Supplementary Online Content

Jorgensen A, Baago IB, Rygner Z, et al. Association of oxidative stress–induced nucleic acid damage with psychiatric disorders in adults: a systematic review and meta-analysis. *JAMA Psychiatry*. Published online August 3, 2022. doi:10.1001/jamapsychiatry.2022.2066

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Search Strategy, Data Extraction, and Covariates

Search strategy

PubMed and MEDLINE

Last search day: November 16, 2021

Search terms: (Deoxyribonucleic acid OR Ribonucleic acid OR DNA OR RNA OR nucleic acid)
AND
(oxidative OR oxidation OR oxidatively OR free radical OR reactive oxygen species OR ROS OR 8-oxo-7,8-dihydro-2-deoxyguanosine OR 8-oxo-7,8-dihydroguanosine OR 8OhdG OR 8-OhdG OR 8oxodG OR 8-oxodG OR 8OHG OR 8-OHG OR 8oxoGuo OR 8-oxoGUO)
AND
(mental disorders [Mesh] OR psychiatry [Mesh] OR depressive disorder [Mesh] OR anxiety disorders [Mesh] OR bipolar disorder [Mesh] OR stress, psychological [Mesh] OR obsessive-compulsive disorder [Mesh] OR schizophrenia [Mesh] OR psychotic disorders [Mesh] OR personality disorders [Mesh])

No limitations were made.

PsycINFO and EMBASE

Last search day: November 16, 2021

Search terms: (Deoxyribonucleic acid OR Ribonucleic acid OR DNA OR RNA OR nucleic acid)
AND
(oxidative OR oxidation OR oxidatively OR free radical OR reactive oxygen species OR ROS OR 8-oxo-7,8-dihydro-2-deoxyguanosine OR 8-oxo-7,8-dihydroguanosine OR 8OhdG OR 8-OhdG OR 8oxodG OR 8-oxodG OR 8OHG OR 8-OHG OR 8oxoGuo OR 8-oxoGUO)
AND
(mental disorders OR psychiatry OR depressive disorder OR anxiety disorders OR bipolar disorder OR stress, psychological OR obsessive-compulsive disorder OR schizophrenia OR psychotic disorders OR personality disorders)

No limitations were made.

Data extraction

Two authors (IBB and AJ) screened the articles for relevance by title and abstract. The selected articles were read in detail and assessed for eligibility following the inclusion criteria by two senior authors (HEP and AJ)). In case of disagreement, a consensus decision was made. A specific data extraction sheet was made for the study. The data extraction sheet was pilot tested on ten studies and subsequently refined. Data extraction was made by two authors independently (IBB+ZR) to eliminate errors and ensure validity. In case of disagreement, a senior co-author was consulted (HEP or AJ).

In the case of missing data regarding the main outcome measures, authors were contacted (twice of necessary) with a data request. If the authors did not respond or were unable to provide the data, but data were presented in a graph, we extracted numerical values from the graphs using an online tool (https://plotdigitizer.com/app). In all continuous variables, the preferred data format was mean and standard deviation (SD), and if the median, minimum-maximum values, standard error of the mean, and/or interquartile range were provided, data were transformed to mean and SD [1,2].

Covariates

The study characteristics extracted were first author name, year of publication; study design, and - where relevant - type of intervention. Biological matrix (plasma/serum, blood cells, urine, saliva, cerebrospinal fluid, and brain) was recorded, and anatomical brain regions were recorded and classified as cortical, hippocampal, or cerebellar. We extracted information on measurement methodology, classified as chromatography, ELISA, comet assay, immunostaining, or other. If multiple comet assay outcomes were reported for the same sample, only one measure (preferentially total strand breaks as measured by tail length) was extracted for analysis.

We assessed study quality with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) score [3]. STROBE score was rated by the two data extractors (IBB and ZR) independently. In the case of disagreement between the data extractors of ≤ 2 points, the highest score was used. In the case of disagreement with > 2 points, a senior co-author (AJ) scored the paper. Using cut-offs based on the STROBE score tertiles, we categorized studies as low, medium or high quality.

For each patient and control group, the covariates extracted were number of participants; age (mean and SD); gender distribution (percent females); smoking status (percent smokers); and body mass index (BMI) (mean and SD). The diagnoses of patient groups were extracted and allocated to five overall diagnostic categories, which corresponded to the World Health Organization's International Classification of Diseases (ICD)-10 F0-F4

categories: Dementias (DEM), substance use disorders (SUB), schizophrenia and other psychotic disorders (PSY), major depressive disorder (MDD), bipolar affective disorders (BIP), and anxiety disorders (ANX).
We extracted psychometric scale name(s) and score(s) (mean and SD). If more than one rating scale were used, a senior psychiatrist selected – if possible - the one considered the most clinically relevant. Standard cut-offs scores of each scale, if available, were used to categorize illness as mild, moderate or severe (eTable 1). In bipolar patients rated with both a mania and depression scale, patients were categorized by the more severe score. Finally, we extracted information on concurrent pharmacological treatment (Y/N), where no treatment was defined as no individuals in the population used medication for the disorder in question, but other medication was allowed; and active treatment was defined as ≥ 50% of the population used medication for the disorder in question. In other or unclear situations, the variable was rated “NA”.

eReferences

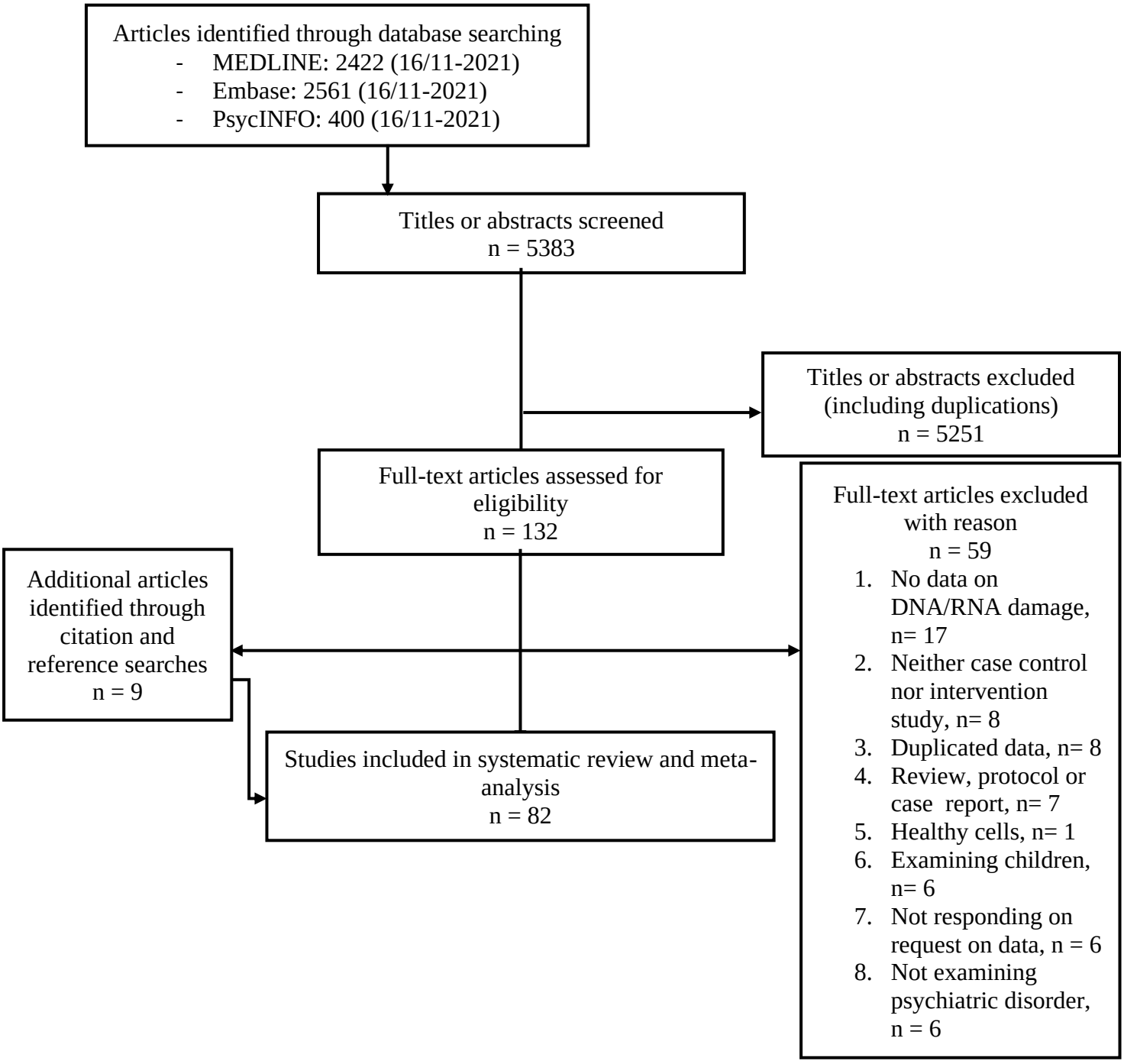
1. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res.* 2018;27(6):1785-1805.
2. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol.* 2014;14:135.
3. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 2007;370(9596):1453-1457.

eTable 1. Illness Severity

The following cut-off values were used to categorize severity of disease in patients. Only scales with established cut-offs for mild, moderate, and severe illness were included. In studies with other or no rating scale data, no severity measure was included.

