8-Hydroxy-2'-Deoxyguanosine and Reactive Oxygen Species as Biomarkers of Oxidative Stress in Mental Illnesses: A Meta-Analysis

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Objective   Mental illnesses may be caused by genetic and environmental factors. Recent studies reported that mental illnesses were accompanied by higher oxidative stress level. However, the results were inconsistent. Thus, present meta-analysis aimed to analyse the association between oxidative DNA damage indicated by 8-hydroxy-2'-deoxyguanosine (8-OHdG) or 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), which has been widely used as biomarker of oxidative stress, and mental illnesses, including schizophrenia, bipolar disorder and depression. As oxidative DNA damage is caused by reactive oxygen species (ROS), systematic review and meta-analysis were also conducted to analyse the relationship between ROS and these three mental illnesses.

Methods   Studies from 1964 to 2020 (for oxidative DNA damage) and from 1907 to 2021 (for ROS) in Pubmed and Scopus databases were selected and analysed using Comprehensive Meta-Analysis version 2 respectively. Data were subjected to meta-analysis for examining the effect sizes of the results. Publication bias assessments, heterogeneity assessments and subgroup analyses based on biological specimens, patient status, illness duration and medication history were also conducted.

Results   This meta-analysis revealed that oxidative DNA damage was significantly higher in patients with schizophrenia and bipolar disorder based on random-effects models whereas in depressed patients, the level was not significant. Since heterogeneity was present, results based on random-effects model was preferred. Our results also showed that oxidative DNA damage level was significantly higher in lymphocyte and urine of patients with schizophrenia and bipolar disorder respectively. Besides, larger effect size was observed in inpatients and those with longer illness duration and medication history. Significant higher ROS was also observed in schizophrenic patients but not in depressive patients.

Conclusion   The present meta-analysis found that oxidative DNA damage was significantly higher in schizophrenia and bipolar disorder but not in depression. The significant association between deoxyguanosines and mental illnesses suggested the possibility of using 8-OHdG or 8-oxodG as biomarker in measurement of oxidative DNA damage and oxidative stress. Higher ROS level indicated the involvement of oxidative stress in schizophrenia. The information from this study may provide better understanding on pathophysiology of mental illnesses.   **Psychiatry Investig 2021;18(7):603-618**

Key Words   Mental illness, Schizophrenia, Bipolar disorder, Depression, DNA damage, Meta-analysis, 8-OHdG.

INTRODUCTION

Mental illnesses have been affecting 970 million of people all over the world in recent decades.[1] The prevalence (point estimate per 100,000) of severe mental illnesses such as schizophrenia, bipolar disorder and depression is 282, 594, and 3,627

respectively.[2] These disorders had been also listed as main contributors of burden of disability with the percentage of 2.8% in schizophrenia, 2.4% in bipolar disorder and 11.8% in depression.[3] However, the underlying pathophysiology of these mental illnesses remains unknown. Lately, rising evidence postulate the involvement of oxidative stress in developing mental illnesses as brain is vulnerable to oxidative stress due to its structures (i.e., rich with lipid) and functions (i.e., high consumption of oxygen, moderate antioxidant system, presence of reducing agents such as iron and copper, and presence of neurotransmitters with reduced capacity).[4-6]

Oxidative stress occurs when there is imbalance between oxidative and antioxidative systems, leading to the damage to cells, lipids, deoxyribonucleic acids (DNAs) or other compo-

nents.[7,8] This imbalance occurs when reactive oxygen species (ROS) such as superoxide radical, hydroxyl radical, and hydrogen peroxide (H_2O_2) are overproduced. Due to shorter lifespan and higher reactivity, the direct measurement of ROS may not be accurate. Thus, indirect measurement of oxidative stress using parameter of oxidative damage becomes the substitution.[9]

Oxidative DNA damage which is one of the consequences of oxidative stress usually occurs on guanine nucleobase as it is easier to be oxidised compared to others.[10] The excess ROS will hydroxylate guanine bases and form 8-hydroxyguanine (8-OH-Gua), producing 8-hydroxy-2'-deoxyguanosine (8-OHdG) through electron abstraction or 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) via keto-enol tautomerism of 8-OHdG. However, the terms of 8-OHdG and 8-oxodG are usually used as the same compound in most of the literatures. This production results in oxidative DNA damage, one of the main forms of DNA damage leading to DNA modification with altered functions.[11,12] Since these mutagenic deoxyguanosines can cross the cell membrane easily, they are more often referred as the indicator of oxidative damage[13] and further classified as a biomarker in early detection of various diseases.[14]

Weakened antioxidative defence system including decreased antioxidants and antioxidant enhancing enzymes is involved in mental illnesses.[15] Besides, the association between higher level of oxidative stress markers with mental illnesses further suggests the involvement of oxidative stress in pathophysiology of mental illnesses.[8,16,17] Increased oxidants and decreased antioxidants have been reported in brain and peripheral tissues of patients.[15] Oxidative damage has been strongly associated with mental illnesses. Both genetic and environmental factors may cause defects in DNA repair system, thus causing the accumulation of DNA damage which will further lead to changes in neuronal structures and functions.[11] This relationship was also reported by Christensen et al.,[18] in which 8-oxodG level was significantly higher in urine and cerebrospinal fluid of deceased patients with severe mental illnesses, thus indicating oxidative DNA damage was the major oxidative damage.

There are now several studies published that address oxidative DNA damage in patients with mental illnesses using various samples. Due to different methodological approaches and perspectives, these studies come to inconsistent conclusions. Hence, this present meta-analysis study aimed to analyse the association between oxidative DNA damage indicated by 8-OHdG or 8-oxodG level in patients with mental illnesses, particularly schizophrenia, bipolar disorder and depression. Furthermore, as oxidative DNA damage is caused by excess ROS, we also aimed to systematically review and analyse the association between ROS and each mental illness for further evidence of oxidative stress in each mental illness.

METHODS

Study search and selection
Databases of PubMed and Scopus were used to search for studies. For meta-analysis of oxidative DNA damage, studies published between 1964 and August 2020 were selected, using keywords of ("8-hydroxy-2'-deoxyguanosine" OR "8-OHdG" OR "oxidative damage" OR "DNA damage") AND ("major mental illness" OR "schizophrenia" OR "bipolar disorder" OR "depression" OR "depressive disorder"). Meanwhile for systematic review and meta-analysis of ROS, keywords of ("reactive oxygen species" OR "ROS" OR "hydrogen peroxide" OR "superoxide radical" OR "hydroxyl radical") AND ("major mental illness" OR "schizophrenia" OR "bipolar disorder" OR "depression" OR "depressive disorder") were used to search for studies published between 1907 and March 2021. Articles of non-English language, non-human subjects such as in vitro or animal studies, and non-research such as review, meta-analysis, overview, book, chapter, editorial or letter were excluded using filter option of database. The studies met the following inclusion criteria were selected: 1) articles were published in peer-reviewed journal, 2) diagnostic methods were reported, 3) both cohort and healthy subjects were included, 4) level of 8-OHdG or 8-oxodG or ROS in living subjects was presented, and 5) enough data to calculate effect size were provided (for meta-analysis only). The flow diagrams of study selection for oxidative DNA damage and ROS are shown in Figures 1 and 2 respectively.

