# 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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**ABSTRACT**

***Objective:*** To investigate the role of oxidative stress and antioxidants in depression.

***Data Sources:*** We searched the literature without language restrictions through MEDLINE/PubMed, Cochrane Library, Fisterra, and Galenicom from database inception until December 31, 2013, supplemented by a hand search of relevant articles. Search terms included (1) *oxidative stress, antioxidant*, nitrosative stress, nitrative stress, nitro-oxidative stress, free radical*,* and names of individual oxidative stress markers/antioxidants and (2) *depression* and related disorders and *antidepressant*.

***Study Selection:*** Included were studies in patients with depression comparing antioxidant or oxidative stress markers with those in healthy controls before and after antidepressant treatment.

***Data Extraction:*** Two authors independently extracted the data for antioxidant or oxidative stress markers. Standardized mean differences (SMDs) ± 95% confidence intervals (CIs) for results from ≥ 3 studies were calculated.

***Data Synthesis:*** Altogether, 29 studies (N = 3,961; patients with depression = 2,477, healthy controls = 1,484) reported on the oxidative stress marker malondialdehyde (MDA) and total nitrites, the antioxidants uric acid and zinc, or the antioxidant-enhancing enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). When patients with depression were compared with healthy controls, depression was associated with higher oxidative stress MDA levels (8 studies; n = 916; SMD = 1.34; 95% CI, 0.57 to 2.11; $P < .001$), lower antioxidant uric acid (4 studies; n = 512; SMD = −0.64; 95% CI, −1.22 to −0.06; $P = .030$) and zinc levels (13 studies; n = 2,002; SMD = −0.66; 95% CI, −0.98 to −0.34; $P < .0001$), and higher antioxidant-enhancing enzyme SOD levels (11 studies; n = 902; SMD = 0.62; 95% CI, 0.07 to 1.17; $P = .028$), while differences in total nitrites and CAT and GPX were nonsignificant. Antidepressant treatment, which significantly reduced Hamilton Depression Rating Scale scores (24.6 ± 0.7 to 16.2 ± 1.6; SMD = 2.65; 95% CI, 1.13 to 4.15; $P = .00065$), reduced MDA (4 studies; n = 194; SMD = −1.45; 95% CI, −2.43 to −0.47; $P = .004$) and increased uric acid (3 studies; n = 212; SMD = 0.76; 95% CI, 0.03 to 1.49; $P = .040$) and zinc levels (3 studies; n = 65; SMD = 1.22; 95% CI, 0.40 to 2.04, $P = .004$), without differences in MDA ($P = .60$), uric acid ($P = .10$), and zinc ($P = .163$) levels compared to healthy controls.

***Conclusions:*** Results suggest that oxidative stress plays a role in depression and that antidepressant activity may be mediated via improving oxidative stress/antioxidant function.

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Depression is among the most frequent mental disorders, with 12-month prevalence rates of 5.6% in the world population and 3.9% in Europe.[1] Moreover, depression is highly incapacitating, being the second leading cause of years lived with disability in 2010.[1] Further, depression is significantly associated with cardiovascular disease, cancer,[2] and all-cause mortality.[1] Several lines of research suggest that the adverse impact of depression on general health is mediated by inflammation and an up-regulated immune response,[3,4] as well as a dysregulated neuro-endocrinologic system.[5–8]

In addition, oxidative stress, which is also regulated via inflammation and an imbalance between antioxidant activity and free radical production, has been associated with depression.[9] Oxidative stress is implicated in the aging process and in numerous human diseases, including cancer and cardiovascular and neuropsychiatric diseases.[10–12] The brain may be particularly vulnerable to oxidative stress, due to its high oxygen needs, which represent around 20% of the body's total oxygen consumption, and the high content of polyunsaturated fatty acids in neuron membranes makes these neuronal membranes especially sensitive to the peroxidation process triggered by reactive species.[13–16]

The interaction between oxidative-nitrosative stress pathways and immune-inflammatory pathways very likely contributes to a decline of neuroplasticity and neurogenesis and an increase of neurodegeneration and neuronal apoptosis in both depression and bipolar disorders.[17–20] These mood disorders have similar molecular alterations, which suggest that shared mechanisms are involved in their pathogeneses.[21]

Moreover, both antidepressants and mood stabilizers, such as lithium and valproate, contribute to stopping and reversing these alterations.[22–26]

Subsequently, antioxidants may be up-regulated to counterbalance reactive species.[11,27,28] For example, oxidative stress damage has been implicated in the hippocampus volume decrease in depressed patients.[29] Although there are several antioxidant mechanisms in the brain that can scavenge free radicals, these antioxidant mechanisms appear to be less efficient in patients with depression.[30]

Currently, it is unknown whether oxidative stress precedes depression or is a result of depression. Nevertheless, long-term antidepressant treatment that restores normal monoamine metabolism in the brain may aid scavenging of free radicals and reduce oxidative stress.[31] The findings of the inhibitory effect of antidepressants on the immune system[26,32] and their well-known effect on cytochrome inhibition[33,34] suggest that antidepressant treatment may affect antioxidant activity,[30,35] although research has been contradictory.[36,37]

Oxidative stress results from an imbalance among endogenous cellular defense systems. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are products of normal cellular function, which play a special role in cellular response to protect living cells against external or internal toxins. However, in high concentrations, reactive species may act against living cells with resulting damage in deoxyribonucleic acid (DNA) molecules, lipids, and proteins.[27,38] To avoid cell damage, the body needs defense mechanisms against constantly produced free radicals, such as oxygen, superoxide, hydroxide, hydrogen peroxide, and nitric oxide; those protective mechanisms maintain a balance between antioxidant activities and intracellular reactive species (Figure 1). Enzymatic and nonenzymatic antioxidant defenses are expressed in the periphery and in the brain. Antioxidant enzymes include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and xanthine oxidase (Figure 2). Nonenzymatic antioxidants are represented by bilirubin, uric acid, glutathione (GSH), and vitamins A, C, and E, among others.[27,39]

Glutathione is an important antioxidant and redox buffer, which performs its function coupled with its oxidized form, glutathione disulfide (GSSG). The GSH/GSSG ratio is a good measure of oxidative stress.[40] Similarly, malondialdehyde (MDA), which results from lipid degradation, has been accepted as an indicator of oxidative stress[18] and, acting as a mutagenic substance, contributes to the damage caused by free radicals. Kotan et al[36] recently reported that MDA correlates with severity of depression and suggest that MDA could play a role as a marker of disease activity. Additional oxidative stress indicators include nitrate and thiobarbituric acid reactive substances (TBARS) (Table 1).

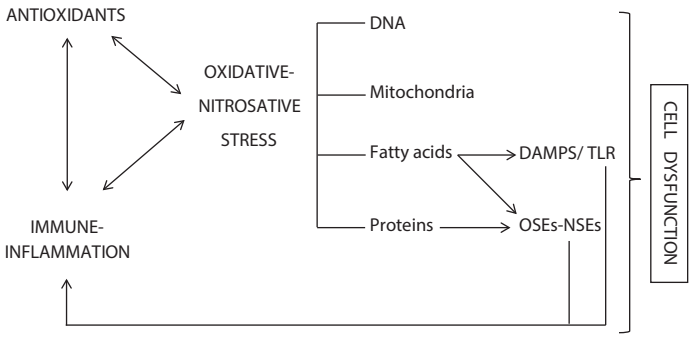
Recently, Palta et al[9] meta-analyzed 23 studies, pooling effect sizes across all reported oxidative stress markers and all antioxidant agents into 2 global metrics. The authors found that patients with depression had significantly higher global levels of oxidative stress and significantly lower global levels of antioxidants than controls. While these results are interesting, the pooling of all individual markers could be problematic as the mean scores may be confusing because information is lost regarding increased, decreased, or nonelevated individual markers. Moreover, since only selected markers were available from a variety of studies that often used different markers, the total mean values are incomplete and not equally weighted. Hence, pooling results across studies that did not report on the same markers complicates the interpretation that higher effect sizes of oxidative stress markers than of antioxidant levels indicate a greater global imbalance toward oxidative stress. Finally, the lack of information on individual markers precludes the identification of potential targets for specific drug development.