Scale	Mild	Moderate	Severe
HAMD-17	<17	17-23	>23
HAMD-21	<19	19-25	>25
MADRS	<20	20-34	>34
BDI	<20	20-28	>28
YMRS	<26	27-37	<37
Y-BOCS	<14	14-25	>25
CGI	<4	4-5	>5
PANSS	<85	85-105	>105
MMSE	>21	11-21	<11
Braak stage	1-2	3-4	5-6

eFigure 1. PRISMA Flow Diagram of the Literature Search and Study Selection



eTable 2. Characteristics of Included Cross-sectional Studies

Summary

The studies were published from 1994-2021. The most commonly studied biological matrix was brain (number of patient-control group comparisons (NC) = 92), followed by urine (NC = 38), plasma/serum (NC = 35), blood cells (NC = 32), CSF (NC = 6), and saliva (NC = 2). The most commonly studied nucleic acid was nDNA (NC = 140), followed by RNA (NC = 53), and mtDNA (NC = 12). Dementias (DEM) were the most commonly studied diagnostic group (NC = 90), followed by schizophrenia and other psychotic disorders (PSY) (NC = 50), major depressive disorder (MDD) (NC = 27), bipolar affective disorders (BIP) (NC = 26), substance use disorders (SUB) (NC = 10), and anxiety disorders (ANX) (NC = 2). Nine matrix/molecule combinations (blood cell RNA and mtDNA, CSF RNA, plasma/serum RNA, salivary DNA, RNA and mtDNA, cerebellar mtDNA, and hippocampal mtDNA) contained =< 2 studies and were not meta-analyzed. Thirty studies were classified as low; 28 as medium and 24 as high quality (see eAppendix for definitions)

ID	Author, year	Country	STROBE score	Study quality	Disorder	Controls	n	Age	Female	Severity scale	Scale points	Patient severity	Drugs	Smokers	BMI	Matrix	Method	Nucleic acid	Marker
1	**Afifi et al. 2018**	Saudi Arabia	16	Medium	BIP	Healthy volunteers	P: 40 C: 25	P: 32.6±8.2 C: 24.4±4.6	P: 52.5 % C: 44.0 %	*NA*	*NA*	*NA*	P: Yes C: No	P: *NA* C: 0 %	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
2	**Ahmadimaneshet al. 2019**	Iran	19	High	MDD	Healthy volunteers	P: 25 C: 14	P: 37.0±8.7 C: 34.8±8.9	P: 64.0 % C: 50.0 %	HAM-D_{21}	P: 27.7±8.1 C: *NA*	Severe	P: No C: *NA*	P: 0 % C: 0 %	P: 26.2±4.6 C: 22.7±6.3	Blood cells	Comet	DNA	Strand breaks
																Plasma/serum	ELISA	DNA	8-OHdG
3	**Akkaya et al. 2017**	Turkey	13	Low	DEM	Elderly cases without history of neurological disorders	P: 67 C: 42	P: 73.2±18.9 C: 75.0±18.9	P: 50.0 % C: 73.8 %	MMSE	*NA*	*NA*	P: Yes C: *NA*	P: 0 % C: 0 %	*NA*	Blood cells	Comet	DNA	Strand breaks
4	**Alici et al. 2016**	Turkey	18	High	ANX	Healthy volunteers	P: 42 C: 38	P: 33.0±9.0 C: 33.0±7.0	P: 66.7 % C: 63.2%	Y-BOCS	P: 21.0±8.9 C: *NA*	Moderate	P: Yes C: *NA*	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
5	**Andreazza et al. 2007**	Brazil	15	Medium	BIP	Healthy volunteers	P: 32 C: 32	P: 43.3±12.7 C: 43.5±14.2	P: 71.9 % C: 59.4 %	HAM-D_{17}, YMRS	P: 6.3±7.4, 3.6±3.0 C: *NA*	Mild	P: Yes C: No	P: 0 % C: 0 %	*NA*	Blood cells	Comet	DNA	Damage
6	**Black et al. 2017**	The Netherlands	19	High	MDD	Healthy controls	P_1: 1,619 P_2: 610 C: 612	P_1: 41.2±12.4 P_2: 44.4±12.9 C: 41.1±14.8	P_1: 67.1 % P_2: 69.7 % C: 60.9 %	IDS-SR	P_1: 29.2±12.4 P_2: 14.3±9.0 C: 8.4±7.4	*NA*	P_1: No P_2: No C: *NA*	P_1: 44.9 % P_2: 35.4 % C: 26.3 %	*NA*	Plasma/serum	Chrom	DNA	8-OHdG
7	**Bradley-Whitman et al. 2013**	USA	16	Medium	DEM	Normal controls	P_1: 14 P_2: 7 P_3: 15 P_4: 12 C: 15	P_1: 85.8±6.4 P_2: 91.0±5.0 P_3: 80.8±5.4 P_4: 68.9±16.6 C: 86.3±5.4	P_1: 78.6 % P_2: 71.4 % P_3: 53.3 % P_4: 41.7 % C: 73.3 %	Median Braak Score	*NA*	*NA*	*NA*	*NA*	*NA*	Brain: TC, PC, CB	Chrom	RNA	8-OHG
8	**Ceprnja et al. 2011**	Croatia	15	Medium	ANX	Healthy controls	P: 46 C: 28	P: 43.0±6.0 C: 39.0±7.0	P: 0 % C: *NA*	*NA*	*NA*	*NA*	P: Yes C: *NA*	*NA*	*NA*	Urine	ELISA	DNA	8-OHdG
9	**Ceylan et al. 2018**	Turkey	18	High	BIP	Non-psychiatric controls	P_1: 37 P_2: 18 P_3: 20 C: 60	P_1: 36.3±10.3 P_2: 36.3±10.3 P_3: 40.8±9.2 C: 36.4±11.4	P_1: 64.9 % P_2: 66.7 % P_3: 35.0 % C: 55.0 %	HAM-D_{17}, YMRS	P_1: 1.7±1.6, 0.4±0.8 P_2: 0.5±0.9, 25.5±7.8 P_3: 23.0±4.6, 0.2±0.7 C: *NA*	Mild, moderate	P_1: Yes P_2: Yes P_3: Yes C: *NA*	P_1: 48.6 % P_2: 38.9 % P_3: 60.0 % C: 29.8 %	P_1: 26.9±4.9 P_2: 29.3±6.5 P_3: 22.7±10.3 C: 25.9±4.7	Blood cells	ELISA	DNA	8-OHdG
10	**Chang et al. 2015**	Taiwan	19	High	MDD	Medically healthy controls without history of major psychiatric disorders	P: 40 C: 70	P: 42.4±15.2 C: 38.0±12.5	P: 70.0 % C: 60.0 %	CGI	*NA*	*NA*	P: Yes C: No	P: 17.5 % C: 0 %	P: 22.1±3.3 C: 23.0±2.7	Blood cells	Other	mtDNA	8-OHdG
11	**Chang et al. 2014**	Taiwan	18	High	BIP	Medically healthy controls without history of major psychiatric disorders	P: 40 C: 70	P: 41.5±14.6 C: 38.0±12.5	P: 55.0 % C: 60.0 %	CGI	*NA*	*NA*	P: Yes C: No	P: 12.5 % C: 0 %	*NA*	Blood cells	Other	mtDNA	8-OHdG
12	**Che et al. 2010**	China	20	High	PSY, BIP, MDD	Non-neurologic non-psychiatric controls	P_1: 15 P_2: 15 P_3: 15 C: 15	P_1: 45.0±12.8 P_2: 42.0±11.2 P_3: 47.0±8.9 C: 48.0±10.5	P_1: 40.0 % P_2: 40.0 % P_3: 40.0 % C: 40.0 %	*NA*	*NA*	*NA*	P_1: Yes P_2: Yes P_3: Yes C: *NA*	*NA*	*NA*	Brain: ML	IHC	RNA	8-OHG 8-OHdG
13	**Chen et al. 2011**	Taiwan	17	Medium	SUB	Healthy controls without known physical or psychiatric illnesses	P: 79 C: 63	P: 41.0±7.0 C: 40.7±8.3	P: 15.2 % C: 7.9 %	CIWA-Ar-C	P: 10.7±5.9 C: *NA*	*NA*	*NA*	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
14	**Chestkov et al. 2018**	Russia	14	Low	PSY	Healthy controls with no history of any psychiatric disorder	P_1: 55 P_2: 55 C: 60	P_1: 38.0±13.0 P_2: 38.0±13.0 C: 37.0±12.0	P_1: 0 % P_2: 0 % C: 0 %	PANSS	*NA*	*NA*	P_1: No P_2: Yes C: *NA*	*NA*	*NA*	Blood cells	Other	DNA	8-oxodG