Data extraction and analysis
First author's name, publication year, demographic characteristics (age and gender), diagnostic method, disease type, patient status, illness duration, medication and specimen were extracted from each study. The mean and standard deviation or other data forms of 8-OHdG or 8-oxodG and ROS levels were extracted to calculate each effect size respectively. The characteristics of studies included in analysis of oxidative DNA damage and ROS are shown in Tables 1 and 2 respectively.

Comparison of 8-OHdG or 8-oxodG and ROS levels between patients with mental illnesses (schizophrenia, bipolar disorder and depression respectively) and healthy controls were analysed in present study using Comprehensive Meta-Analysis (CMA) version 2 (Biostat, Englewood, NJ, USA). Effect sizes (Hedges' g) and 95% confidence intervals were pooled using fixed-effect and random-effects models. A random-effects model was preferred when high heterogeneity was present,[19] whereas a fixed-effect model was preferred for analysing small number of studies.[20] A p-value of less than 0.05 ($p<0.05$) was considered significant. The heterogeneity was tested using Q statistic value and I-squared (I^2), in which $I^2 \leq 25\%$, $25\% < I^2 \leq 50\%$ and high $I^2 > 50\%$ indicating low, moderate and high heterogeneity
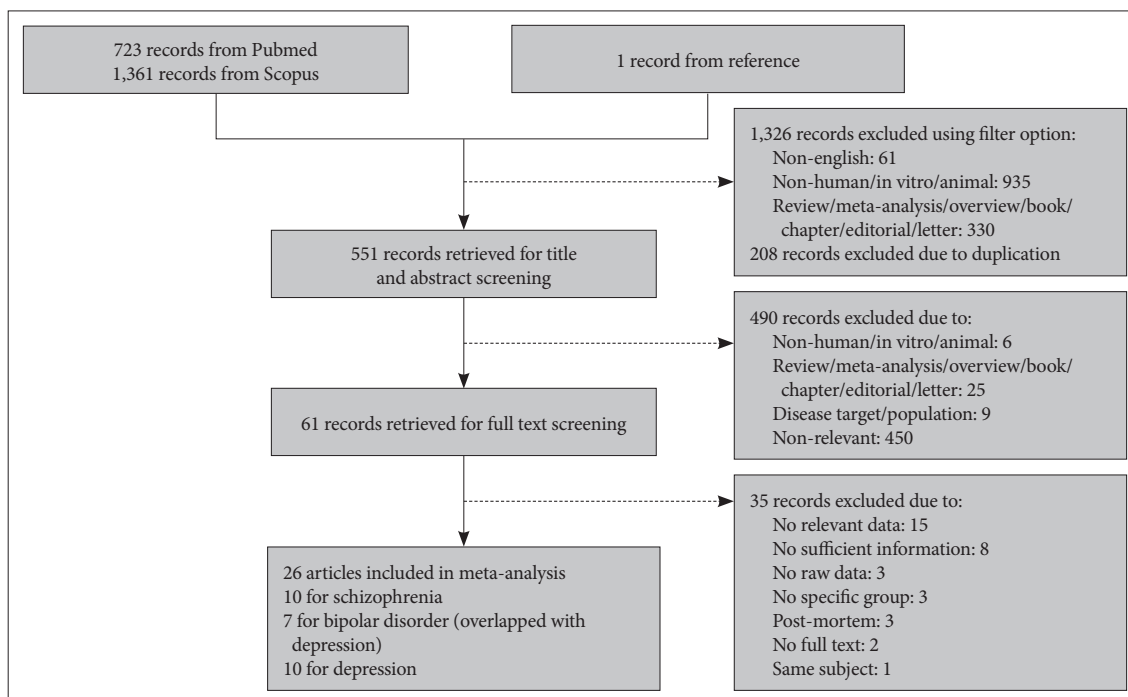
Figure 1. Flow diagram of study selection for meta-analysis of oxidative DNA damage.

respectively. Publication bias was checked using Egger's test[21] and it was adjusted using trim-and-fill test[22] if bias was present. Besides, subgroup analyses were performed in order to examine the 8-OHdG or 8-oxodG level according to specimens (lymphocyte, plasma/serum and urine), patient status (inpatients and outpatients), illness duration (less than 10 years and below, more than 10 years) and medication (no medication and on medication) in each illness, with minimum of two studies for each category. Subgroup analysis was also performed to examine ROS level according to medication history.

RESULTS

Meta-analysis of oxidative DNA damage

Oxidative DNA damage in schizophrenia

After screening, 10 studies with total of 1,026 subjects (546 patients and 480 controls) were included in the schizophrenic group. The 8-OHdG or 8-oxodG level was significantly higher (random-effects, Hedges's g=1.310, 95% CI=0.491 to 2.130, p=0.002) in schizophrenic patients compared to healthy controls (Figure 3A) with the heterogeneity I^2 of 97.7% [Q=609.08; df(Q)=14; p<0.001]. Publication bias tested using Egger's test was not significant (p=0.967).

Oxidative DNA damage in bipolar disorder

The literature search produced 7 studies with total subjects of 874, consisting of 513 patients and 361 controls. The oxida-

tive DNA damage level was significantly increased (random-effects, Hedges's g=0.463, 95% CI=0.263 to 0.622, p<0.001) in patients with bipolar disorder (Figure 3B). The heterogeneity I^2 was 62.6% [Q=32.08; df(Q)=12; p=0.001]. In addition, there was no evidence of publication bias (p=0.771).

Oxidative DNA damage in depression

A total of 10 studies were included in present analysis, with 2,176 total subjects (671 patients and 1,505 controls). Mean effect size (Hedges' g) on oxidative DNA damage was -0.410 (95% CI=-0.495 to -0.324) in the fixed-effects model with no significant difference in the random-effects model (Figure 3C). Due to high heterogeneity [I^2=98.8%, Q=895.45; df(Q)=11; p<0.001], the random-effects model was chosen. Publication bias was significant (p=0.007). The funnel plot was asymmetric, and it was suggested that 5 studies were missing at the left side using Trim-and-Fill test (Figure 4). After adjustment, the imputed point estimate was -0.658 (95% CI=-0.737 to 0.579) based on the fixed-effect model whereas the imputed point estimate was -0.414 (95% CI=-1.088 to 0.260) based on the random-effects model.

Subgroup analyses

The results of all subgroup analyses were summarised in Table 3.