Therefore, to fill this gap in the literature and address the issues raised above, we conducted a comprehensive meta-analysis of individual stress markers and endogenous antioxidants in patients with depression compared to controls and in patients with depression before and after treatment with antidepressants. We hypothesized that certain oxidative stress markers would be elevated compared to controls, while certain antioxidants would

**Clinical Points**

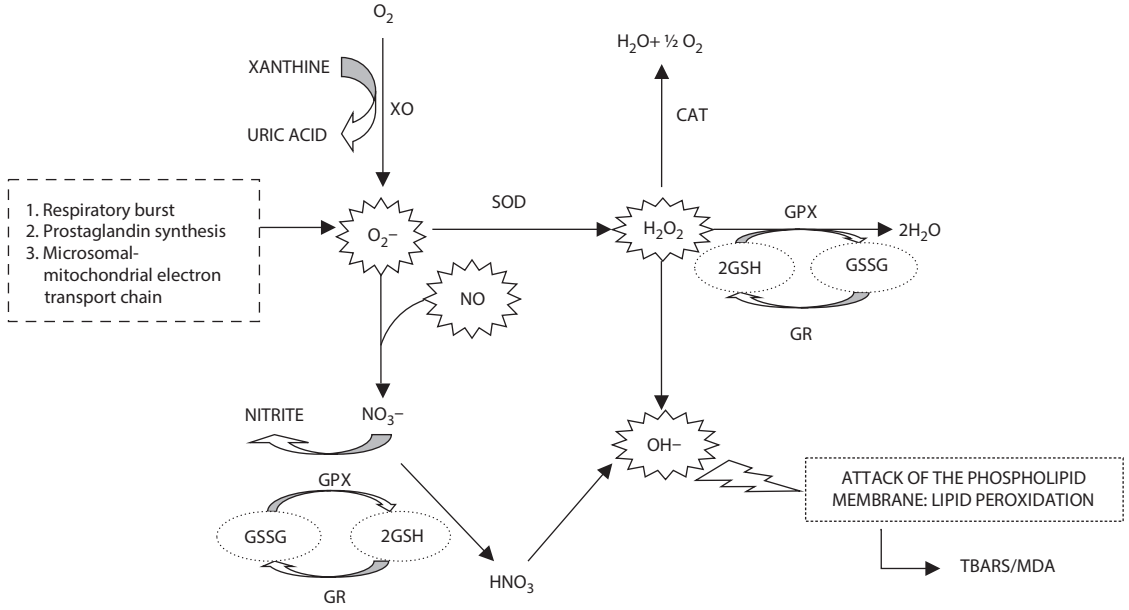
- Our meta-analysis of 29 studies and 3,961 individuals shows that compared to healthy control subjects, patients with depression have a dysbalance between significantly elevated oxidative stress markers and lower levels of antioxidants.
- Clinicians should consider that effective antidepressant treatment can reduce oxidative stress and increase nonenzymatic antioxidants, some of which seem to normalize to the levels of healthy controls.
- Research knowledge about specific oxidative stress/antioxidant imbalances and effective ways to normalize them can guide the development of novel treatments for depression.

**Figure 1. Association Between Oxidative-Nitrosative Stress and Inflammation-Immune Pathways**




Abbreviations: DAMPS = damage-associated molecular patterns, DNA = deoxyribonucleic acid, NSEs = nitrosative-specific epitopes, OSEs = oxidative-specific epitopes, TLR = toll-like receptor.

**Figure 2. Oxidative Stress Pathways**




be reduced. Moreover, we hypothesized that certain markers found to be abnormal in depressed patients would change in the direction of controls after antidepressant treatment.

## METHOD

### Search Strategy

We conducted an electronic literature search without language restrictions using MEDLINE/PubMed, Cochrane Central Register of Controlled Trials, Fisterra, and Galenicom from database inception until December 31, 2013, supplemented by a hand search of reference lists of included and relevant review articles. Search terms included (1) *oxidative stress, antioxidant*, nitrosative stress, nitrative stress, nitro-oxidative stress, free radical**, and different oxidative stress markers, including *MDA, TBARS, NO* (nitric oxide), *SOD, CAT, GPX, GSSG, GSH, uric acid,* and *zinc*; and (2) *depression* and related disorders (major depressive disorder, depressive syndrome, unipolar depression) and *antidepressant*. Authors of identified studies were contacted to obtain missing data required for the meta-analysis.

### Study Selection/Inclusion Criteria

We included studies with the following characteristics: (1) patients diagnosed with depression; (2) quantitative data (mean ± SD) for oxidative stress marker or antioxidant levels in serum, plasma, or red blood cells (RBC); (3) data available in a healthy control group in cross-sectional studies or baseline and follow-up data available before and after antidepressant treatment in longitudinal studies. Excluded were studies in which patients with depression were also diagnosed with any other important psychiatric disease (eg,

**Table 1. Consequences of ROS/RNS at a Cellular Level and the Molecules to Measure Them**

| Damaged Targets | Parameters That Indirectly Allow Quantification of ROS/RNS |
|---|---|
| Fatty acids | MDA and TBARS<br>Omega-3 fatty acids<br>8-iso-Prostaglandin F2α<br>4HNE |
| Proteins | Nitrotyrosine |
| DNA | 8-OHdG |
| **Molecules of Origin** | **Determination of Autoimmune Reactions Against Neoepitopes** |
| Fatty acids | IgG antibodies against oxidized LDL<br>IgM against OSEs (phosphatidylinositol and oleic, palmitic, and myristic acid) |
| Proteins | IgM against NSEs (NO-tyrosine, NO-tryptophan, and NO-albumin) |

Abbreviations: DNA = deoxyribonucleic acid; 8-OHdG = 8-hydroxy-2´-deoxyguanosine; 4HNE = 4-hydroxynonenal; IgG = immunoglobulin G; IgM = immunoglobulin M; LDL = *low-density lipoprotein,* MDA = malondialdehyde; NSEs = nitrosative-specific epitopes; OSEs = oxidative-specific epitopes; ROS/RNS = reactive oxygen species/reactive nitrogen species; TBARS = thiobarbituric acid reactive substances.

schizophrenia) or physical disease (eg, cancer), which affect oxidative stress.

### Data Extraction and Outcomes

One author (S.J-F.) extracted and entered data on oxidative stress marker or antioxidant levels, and a second author (C.U.C.) verified the information. Any inconsistency was resolved by consensus.

### Quality Assessment of Included Studies

We followed guidelines from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to assess study quality using the following items[41]: (1) clear description of patient inclusion criteria and, for case-control studies, case ascertainment based on psychometric methods and comparable control selection; (2) diagnosis and measurement of depression utilizing reliable instruments; (3) clear description of oxidative stress measurements; (4) clear description of how depression and oxidative stress variables were handled in the analyses; and (5) control for potential confounders, either by exclusion criteria or statistical adjustment, including smoking status, body mass index (BMI)/obesity, recent infections, other chronic medical diseases, or medication use, which can each affect oxidative stress.

### Data Analysis

We carried out separate meta-analyses for each oxidative stress and antioxidant parameter for which ≥ 3 studies provided data, comparing levels (1) in patients with depression with those in healthy controls, (2) before and after antidepressant treatment in patients with depression, and (3) in patients with depression after antidepressant treatment with those in healthy controls (in order to assess if antidepressant treatment normalized the values). For the latter, we also meta-analytically calculated the effect size for the change in the depression rating scale from baseline to endpoint.