15	**Choromanska et al. 2017**	Poland	17	Medium	DEM	Patients attending follow up visits	P: 80 C: 80	P: 80.1±6.7 C: 80.1±6.7	P: 68.8 % C: 68.8 %	MMSE	P: 13.5±2.9 C: 27.4±3.1	Moderate	P: Yes C: Yes	P: 0 % C: 0 %	*NA*	Saliva, plasma/serum	ELISA	DNA	8-OHdG
16	**Christensen et al. 2018**	Denmark	19	High	PSY	Mentally healthy living controls	P_1: 107 P_2: 112 C: 321	P_1: 46.8±13.5 P_2: 52.4±12.5 C: 47.0±12.6	P_1: 21.5 % P_2: 72.3 % C: 21.5 %	*NA*	*NA*	*NA*	*NA*	*NA*	P_1: 25.5±1.4 P_2: *NA* C: 26.1±0.8	Urine	Chrom	DNA, RNA	8-oxodG 8-oxoGuo
17	**Coello et al. 2021**	Denmark	19	High	BIP	Healthy controls without personal or first-degree family history of psychiatric disorders	P: 360 C: 197	P: 30.6±9.5 C: 24.9±8.8	P: 65.0 % C: 64.5 %	HAM-D_{17}, YMRS	P: 9.7±7.4, 3.4±5.2 C: 0.7±1.5, 0.4±0.7	Mild	P: Yes C: *NA*	P: 43.9 % C: 11.2 %	P: 24.5±3.7 C: 24.0±3.0	Urine	Chrom	DNA, RNA	8-oxodG 8-oxoGuo
18	**Copoglu et al. 2015**	Turkey	15	Medium	PSY	Healthy volunteers with no history of any psychiatric disorder	P_1: 26 P_2: 38 C: 80	P_1: 34.7±7.7 P_2: 35.6±10.2 C: *NA*	P_1: 38.5 % P_2: 31.6 % C: *NA*	PANSS	*NA*	*NA*	P_1: Yes P_2: Yes C: *NA*	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
19	**Cui et al. 2020**	China	12	Low	PSY	Healthy controls	P: 54 C: 54	P: 38.4±11.6 C: 33.6±9.9	P: 66.7 % C: 75.9 %	*NA*	*NA*	*NA*	P: No C: *NA*	P: 16.7 % C: 14.8 %	P: 21.2±2.6 C: 21.3±2.3	Plasma/serum	ELISA	DNA	8-OHdG
20	**Czarny et al. 2015**	Poland	14	Low	MDD	Healthy controls without psychiatric disturbances	P: 40 C: 46	P: 40.8±15.0 C: 40.8±15.0	*NA*	*NA*	*NA*	*NA*	P: Yes C: *NA*	*NA*	*NA*	Blood cells	Comet	DNA	Strand breaks Alkali-labile sites
21	**Ding et al. 2006**	USA	10	Low	DEM	Control subjects	P_1: 6 P_2: 6 C: 6	P_1: 90.2±5.2 P_2: 81.1±8.8 C: 82.0±7.5	P_1: 66.7 % P_2: 66.7 % C: 50.0 %	Braak stage	P_1: 3.3±0.5 P_2: 5.8±0.4 C: 1.2±0.4	Moderate, severe	*NA*	*NA*	*NA*	Brain: PC	Other	RNA	8-OHG
22	**Dorszewska et al. 2009**	Poland	12	Low	DEM	Controls without verifiable symptoms of dementia or any other neurological disorder	P: 41 C: 51	P: 72.5±11 C: 51.1±21	P: 39.0 % C: 39.2 %	MMSE	*NA*	*NA*	*NA*	*NA*	*NA*	Blood cells	Chrom	DNA	8-oxo2dG
23	**Ershova et al. 2017**	Russia	16	Medium	PSY	Healthy controls with no history of any psychiatric disorder	P_1: 58 P_2: 11 P_3: 14 C: 30	P_1: 41.5±10.2 P_2: 41.8±10.3 P_3: 43.2±6.7 C: 41.0±12.0	P_1: 0 % P_2: 0 % P_3: 0 % C: 0 %	PANSS	*NA*	*NA*	P_1: No P_2: No P_3: No C: *NA*	*NA*	*NA*	Blood cells, plasma/serum	Other	DNA	8-oxodG
24	**Forlenza et al. 2006**	Canada	18	High	MDD	Healthy controls with no history of psychiatric illness	P: 84 C: 85	P: 28.7±9.0 C: 28.9±8.9	P: 81.0 % C: 81.2 %	HAM-D_{17}	P: 19.0±5.1 C: 0.4±0.9	Moderate	P: No C: No	P: 32.1 % C: 5.9 %	P: 29.2±9.7 C: 26.8±6.5	Plasma/serum	ELISA	DNA	8-OHdG
25	**Gabbita et al. 1998**	USA	14	Low	DEM	Controls without history of dementia or other neurological disorders or systemic diseases affecting the brain	P: 9 C: 11	P: 83.5±2.0 C: 77.6±2.6	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	Brain: FC, PC, TC, CB	Chrom	DNA	8-hydroxyguanine
26	**Gackowski et al. 2008**	Poland	13	Low	DEM	Controls matched by eating habits, age, body	P: 18 C: 33	P: 71.8±7.8 C: *NA*	P: 55.6 % C: 57.6 %	MMSE	*NA*	*NA*	*NA*	*NA*	*NA*	Blood cells, urine, CSF	Chrom	DNA	8-oxodG

						weight, smoking status													
27	**Götz et al. 2001**	Germany	14	Low	SUB	Controls without history or neuropathological evidence of neurologic or psychiatric disorders who had consumed alcohol only on special occasions	P: 12 C: 17	P: 62.9±9.0 C: 66.9±11.3	P: 25.0 % C: 41.2 %	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	Brain: FC, TC, PC, CB	Chrom	DNA, mtD NA	8-OHdG
28	**Hosseini-Ghalibaf et al. 2019**	Iran	19	High	BIP	Controls	P: 35 C: 35	P: *NA* C: 38.2±8.4	*NA*	MADRS	*NA*	*NA*	*NA*	*NA*	*NA*	Urine, saliva	ELISA	DNA	8-OHdG
29	**Huang et al. 2018**	Taiwan	17	Medium	SUB	Healthy controls with no known physical or psychiatric illnesses not fulfilling the diagnostic criteria for drug or alcohol abuse	P: 182 C: 71	P: 31.1±8.3 C: 27.1±7.7	P: 21.4 % C: 4.2 %	AUDIT	P: 4.0±6.0 C: *NA*	*NA*	*NA*	P: 95.2 % C: *NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
30	**Huang et al. 2014**	Taiwan	17	Medium	SUB	Alcohol dependence without delirium tremens	P: 16 C: 58	P: 44.4±8.4 C: 40.6±5.9	P: 0 % C: 12.1 %	CIWA-Ar-C	P: 30.4±7.2 C: 14.0±7.3	*NA*	*NA*	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
31	**Huzayyin et al. 2014**	Canada	16	Medium	BIP	Healthy controls with no personal or family history of psychiatric illness among 1st and 2nd degree relatives	P: 14 C: 16	P: 44.7±10.9 C: 45.8±13.5	P: 42.9 % C: 60.0 %	*NA*	*NA*	*NA*	P: Yes C: *NA*	*NA*	*NA*	Blood cells	ELISA	DNA	8-OHdG
32	**Ibrahim et al. 2020**	Egypt	14	Low	PSY	Healthy volunteers with no evidence of mental illness	P_1: 150 P_2: 150 C: 150	P_1: 51.6±4.0 P_2: 53.1±4.0 C: 51.5±3.8	P_1: 0 % P_2: 0 % C: 0 %	PANSS	P_1: 73.2±11.5 P_2: 80.1±10.0 C: *NA*	Mild	P_1: Yes P_2: Yes C: *NA*	P_1: 28.0 % P_2: 54.0 % C: 8.0 %	P_1: 23.7±3.0 P_2: 24.7±3.4 C: 23.3±2.9	Plasma/serum	ELISA	DNA	8-OHdG
33	**Irie et al. 2005**	Japan	19	High	MDD	Healthy controls	P: 30 C: 60	P: 49.4±13.7 C: 48.1±11.7	P: 33.3 % C: 33.3 %	CES-D	P: 21.4±11.3 C: 13.7±6.5	*NA*	P: Yes C: *NA*	P: 43.3 % C: 31.7 %	P: 23.1±3.5 C: 22.5±2.4	Blood cells	Chrom	DNA	8-OHdG
34	**Isobe et al. 2009**	Japan	13	Low	DEM	Neurologically normal patients who underwent lumbar anesthesia for minor surgery	P: 18 C: 15	P: 67.4±9.2 C: 65.7±9.2	P: 61.1 % C: 40.0 %	MMSE	P: 16.5±3.5 C: *NA*	Moderate	P: No C: *NA*	*NA*	*NA*	CSF, plasma/serum	Chrom	RNA	8-OHG
35	**Isobe et al. 2010**	Japan	13	Low	DEM	Controls with no neurological disease	P: 30 C: 30	P: 69.0±4.1 C: 64.8±16.4	P: 56.7 % C: 53.3 %	MMSE	P: 18.4±2.1 C: *NA*	Moderate	P: No C: *NA*	*NA*	*NA*	CSF	Chrom	DNA	8-OHdG
36	**Jacoby et al. 2016**	Denmark	18	High	BIP	Healthy controls	P: 54 C: 35	P: 41.9±11.9 C: 36.7±11.6	P: 40.7 % C: 42.9 %	HAM-D_{17}, YMRS	P: 5.1±5.5, 23.8±6.4 C: 1.7±1.9, 1.0±1.7	Mild	P: Yes C: *NA*	P: 57.4 % C: 20.0 %	P: 26.3±4.9 C: 22.6±4.0	Urine	Chrom	DNA, RNA	8-oxodG 8-oxoGuo