Biological specimens

Oxidative DNA damage levels in lymphocyte, plasma/serum

1,453 records from Pubmed
1,969 records from Scopus

2,127 records excluded using filter
option:
    Non-english: 106
    Non-human/in vitro/animal:
      1,550
    Review/meta-analysis/overview/
    book/chapter/editorial/
    letter: 471
254 records excluded due to
duplication

1,041 records retrieved for
title and abstract screening

1,020 records excluded due to:
    Non-human/in vitro/animal:
    241
    Review/meta-analysis/overview/
    book/chapter/editorial/letter:
    190
    Disease target/population: 129
    Non-relevant: 460

21 records retrieved for
full text screening

12 records excluded due to:
    No relevant data: 5
    No control: 4
    No mentioned diagnostic
      method: 1
    Non-living tissue: 1
    Overlapping sample: 1

9 articles included in
systematic review

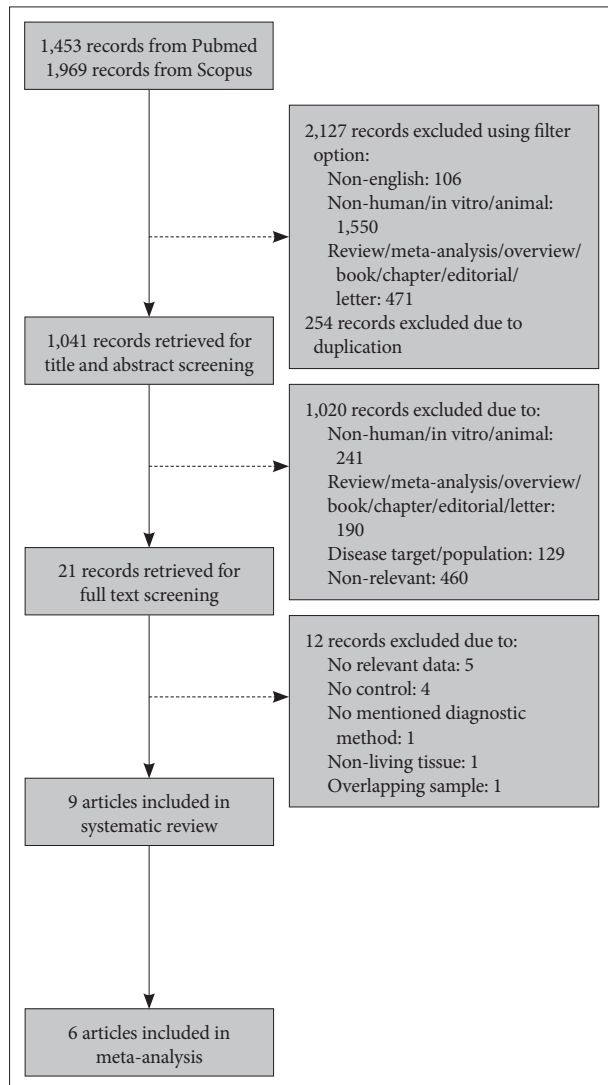6 articles included in
meta-analysis

Figure 2. Flow diagram of study selection for systematic review and meta-analysis of reactive oxygen species (ROS).

and urine were analysed as there were minimum of two studies for each specimen. Due to expected heterogeneity, a random-effects model was adopted for subgroup analyses. It can be seen that level of 8-OHdG or 8-oxodG was significantly increased in lymphocyte (p=0.013) of schizophrenic patients. Meanwhile in bipolar disorder, significant higher oxidative DNA damage level was observed in urine specimen only (p<0.001). In depressed patients, no significant changes of 8-OHdG or 8-oxodG level were detected in their plasma/serum or urine.

Patient status

Based on this subgroup analysis, significant oxidative DNA damage occurred only in the inpatients with schizophrenia and bipolar disorder (p<0.001 for both). There was no subgroup analysis for inpatients of depression as there was only one study.

Illness duration

Patients with schizophrenia (p=0.016) and bipolar disorder (p<0.001) for more than 10 years showed significantly larger effect size in oxidative DNA damage. No subgroup analysis was carried out for bipolar disorder patients with illness duration of 10 years and below as there was only one study.

Medication history

Schizophrenia patients, as well as bipolar disorder patients, who received medication showed significantly higher (p<0.001) oxidative DNA damage. No significant association was found in those without medication. In this subgroup analysis, only unmedicated depressed patients were included, as there was only one study that reported medicated patients.

Systematic review and meta-analysis of ROS

A total of 9 articles were included in present systematic review after screening. As 3 articles were not providing raw data,[49,50,54] thus only 6 articles were included in meta-analysis. The study outcomes are shown in Table 2.

In schizophrenia, ROS was significantly higher in patients in comparison to healthy controls (fixed-effect, Hedges's g=0.712, 95% CI=0.269 to 1.154, p=0.002) (Figure 5A). As heterogeneity was low, thus fixed-effect model was chosen [I^2=16.2%, Q= 1.193; df(Q)=1; p=0.275].

In depression, ROS was not significantly different between patients compared to healthy controls (random-effects, Hedges's g=0.306, 95% CI=-0.239 to 0.851, p=0.271) (Figure 5B). The heterogeneity I^2 was 87.2% [Q=54.527; df(Q)=7; p<0.001]. Publication bias tested using Egger's test was not significant (p=0.751).

As schizophrenia group was only comprised of unmedicated patients, thus subgroup analysis based on medication history was only conducted in depression group (Table 4). However, no significant difference was observed in both medicated and unmedicated depressive patients.

DISCUSSION

The present meta-analysis found enhanced oxidative DNA damage indicated by 8-OHdG or 8-oxodG level in both schizophrenia and bipolar disorder patients. Our results were in agreement with the findings of previous meta-analyses on oxidative stress.[8,16,58-60] To the best of our knowledge, this is the first meta-analysis study of the association between 8-OHdG or 8-oxodG level with schizophrenia. Redox imbalances, oxidative stress and impaired DNA damage repair, which may initiate cellular stress responses, have been observed in schizophrenia patients,[30,61] especially those with a family history of schizophrenia.[62] This high neuronal oxidative stress may cause poor prognosis by