We calculated standardized mean differences (SMD) weighted for sample size (± 95% confidence intervals [CIs]), yielding Hedges *g* effect sizes. Heterogeneity between studies was explored with a $\chi^2$ test of homogeneity together with the $I^2$ statistic, with an $I^2 \geq 50\%$ indicating significant heterogeneity. In the primary analyses, we pooled data irrespective of the medium that the target parameter's analyses were based on, ie, serum, plasma, whole blood, or RBC. Whenever a study presented data from more than 1 of the 4 possible sources, we used data from the source that was used by the majority of the remaining studies for that specific outcome. Finally, 3 sensitivity analyses were conducted whenever at least 3 studies remained analyzable: (1) after removal of outlying results, defined as effect sizes ≥ 2; (2) focusing only on RBC samples, on which the majority of data were based; and (3) analyzing only results of high-quality studies (only possible for zinc). We used funnel graphs (trial effect against trial size) to investigate the likelihood of overt publication bias. All data were analyzed using Review Manager 5.1 (http://tech.cochrane.org).

## RESULTS

### Search Results

The electronic search yielded 3,766 articles, and 3,696 articles were excluded based on title and abstract review. (See Supplementary eFigure 1 at PSYCHIATRIST.COM for a flowchart showing the study selection process.) Of 70 potentially eligible studies, 41 were excluded after full-text review because of at least 1 of the following reasons: (1) data presented were not related to oxidative stress; (2) diagnosis was not depression; or (3) they were studies in animals, genetic studies, cultured cells or in-vitro studies, postmortem studies, or review articles, leaving 29 eligible studies.[17,30,35–37,42–65]

### Depressed Patients Compared to Healthy Control Subjects

***Study and patient characteristics.*** All 29 identified studies provided data on the comparison between depressed patients (n = 2,477; mean ± SD age = 36.76 ± 10.89 years; 66.19% females; mean ± SD illness duration = 6.21 ± 5.74 years) and healthy controls (n = 1,484; mean ± SD age = 38.04 ± 12.89 years; 58.2% females) (for details, see Supplementary eTable 1). Patients with depression and healthy controls were matched on sex and age in 21 studies and matched on sex, age, BMI, and smoking in 4 studies, while matching criteria were either not mentioned or not applied in 4 studies. *DSM-IV* criteria were used in 16 studies to determine the diagnosis of major depressive disorder (MDD). At baseline, patients were medication-free in 11 studies (37.9%) and treated with antidepressants in 13 studies (44.8%) (ie, selective serotonin reuptake inhibitors [SSRIs] = 4 studies, serotonin-norepinephrine reuptake inhibitors [SNRIs] = 4 studies, norepinephrine reuptake inhibitor [NRI] = 1 study, tricyclic antidepressants [TCAs] = 4 studies, or the antidepressant used was not specified in 4 studies). The mean ± SD Hamilton Depression Rating Scale (HDRS) score at baseline was 24.1 ± 11.88 (13 studies; n = 699).

Studies reported on uric acid (4 studies; 3 analyzing outcomes in serum, 1 in plasma), zinc (13 studies; 9 analyzing outcomes in serum and 2 each in plasma or in an unspecified source), enzymes involved in increasing antioxidant peripheral defenses (SOD [10 studies; 5 each analyzing outcomes in either RBC or serum], CAT [3 studies; 2 analyzing outcomes in RBC, 1 in serum], and GPX [6 studies; 4 analyzing outcomes in RBC, and 1 each in serum, plasma, or whole blood]), and/or oxidative stress markers, including MDA (8 studies; 4 each analyzing outcomes in RBC or plasma, 2 in serum [several studies analyzed outcomes in more than 1 medium]) and total nitrites (3 articles; 2 analyzing outcomes in plasma and 1 in serum). There were fewer than 3 articles reporting data on gluthatione reductase or TBARS, which is why we did not meta-analyze them (Supplementary eTable 1).

Overall, the quality of the included studies was medium. Among the 29 articles included, 11 met all the criteria for quality assessment. The methods/sources of participant

selection were not clearly defined in 4 studies,[30,35,57,58] and assessment of depression was unclear in 8 studies.[17,30,46,48,56–58,65] Except for 1,[57] all studies provided a clear description of oxidative stress measures. A description of the handling of depression and oxidative stress in the analyses was not provided in 3 studies[53,54,60] (see Supplementary eTable 2).

***Malondialdehyde (oxidative stress marker).*** Compared with healthy controls, patients diagnosed with depression had significantly higher MDA levels (8 studies; n = 916; SMD = 1.34; 95% CI, 0.57 to 2.11; $P < .0001$; $I^2 = 96\%$) (see Figure 3). When the analysis was restricted to RBC samples, results remained highly significant with a large effect size (4 studies; n = 328; SMD = 1.02; 95% CI, 0.63 to 1.41; $P < .001$), but the result became less heterogeneous ($I^2 = 57\%$). After removing 1 outlier study, results were expectedly somewhat attenuated but remained robust (7 studies; n = 814; SMD = 0.76; 95% CI, 0.32 to 1.20; $P < .001$; $I^2 = 87\%$).

***Total nitrites (oxidative stress marker).*** Total nitrites were not significantly different between depressed patients and healthy controls (3 studies; n = 426; SMD = −0.43; 95% CI, −1.26 to 0.40; $P = .31$; $I^2 = 87\%$) (see Figure 3).

***Uric acid (nonenzymatic antioxidant).*** Patients had significantly lower uric acid levels than healthy controls (4 studies; n = 512; SMD = −0.64; 95% CI, −1.22 to −0.06; $P = .030$; $I^2 = 89\%$) (Figure 3).

***Zinc (nonenzymatic antioxidant).*** Zinc levels were significantly lower in depressed patients than healthy controls (13 studies; n = 2,002; SMD = −0.66; 95% CI, −0.98 to −0.34; $P < .0001$; $I^2 = 85\%$) (Figure 3). After repeating the analyses in the 6 studies with high quality ratings, results remained consistent (n = 620; SMD = −0.74; 95% CI, −1.41 to −0.07; $P = .03$; $I^2 = 90\%$).

***Enzymatic antioxidants: superoxide dismutase, catalase, and glutathione peroxidase.*** Compared with healthy controls, patients diagnosed with depression had significantly higher SOD levels (11 studies; n = 902; SMD = 0.62; 95% CI, 0.07 to 1.17; $P = .028$; $I^2 = 93\%$) (Figure 3). In the sensitivity analysis focused on RBC, SOD levels continued being significantly higher in depressed patients versus controls (5 studies; n = 420; SMD = 0.70; 95% CI, 0.04 to 1.37; $P = .040$), although results remained heterogeneous ($I^2 = 90\%$).

CAT activity and GPX activity were not significantly different between depressed patients and healthy controls (CAT: 3 studies; n = 181; SMD = 0.94; 95% CI, −0.25 to 2.13; $P = .12$ and GPX: 6 studies; n = 384; SMD = −0.16; 95% CI, −0.66 to 0.34; $P = .53$) (Figure 3).

Results remained nonsignificant in analyses focusing on RBC results (CAT: 2 studies; n = 122; SMD = 0.41; 95% CI, −0.66 to 1.47; $P = .45$; $I^2 = 88\%$ and GPX: 4 studies; n = 270; SMD = −0.05; 95% CI, −0.77 to 0.65; $P = .88$; $I^2 = 87\%$).

## Comparison Before and After Antidepressant Treatment and After Antidepressant Treatment Compared to Healthy Controls

***Study and patient characteristics.*** Altogether, 11 studies provided data in depressed patients (n = 466; mean age = 39.04 ± 11.55 years; 62.74% female, mean illness duration = 5.1 ± 3.6 years [based on 3 studies with data]) before and after antidepressant treatment (mean treatment duration: 10.38 weeks) (Supplementary eTable 3). *DSM-IV* criteria to determine the diagnosis of MDD were used in 8 studies. At baseline, patients were medication-free in 7 studies (63.64%). The mean HDRS scores in the 3 studies with both baseline and endpoint data decreased from 24.6 ± 0.7 to 16.2 ± 1.6, resulting in a large effect size for antidepressant action (SMD = 2.65; 95% CI, 1.13 to 4.15; $P = .00065$).