37	**Jørgensen et al. 2018**	Denmark	20	High	PSY, BIP, MDD	Type 2 diabetes mellitus and no psychiatric illness	P_1: 28 P_2: 8 P_3: 4 C: 1,312	P_1: 61.7±10.4 P_2: 59.0±11.9 P_3: 59.0±9.5 C: 64.7±11.5	P_1: 67.9 % P_2: 50.0 % P_3: 75.0 % C: 46.4 %	*NA*	*NA*	*NA*	*NA*	P_1: 63.0 % P_2: 42.9 % P_3: 50.0 % C: 33.9 %	P_1: 32.3±7.3 P_2: 29.8±4.9 P_3: 32.2±9.3 C: 29.6±5.2	Urine	Chrom	DNA, RNA	8-oxodG 8-oxoGuo
38	**Jørgensen et al. 2013**	Denmark	20	High	MDD	Healthy controls	P_1: 26 P_2: 29 C: 28	P_1: 41.7±8.5 P_2: 46.2±17.0 C: 38.9±13.7	P_1: 57.7 % P_2: 51.7 % C: 60.7 %	HAM-D_{17}	P_1: 18.6±2.4 P_2: 26.9±4.5 C: 1.0±1.4	Moderate, severe	P_1: No P_2: Yes C: *NA*	P_1: 42.3 % P_2: 44.8 % C: 10.7 %	P_1: 27.5±5.2 P_2: 24.3±4.7 C: 26.8±7.6	Urine	Chrom	DNA, RNA	8-oxodG 8-oxoGuo
39	**Jørgensen et al. 2013**	Denmark	18	High	PSY	Healthy controls	P: 40 C: 40	P: 33.0±10.7 C: 31.4±9.8	P: 50.0 % C: 50.0 %	PANSS	P: 89.1±16.5 C: *NA*	Moderate	P: Yes C: *NA*	P: 55.0 % C: 21.0 %	P: 27.2±5.7 C: 25.1±3.8	Urine	Chrom	DNA, RNA	8-oxodG 8-oxoGuo
40	**Kadioglu et al. 2004**	Turkey	13	Low	DEM	Healthy elderly people without verifiable symptoms of dementia or other neurological disorders	P: 24 C: 21	P: 72.2 C: 68.4	*NA*	MMSE	*NA*	*NA*	*NA*	P: 4.2 % C: 4.8 %	*NA*	Blood cells	Comet	DNA	Single strand breaks
41	**Kilic et al. 2019**	Turkey	18	High	PSY	Healthy volunteers	P_1: 27 P_2: 27 C: 27	P_1: 35.7±7.4 P_2: 35.0±9.2 C: 32.1±5.2	P_1: 40.7 % P_2: 37.0 % C: 37.0	CGI	P_1: 5.0±1.0 P_2: 2.4±0.6 C: *NA*	Moderate, mild	P_1: Yes P_2: Yes C: *NA*	P_1: 55.6 % P_2: 51.9 % C: 48.1 %	P_1: 29.1±4.3 P_2: 29.3±4.3 C: 28.6±4.5	Plasma/serum	ELISA	DNA	8-OHdG
42	**Knorr et al. 2019**	Denmark	19	High	BIP	Healthy controls with no personal or first-degree family history of psychiatric disorders	P: 86 C: 44	P: 33.4±12.8 C: 32.1±13.0	P: 51.0 % C: 54.0 %	HAM-D_{17}, YMRS	P: 3.0±3.0, 1.0±1.5 C: 0±0, 0±0	Mild	P: Yes C: *NA*	P: 34 % C: 18 %	P: 25.3±4.9 C: 24.9±3.4	CSF, urine	Chrom	DNA, RNA	8-oxodG 8-oxoGuo
43	**Kume et al. 2012**	Japan	18	High	DEM	Non-demented elderly controls	P: 33 C: 35	P: 80.3±4.9 C: 79.5±6.4	P: 48.5 % C: 60.0 %	MMSE	P: 21.8±4.0 C: 27.1±2.4	Mild	*NA*	P: 12.1 % C: 25.7 %	*NA*	Urine	Chrom	DNA	8-OHdG
44	**Kupper et al. 2009**	The Netherlands	18	High	MDD	Chronic heart failure and no depression	P: 38 C: 72	*NA*	*NA*	BDI	*NA*	*NA*	*NA*	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
45	**Kwiatkowski et al. 2016**	Poland	14	Low	DEM	Randomly selected patients from other departments	P: 105 C: 130	P: 82.3±7.3 C: 78.4±10.3	P: 55.2 % C: 56.9 %	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	Blood cells	Comet	DNA	Total basal damage
46	**Lee et al. 2007**	South Korea	12	Low	DEM	Healthy people with no verifiable symptoms of dementia or other neurological disorders	P: 36 C: 34	P: 77.1±7.4 C: 76.4±7.3	P: 100 % C: 100 %	MMSE	P: 17.5±4.2 C: 29.4±2.8	Moderate	*NA*	P: 4.9 % C: 4.0 %	*NA*	Urine	Chrom	DNA	8-OHdG
47	**Lindqvist et al. 2017**	USA	20	High	MDD	Healthy controls	P: 50 C: 55	P: 39.6±14.7 C: 37.6±13.9	P: 54.0 % C: 60.0 %	HAM-D_{17}	P: 20.2±3.3 C: *NA*	Moderate	P: No C: *NA*	P: 26.0 % C: 6.0 %	P: 26.1±4.5 C. 24.4±4.9	Plasma/serum	Chrom	DNA	8-OHdG
48	**Liu et al. 2018**	China	18	High	MDD	No post-stroke depression	P: 70 C: 171	P: 64.0±10.6 C: 63.3±10.5	P: 35.7 % C: 35.7 %	HAM-D_{17}	*NA*	*NA*	P: No C: No	P: 30.0 % C: 29.2 %	P: 24.5±3.7 C: 24.2±3.0	Plasma/serum	ELISA	DNA	8-OHdG

49	**Lovell et al. 2011**	USA	17	Medium	DEM	Normal controls	P: 10 (4) C: 8 (5)	P: 86.0±6.6 C 83.9±5.4	P: 80.0 % C: 87.5 %	MMSE	P: 28.5±1.3 C: 28.1±1.4	Mild	*NA*	*NA*	*NA*	Brain: ML	IHC	DNA, RNA	8-OHG
																	Chrom	DNA	8-OHG
50	**Lovell et al. 2001**	USA	13	Low	DEM	Controls without a history of dementia or other neurological disorders	P: 18 C: 7	P: 79.9±10.6 C: 80.0±6.9	P: 61.1 % C: 42.9 %	Mean Braak Stage	P: 5.7±0.9 C: 1.3±1.3	Severe	*NA*	*NA*	*NA*	CSF	Chrom	DNA	8-OHG
51	**Lyras et al. 1997**	England	16	Medium	DEM	Controls with no history of psychiatric or neurological illness	P: 10 C: 10	P: 79.9±6.1 C: 74.1±16.0	P: 80.0 % C: 60.0 %	*NA*	*NA*	*NA*	P: No C: No	*NA*	*NA*	Brain: FC, PC, TC, OC	Chrom	DNA	8-hydroxyguanine
							P: 12 C: 9	P: 78.3±9.2 C: 69.5±9.4	P: 66.7 % C: 22.2 %	*NA*	*NA*	*NA*	P: No C: No	*NA*	*NA*	Brain: TC	Chrom	DNA	8-hydroxyguanine
							P: 12 C: 8	P: 78.3±9.2 C: 69.5±10.1	P: 66.7 % C: 25.0 %	*NA*	*NA*	*NA*	P: No C: No	*NA*	*NA*	Brain: TC	Chrom	DNA	8-hydroxyguanine
							P: 7 C: 8	P: 77.6±9.3 C: 68.5±9.5	P: 85.7 % C: 25.0 %	*NA*	*NA*	*NA*	P: No C: No	*NA*	*NA*	Brain: ML	Chrom	DNA	8-hydroxyguanine
52	**Lyras et al. 1998**	England	14	Low	DEM	Controls	P: 8 C: 8	P: 78.5±7.1 C: 70.8±10.0	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	Brain: FC, PC	Chrom	DNA	Guanine base products
							P: 4 C: 4	P: 74.0±4.2 C: 64.5±8.1	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	Brain: TC	Chrom	DNA	Guanine base products
							P: 6 C: 6	P: 77.3±6.1 C: 69.3±7.9	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	Brain: OC	Chrom	DNA	Guanine base products
53	**Mecocci et al. 2002**	Italy	12	Low	DEM	Healthy aged controls	P: 40 C: 39	P: 75.9±5.4 C: 74.8±6.3	P: 50.0 % C: 51.3 %	MMSE	P: 17.3±2.1 C: *NA*	Moderate	*NA*	P: 0 % C: 0 %	*NA*	Blood cells	Chrom	DNA	8-OHdG
54	**Mecocci et al. 1994**	USA	11	Low	DEM	Controls	P: 13 C: 13	P: 71.4±4.7 C: 75.4±9.7	P: 38.5 % C: 38.5 %	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	Brain: FC, PC, TC, CB	Chrom	DNA, mtDNA	8-OHdG
55	**Migliore et al. 2005**	Italy	13	Low	DEM	Healthy controls	P_1: 20 P_2: 15 C: 15	P_1: 71.1±6.7 P_2: 66.5±6.8 C: 65.8±9.1	P_1: 70.0 % P_2: 40.0 % C: 60.0 %	MMSE	P_1: 17.7±4.7 P_2: 25.2±4.5 C: *NA*	Moderate, mild	P_1: No P_2: No C: *NA*	*NA*	*NA*	Blood cells	Comet	DNA	Single strand breaks
56	**Mórocz et al. 2002**	Hungary	14	Low	DEM	Controls with no verifiable symp-toms of dementia or other inter-nal and neurological disorders	P: 27 C: 12	P: 72.0±6.7 C: 72.3±9.4	P: 63.0 % C: 58.3 %	MMSE	P: 18.6±4.3 C: 27.5±1.1	Moderate	P: No C: No	P: 0 % C: 0 %	*NA*	Blood cells	Comet	DNA	Single strand breaks
57	**Munkholm et al. 2015**	Denmark	19	High	BIP	Healthy controls with no history of psychiatric disorder in the subjects or their first-degree relatives	P: 37 C: 40	P: 40.9±12.3 C: 36.3±12.5	P: 67.6 % C: 57.5 %	HAM-D_{17}, YMRS	*NA*	*NA*	P: Yes C: *NA*	P: 76.0 % C: 0 %	P: 24.6±3.6 C: 24.9±3.9	Urine	Chrom	DNA, RNA	8-oxodG 8-oxoGuo
58	**Muraleedharan et al. 2015**	India	17	Medium	PSY	Healthy controls screened negative for psychiatric morbidity	P: 40 C: 40	P: 30.6±8.5 C: *NA*	P: 47.5 % C: 47.5 %	*NA*	*NA*	*NA*	P: No C: *NA*	P: 20.0 % C: *NA*	*NA*	Blood cells	Comet	DNA	Comet
59	**Mutlu-Türkoglu et al. 2000**	Turkey	11	Low	SUB	Controls	P: 28 C: 15	P: 39.2±8.7 C: 38.3±13.4	P: 14.3 % C: 20.0 %	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	Blood cells	Comet	DNA	Damage
60	**Nishioka et al. 2004**	USA	16	Medium	PSY	Elderly non-psychiatric controls	P: 10 C: 13	P: 75.2±9.9 C: 75.5±9.9	P: 70.0 % C: 69.0 %	*NA*	*NA*	*NA*	P: Yes C: *NA*	*NA*	*NA*	Brain: ML	IHC	DNA	8-OHdG
61	**Nordholm et al. 2016**	Denmark	17	Medium	PSY	Healthy controls without severe mental illness	P_1: 41 P_2: 35 C: 29	P_1: 23.9±4.7 P_2: 23.3±5.6 C: 24.7±4.9	P_1: 56.1 % P_2: 45.0 % C: 41.3 %	PANSS	P_1: 79.7±14.1 P_2: *NA* C: *NA*	Mild	P_1: No P_2: No C: *NA*	*NA*	*NA*	Urine	Chrom	DNA, RNA	8-oxodG 8-oxoGuo