Table 1. Study characteristics of meta-analysis of oxidative DNA damage

Author (year)	Sample size (N)		Mean age (SD) (years)		Gender (male/female)		Diagnostic method	Disease type	Patient status	Illness duration (years/months)	Medication	Specimen
	Patient	Control	Patient	Control	Patient	Control						
Chestkov et al.[23] (2018)	55	30	38 (13)	37 (12)	55 males	30 males	ICD-10; DSM-IV	Paranoid	Outpatients	<3 years (N=24); 3–10 years (N=20); >10 years (N=66)	No medication	Lymphocyte
Ershova et al.[24] (2017)	69	30	Paranoid=41.5 (10.2); schizophreniform psychotic disorder= 41.8 (10.3)	41 (12)	69 males	30 males	ICD-10	Paranoid (N=58); schizophreniform psychotic disorder (N=11)	Inpatients	1–3 years (N=20); 3–10 years (N=15); 10–20 years (N=23)	No medication for at least one week prior to hospitalization	Lymphocyte/ plasma
Shmarina et al.[25] (2020)	40	25	40.4 (9.8)	18–63	40 males	25 males	ICD-10; DSM-IV	First episode of paranoid	Inpatients	NA	No appropriate treatment	Mononuclear cells
Jorgensen et al.[26] (2013)	40	40	33.0 (10.7)	31.4 (9.8)	20/20	20/20	ICD-10	Schizophrenia	Inpatients (60%) & outpatients	76 (36–189) months	40 patients on second-generation antipsychotics	Urine
Nordholm et al.[27] (2016)	35	30	23.3 (5.6)	24.7 (4.9)	18 males	19 males	ICD-10	First-episode schizophrenia	Outpatients	NA	Antipsychotics naïve	Urine
Ibrahim et al.[28] (2020)	150	150	Chronic schizophrenia with acute ischemic stroke=53.1 (3.9); chronic schizophrenia without acute ischemic stroke=51.6 (3.99)	51.5 (3.76)	150 males	150 males	DSM-IV	Chronic schizophrenia with acute ischemic stroke (N=150); chronic schizophrenia without acute ischemic stroke (N=150)	Inpatients	Chronic schizophrenia with acute ischemic stroke=13.8 (1.66) years; chronic schizophrenia without acute ischemic stroke=14.5 (2) years	Patients on antipsychotics	Serum
Ma et al.[29] (2020)	44	45	<25=4; 25–29=10; 30–34=10; ≥35=20	<25=4; 25–29=18; 30–34=10; ≥35=13	15/29	9/36	ICD-10	Schizophrenia	NA	100.9 (92.8) months	18 drug naïve; 26 medicated	Serum
Copoglu et al.[30] (2015)	64	80	Symptomatic remission=34.69 (7.69); without symptomatic remission=35.61 (10.2)	NA	42/22	NA	DSM-IV	Symptomatic remission (N=26); without symptomatic remission (N=38)	Outpatients	Symptomatic remission=12.08 (8.70); without symptomatic remission=11.84 (8.98)	All patients on antipsychotics	Serum
Şimşek et al.[31] (2016)	20	20	14.5 (1.6)	14.4 (1.5)	8/12	8/12	DSM-IV	First-episode psychosis	NA	13.1 (14.3) months	Antipsychotics naïve	Serum

Table 1. Study characteristics of meta-analysis of oxidative DNA damage (continued)

Author (year)	Sample size (N) Patient	Sample size (N) Control	Mean age (SD) (years) Patient	Mean age (SD) (years) Control	Gender (male/female) Patient	Gender (male/female) Control	Diagnostic method	Disease type	Patient status	Illness duration (years/months)	Medication	Specimen
Miyaoka et al.[32] (2015)	29	30	47.76 (12.50)	42.43 (14.42)	13/16	11/19	DSM-IV	Chronic schizophrenia	Inpatients & outpatients	17.76 (10.25) years	25 on antipsychotics; 4 no medication	Urine
Jacoby et al.[33] (2016)	148	70	41.9 (11.9)	36.7 (11.6)	32/22	20/15	ICD-10	Euthymic (N=77); depressive state (N=18); manic state (N=43); mixed state (N=10)	Inpatients & outpatients	15 (11.0) years	Patients on lithium, anticonvulsants, antipsychotics, selective serotonin reuptake inhibitor (SSRI)	Urine
Munkholm et al.[34] (2015)	168	80	40.9 (12.3)	36.3 (12.5)	25/12	23/17	DSM-IV	Euthymic (N=75); depressive state (N=63); manic state (N=24); mixed state (N=6)	Inpatients & outpatients	21.2 (13.0) years	Patients on lithium, anticonvulsants, antipsychotics, SSRI	Urine
Knorr et al.[35] (2019)	86	44	33 (25–42)	31 (24–41)	86 females	44 females	ICD-10; DSM-IV	49 bipolar type I; 37 bipolar type II	Outpatients	12.4 (9.8) years	Patients on antipsychotics, anticonvulsants, antidepressants, benzodiazepines	Urine
Soeiro-de-Souza et al.[36] (2013)	50	50	26.8 (4.5)	26.0 (4.0)	17/33	25/25	DSM-IV	Bipolar type I 26 in mania 24 in depressive	NA	5.0 (3.7) years	Pre-treatment	Plasma
Tsai and Huang[37] (2015)	23	40	41.3 (12.0)	30.4 (5.0)	13/10	20/20	DSM-IV	Bipolar type I (manic phase)	Inpatients	NA	Pre-treatment	Serum
Huzayyin et al.[38] (2014)	14	16	44.7 (10.9)	45.8 (13.5)	8/6	10/6	DSM-IV	10 bipolar type I; 4 bipolar type II	NA	NA	Lithium treatment	Lymphocyte
Ceylan et al.[39] (2020)	24	61	32.88 (7.80)	27.92 (8.21)	70.8% females	61.3% females	DSM-IV	Bipolar depression	Outpatients	NA	26% were drug free. Some patients on antidepressants, stabilizers, antipsychotics	Urine
Yi et al.[40] (2012)	179	332	Male=43.4 (10.3); female=41.5 (10.0)	Male=44.4 (11.1); female= 40.4 (10.7)	105/74	196/136	CES-D	Depressive symptoms	Outpatients	NA	NA	Urine

Table 1. Study characteristics of meta-analysis of oxidative DNA damage (continued)

Author (year)	Sample size (N)		Mean age (SD) (years)		Gender (male/female)		Diagnostic method	Disease type	Patient status	Illness duration (years/months)	Medication	Specimen
	Patient	Control	Patient	Control	Patient	Control						
Black et al.[41] (2017)	107	562	Remitted major depressive disorder= 44.4 (12.9); current major depressive disorder=41.2 (12.4)	41.1 (14.8)	Remitted major depressive disorder=69.7% females; current major depressive disorder=67.1% females	Remitted major depressive disorder= 60.9% females	CIDI	Remitted major depressive disorder (N=107); current major depressive disorder (N=316)	Outpatients	NA	Majority patients (remitted=86.6%; current=61.6%) no medication. Some on antidepressants, selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA)	Plasma
van Velzen et al.[42] (2017)	66	231	37.73 (10.06)	NA	33% males	NA	DSM-IV	Major depressive disorder and/or anxiety	Outpatients	NA	22% on SSRI	Plasma
Lindqvist et al.[43] (2017)	49	55	39.6 (14.7)	37.6 (13.9)	54% females	60% females	DSM-IV	Major depressive disorder	Outpatients	NA	Pre-treatment	Plasma
Forlenza and Miller[44] (2006)	84	85	28.7 (9.0)	28.9 (8.9)	16/68	16/69	DSM-IV	Depression	Outpatients	NA	No medication	Serum
Tsai and Huang[45] (2016)	21	40	49.6 (7.0)	33.0 (5.7)	4/17	10/30	DSM-IV	Major depressive disorder	Inpatients	NA	NA	Serum
Wei et al.[46] (2009)	52	30	55.95 (13.90)	NA	1.26 (0.46) male/ female ratio	NA	HAMD, SDS, SAS, SCL-90	Colorectal adenocarcinoma with depression	NA	NA	Pre-treatment	Serum
Wei et al.[47] (2009)	63	63	54.94 (14.67)	NA	1.33 (0.50) male/ female ratio	NA	HAMD, SDS, SAS, SCL-90	Gastric adenocarcinoma with depression	NA	NA	Pre-treatment	Serum
Liu et al.[48] (2014)	17	46	54.71 (8.10)	51.22 (8.32)	10/7	19/27	HADS-D screening	Type II diabetes mellitus with depression	NA	NA	NA	Leukocyte DNA

