0.88	<0.01	66%	19—86%
Correction for confounders	Unadjusted	5	0.43	−0.07, 0.92		80%	53—92%
	Adjusted	5	0.23	−0.04, 0.51	0.50	69%	36—85%
Risk of bias score[d]	"Low" risk of bias	3	0.06	−0.15, 0.27		35%	0—74%
	"High" risk of bias	7	0.53	0.19, 0.87	0.02	72%	40—87%
F2-isoprostanes[e]		N studies	Hedges' g	95% CI	p	I^2	95% CI
All studies (depressive symptoms, MDD)		8	0.48	0.19, 0.77	0.001	73%	47—86%
Egger's test for publication bias[a]		8			0.13		
Subgroup analyses		N samples	Hedges' g	95% CI	p[f]	I^2	95% CI
Depression	Depressive symptoms	3	0.24	−0.05, 0.53		56%	0—86%
	MDD	5	0.70	0.28, 1.12	0.08	66%	13—87%
Biological specimen[c]	Urine	3	0.41	−0.06, 0.89		80%	48—92%
	Plasma/serum	4	0.49	0.08, 0.89	0.82	67%	3—89%
Laboratory method	Immunoassay	4	0.51	0.10, 0.92		81%	57—92%
	Chromatography	4	0.45	0.00, 0.90	0.84	61%	0—87%
Correction for confounders		NA					
Risk of bias score[d]	"Low" risk of bias	3	0.51	−0.10, 1.11		74%	40—89%
	"High" risk of bias	5	0.46	0.11, 0.81	0.90	77%	24—93%

BD, bipolar disorder; DS, depressive symptoms; MD, major depressive disorder; NA, not applicable; no or insufficient studies to perform the subgroup analysis.

[a] *See Appendix D for funnel plots.* [b] *Jorgensen et al. (2013) is counted in two categories because it describes stratified analyses of both MDD and BD patient*[c] *studies using specimens from others sources were excluded from this analysis (Irie et al., 2005; Huzayyin et al., 2014; Pomara et al., 2012).*

[d] *See Appendix C for risk of bias scores.*

[e] *Results of sensitivity analyses, excluding Pomara et al. (2012) with specimens from CSF (cerebrospinal fluid): all studies: Hedges' g 0.44, p 0.004; Egger's test: p 0.22. MDD: Hedges' g 0.66, p between subgroups 0.17; immunoassay: Hedges' g 0.44, p between subgroups 0.98, ''High'' risk of bias: Hedges' g 0.39, p between subgroups 0.75.*

[f] *p value between subgroups.*

Figure 2 *(a) Meta-analysis of 8-OHdG in depression (major depressive disorder [MDD], bipolar disorder [BD] and depressive symptoms [DS]) with effect sizes Hedges' g and 95% confidence intervals for the comparison of 8-OHdG levels with controls. (b). Meta-analysis of F2-isoprostanes in depression (major depres- sive disorder [MDD] and depressive symptoms [DS]) with effect sizes Hedges' g and 95% confidence intervals for the comparison of F2-isoprostane levels with controls.CI 0.19, 0.77), I^2 = 73% (95% CI 47—86%), indicating that*

F2-isoprostanes are significantly increased in depression (Fig. 2b and Table 3). Egger's test was not significant (p = 0.13) and the effect size adjusted for publication bias by Duval and Tweedie's trim and fill procedure (no trimmed studies) was unchanged, indicating no significant effects of publication bias (see Appendix D for funnel plot).

A sensitivity analysis was performed excluding one study (Pomara et al., 2012) as this study measured oxidative stress centrally (in cerebrospinal fluid) as opposed to periph- eral measurements (blood and urine) used in all others. Exclusion of this study did not affect the overall results (Hedges' g 0.44, p = 0.004; Table 3). Subgroup analyses in F2-isoprostanes showed a trend level difference between studies assessing depressive symptoms vs. MDD with the MDD studies showing a larger effect size (p = 0.08). Subgroup anal- yses by biological specimen used, laboratory method for oxidative stress measurement and risk of bias score revealed no significant differences (Table 3). No subgroup analyses were performed based on correction for confounders as only one study was defined as uncorrected.