62	**Nunomura et al. 2004**	Japan	11	Low	DEM	Controls without dementia	P: 13 C: 15	P: 59.0 C: 66.0	P: 84.6 % C: 53.3 %	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	Brain	IHC	RNA	8-OHG
63	**Nunomura et al. 2012**	Japan	13	Low	DEM	Controls with normal cognitive functions free of amyloid plaques and neurofibrillary tangles	P_1: 4 P_2: 6 P_3: 5 C: 5	P_1: 88.8±4.3 P_2: 93.5±4.5 P_3: 85.4±8.1 C: 88.4±5.7	*NA*	CDR	P_1: 0 P_2: 0.5 P_3: 1.0 C: 0	*NA*	*NA*	*NA*	*NA*	Brain: TC, CB	IHC	RNA	8-OHG
64	**Peña-Bautista et al. 2019**	Spain	17	Medium	DEM	Elderly controls with absence of cognitive disturbances	P: 53 C: 27	P: 70.5±5.8 C: 66.0±8.0	P: 60.4 % C: 37.0 %	MMSE	P: 24.0±6.0 C: 30.0±2.0	Mild	P: Yes C: Yes	P: 34.0 % C: 44.0 %	*NA*	Urine	Chrom	DNA	8-OHdG
65	**Psimadas et al. 2004**	Greece	13	Low	PSY	Controls	P_1: 11 P_2: 9 C: 20	P_1: 38.3±1.1 P_2: 39.7±1.5 C: 38.8±2.2	P_1: 0 % P_2: 0 % C: 0 %	*NA*	*NA*	*NA*	P_1: Yes P_2: Yes C: *NA*	P_1: 100 % P_2: 100 % C: 100 %	*NA*	Blood cells	Comet	DNA	Damage
66	**Shimanoe et al. 2017**	Japan	18	High	MDD	Depressive symptoms low	P: 1,449 C: 5,068	*NA*	P: *NA* C: 62.4 %	SDS	*NA*	*NA*	*NA*	*NA*	*NA*	Urine	Chrom	DNA	8-OHdG
67	**Shmarina et al. 2020**	Russia	11	Low	PSY	Healthy controls without somatic or neurological pathology	P_1: 40 P_2: 22 C: 25	P_1: 40.4±9.8 P_2: 42.2±5.9 C: *NA*	P_1: 0 % P_2: 0 % C: 0 %	PANSS	*NA*	*NA*	P_1: No P_2: No C: *NA*	*NA*	*NA*	Blood cells, plasma/serum	Other	DNA	8-oxodG
68	**Silva et al. 2014**	Brazil	14	Low	DEM	Controls without neuropatho-logical Alzheimer's disease and normal cognitive function	P_1: 19 P_2: 12 C: 31	P_1: 86.1±5.9 P_2: 85.3±5.0 C: 84.6±4.3	P_1: 84.2 % P_2: 61.5 % C: 51.6 %	Braak	P_1: 5.1±0.9 P_2: 4.3±0.9 C: 2.0±0.8	Severe, moderate	*NA*	*NA*	*NA*	Brain: ML	IHC	DNA	8-OHdG
69	**Sliwinska et al. 2016**	Poland	15	Medium	DEM	Healthy volunteers without neurodegenerative disorders or a family history of AD	P: 100 C: 110	P: 79.2±4.9 C: 77.1±7.3	P: 56.0 % C: 58.2 %	*NA*	*NA*	*NA*	P: Yes C: *NA*	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-oxoG
70	**Soeiro-de-Souza et al. 2013**	Brazil	17	Medium	BIP	Healthy volunteers with no current or past psychiatric disorder, no family history of mood or psychotic disorders, and no recent treatment	P: 50 C: 50	P: 26.8±4.5 C: 26.0±4.0	P: 66.0 % C: 50.0 %	MADRS, YMRS	P: 20.1±9.0, 14.1±8.3 C: *NA*	Moderate	P: No C: No	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
71	**Szebeni et al. 2017**	USA	17	Medium	MDD, PSY	Psychiatrically normal controls donors	P_1: 10 P_2: 10 C: 13	P_1: 50.5±5.0 P_2: 39.7±5.1 C: 47.9±4.1	P_1: 0 % P_2: 20.0 % C: 15.4 %	*NA*	*NA*	*NA*	*NA*	P_1: 60.0 % P_2: 70.0 % C: 30.8 %	*NA*	Brain: PC	ELISA	DNA	8-OHdG
72	**Te Koppele et al. 1996**	The Netherlands	15	Medium	DEM	Controls with no history of	P: 3-7 C: 2-8	P: 83.8±7.3 C: 68.2±15.3	P: 75.0 % C: 37.5 %	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	Brain: OC, TC, FC, ML	Chrom	DNA	8-OHdG

						neurological or psychiatric disorders												
73	**Topak et al. 2018**	Turkey	16	Medium	PSY	Healthy volunteers with normal mental capacities, no physical neurological or psychiatric disease, and no medication	P_1: 30 P_2: 30 C: 30	P_1: 39.4±7.8 P_2: 35.6±9.8 C: 36.7±6.8	P_1: 30.0 % P_2: 53.3 % C: 56.7 %	PANSS	*NA*	*NA*	P_1: Yes P_2: Yes C: No	P_1: 53.3 % P_2: 56.7 % C: 46.7 %	P_1: 28.2±4.5 P_2: 27.1±4.0 C: 28.2±5.5	Blood cells	Comet	DNA	Damage
74	**Valentina et al. 2020**	Russia	11	Low	BIP	Healthy controls without chronic somatic diseases	P: 19 C: 20	P: 38.0 C: 34.5	*NA*	*NA*	*NA*	*NA*	P: Yes C: *NA*	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
75	**Vieira et al. 2021**	Canada	16	Medium	MDD	Healthy controls with no history of major psychiatric disorders or neurocognitive impairment	P: 57 C: 35	P: 73.2±7.7 C: 70.5±7.4	P: 87.7 % C: 91.4 %	HAM-D_{21}	P: 18.7±6.3 C: 1.6±2.2	Mild	P: Yes C: *NA*	*NA*	P: 27.3 C: 26.8±4.6	Plasma/serum	ELISA	DNA	8-oxodG
76	**Wang et al. 2006**	USA	14	Low	DEM	Controls neuro-psychologically normal	P: 8 C: 6	P: 89.5±13.6 C: 81.0±9.3	P: 50.0 % C: 33.3 %	Braak stage	*NA*	*NA*	*NA*	*NA*	*NA*	Brain: FC, PC, TC, CB	Chrom	DNA, mtDNA	8-OHdG
77	**Wei et al. 2009**	China	15	Medium	MDD	Non-depression in patients with gastric adenocarcinoma stage III	P: 63 C: 43	P: 54.9±14.7 C: 48.6±12.1	*NA*	SCL-90	P: 82.4±43.1 C: 27.8±12.0	*NA*	*NA*	P: 0 % C: 0 %	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
78	**Wei et al. 2009**	China	15	Medium	MDD	Non-depression in patients with colorectal carcinoma	P: 52 C: 30	P: 56.0±13.9 C: 58.5±11.3	*NA*	SCL-90	P: 86.9±45.7 C: 22.3±15.0	*NA*	*NA*	P: 0 % C: 0 %	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
79	**Weidner et al. 2011**	USA	12	Low	DEM	Non-cognitively impaired controls	P: 12 C: 10	P: 83.0±6.7 C: 90.0±5.6	P: 83.3 % C: 90.0 %	MMSE	P: 6.9±7.2 C: 28.0±1.6	Severe	*NA*	*NA*	*NA*	Brain: FC, ML, PC, TC, CB	Chrom	RNA	8-OHG
80	**Yi et al. 2012**	Japan	18	Medium	MDD	Non-depression in male workers	P: 105 C: 196	P: 43.4±10.3 C: 44.4±11.1	P: 0 % C: 0 %	CES-D	*NA*	*NA*	*NA*	P: 48.6 % C: 43.9 %	P: 23.1±3.5 C: 23.8±3.2	Urine	Chrom	DNA	8-OHdG
						Non-depression in female workers	P: 74 C: 136	P: 41.5±10.0 C: 40.4±10.7	P: 100 % C: 100 %	CES-D	*NA*	*NA*	*NA*	P: 0 % C: 2.9 %	P: 21.1±3.2 C: 21.0±3.1	Urine	Chrom	DNA	8-OHdG
81	**Young et al. 2007**	UK	16	Medium	PSY	Apparently healthy controls	P: 16 C: 17	P: 37.9±11.0 C: 38.9±9.2	P: 25.0 % C: 29.4 %	PANSS	*NA*	*NA*	P: Yes C: *NA*	*NA*	*NA*	Blood cells	Comet	DNA	Damage
82	**Zengi et al. 2012**	Turkey	16	Medium	DEM	Healthy elderly volunteers with negative psychiatric anamnesis	P: 21 C: 20	P: 76.0±7.8 C: 81.0±7.2	P: 52.4 % C: 45.0 %	MMSE	P: 14.2±3.2 C: *NA*	Moderate	*NA*	P: 0 % C: 0 %	*NA*	Urine	Chrom	DNA	8-OHdG