ICD: International Classification of Diseases, DSM: Diagnostic and Statistical Manual of Mental Disorders, CES-D: Center for Epidemiological Studies-Depression Scale, HAMD: Hamilton Depression Rating Scale, SDS: Self-Rating Depression Scale, SAS: Self-Rating Anxiety Scale, SCL-90: Symptom Checklist-90, HADS-D: Hospital Anxiety and Depression Scale, SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressant, DNA: deoxyribonucleic acid, N: number of patients, SD: standard deviation, NA: not available

Table 2. Study characteristics and outcomes of systematic review and meta-analysis of ROS

Author (year)	Sample size (N)		Mean age (SD) (years)		Gender (male/female)		Diagnostic method	Disease type	Patient status	Illness duration (years/months)	Medication	Specimen (parameter)	Study outcomes
	Patient	Control	Patient	Control	Patient	Control							
Dietrich-Muszalska et al.[49] (2005)	31	14	18–36	NA	NA	NA	DSM-IV	Paranoid schizophrenia	Inpatients	4 years	Patients were treated with atypical antipsychotics (risperidone, quetiapine, olanzapine)	Platelets (ROS: superoxide anion, H_2O_2, singlet oxygen, organic radicals)	ROS level in resting platelets was significantly higher in patients compared to healthy controls (p<0.05). After stimulated with thrombin, platelets from patients (increased 53%) showed decreased chemiluminescence compared to healthy controls (increased 101.5%).
Dietrich-Muszalska and Olas[50] (2009)	35	25	31.4 (7.3)	31.0 (6.8)	21/14	15/10	DSM-IV	Paranoid schizophrenia	Inpatients	8.9 (4.5) years	Patients were treated with atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine)	Platelets (superoxide anion radicals)	Superoxide anion radicals level was lower in patients compared to healthy controls (p=0.05). They suggested that the reduced level could be due to the formation of RNS.
Melamed et al.[51] (1998)	29	17	39.1 (6.3)	39.4 (6.1)	19/10	9/8	DSM-III	Schizophrenia	NA	9.5 (2.4) years	The patients did not take antipsychotics prior to hospitalization	Neutrophils (superoxide anion)	Superoxide anion production was significantly higher (with 34% more production) in patients in comparison to healthy controls (p=0.003).
Sirota et al.[52] (2003)	18	15	36.2 (5.8)	36.8 (5.6)	15/3	12/3	DSM-IV	Schizophrenia	NA	11 (9) years	The patients had not taken anti-psychotic medications prior to hospitalization for at least 3 months	Neutrophils (superoxide anion)	Superoxide anion production was significantly higher in patients compared to healthy controls (p=0.012).
Szuster-Ciesielska et al.[53] (2008)	29	30	48.2 (11.2)	41.3 (4.4)	14/15	15/15	DSM-IV	Unipolar depression & bipolar depression	NA	NA	Most of the patients had not taken medication for 3–7 days before the examination; 4 patients received different combinations of amitriptyline, sulpiride, clomipramine, perazine, levomepromazine, or imipramine	Polymorphonuclear cells (ROS: superoxide anion & H_2O_2)	Superoxide anion (p<0.05) and H_2O_2 (p<0.05) productions were significantly higher in patients compared to healthy controls.

Table 2. Study characteristics and outcomes of systematic review and meta-analysis of ROS (continued)

Author (year)	Sample size (N) Patient	Control	Mean age (SD) (years) Patient	Control	Gender (male/female) Patient	Control	Diagnostic method	Disease type	Patient status	Illness duration (years/months)	Medication	Specimen (parameter)	Study outcomes
Alcocer-Gómez et al.[54] (2014)	40	20	Non-treated= 54.4 (10.1); amitriptyline= 53.5 (9.8)	57 (3)	Non-treated =2/18; amitriptyline =1/19	2/18	DSM-IV	Melancholic depression	Outpatients	NA	20 patients were without treatment; 20 were treated with amitriptyline for 12.1 (2.3) months	Peripheral blood mononuclear cells (mitochondrial superoxide)	Mitochondrial superoxide production was significantly higher in unmedicated patients in comparison to healthy controls ($p<0.001$). Significantly increased production was also observed in patients treated with amitriptyline ($p<0.05$ between unmedicated and medicated patients; $p<0.001$ between medicated patients and healthy controls).
Atanackovic et al.[55] (2004)	10	11	33.0 (7.4)	28.0 (4.2)	2/8	4/7	ICD-10	Minor depression	Inpatients	NA	Patients were on psychotherapy but not on psychopharmacological treatment	Phagocytes (ROS)	No significant difference in ROS production was observed between patients and healthy controls.
Chang et al.[56] (2015)	35	35	39.14 (10.23)	39.37 (8.5)	13/22	11/24	DSM-IV	First-episode major depressive disorder	Outpatients	NA	Patients were under sertraline treatment for 12 weeks	Blood (superoxide radicals and hydroxyl radicals)	No significant differences in superoxide radicals ($p=0.38$) and hydroxyl radicals ($p=0.26$) levels were observed between patients before treatment of sertraline and healthy controls. However, both levels were significantly decreased after treatment of sertraline for 12 weeks ($p<0.001$).
Rybka et al.[57] (2013)	15	19	59.7 (1.91)	62.3 (2.84)	NA	NA	ICD-10	Recurrent depressive disorder	NA	NA	60% were treated with selective serotonin reuptake inhibitor (SSRIs), 35% with serotonin-norepinephrine reuptake inhibitor (SNRIs), and 15% with tricyclic antidepressant (TCAs), either as monotherapies or in various combinations	Plasma (H_2O_2)	Plasma H_2O_2 concentration was significantly higher in patients in comparison to healthy controls ($p=0.005$).