Studies reported on uric acid (3 studies; 2 analyzing outcomes in serum, 1 in plasma), zinc (3 studies; 2 analyzing outcomes in plasma, 1 in serum), enzymes involved in increasing antioxidant peripheral defenses (SOD [5 studies; 3 analyzing outcomes in RBC, 2 in serum], CAT [2 studies, each

**Figure 3. Pooled Standardized Mean Differences of Specific Oxidative Stress Markers, Nonenzymatic Antioxidants, and Enzymatic Antioxidants Between Patients With Depression and Healthy Controls**

| Parameter | Statistics for Each Parameter | | | | | | |
|---|---|---|---|---|---|---|---|
| | Standardized Difference in Means | Standard Error | Variance | Lower Limit | Upper Limit | Z Value | P Value |
| Zinc (13 studies, n = 2,002) | −0.660 | 0.163 | 0.027 | −0.980 | −0.340 | −4.045 | <.001 |
| Uric acid (4 studies, n = 512) | −0.640 | 0.295 | 0.087 | −1.219 | −0.061 | −2.168 | .030 |
| Total nitrites (3 studies, n = 426) | −0.430 | 0.425 | 0.180 | −1.263 | 0.403 | −1.012 | .311 |
| Glutathione peroxidase (6 studies, n = 384) | −0.160 | 0.257 | 0.066 | −0.663 | 0.343 | −0.623 | .533 |
| Superoxide dismutase (11 studies, n = 902) | 0.620 | 0.283 | 0.080 | 0.066 | 1.174 | 2.192 | .028 |
| Catalase (3 studies, n = 181) | 0.940 | 0.606 | 0.367 | −0.247 | 2.127 | 1.552 | .121 |
| Malondialdehyde (8 studies, n = 916) | 1.340 | 0.395 | 0.156 | 0.566 | 2.114 | 3.393 | <.001 |

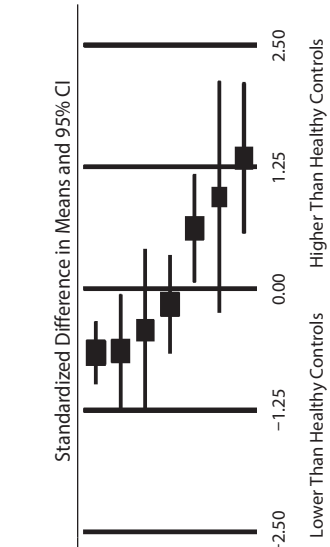


**Figure 4. Pooled Standardized Mean Differences of Specific Oxidative Stress Markers, Nonenzymatic Antioxidants, and Enzymatic Antioxidants in Patients With Depression Before and After Antidepressant Treatment (A) and Between Patients With Depression After Antidepressant Treatment and Healthy Controls (B)**

A. Patients With Depression Before vs After Antidepressant Treatment

| Parameter | Standardized Difference in Means | Standard Error | Variance | Lower Limit | Upper Limit | Z Value | P Value |
|---|---|---|---|---|---|---|---|
| Malondialdehyde (4 studies, n = 194) | −1.450 | 0.499 | 0.249 | −2.429 | −0.471 | −2.903 | .004 |
| Glutathione peroxidase (3 studies, n = 130) | 0.040 | 0.169 | 0.029 | −0.292 | 0.372 | 0.236 | .813 |
| Superoxide dismutase (5 studies, n = 130) | 0.450 | 0.425 | 0.180 | −0.382 | 1.282 | 1.060 | .289 |
| Uric acid (3 studies, n = 210) | 0.760 | 0.373 | 0.139 | 0.029 | 1.491 | 2.038 | .042 |
| Zinc (3 studies, n = 65) | 1.220 | 0.420 | 0.177 | 0.396 | 2.044 | 2.901 | .004 |




B. Patients With Depression After Antidepressant Treatment vs Healthy Controls

| Parameter | Standardized Difference in Means | Standard Error | Variance | Lower Limit | Upper Limit | Z Value | P Value |
|---|---|---|---|---|---|---|---|
| Uric acid (3 studies, n = 332) | −0.370 | 0.226 | 0.051 | −0.813 | 0.073 | −1.636 | .102 |
| Malondialdehyde (3 studies, n = 236) | 0.070 | 0.135 | 0.018 | −0.194 | 0.334 | 0.520 | .603 |
| Zinc (3 studies, n = 135) | 0.240 | 0.172 | 0.030 | −0.097 | 0.577 | 1.396 | .163 |
| Superoxide dismutase (5 studies, n = 360) | 0.700 | 0.252 | 0.063 | 0.207 | 1.193 | 2.780 | .005 |




analyzing outcomes in RBC], GPX [3 studies; 2 analyzing outcomes in RBC, 1 in plasma]), and the oxidative stress markers MDA (4 studies; 3 each analyzing outcomes in RBC or plasma, 1 in serum [several studies analyzed outcomes in more than 1 medium]) and total nitrites (2 studies, each analyzing data in serum and plasma) (Supplementary eTable 3).

***Malondialdehyde (oxidative stress marker).*** After antidepressant treatment, MDA decreased significantly (4 studies; n = 194 patients evaluated twice; SMD = −1.45; 95% CI, −2.43 to −0.47; $P = .004$; $I^2 = 94\%$) (Figure 4A), not remaining higher than in healthy controls (3 studies; n = 236; SMD = 0.07; 95% CI, −0.19 to 0.33; $P = .60$; $I^2 = 4\%$) (Figure 4B). The effect size remained large and significant, even after removing 1 outlying study (3 studies; n = 130 patients evaluated twice; SMD = −0.90; 95% CI, −1.16 to −0.65; $P < .001$; $I^2 = 0\%$).

***Uric acid (nonenzymatic antioxidant).*** After antidepressant treatment, uric acid levels increased significantly (3 studies; n = 212 patients evaluated twice; SMD = 0.76; 95% CI, 0.03 to 1.49; $P = .042$; $I^2 = 91\%$) (Figure 4A), no longer being significantly lower than in healthy controls (3 studies; n = 332; SMD = −0.37; 95% CI, −0.81 to 0.07; $P = .10$; $I^2 = 72\%$), although the confidence interval was large (Figure 4B).

***Zinc (nonenzymatic antioxidant).*** Zinc levels increased significantly after antidepressant treatment (3 studies; n = 65 patients evaluated twice; SMD = 1.22; 95% CI, 0.40 to 2.04; $P = .004$; $I^2 = 75\%$) (Figure 4A), and there was no longer a significant difference from healthy controls (3 studies; n = 135; SMD = 0.24; 95% CI, −0.10 to 0.58; $P = .16$; $I^2 = 0\%$) (Figure 4B).

***Enzymatic antioxidants: superoxide dismutase, catalase, and glutathione peroxidase.*** After antidepressant treatment, SOD and GPX levels did not change significantly (SOD: 5 studies; n = 130 patients evaluated twice; SMD = 0.45; 95% CI, −0.38 to 1.28; $P = .29$; $I^2 = 94\%$ and GPX: 3 studies; n = 130 patients evaluated twice; SMD = 0.04; 95% CI, −0.29 to 0.37; $P = .81$; $I^2 = 46\%$) (Figure 4A). Moreover, after antidepressant treatment, SOD levels remained significantly higher compared to healthy controls (5 studies; n = 360; SMD = 0.70; 95% CI, 0.21 to 1.19; $P = .005$; $I^2 = 81\%$) (Figure 4B). However, the sensitivity analysis of SOD in RBC showed a significant decrease (3 studies; n = 130 patients evaluated twice; SMD = −0.41; 95% CI, −0.65 to −0.16; $P = .001$; $I^2 = 0\%$). Although in these 3 studies with RBC assays, SOD levels were no longer significantly higher compared to healthy controls (SMD = 0.59; 95% CI, −0.06 to 1.24; $P = .07$; $I^2 = 83\%$), levels were still marginally higher and confidence intervals were large.