Values are expressed as number (%) or mean±sd.
Abbreviations. DEM: dementia, SUB: substance misuse, PSY: psychotic disorder, BD: bipolar disorder, MDD: major depressive disorder, ANX: anxiety. P: patients, C: controls. AUDIT: Alcohol Use Disorders Identification Test, BDI: Beck Depression Inventory, CDR: Clinical Dementia Rating, CES-D: Center for Epidemiologic Studies

Depression Scale, CGI: The Clinical Global Impressions Scale, CIWA-Ar-C: Clinical Institute Withdrawal Assessment for Alcohol Revised, HAM-D: Hamilton Depression Rating Scale, IDS-SR: Inventory of Depressive Symptomatology Self-Report, MADRS: Montgomery-Asberg Depression Rating Scale, MMSE: Mini Mental State Examination, PANSS: Positive and Negative Syndrome Scale, Y-BOCS: Yale-Brown Obsessive-Compulsive Scale, YMRS: Young Mania Rating Scale, SDS: Self-Rating Depression Scale, SCL-90: Symptom Checklist-90. FC: frontal cortex, TC: temporal cortex, PC: parietal cortex, OC: occipital cortex, ML: middle lobe, CB: cerebellum. Chrom: chromatography, Comet: comet assay, ELISA: Enzyme-Linked Immunosorbent Assay, IC: immunohistochemistry. mtDNA: mitochondrial DNA. 8-OHdG, 8-oxodG, 8-oxo2dG: 8-hydroxy-2'-deoxyguanosine, 8-OHG: 8-hydroxyguanosine, 8-oxoGuo, 8-oxoG: 8-oxo-7,8-dihydroguanosine. *NA*: not applicable.

eTable 3. Characteristics of Included Intervention Studies

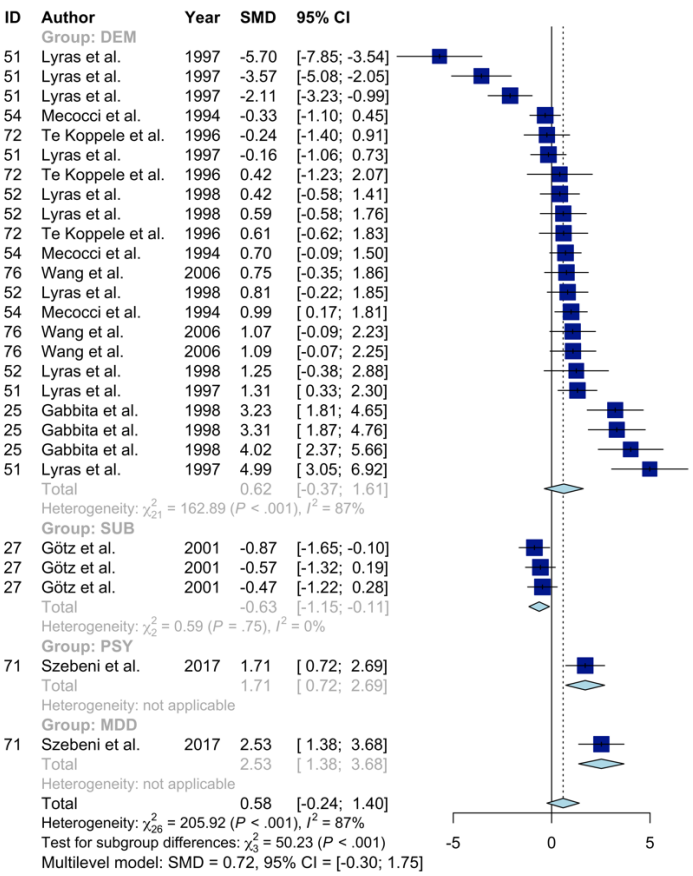
ID	Author, year	Country	STROBE score	Study quality	Disorder	Intervention & randomization	n	Age	Female	Severity scale	Scale points	Severity	Drugs	Smokers	BMI	Matrix	Method	Nucleic acid	Marker
2	**Ahmadimanesh et al. 2019**	Iran	19	High	MDD	Treatment with citalopram, randomized	25	37.0±8.7	64.0 %	HAM-D_{21}	Pre: 27.7±8.1 Post: 19.8±9.0	Pre: Severe Post: Moderate	Pre: No Post: Yes	0 %	Pre: 26.2±4.6 Post: 26.1±4.7	Blood cells	Comet	DNA	Strand breaks
																Plasma/serum	ELISA	DNA	8-OHdG
						Treatment with sertralin, randomized	20	34.4±9.1	80.0 %	HAM-D_{21}	Pre: 26.9±11.4 Post: 17.4±9.2	Pre: Severe Post: Moderate	Pre: No Post: Yes	0 %	Pre: 25.4±5.4 Post: 25.6±5.6	Blood cells	Comet	DNA	Strand breaks
																Plasma/serum	ELISA	DNA	8-OHdG
13	**Chen et al. 2011**	Taiwan	17	Medium	SUB	1 week alcohol detoxification, not randomized	79	41.0±7.0	15.2 %	CIWA-Ar-C	Pre: 10.7±5.9 Post: *NA*	*NA*	*NA*	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
28	**Hosseini-Ghalibaf et al. 2019**	Iran	19	High	BIP	Coenzyme Q10 supplementation, randomized	36	37.5±10.7	77.8 %	MADRS	*NA*	*NA*	Yes	22,2 %	*NA*	Urine, saliva	ELISA	DNA	8-OHdG
						Placebo, randomized	33	39.5±10.8	90.9 %	MADRS	*NA*	*NA*	Yes	21,2 %	*NA*	Urine, saliva	ELISA	DNA	8-OHdG
29	**Huang et al. 2018**	Taiwan	17	Medium	SUB	2 weeks of methamphetamine abstinence, not randomized	182	31.1±8.3	21.4 %	AUDIT	Pre: 4.0±6.0 Post: *NA*	*NA*	*NA*	95,2 %	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
30	**Huang et al. 2014**	Taiwan	17	Medium	SUB	1 week of alcohol detoxification, not randomized	16	44.4±8.4	0 %	CIWA-Ar-C	Pre: 30.4±7.2 Post: *NA*	*NA*	*NA*	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
							58	40.6±5.9	12.1 %	CIWA-Ar-C	Pre: 14.0±7.3 Post: *NA*	*NA*	*NA*	*NA*	*NA*	Plasma/serum	ELISA	DNA	8-OHdG
38	**Jorgensen et al. 2013**	Denmark	20	High	MDD	ECT, not randomized	29	46.2±17.0	51.7 %	HAM-D_{17}	Pre: 26.9±4.5 Post: 11.7±6.8	Pre: Severe Post: Mild	Yes	44,8 %	Pre: 24.3±4.7 Post: *NA*	Urine	Chrom	RNA	8-oxodG
																			8-oxoGuo
47	**Lindqvist et al. 2017**	USA	20	High	MDD	8-week SSRI-treatment, not randomized	19	*NA*	*NA*	HAM-D_{17}	*NA*	*NA*	*NA*	*NA*	*NA*	Plasma/serum	Chrom	DNA	8-OHdG

Values are expressed as number (%) or mean±sd.
Abbreviations. MDD: major depressive disorder, SUB: substance misuse, BIP: bipolar disorder. HAM-D: Hamilton Depression Rating Scale, CIWA-Ar-C: Clinical Institute Withdrawal Assessment for Alcohol Revised, MADRS: Montgomery-Asberg Depression Rating Scale, AUDIT: Alcohol Use Disorders Identification Test. Comet: comet assay, ELISA: Enzyme-Linked Immunosorbent Assay, Chrom: chromatography. 8-OHdG, 8-oxodG: 8-hydroxy-2'-deoxyguanosine, 8-OHG: 8-hydroxyguanosine, 8-oxoGuo: 8-oxo-7,8-dihydroguanosine. *NA*: not applicable.

eFigure 2. Forest Plots and Meta-analyses of Central Nervous System Markers

Forest plots and meta-analyses of cortical DNA (A), cortical RNA (B), cortical mtDNA (C), hippocampal DNA (D), hippocampal RNA (E), cerebellar DNA (F), cerebellar RNA (G), and CSF DNA markers (H). Results are standardized mean differences (Hedges g) with 95% confidence intervals. Heterogeneity is expressed by the I^2 statistic. Results from the multilevel meta-analysis are given below each plot. DEM: Dementia disorders; SUB: Substance use disorders; PSY: Psychotic disorders; BIP: Bipolar disorders; MDD: Major Depressive Disorders; ANX: Anxiety disorders. The study ID refers to eTable 2, which provides study details.