DSM: Diagnostic and Statistical Manual of Mental Disorders, ICD: International Classification of Diseases, ROS: reactive oxygen species, H_2O_2: hydrogen peroxide, N: number of patients, SD: standard deviation
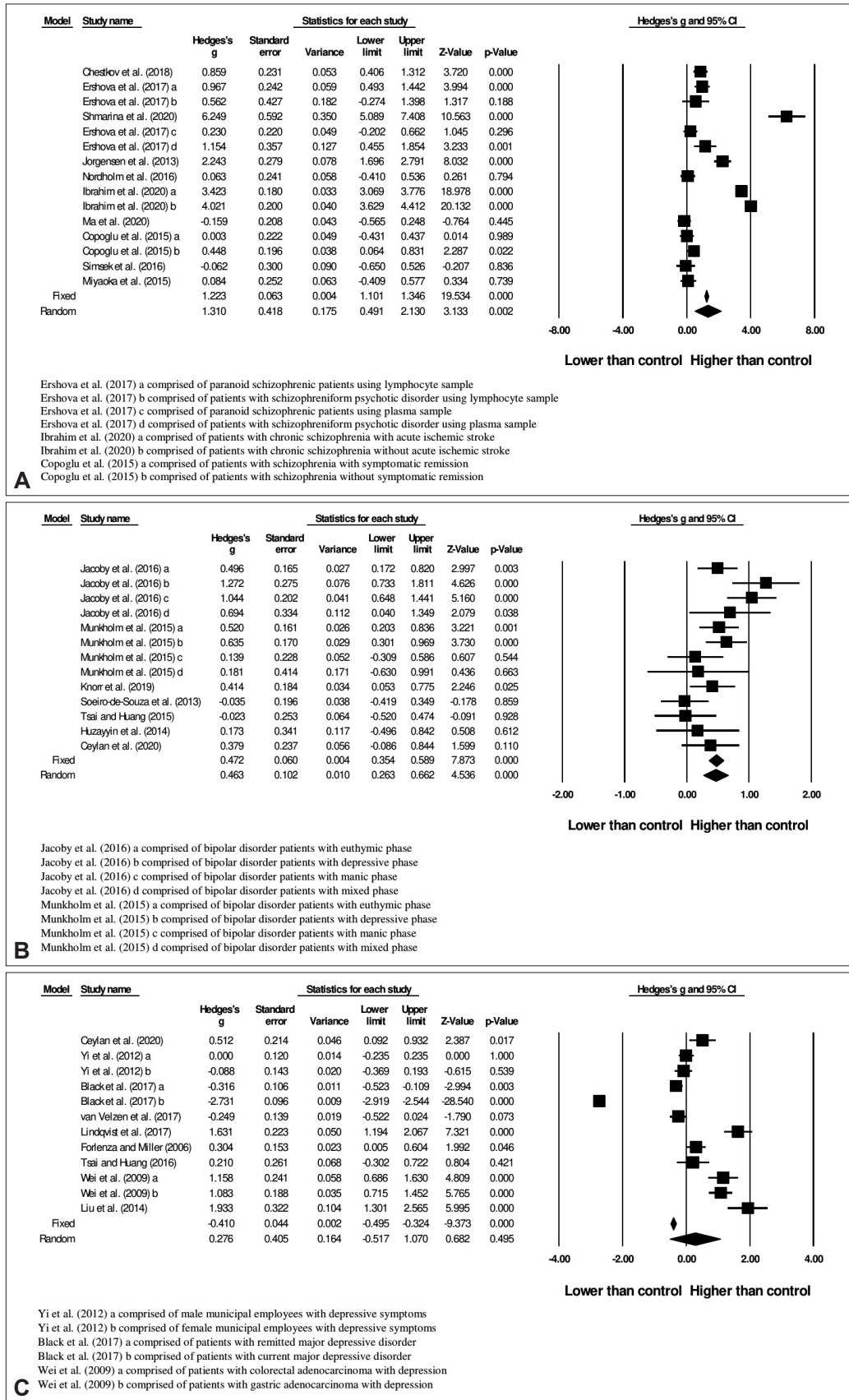
Figure 3. Meta-analysis of oxidative DNA damage (8-OHdG or 8-oxodG) in (A) schizophrenia, (B) bipolar disorder, and (C) depression.[23-48]
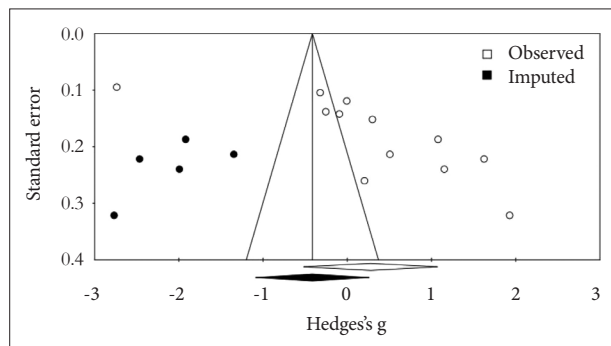
Figure 4. Funnel plot of oxidative DNA damage in depression (random-effects model).

disturbing metabolic activity, gene expression and cellular dysfunction. Besides, association between oxidative DNA damage and schizophrenia was also supported by previous post-mortem finding, that increased 8-OHdG was found in neuronal cytoplasm in hippocampus of elderly schizophrenic patients with poorer outcome.[63]

Bipolar disorder is the mental illness characterised by periodic episodes of mania (bipolar type I) or hypomania (bipolar type II) and depression.[64] The symptom severity was found to be correlated with DNA damage.[65] In a twin-case report, higher level of oxidative stress markers which may lead to lipid and protein oxidation with consequence of increased DNA damage was observed.[66] Increased DNA damage was also found in twins as a trait because the lesion remained higher in comparison to healthy controls even after treatment of mood stabilization. Previous meta-analysis[16] had first reported a larger effect size of DNA and RNA damage than our current study, due to their inclusion of both peripheral blood samples and post-mortem brain samples as well as measurements other than 8-OHdG or 8-oxodG. Post-mortem studies also demonstrated the involvement of DNA damage in bipolar disorder, particularly DNA fragmentation in anterior cingulate cortex[67] as well as in frontal cortex, pons, medulla, and thalamus.[68] From our result, it can be seen that the effect size of bipolar disorder was smaller than that of schizophrenia. This could be due to the occurrence of peripheral oxidative imbalance in the active phases of bipolar disorder only.[69]

It has been hypothesized that stressful life events leading to oxidative stress that involved in the pathophysiology of depression.[70,71] Previous meta-analyses found that increased oxidative stress and decreased antioxidant level were associated with greater depressive symptoms.[17,72,73] As we discussed before, high oxidative stress level is associating with oxidative DNA damage. However, no association between oxidative DNA damage with depression was found in present study according to random-effects model. It contrasted with the findings of previous meta-analysis study.[74] This may be due to the different inclusion criteria used. In previous study, bipolar disorder, major depres-