4. Discussion

This meta-analysis found that both oxidative stress mark- ers, 8-OHdG and F2-isoprostanes, are increased in subjects with depression (major depressive disorder, bipolar disorder and depressive symptoms) compared to controls, with effect sizes in the small to moderate range (Cohen, 1988). In addi- tion, subgroup analyses of the 8-OHdG studies revealed that some of the variation in the results may be explained by the type of the biological specimen and/or the laboratory method for oxidative stress measurement, and that studies with lower risk of bias reported significantly smaller effect sizes. Findings for F2-isoprostanes however, did not differ when analyzed by type of depression, biological specimen, laboratory method or quality.

The results indicate that depression is associated with increased oxidative damage to DNA and lipids (reflected by 8-OHdG and F2-isoprostanes respectively). These find- ings are in line with previous meta-analytic studies that reported decreased anti-oxidants and anti-oxidant enzymes in unipolar depression, and increased oxidative stress in both uni- and bipolar depression (Andreazza et al., 2008; Palta et al., 2014). Previously DNA damage in bipolar dis- order has been reported measured by increased levels of DNA strand breakage with the comet assay (Andreazza et al., 2007). Oxidative damage to proteins determined by the protein carbonyl assay has not yet been as widely studied, but increased levels have been reported in MDD and BD (Kapczinski et al., 2011; Magalhaes et al., 2012), however not consistently (Andreazza et al., 2009; Gubert et al., 2013). The oxidative stress markers used in this meta-analysis are among the most robust markers of oxida- tive stress currently available and have recognized roles in the pathophysiology various somatic diseases such as cardiovascular disease, cancer and diabetes (Dalle-Donne et al., 2006; Valavanidis et al., 2009). 8-OHdG is a biologi- cally important mutagenic DNA lesion, while F2-isoprostanes are known to be increased in atherosclerotic lesions and may also be biologically active in the pathogenesis of atherosclerosis (Ho et al., 2013). It should be noted that although both markers reflect oxidative damage they are not necessarily associated with each other. One study included in our meta-analysis (Yager et al., 2010) found no correlation between the two, suggesting that 8-OHdG and F2-isoprostanes reflect specific aspects of oxidative imbalance.

Although the main findings of this study are unlikely to be greatly influenced by publication bias, considerable heterogeneity between studies was found for both 8-OHdG and F2-isoprostanes. This heterogeneity may be explained by several factors. In the studies that examined 8-OHdG, patients in three bipolar disorder studies (Ceylan et al., 2012; Soeiro-de-Souza et al., 2013; Huzayyin et al., 2014) were not all currently depressed, but some were in a manic or euthymic state. This may account for the fact that two of these studies' results have the highest and lowest effect sizes included in the meta-analysis. In addition, the sub- group analyses in 8-OHdG studies demonstrated significant differences between studies based on risk of bias, with the studies with lower risk of bias finding smaller effects. There was also a significant difference in effect size in the subgroup analyses by biological specimen (higher in

plasma/serum than in urine) and by laboratory method used to measure oxidative stress (higher in immuno-assays than chromatography). With only one exception however, all the measurements using chromatography were done in urine samples, whereas all the immuno-assays for the measure- ment of 8-OHdG in were done in plasma or serum. Therefore, it cannot be determined whether this difference is based on the biological specimen or laboratory technique. 8-OHdG levels determined by immuno-assays are higher than those measured by chromatography, with the latter considered the gold standard. The correlation between the two methods is generally high (Yoshida et al., 2002) and so may not neces- sarily affect the strength of the association with depression. It has been reported that urinary 8-OHdG levels are more stable than those in plasma or serum, and therefore pos- sibly more reliable (Matsumoto et al., 2008). Although the subgroup analyses may help to explain the heterogeneity observed, the findings should be interpreted with consider- able caution, as the number of studies in the subgroups is small.