A



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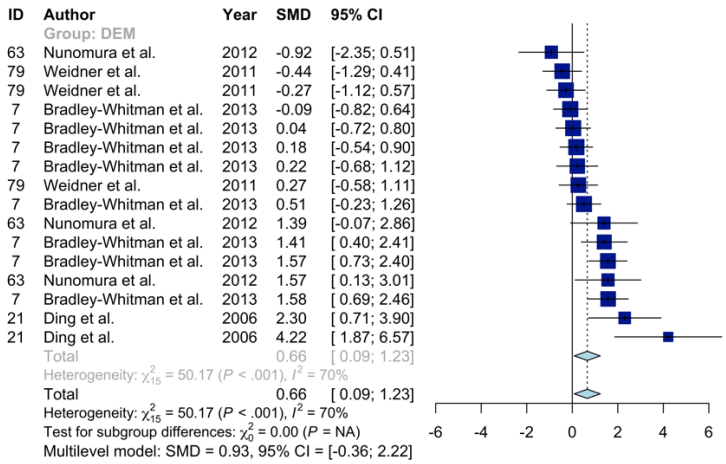
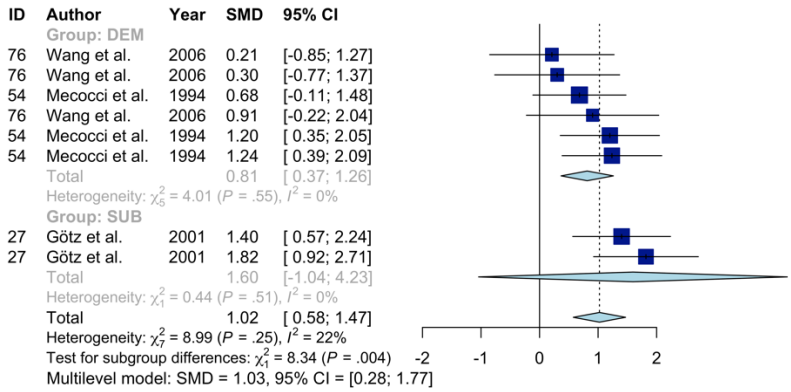
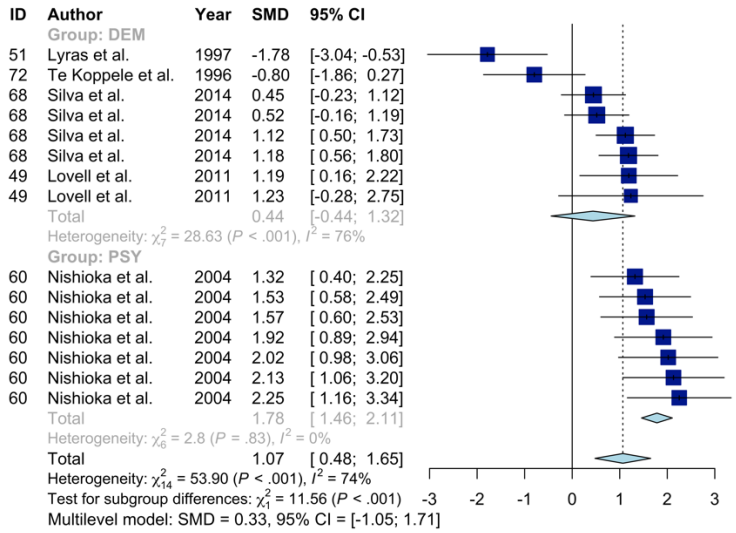


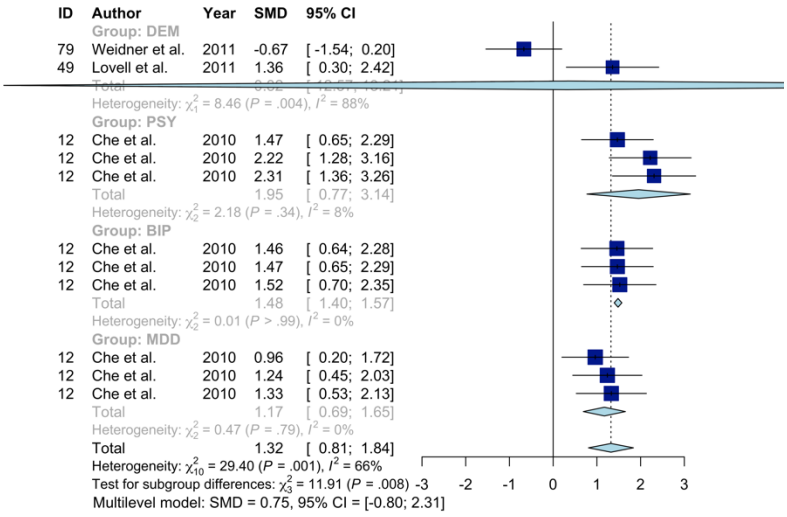
C



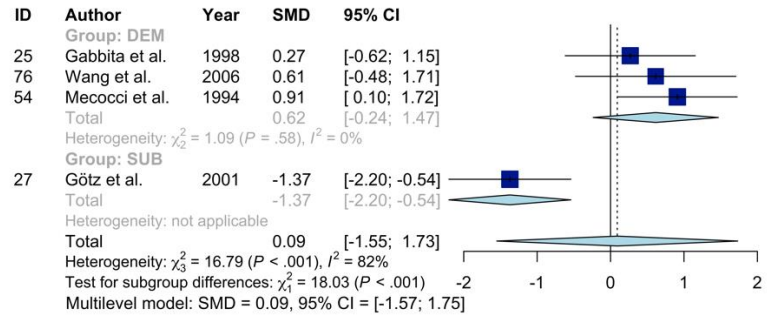
D



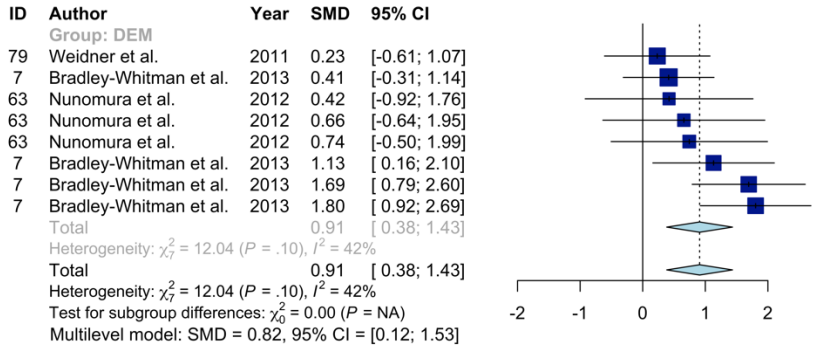
E



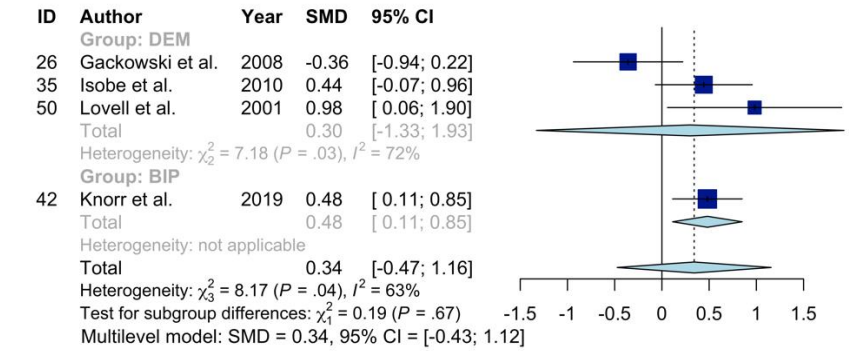
F



G



H



eTable 4. Multilevel Meta-analyses and Sensitivity Analysis for Central Nervous System Markers