Table 3. Subgroup analyses for oxidative DNA damage in each illness

Subgroup	Category	Effect model	Schizophrenia				Bipolar Disorder				Depression			
			Number of studies	Hedges' g (95% CI)	p-value	I² (%)	Number of studies	Hedges' g (95% CI)	p-value	I² (%)	Number of studies	Hedges' g (95% CI)	p-value	I² (%)
Specimen	Lymphocyte	Random	3	2.073 (0.441 to 3.704)	0.013*	96.2	-	-	-	-	-	-	-	-
	Plasma/serum	Random	5	1.136 (-0.127 to 2.399)	0.078	98.5	2	-0.030 (-0.440 to 0.381)	0.887	0	7	0.128 (-0.864 to 1.120)	0.801	99.1
	Urine	Random	3	0.791 (-0.564 to 2.146)	0.253	95.4	4	0.581 (0.397 to 0.764)	<0.001*	51.1	2	0.140 (-1.478 to 1.757)	0.866	65.2
Patient status	Inpatients	Random	4	2.312 (1.341 to 3.283)	<0.001*	97.7	3	0.564 (0.332 to 0.796)	<0.001*	64.5	-	-	-	-
	Outpatients	Random	3	0.343 (-1.008 to 1.695)	0.619	66.6	2	0.398 (-0.072 to 0.868)	0.097	0	6	-0.124 (-1.070 to 0.822)	0.798	99.0
Duration of illness	10 years and below	Random	5	0.723 (-0.312 to 1.758)	0.171	88.6	-	-	-	-	-	-	-	-
	More than 10 years	Random	3	1.601 (0.304 to 2.899)	0.016*	98.9	3	0.603 (0.393 to 0.813)	<0.001*	54.7	-	-	-	-
Medication history	No medication	Random	4	0.538 (-0.628 to 1.703)	0.366	66.3	2	-0.030 (-0.440 to 0.381)	0.887	0	6	0.119 (-1.102 to 1.339)	0.849	99.2
	On medication	Random	6	1.982 (0.893 to 3.071)	<0.001*	98.6	5	0.559 (0.380 to 0.737)	<0.001*	49.3	-	-	-	-

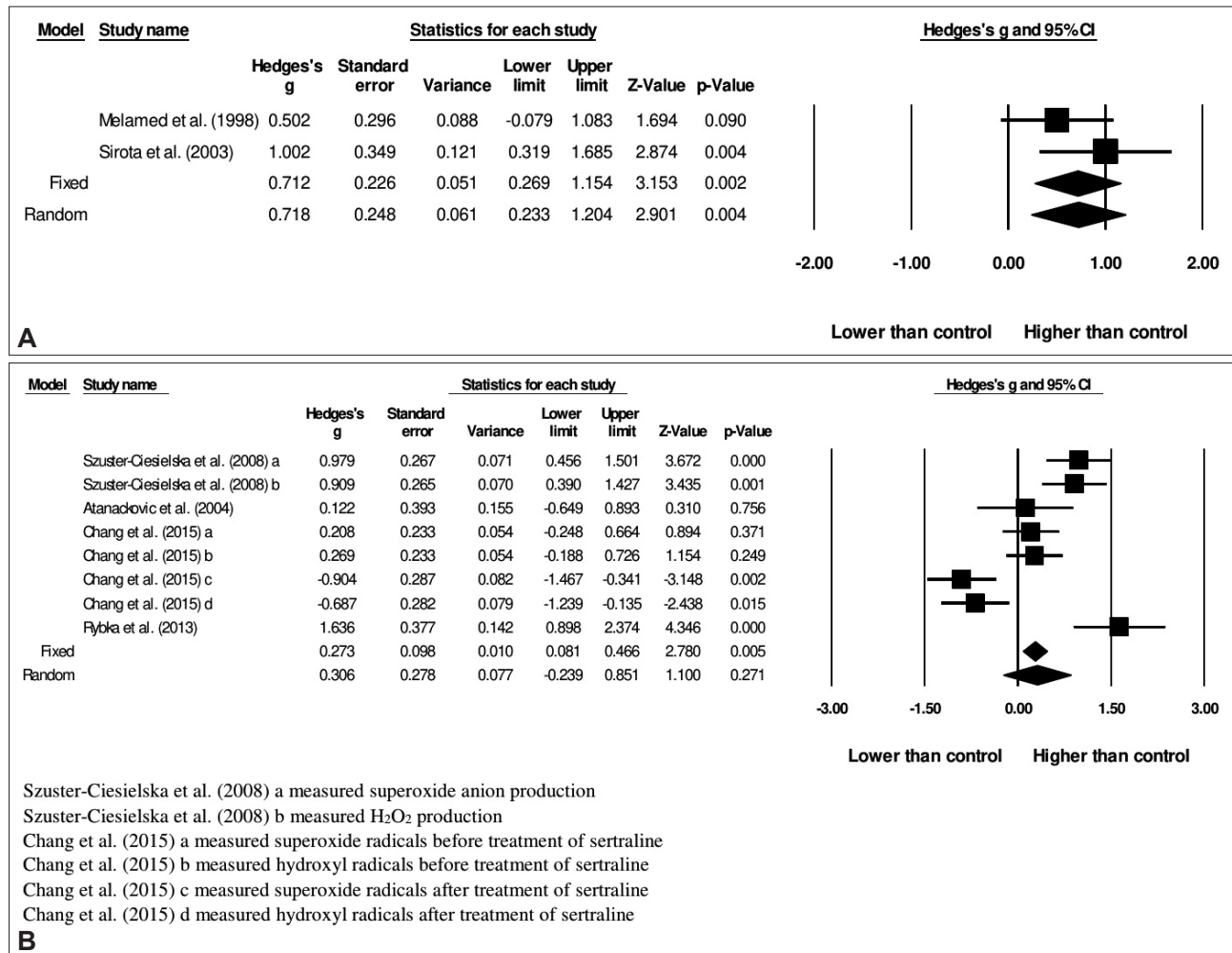*p<0.05 indicating significant result. CI: confidence interval, I²: I-square

Figure 5. Meta-analysis of reactive oxygen species in (A) schizophrenia and (B) depression.[49-57]

Table 4. Subgroup analyses for reactive oxygen species in depression

Subgroup	Category	Effect model	Depression			
			Number of studies	Hedges' g (95% CI)	p-value	I^2 (%)
Medication history	No medication	Random	3	0.504 (-0.143 to 1.152)	0.127	56.0
	On medication	Random	2	-0.040 (-0.892 to 0.812)	0.926	93.9

CI: confidence interval, I^2: I-square

sive disorder and depression were classified as the same category, whereas we excluded bipolar disorder in the present analysis. Among the patients with major depressive disorder, the antidepressant users contrarily showed lower oxidative DNA damage. However, the precise roles of antidepressants in anti-inflammation and antioxidative action are not fully understood.[41]

Due to the presence of heterogeneity and the wide distribution of data in forest plot, results obtained with random-effects model were preferred. High heterogeneity found in the present analysis may be due to several reasons such as clinical differences and single study designs.[75] The different effect sizes found in subgroup analyses may also indicate the heterogeneity. On the other hand, since publication bias was not significant in the analyses of schizophrenia and bipolar disorder, thus it was not the reason causing high heterogeneity. However, significant publication bias may contribute certain extents to high heterogeneity in the analysis of depression. This publication bias may be due to the design of single studies, submission of results by researchers, rejection of negative studies by journals, source funding of studies and design of reviews or meta-analyses.[76] The adjustment using Trim-and-Fill test showed that studies were missing at the left side of funnel plot. Thus, this significant publication bias might increase awareness in future to publish any results especially negative results (no effect or opposite ef-

fects) which are failed to prove their hypotheses.[77]