This meta-analysis confirms oxidative stress markers are increased in subjects with depression in cross-sectional stud- ies, but the underlying mechanisms explaining this link need to be examined further. Many behavioural factors that are related to increased exposure to ROS (smoking, alcohol use, overweight, physical activity)(Maritim et al., 2003; Dalle- Donne et al., 2006; Valko et al., 2007) are also

associated with depression (Glassman et al., 1990; Abu-Omar et al., 2004; Sullivan et al., 2005; Luppino et al., 2010). It cannot be ruled out that the association is partially driven by these or other lifestyle confounders. The majority of the included studies took some, but few took all of these potential con- founders into account. The results of studies that did correct for confounders did not differ significantly from studies that did not, strengthening the observation that an association between depression and oxidative stress is present inde- pendent of these life-style factors. The observed increased levels of oxidative stress in depression might be under- stood within the concepts of allostasis and allostatic load. The former refers to the physiological adaptation to physi- cal, psychological, social and environmental stressors. The latter refers to the physical ''wear and tear'' induced by prolonged exposure to the stress response (McEwen and Wingfield, 2003). Depression has been found to be associ- ated with increased ''wear and tear'' or accelerated cellular ageing reflected by decreased telomere length in depressed patients (Verhoeven et al., 2013). Dysregulations in the major stress systems (hypothalamic-pituitary-adrenal axis activity, autonomic nervous system function and inflam- matory functions) have been demonstrated in depression (Penninx et al., 2013) and these could be contributing to increased oxidative stress. Oxidative stress is closely related to the inflammatory pathway in particular. Pro-inflammatory cytokines are produced in reaction to oxidative stress and oxidative stress in turn amplifies the inflammatory response. High cortisol levels have been associated with increased levels of oxidative damage (Joergensen et al., 2011). The damage caused by this allostatic load experienced dur- ing mood episodes is hypothesized to render an individual more vulnerable to developing a following episode and at higher risk to develop somatic disease (Maes et al., 2011; Grande et al., 2012). The brain is particularly vulnerable to oxidative damage due to its high oxygen consumption and low anti-oxidants defences. There is evidence from post-mortem studies suggesting that in depression oxida- tive stress is increased (Wang et al., 2009; Che et al., 2010; Michel et al., 2012) and anti-oxidants are decreased (Gawryluk et al., 2011) in the brain.

This meta-analysis' strength lies in the focus on robust oxidative stress markers and in the comprehensive search that was conducted to identify all studies on the association of 8-OHdG and F2-isoprostanes with depression. Through additional data requests the number of studies eligible for inclusion was increased, and where possible adjusted data was obtained, mitigating the effects of possible pub- lication bias and increasing the reliability of the overall results.

There are also a number of important limitations. As is apparent from the number of included studies and subjects the evidence on 8-OHdG and F2-isoprostanes in depression is limited. The studies that were excluded because they only reported on depressive symptoms as a continuous measure (Irie et al., 2001, 2003; Iida et al., 2011) all found a positive association. Therefore it is most likely that they would not have altered the overall result. Furthermore, the covariates used in the adjusted analyses varied widely. Therefore it was not possible to assess the effects of adjustment on the results satisfactorily. Information on diet and anti-oxidant supplement use was not available for most studies and there- fore it cannot be ruled out this factor may have had an effect. In addition, the use of antidepressants or mood stabi- lizers could also be sources of confounding that were often not investigated. There is some evidence to suggest that antidepressants, lithium and other mood stabilizers protect against oxidative stress (Behr et al., 2012; Khairova et al., 2012; de Sousa et al., 2014) Studies addressing their effects on F2-isoprostanes however found an increase (Chung et al., 2013) or no effect on oxidative stress levels (Rawdin et al., 2013).

In conclusion, the finding that both 8-OHdG and F2- isoprostanes are increased in depression strongly suggests that depression is accompanied by increased oxidative dam- age. This finding supports the hypothesis that increased metabolic stress is present in depression, which could poten- tially contribute to the higher risk of somatic morbidity and mortality in sufferers. There is a need for future larger scale studies on oxidative stress in depression, in which the role of treatment effects should be addressed.

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