## DISCUSSION

### Main Findings

This comprehensive meta-analysis of oxidative stress and antioxidant markers in patients with depression has 2 main findings. First, several oxidative stress indicators are abnormal in individuals with depression compared to healthy control subjects. These include significantly elevated levels of the oxidative stress indicator MDA, the final product of lipid degradation; lower levels of the antioxidants zinc and uric acid; and up-regulated levels of the free radical–eliminating enzyme SOD. Second, effective antidepressant treatment improved some of these abnormalities. For example, the oxidative stress marker MDA decreased significantly; levels of the antioxidant–producing enzyme SOD decreased, at least in RBC; and the nonenzymatic antioxidants uric acid and zinc increased significantly. After antidepressant treatment, MDA, zinc, and uric acid levels were comparable to those of healthy controls, although antidepressant did not fully normalize levels of the enzymatic antioxidant SOD compared to controls. Altogether, these findings suggest specific abnormalities in the oxidative stress–antioxidant balance and specific antidepressant effects for some, but not other, components of this dysregulated homeostasis in patients with depression.

We conducted sensitivity analyses in erythrocyte samples because it has been suggested that oxidative stress status of RBC may best reflect the status in brain.[66] RBCs are very sensitive to prooxidant challenges and, contrary to brain tissue, can be easily studied.[66] In general, these analyses confirmed pooled analyses irrespective of the analyzed samples, reducing some heterogeneity and revealing the finding of significantly increased SOD levels.

Free radicals, which attack proteins and lipids, increase during enhanced oxidative stress (Figure 1). The body compensates for this excess of free radicals by activation of antioxidant enzymes and through the action of multiple blood circulating antioxidant substances, like uric acid and bilirubin, or buffering substances, like GSH.[27] Our results in depressed patients regarding MDA, uric acid, zinc, and SOD are consistent with this interpretation and suggest that depression is associated with increased levels of oxidative stress and decreased antioxidant levels. However, we did not find significant differences in the oxidative stress parameter total nitrites and the antioxidant enzymes CAT or GPX compared to healthy subjects or after antidepressant treatment. This divergence in the results could be a type II error due to limited power, could be due to the difficulties to control for confounding factors, or might point to specific patterns of oxidative stress in depression, including a potentially pathological lack of compensatory up-regulation of antioxidant enzyme pathways. If larger studies and meta-analyses can substantiate that specific oxidative stress/antioxidant signatures are involved in the pathophysiology of depression and/or improvements in depression, the door would open for targeted antidepressant drug development with novel mechanisms.

However, our results also need to be interpreted within the light of studies and meta-analyses in other severe psychiatric disorders so that the potential specificity of individual oxidative stress marker and antioxidant findings can be assessed. When comparing our results with those from previous meta-analyses in patients with schizophrenia[67] and bipolar disorder,[68] both similarities and differences emerge. Consistent with our findings in depression, MDA levels were significantly higher in schizophrenia patients, independent of illness duration and acuity.[67] No data were available for the effect of antipsychotics or in bipolar disorder patients. Similar to our findings, at least in first-episode schizophrenia patients, uric acid was also decreased,[67] while no meta-analytic results were available for bipolar disorder. SOD levels, which in depressed patients were either nonsignificantly different from controls or significantly higher than in controls considering RBC samples, were not different from controls in bipolar disorder patients.[68] SOD levels were either no different or decreased (as opposed to increased) in RBC samples in patients with schizophrenia relative to controls.[67] However, in plasma-derived analyses, SOD levels were higher in first-episode patients, chronically ill inpatients, and acutely relapsed patients with schizophrenia compared to controls, while SOD was decreased in stably medicated outpatients, yielding contradictory results.[67] Finally, like our results in depressed patients, CAT and GPX levels in bipolar disorder patients were not different from controls, while in schizophrenia, results were again heterogeneous but showing mostly decreased CAT or GPX levels.[68]

Furthermore, our results provide support for the hypothesis that oxidative stress and nitrosative stress are activated in depression, resulting in an increase of reactive nitrogen and oxygen species, which enhances the expression of endogenous antioxidants and the increase of inflammatory mediators.[69] This is relevant, as reactive oxygen and nitrogen species directly attack different cell components, such as DNA, proteins, and amino acids, causing serious damage in cell membranes, anchorage molecules, functional proteins, and mitochondrial activity by ROS-RNS and their inflammation-enhanced reactions. The activated immune-inflammatory pathways are interacting with the oxidative-nitrosative stress status and exacerbating each other via different ways: (1) Depression has been associated with increased blood mononuclear cells (activated phagocytes and macrophages and T helper-1 and 17-like cells) that produce large quantities of cytokines and ROS.[3,20] (2) As a result of the attack of ROS-RNS on fatty acids and proteins, new oxidative- and nitrosative-specific epitopes are formed, which mediate autoimmune responses enhancing serious cell dysfunction.[70,71] (3) Patients with depression have higher immune response to lipopolysaccharides from bacterial translocation that belongs to the normal gut flora.[72] Lipopolysaccharides activate toll-like receptors (TLR2/TLR4), which are an important part of the host defense system.[73] Further, these receptors are also activated by damage-associated molecular patterns that are produced during the lipid peroxidation.[74] In central nervous

system cells, the resultant cell alterations and cell dysfunction trigger a neurodegeneration process[75,76] and neuronal apoptosis. Furthermore, immune-inflammatory pathways affect the expression of neurotransmitters that are involved in depression. In this context, it is notable that depression is associated with single-nucleotide polymorphisms in prooxidant and antioxidant genes that increase susceptibility to depression.[77] Moreover, several single-nucleotide polymorphisms of cytokine proinflammatory genes may be related to response to antidepressant treatment.[78] Further, environmental interactions, which are currently almost unknown, may also play an important role, which requires further elucidation.

### Strengths and Limitations

The results of this meta-analysis need to be interpreted within its limitations. These include, foremost, the still relatively small number of studies and participants, as well as the related heterogeneity of the results that may also be a consequence of the heterogeneity of the studied populations that were not separated by illness duration or acuity, biological sources, and employed assays. Further, we were unable to analyze the effect of specific antidepressants on the oxidative stress balance because most studies did not report separate results for each antidepressant. Moreover, only 11 studies (37.9%) were of high quality, and most studies did not match patients and controls on or control for potentially confounding factors, such as tobacco use, BMI, and diet, which may alter oxidative stress/antioxidant parameters in the pre- versus postantidepressant treatment analyses.[79–81] Finally, we were unable to account for different genetic factors; for instance, an association of SOD polymorphism has been demonstrated in patients with depressive disorders.[82]

However, despite these limitations, strengths of this study include that we (1) independently analyzed 2 specific oxidative stress markers (MDA and total nitrites) and 5 specific antioxidants (3 antioxidant enzymes [SOD, CAT, and GPX] and 2 nonenzymatic antioxidants [zinc and uric acid]), (2) examined the effect of antidepressant treatment, (3) evaluated the degree of normalization of the examined markers after antidepressant treatment compared to healthy controls, and (4) assessed results depending on different biological source samples. These strengths are also the main differences to the recently published meta-analysis on oxidative stress in depression[9] in which levels from a variety of different markers, each measured in only some of the included studies, were pooled into 2 single effect sizes compared to controls, 2 for oxidative stress levels and 2 for antioxidant levels. Furthermore, compared to the prior meta-analysis,[9] we included 8 additional articles meeting our selection criteria. By contrast, we decided to exclude several studies that were included in Palta and colleagues' meta-analysis[9] for the following reasons: (1) patients had comorbidities that could potentially alter oxidative stress parameters[83,84]; (2) the diagnoses were not circumscribed to unipolar depression[85–87]; (3) individual oxidative stress or antioxidant parameters were not reported in at least 3 studies[88–92]; and (4) data were extracted from sources different from those that we focused on in order to minimize possible confounders.[93]

## CONCLUSIONS AND FUTURE DIRECTIONS

Taken together, the meta-analyzed results suggest that depression has an oxidative stress signature and that antidepressants can improve this abnormality to some degree. Moreover, the results indicate a possible similarity in oxidative stress/antioxidant dysbalances between depression and bipolar disorder. In particular, SOD, CAT, and GPX levels were not significantly different from those of healthy controls in either depressed patients in our results or bipolar disorder patients in a prior meta-analysis.[68] However, there seems to be less resemblance between depression and schizophrenia.[67]

Nevertheless, these results also suggest that, in addition to potential disease-specific alterations, nonspecific oxidative stress abnormalities may cut across different severe psychiatric disorders, as has been observed for increased markers of inflammation.[91] Therefore, further research is needed in order to identify common and unique oxidative stress pathways that may help either to focus the search for general/nonspecific preventive and treatment targets or to guide novel, disease-specific interventions. However, for such data to be informative, it will be crucial that, in future studies, relevant confounding variables are measured and controlled for; that populations are stratified by illness phase, acuity, severity, and specific treatment(s); and that specific effects of available treatments are being assessed. Moreover, such studies need to be sufficiently large and should analyze a comprehensive array of relevant markers (see Figure 2) in serum, plasma, and RBC concurrently. It is hoped that increased research knowledge will aid the development of novel treatments that can modify dysregulated oxidative stress pathways and thereby improve outcomes in at least subgroups of patients with depression and, possibly, other severe mental disorders.