Subgroup analyses were performed to determine the oxidative DNA damage in different biological specimens, patient status, illness duration and medication history for each mental illness. We found significant oxidative DNA damage in lymphocyte of schizophrenia patients and in urine of bipolar disorder patients. It may reflect the possibility of different mechanisms of oxidative DNA damage in each mental illness. As the major product of oxidative DNA damage, 8-OHdG or 8-oxodG will be released into bloodstream after being repaired and then be excreted by kidneys into urine. Hence, the plasma level of these deoxyguanosines may indicate how much oxidative stress has been exposed. It may represent the balance between DNA repair and clearance into urine within a period of time. However, some claimed that non-invasive urinary 8-oxodG originated from DNA of various tissues is better alternative in reflecting general oxidative stress as it is not dependent on changes of DNA repair and plasma clearance.[78,79] On the other hand, peripheral lymphocytes are also being suggested in reflecting overall oxidative stress status of a whole organism because of their circulation in the body.[80] Since many are questioning about the most favourable body samples to be selected in determining the level of deoxyguanosines,[81] our findings may help future studies in choosing specific samples for each mental illness.

In this study, only inpatients of schizophrenia and bipolar disorder had significant oxidative DNA damage whereas no significant association was found in depression. The higher oxidative DNA damage among inpatients was accordance with the previous meta-analysis[59] that chronic schizophrenia inpatients had lower antioxidants and higher oxidants whereas higher concentration of antioxidants was found in the stable medicated outpatients even though their lipid peroxidation was high. It was also suggested that longer illness duration might have cumulative effect in oxidative stress.[82-84] Our subgroup analyses also showed that higher oxidative DNA damage was significantly evident in both schizophrenic and bipolar disorder patients with illness duration of more than 10 years. Interestingly, medicated schizophrenic and bipolar disorder patients showed more oxidative DNA damage. This is evidenced by the role of clozapine in increasing oxidative stress and DNA damage due to long-term use of high doses, accompanied with reduced glutathione (GSH) level and glutathione peroxidase (GSH-Px) activity that function as ROS scavengers.[85] In addition, N-methyl-D-aspartate receptor (NMDAR) hypofunction may be inversely associated with oxidative stress in pathophysiology of schizophrenia. To enhance NMDAR efficacy, the inhibition of D-amino acid oxidase (DAAO) activity was suggested.[86] It is known that the metabolism of D-amino acids by DAAO generates hydrogen peroxide which may result in oxidative damage.[87] The application of sodium benzoate as DAAO inhibitor

in clozapine-resistant schizophrenia increased catalase activity in decomposing hydrogen peroxide.[88] Among antipsychotic medications, only blonanserin and risperidone owned stronger DAAO inhibitory effects based on in vitro study.[89] Besides, animal study also demonstrated that increased oxidative damage in rat brain was induced by haloperidol and clozapine but not by olanzapine and aripiprazole.[90] Antidepressant hydrazines such as isocarboxazid and phenelzine were also found to have a role in inactivating DNA when they react with oxygen and produce hydrogen peroxide.[91] Therefore, it can be assumed that the positive association between oxidative DNA damage and medication was correlated with patient status and illness duration. This could be due to the higher usage of antipsychotics in inpatients compared to outpatients.[92] Patients with longer illness duration were also assumed in taking more medications. No significant result was observed in depression as most of the patients were not hospitalized and not on medication.

As discussed, oxidative DNA damage is the consequence of oxidative stress that involves excessive ROS or RNS in impaired antioxidant mechanism.[93] To the best of our knowledge, there was no systematic review or meta-analysis done on ROS in schizophrenia, bipolar disorder and depression yet. The present study revealed that higher ROS level was found in particularly unmedicated schizophrenic patients. However, studies[49,50] also suggested the involvement of higher RNS level in schizophrenic patients treated with atypical antipsychotics. This was consistent with previous meta-analysis[8] which found increased nitric oxide (NO) which is one of the RNS in medicated schizophrenic patients. Hence, these excess ROS/RNS levels may be correlated with increased oxidative DNA damage in schizophrenia found in present meta-analysis. On the other hand, direct measurement of ROS has been less studied compared with NO[16] in patients with bipolar disorder. Meanwhile the current meta-analysis revealed that in depression, the non-significant differences in ROS level and oxidative DNA damage might be contributed by medication. Previous meta-analysis[17] also reported that there was no significant difference in NO level between depressed patients and healthy controls. Therefore, we can postulate that different types of antidepressant may affect oxidative stress level, for instance amitriptyline increased ROS production,[54] and sertraline decreased levels of superoxide radicals and hydroxyl radicals.[56] This could be also supported by in vitro study which found tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitor (SSRIs) induced oxidative stress by increasing production of ROS and reducing glutathione level.[94]

Our present study has several limitations. First, some studies were excluded in present analysis as the information was insufficient or raw data were not provided. Thus, there might be certain influences on the overall result. Second, the associ-

ation between oxidative DNA damage and other risk factors such as age[95] or smoking status[96] which have been found to have positive correlation with the damage was not analysed. We cannot rule out the possible effects of external factors such as diet or lifestyle on oxidative DNA damage to determine whether the damage is formed as the consequence of the illness. Besides, we were unable to evaluate the effect of specific antipsychotics drug as the subjects in studies were treated with variety of treatment. Furthermore, as there was insufficient number of studies, we were unable to conduct analysis of ROS level in bipolar disorder.

In conclusion, the present meta-analysis revealed that schizophrenia with the largest effect size and bipolar disorder were associated with increased oxidative DNA damage whereas no association between oxidative DNA damage and depression was observed. Subgroup analyses of oxidative DNA damage level in different biological specimens may indicate different mechanisms of lesion occurrence in different mental illness and may help future studies in choosing specific specimen for a particular mental illness. Other factors such as patient status, illness duration and medication history that may contribute certain effects on oxidative DNA damage need further investigation. The present study also revealed the relationship between high ROS level and schizophrenia but not in depression. More association studies between direct measurement ROS and oxidative DNA damage can be conducted in future to further confirm that 8-OHdG or 8-oxodG may have the potential to be used as biomarker of oxidative DNA damage and oxidative stress in mental illness, as well as to help in understanding the underlying pathophysiology of mental illnesses.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: all authors. Data curation: Xue Xin Goh. Formal analysis: Xue Xin Goh. Funding acquisition: Shiau Foon Tee. Investigation: all authors. Methodology: Xue Xin Goh. Project administration: Pek Yee Tang, Shiau Foon Tee. Resources: Pek Yee Tang, Shiau Foon Tee. Supervision: Pek Yee Tang, Shiau Foon Tee. Validation: Pek Yee Tang, Shiau Foon Tee. Writing—original draft: Xue Xin Goh. Writing—review & editing: Pek Yee Tang, Shiau Foon Tee.

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