Cortex, DNA markers						
	All studies (NC = 27)			**Medium and high-quality studies (NC = 11)**		
	g	**95% CI**	***I²***	***g***	**95% CI**	***I²***
DEM	0.76	[-0.44; 1.98]		-0.48	[-2.74; 1.78]	
SUB	-0.64	[-3.65; 2.38]		NA	NA	
PSY	1.71	[-2.52; 5.93]		1.71	[-4.98; 8.39]	
BIP	NA	NA		NA	NA	
MDD	2.53	[-1.74; 6.79]		2.526	[-4.19; 9.24]	
ANX	NA	NA		NA	NA	
Total	0.72	[-0.30; 1.75]	93%	0.004	[-1.89; 1.90]	95%
Cortex, RNA markers						
	All studies (NC = 16)			**Medium and high-quality studies (NC = 8)**		
	g	**95% CI**	***I²***	***g***	**95% CI**	***I²***
DEM	0.93	[-0.36; 2.22]		**0.64**	**[0.05; 1.23]**	
SUB	NA	NA		NA	NA	
PSY	NA	NA		NA	NA	
BIP	NA	NA		NA	NA	
MDD	NA	NA		NA	NA	
ANX	NA	NA		NA	NA	
Total	0.93	[-0.36; 2.22]	87%	**0.64**	**[0.05; 1.23]**	66%
Cortex, mtDNA markers						
	All studies (NC = 8) *			**Medium and high-quality studies (NC = 8) ***		
	g	**95% CI**	***I²***	***g***	**95% CI**	***I²***
DEM	**0.78**	**[0.09; 1.47]**		**0.78**	**[0.09; 1.47]**	
SUB	**1.60**	**[0.57; 2.62]**		**1.60**	**[0.57; 2.62]**	
PSY	NA	NA		NA	NA	
BIP	NA	NA		NA	NA	
MDD	NA	NA		NA	NA	
ANX	NA	NA		NA	NA	
Total	**1.03**	**[0.29; 1.77]**		**1.03**	**[0.29; 1.77]**	49%

Hippocampus, DNA markers						
	All studies (NC = 15)			Medium and high-quality studies (NC = 11)		
	g	**95% CI**	***I²***	***g***	**95% CI**	***I²***
DEM	-0.06	[-1.54; 1.43]		-0.41	[-2.42; 1.59]	
SUB	NA	NA		NA	NA	
PSY	1.79	[-1.04; 4.61]		1.79	[-1.51; 5.08]	
BIP	NA	NA		NA	NA	
MDD	NA	NA		NA	NA	
ANX	NA	NA		NA	NA	
Total	0.33	[-1.05; 1.71]	90%	0.17	[-1.69; 2.03]	90%
Hippocampus, RNA markers						
	All studies (NC = 11) *			**Medium and high-quality studies (NC = 10) ***		
	g	**95% CI**	***I²***	***g***	**95% CI**	***I²***
DEM	0.32	[-2.08; 2.72]		**1.36**	**[0.06; 2.66]**	
SUB	NA	NA		NA	NA	
PSY	1.95	[-1.30; 5.20]		**1.95**	**[1.31; 2.59]**	
BIP	1.48	[-1.76; 4.72]		**1.48**	**[0.89; 2.07]**	
MDD	1.17	[-2.06; 4.41]		**1.17**	**[0.60; 1.74]**	
ANX	NA	NA		NA	NA	
Total	0.75	[-0.80; 2.31]	88%	**1.49**	**[1.19; 1.80]**	0%

Cerebellum, DNA markers						
	All studies (NC = 4)			Medium and high-quality studies (NC = 4)		
	g	**95% CI**	***I²***	***g***	**95% CI**	***I²***
DEM	0.61	[-0.53; 1.77]		0.61	[-0.53; 1.77]	
SUB	-1.37	[-3.18; 0.44]		-1.37	[-3.18; 0.44]	
PSY	NA	NA		NA	NA	
BIP	NA	NA		NA	NA	
MDD	NA	NA		NA	NA	
ANX	NA	NA		NA	NA	
Total	0.09	[-1.57; 1.75]	81%	0.09	[-1.57; 1.75]	81%
Cerebellum, RNA markers						
	All studies (NC = 8)			**Medium and high-quality studies (NC = 4)**		
	g	**95% CI**	***I²***	***g***	**95% CI**	***I²***
DEM	**0.82**	**[0.13; 1.53]**		**1.23**	**[0.15; 2.32]**	
SUB	NA	NA		NA	NA	
PSY	NA	NA		NA	NA	
BIP	NA	NA		NA	NA	
MDD	NA	NA		NA	NA	
ANX	NA	NA		NA	NA	
Total	**0.82**	**[0.13; 1.53]**	50%	**1.23**	**[0.15; 2.32]**	59%

CSF, DNA markers						
	All studies (NC = 4)			Medium and high-quality studies (NC = 4)		
	g	**95% CI**	***I²***	***g***	**95% CI**	***I²***
DEM	0.30	[-1.30; 1.90]		0.30	[-1.30; 1.90]	
SUB	NA	NA		NA	NA	
PSY	NA	NA		NA	NA	
BIP	0.48	[-2.01; 2.97]		0.48	[-2.01; 2.97]	
MDD	NA	NA		NA	NA	
ANX	NA	NA		NA	NA	
Total	0.34	[-0.43; 1.12]	66%	0.34	[-0.43; 1.12]	66%

Multilevel meta-analysis of central nervous system markers of oxidation of nucleic acids in psychiatric disorders, including subgroup analyses and sensitivity analyses excluding low quality studies. Data are standardized mean differences expressed as Hedges' *g* with 95% confidence intervals and heterogeneity expressed by I^2. * Test of subgroup differences significant ($p < 0.05$). Bold type: $p < 0.05$. NC: Number of patient- vs. control-group comparisons.

eTable 5. Meta-regression Analyses of Covariates

Age and gender:

Model Results:

	estimate	95% CI	p
age	0.018	[0.01; 0.02]	<0.0001
gender	-0.004	[-0.01; 0.002]	0.26

Test of Moderators (coefficients 1:2): F(df1 = 2, df2 = 179) = 28.7579, p-val < .0001.

Full (including covariate(s)) vs. reduced (uncorrected) model:

	df	AIC	BIC	LRT	p
Full	4	501.31	514.11		
Reduced	3	499.12	508.71	0.00	1.00

Smoking:

Model Results:

	estimate	95% CI	p
smoking	-0.003	[-0.01; 0.005]	0.43

Full (including covariate(s)) vs. reduced (uncorrected) model:

	df	AIC	BIC	LRT	p
Full	4	133.67	142.24		
Reduced	3	132.22	138.65	0.55	0.47

BMI:

Model Results:

	estimate	95% CI	p
BMI	-0.003	[-0.11; 0.05]	0.4

Full (including covariate(s)) vs. reduced (uncorrected) model:

	df	AIC	BIC	LRT	p
Full	4	80.21	87.35		
Reduced	3	78.69	84.04	0.48	0.49

eTable 6. Meta-analyses of Secondary Outcomes

Measurement methodology:

Model Results:

Method	**estimate**	**95% CI**	**p**
Comet	1.31	[0.80; 1.81]	<.001
IHC	1.15	[0.50; 1.81]	<.001
Other	1.06	[0.35; 1.77]	0.004
ELISA	1.00	[0.64; 1.36]	<.001
Chromatography	0.52	[0.23; 0.80]	<.001

Test of Moderators: F(df1 = 5, df2 = 200) = 17.3933, p < .0001

Study quality:

Model Results:

Level	**estimate**	**95% CI**	**p**
Low	1.03	[0.70; 1.36]	<.001
Medium	0.90	[0.56; 1.24]	<.001
High	0.60	[0.25; 0.95]	<.001

Test of Moderators: F(df1 = 3, df2 = 202) = 24.8624, p < .0001

Illness severity:

Model Results:

Level	**estimate**	**95% CI**	**p**
Mild	1.06	[0.58; 1.54]	<.001
Moderate	0.87	[0.46; 1.30]	<.001
Severe	1.27	[0.69; 1.87]	<.001

Test of Moderators: F(df1 = 3, df2 = 55) = 10.9718, p < .0001

Pharmacological treatment:

Model Results:

	estimate	95% CI	p
No	0.70	[0.24; 1.16]	<.01
Yes	1.03	[0.46; 1.30]	<.001

Test of Moderators: F(df1 = 2, df2 = 99) = 17.9680, p < .0001

BMI controlled studies only:

Model Results:

Group	**estimate**	**95% CI**	**p**
PSY	0.84	[0.31; 1.36]	0.002
BIP	0.60	[0.01; 1.18]	.04
MDD	0.67	[0.21; 1.13]	0.005

Test of Moderators: F(df1 = 3, df2 = 41) = 5.0279, p = 0.0046

Cortical subregions, DNA markers:

Model Results:

Region	**estimate**	**95% CI**	**p**
Frontal cortex	0.20	[-1.28; 1.69]	0.28
Occipital cortex	1.20	[-3.52; 1.12]	0.29
Parietal cortex	1.65	[0.22; 3.08]	0.03
Temporal cortex	0.76	[-0.63; 2.13]	0.27

Test of Moderators: F(df1 = 4, df2 = 23) = 2.0713, p = 0.12

Cortical subregions, RNA markers:

Model Results:

Region	estimate	95% CI	p
Frontal cortex	0.45	[-1.69; 2.61]	0.65
Parietal cortex	0.64	[-0.95; 2.22]	0.40
Temporal cortex	1.35	[-0.22; 2.94]	0.09

Test of Moderators: F(df1 = 3, df2 = 13) = 1.9045, p = 0.1787

Diagnostic group across all matrices:

Model Results:

Group	estimate	95% CI	p
DEM	1.02	[0.68; 1.35]	<.001
PSY	0.93	[0.54; 1.31]	<.001
BIP	0.86	[0.42; 1.30]	<.001
MDD	0.64	[0.24; 1.03]	0.002
SUB	0.48	[-0.36; 1.32]	0.26
ANX	0.37	[-1.00; 1.73]	0.60

Test of Moderators: F(df1 = 6, df2 = 199) = 12.2017, p < .0001

eFigure 3. Funnel Plot of All Included Cross-sectional Studies