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# Supplementary Material

**Article Title:** 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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## List of Supplementary Material for the article

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2. **eTable 1** Studies of Oxidative Stress Marker and Antioxidant Levels in Patients with Depression vs Healthy Controls

3. **eTable 2** Quality Assessment Based on Guidelines from the STROBE Statement

4. **eTable 3** Studies of Oxidative Stress Marker and Antioxidant Levels in Patients with Depression Before and After Antidepressant Treatment

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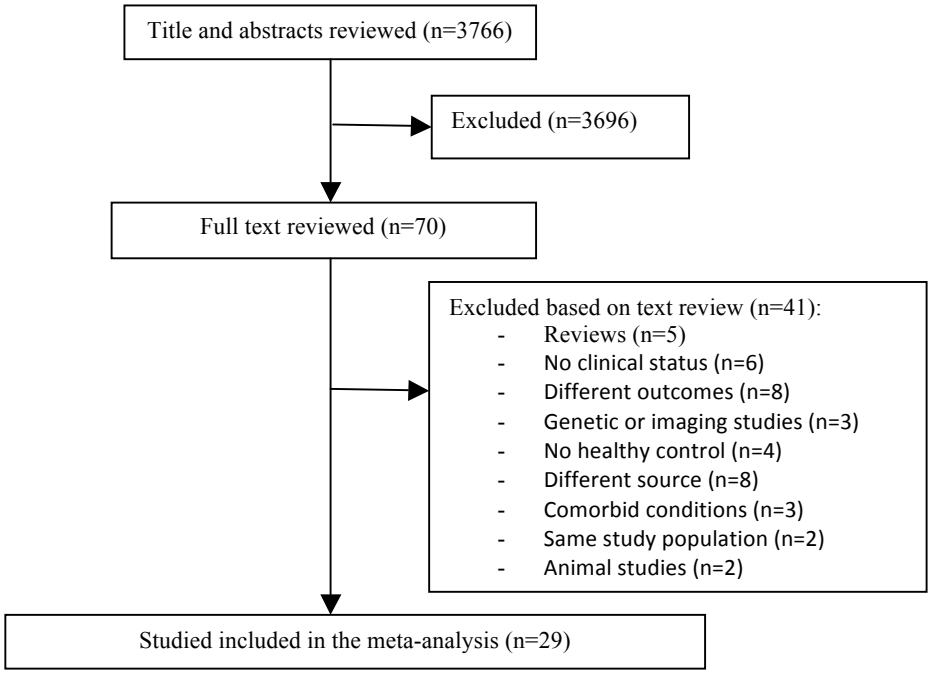
**Supplementary eFigure 1.** Flow chart of study selection process



**Supplementary Table 1.** Studies of Oxidative Stress Marker and Antioxidant Levels in Patients with Depression vs. Healthy Controls

| Study (Country) | Design | N Patients with Depression | N Healthy Controls (variables matched on) | Population | Mean baseline Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness duration (Years) | Antidepressant<br><br>Treatment duration | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Amani et al. (2010)**[42] *(Iran)* | Cross-sectional study | 23 | 23 (sex, age) | Students with moderate to severe depression (Beck´s questionnaire>19) | BDI: 47.2±17.3 | MDD: 20.7±1.6<br><br>HC: 20.2±0.9 | MDD:100<br><br>HC: 100 | NR | No reported AD medication | | | | | | | *Serum:* MDD: 79.6±30.7 HC: 111.6±21.9 |
| **Baek and Park (2013)**[43] (South Korea) | Cross-sectional study | 80 | 80 (sex, age) | MDD (DSM-IV) | CES-D-K: 35.41±0.78 | MDD: 44.85±1.77 HC: 44.47±1.63 | MDD: 73.75<br><br>HC: 65 | NR | NR | | | | *Serum:* MDD: 11.06±3<br><br>HC: 9.37±3 | | | |
| **Bilici et al. (2001)**[30] *(Turkey)* | Cohort 12-week long. study | 30 | 32 (sex, age) | MDD (DSM-IV), AD free during index episode, free of medical illness (including infection, inflammation or allergic reaction)<br>HC: free of any medication ≥2 months. No drinkers or heavy smokers. No PH and FH of psychiatric d/o | HDRS-17: 24.12±3.61 | MDD: 40.3±7<br><br>HC: 42.1±7 | MDD: 70<br>HC: 50 | 6.5±2.4 | SSRI | *Plasma*<br>MDD: 4.32±1.6<br>HC: 2.89±1.1<br><br>*RBC*<br>MDD:149.8±32.2<br>HC: 109.3±32.8 | | *Plasma*<br>MDD: 115.1± 29.3<br>HC: 109.7± 33.6<br>*RBC*<br>MDD: 6.6±1.2<br>HC: 5.5±1.6 | *RBC*<br>MDD: 1250± 153<br>HC: 966± 129 | *RBC*<br>MDD: 283.9± 46.8<br>HC: 290.4± 5.6 | | |
| **Chaudhari et al. (2010)**[44] **(***India)* | Random. parallel group, 12week long. study | 40 | 36 (sex, age,) | MDD (DSM-IV),<br>No other psychiatric diagnoses, no medical illness. Vegetarian diet<br>HC: >50kg body weight, good diet (vegetarian), non-smoker, non-alcoholic, medication free ≥1month. No PH of psychiatric d/o | HDRS-21: 25.33±2.29 | (18-65) | NR | NR | SSRI: fluoxetine 20 mg (n=20) vs citalopram 20 mg (n=20) | | *Serum*<br>MDD 3.765± 0.79<br>HC: 5.256± 1.02 | | | | | |
| **Chrapko et al. (2006)** [45] *(Canada)* | Cohort 8-week long. study | 17 | 12 (sex, age) | MDD (DSM-IV), comorbid with anxiety disorder. Free of psychotropic medication for at least 1 year. No current or past or FH of early cerebrocardiovascular illness | HDRS-21: 20.71±4.25<br><br>BDI: 25.18±4.08 | MDD: 34.50±2.08<br><br>HC: 26.75±2.78 | MDD: 35.3<br><br>HC: 41.6 | NR | SSRI: Paroxetine 20 mg (n=17) | | | | | | *Plasma:* MDD: 5.74±6.0 HC: 23.33±13.01 | |
| **Crayton et al. (2007)** [46] *(USA)* | Cross-sectional study | 485 | 28 (sex, age) | Clinical diagnosis and treated by primary care psysicians or psychiatrists. Excluded BPD or other psychiatric condition | NR | 30-60 | 100 | NR | NR | | | | | | | *NR:* MDD: 73±15 HC: 77±12 |
| **Crayton et al. (2007)** [46] *(USA)* | Cross-sectional study | 328 | 26 (sex, age) | Clinical diagnosis and treated by primary care psysicians or psychiatrists. Excluded BPD or other psychiatric condition | NR | 30-60 | 0 | NR | NR | | | | | | | *NR:* MDD: 78±14 HC: 78±15 |

| Study (Country) | Design | N Patients with Depression | N Healthy Controls (variables matched on) | Population | Mean baseline Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness duration (Years) | Antidepressant<br><br>Treatment duration | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Galecki et al. (2009)** [77] **(***Poland)* | Cohort 12-week long. study | 50 | 30 (sex, age) | MDD (DSM-IV) medication free ≥3 weeks, free of medical illness (including infection, inflammation or allergic reaction)<br>HC: free of any medication ≥2 months. No drinkers or heavy smokers. No PH and FH of psychiatric d/o | HDRS-21: 32.3±2.9 | MDD: 36.7±5.2<br><br>HC: 32.1±4.3 | MDD: 56<br>HC: 53 | NR | SSRI: fluoxetine 20 mg | *RBC*<br>MDD: 0.739± 0.164<br>HC: 0.549± 0.224 | | *RBC*<br>MDD: 74.2±13.5<br>HC: 68.7±16.7 | *RBC*<br>MDD: 2078± 199<br>HC: 1978± 196 | *RBC*<br>MDD:17.4±3.1<br>HC:14.2± 3.5 | | |
| **Grieger et al. (2009)** [47] *(Australia)* | Cross-sectional study | 28 | 43 (NR) | MDD | GDS: 8.1±2.12 | 80.2±10.6 | NR | NR | NR | | | | | | | *Serum:*<br>MDD: 10.1±2.12<br><br>HC: 11.9±3.28 |
| **Herken et al. (2007)** [48] *(Turkey)* | Cohort 8-week long. study | 36 | 20 (sex, age, smoking) | MDD (DSM-IV) medication ceased ≥2 weeks before. No axis I cormobidity. No medical illness or substance use<br>HC: free of medication ≥6 weeks before. No drinkers or heavy smokers or drug consumers. No PH and FH of psychiatric disorder | HDRS (no results given) | (17-62) | MDD: 52.7 | 2.7±4.7 | SSRI: fluoxetine 20 mg (n=11), citalopram 20 mg (n=10), sertraline 50 mg (n=8), fluvoxamine 150 mg (n=7) | | | | *Serum*<br>MDD: 7.7±1.8<br>HC: 9.2±0.5 | | *Serum:*<br>MDD: 66.4±21.3<br>HC:61.6± 9.0 | |
| **Khanzode et al. (2003)** [35] **(***India)* | Random. Parallel group, 12–week long. study | 62 | 40 (NR) | MDD (DSM-IV) medication ceased ≥2 weeks before. No axis I or II comorbidity. No medical illness which can affect free radical status<br>HC: free of any medication ≥1 month. No drinkers, heavy smokers or drug consumers. No PH and FH of psychiatric d/o | HDRS-21: 24.28±4.62 | MDD: 43.8± 12.9<br>HC: 40.8±10.2 | MDD: 55<br>HC: 45 | NR | SSRI: fluoxetine 20 mg (n=32) vs. citalopram 20 mg(n=30) | *Serum*<br>MDD: 6.45±0.94<br>HC: 1.74±0.64 | | | *Serum*<br>MDD: 7.80± 2.64<br>HC: 2±0.87 | | | |
| **Kotan et al. (2011)** [36] **(***Turkey)* | Cohort 24-week long. study | 50 | 44 (sex, age, BMI, smoking) | MDD (DSM-IV). No other axis I or II diagnosis, no alcohol/drug consumption, No physical disease or syndrome, no CVD in first-degree relatives, pregnancy. No BMI ≥30, no regular treatment or heavy smokers (>15 cigarettes/day)<br><br>HC: same characteristics as MDD. | HDRS-17: 30.4±3 | MDD: 33.1±10<br>HC: 33.2±7.9 | MDD: 78<br>HC: 77 | NR | SNRI, SSRI, MAOI, TCA: venlafaxine 125±43.3 mg (n=21); paroxetine 25±7.6 mg (n=8); escitalopram 16.3±5.2 mg (n=8); sertraline 80±27.4 mg (n=5); citalopram 33.3±11.5 mg (n=3); milnacipran 100 mg (n=2); fluoxetine 20 mg (n=1); tianeptin 37.5 mg (n=1); moclobemid 600 mg (n=1) | *Plasma*<br>MDD: 1.93±1.41<br>HC: 1.08±0.58 | *Plasma*<br>MDD: 3.6± 0.9<br>HC: 4.1± 1.3 | *RBC*<br>MDD: 12.4±5.5<br>HC: 13.2±5 | *RBC*<br>MDD: 2331± 1201<br>HC:1 771±477 | | | |
| **Maes et al. (1994)** [49] *(USA)* | Cross-sectional study | 48 | 32 (sex, age) | MDD (DSM-III). No other axis I; no treatment with antionulsants or high dosages of neuroleptics during the previous year; Clinical or laboratory test, ECG, EGG, chest X-ray without | HDRS-17: 19.18±6.0 | MDD: 49.64±11.27<br><br>HC: 43.8±15.3 | NR | NR | Low-dosage of benzodiazepines (n=23) if severe anxiety, agitation or sleep disturbances. | | | | | | | *Serum:*<br>MDD: 1.81±0.28<br>HC: 2.02±0.2 |

| Study (Country) | Design | N Patients with Depression | N Healthy Controls (variables matched on) | Population | Mean baseline Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness duration (Years) | Antidepressant<br><br>Treatment duration | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | alterations. Free of drugs or illness (known to affect immune or endocrines system or zinc metabolism). No allergic or infectious reactions 2 weeks prior to blood test. | | | | | | | | | | | | |
| **Maes et al. (1997)** [50] *(Belgium)* | Cross-sectional study | 36 | 15 (sex, age) | MDD (DSM-III). No other axis I; no treatment with fluoxetine or trazodone during the index episode; free of medical illnesses and free of acute infections and inflammatory or allergic reactions for at least 2 weeks prior to the study. | 24.4±3.9 | MDD: 50.9±14.2 HC: 47.5±15.0 | MDD: 50 HC: 33.3 | 11.5±9.4 | Trazodone 100mg (n=7); trazodone 100 mg + pindolol 7.5 mg (n=8); trazodone 100 mg + fluoxetine 20 mg (n=11) | | | | | | | *Serum* MDD: 95±12 HC:114±13 |
| **Maes et al. (1999)** [51] *(Belgium)* | Cross sectional study | 34 | 14 (sex, age) | MDD (DSM-III-R). No other axis I; no axis-II diagnosis; free of abnormal radiograph or heart/lungs/EGG; no treatment with fluoxetine, trazodone, MAOIs, antipsychotic drugs, antivonvulsants, lithium or ECT the year previous; free of acute or chronic and acute infections or allergic reactions for at least 2 weeks prior to the study; free of low fat diet or cholesterol-lowering drugs; no mediction that affect fatty acid metabolism or endocrine and immune functions; BMI inside normal limits; no heavy smokers; consuming Belgian diet | HDRS-17: | MDD: 52.2±13.6 HC: 48.3±15.2 | MDD: 47.01 HC: 35.71 | NR | No treatment | | | | | | | *Serum:* MDD: 96.4±10.4 HC: 113.6±12.1 |
| **Maes et al. (2011)** [17] *(Thailand)* | Cross-sectional study | 39 | 24 (sex, age) | MDD (DSM-IV) and HC exclusion criteria: 1) medical illnesses; 2) abnormal blood test; 3) inflammatory or allergic reactions last 2 months; 4) treated with AP, AC, MS; 5) dietary supplements | HDRS: (no results given) | MDD: 44.6±12 HC: 45.5±9.9 | MDD: 56 HC: 29 | NR | NR | | | *Whole Blood* MDD:35.1±10.7 HC: 42.4±17.5 | | | | |
| **McLoughlin and Hodge (1990)** [53] *(United Kingdom)* | Cohort long. study | 14 | 14 (sex, age) | MDD. No recent myocardial infaction, abnormal renal function, severe infection, evidence of clinical dehydratation or pregnancy | BDI: 21±6.3<br><br>HDRS-17: 21±2 | MDD: 56.8±16.7<br><br>HC: 56.2±15.6 | MDD: 78.57 | NR | 57.14 % AD (n=8); 7.14% carbamazepine (n=1); 7.14% night sedation | | | | | | | *Plasma:* MDD: 12.3±1.64<br><br>HC: 14.1±1.46 |
| **Narang et al. (1991)** [54] *(India)* | Cohort long. study | 35 | 35 (sex, age) | MDD | HDRS (no results given) | NR | MDD: 40 | NR | NR | | | | | | | *Plasma:* MDD: 107.62±21.94<br><br>HC: 115.8±24.88 |
| **Nguyenet al. (2009)** [55] | Cross sectional study | 182 | 187 (sex, age) | CES-D>16; Women were not admitted if :1) pregnancy; 2) lactation (child within the last | CES-D (no results given) | MDD: 32.8±9.3 | 100 | | NR | | | | | | | *Serum:* MDD: 10.6±2.0 |

| Study (Country) | Design | N Patients with Depression | N Healthy Controls (variables matched on) | Population | Mean baseline Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness duration (Years) | Antidepressant<br><br>Treatment duration | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 3 mo); 3) supplements consumption; 4) chronic diseases; 5) severe anemia | | HC: 29.5±9.2 | | | | | | | | | | HC: 10.5±2.2 |
| **Rybka et al. (2013)** [56] **(***Poland)* | Cross-sectional study | 15 | 19 (sex, age) | Recurrent depressive disorder (ICD-10). No other psychiatric diagnosis (axis I or axis II) or medical illness. All patients and HC were on their usual medication | BDI (no results given) | MDD: 62.3±2.8 HC: 62.3± 2.84 | NR | NR | SSRI (60%), SNRI (35%), TCA (15%) | *RBC* MDD: 0.169± 0.0743 HC: 0.088± 0.0148 | | *RBC* MDD: 12.23± 5.39 HC: 19.01± 4.24 | *RBC* MDD: 2269.9± 643.81 HC: 2637.1± 282.00 | | | |
| **Russo (2010)** [57] *(United States)* | Cohort long. study | 36 | 18 (sex, age) | MDD; HC: no documented mental illness | HDRS (no results given) | MDD: 35.2 HC: 41.7 | MDD: 61.5 HC: 73.7 | NR | NR AD medication; Antioxidant therapy | | | | *Serum* MDD:0.695±0.479 HC:0.326± 0.14 | | | |
| **Salimi et al. (2008)** [58] *(Iran)* | Cross sectional study | 161 | 144 (sex, age) | MDD; No taking psychotropic drugs | NR | MDD: 35.37±10.13 HC: 38.53±10.4 | MDD: 57.76 HC: 58.3 | NR | No treatment | | | | | | | *Serum:* MDD: 64.94±13.9 HC: 69.67±11.29 |
| **Salustri et al. (2010)** [59] *(Italy)* | Cross-sectional study | 13 | 13 (sex, age) | MDD (DSM-IV). No alcoholism, psychotropic drugs abuse and mental retardation. | MADRS HDRS-17 (no results given) | MDD: 54.2±13.5 HC: 55.9±19.3 | MDD: 85 HC: 85 | NR | Immediately after admission started a therapy. | | | | | | | *Serum:* MDD: 107.59±54.85 HC: 86.05±7.22 |
| **Sarandol et al. (2007)** [37] *(Turkey)* | Cross-sectional study | 96 | 54 (sex, age, smoking status) | MDD (DSM-IV) No other axis I or axis II disorder; no known major health problems HC: free of any medication, free of medication ≥3 weeks | HDRS-17: 15-23 | MDD: 40.0±11 HC: 37±9 | MDD: 75 HC: 74 | NR | SNRI, NRI: venlafaxine 150 mg, reboxetine 8 mg, sertraline 50 mg | *Plasma* MDD: 0.88±0.44 HC: 0.64±0.26 *RBC* MDD: 108±30 HC: 84±20 | Whole blood: MDD: 4.2±2.0 HC: 4.1±1.3 | Whole blood: MDD: 4554±2030 HC: 5225±1414 | *RBC* MDD:266.67± 177.78 HC: 100±83.3 | | | |
| **Stanley et al. (2002)** [60] *(Nigeria)* | Cohort long. 7-weeks study | 21 | 20 (NR) | MDD (ICD-10) | NR | 16-50 | NR | NR | TCA: amitryptiline 75 mg AP: Chlorpromzine 100 mg | | | | | | | *Serum:* MDD: 11.9±3.96 HC: 20.1±3.46 |
| **Stefanescu et al. (2012)** [61] **(***Romania)* | Cross-sectional study | 31 | 20 (sex, age) | MDD (DSM-IV): first episode and recurrent episodes. No CVD, CD, hepatic/renal diseases, DM, hypothyroidism, malignancies, alcohol (>30mg/day), supplementation. HC: no PH of psychiatric disorder. Free of medication | HDRS: 21.6±5.6 | MDD: 47.6±8.5 HC: 46.3±7.8 | MDD: 64.5 HC: 65 | 7.1±6.1 | SSRI, SNRI, TCA: FE: mirtazapine 30 mg (n=8); venlafaxine 75 mg (n=7); RR: tianeptine 37.5 mg (n=16); escitalopram 10 mg (n=5); venlafaxine 150 mg (n=5) | *Serum* MDD: 76.66±27.8 HC: 63.33± 16.97 | | *Serum* MDD: 0.084± 0.022 HC: 0.092± 0.04 | *Serum* MDD: 0.34± 0.22 HC: 0.46±0.2 | | | |

| Study (Country) | Design | N Patients with Depression | N Healthy Controls (variables matched on) | Population | Mean baseline Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness duration (Years) | Antidepressant<br><br>Treatment duration | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Szuster-Ciesielska et al. (2008)** [62] *(Poland)* | Cross-sectional study | 29 | 30 (sex, age) | MDD (DSM-IV): No other axis I disorder, free of medical illness, no regular drinker or drug consumer. HC: free of medication ≥1month, free of medical illness, no regular drinker or drug consumer | HDRS-17: 30.4±3.5 | MDD: 48.2±11 HC: 41.3±4.4 | MDD: 51.7 HC: 50 | NR | TCA, AP and different combination of amitriptyline 100-200 mg, sulpiride 100-200 mg, clomipramine 75-150 mg, perazine 25-125 mg, levopromazine 150 mg, imipramine 25 mg | | | | *Serum* MDD: 0.169± 0.03 HC: 0.15± 0.02 | *Serum* MDD: 39.4± 18.6 HC: 10.4±7.6 | | |
| **Vargas et al. (2013)** [63] **(***Brazil)* | Cross-sectional study | 140 | 201 (sex, age, smoking status) | | HDRS: 10.76±9.5 | (18-60) | MDD: 75.8 HC: 58.45 | NR | NR | *Plasma* MDD: 15.62±6.38 HC: 16±5.4 | | | | | *Plasma:* MDD: 3.92±2.18 HC: 4.07±2.4 | |
| **Wen et al. (2012)** [64] **(***China)* | Cohort,. 5-week long. study | 124 | 42 (NR) | Depression: MDD or moderate depression (DSM-IV). Exclusion criteria: treatment with drugs that could increase or affect uric acid | HDRS -24: 34.56±15.23 | MDD: 41. 8 (16-78) HC: 31 (17-66) | MDD: 69 HC: 30 | 5.4±3.6 | AD treatment | | *Serum* MDD: 271.97±77.5 HC: 315.76±87.5 | | | | | |
| **Wiener et al. (2013)** [65] *(Brazil)* | Case-control study | 82 | 94 (sex, age) | MDD: current or euthymic (DSM-IV). HC: exclusion criteria are medical cormobidities and abnormal blood values | HDRS (no results given) | (18-24) | MDD: 76.8 HC: 57.4 | NR | 9 patients were taking psychiatric medications | | *Serum* MDD: 4.004± 3.44 (Eu-thymia: 3.846±-3.0) HC: 4.135±-3.82 | | | | | |
| **Total (means, SDs and percentages are weighted with n values)** | 30 studies: 12 cohort studies; 17 cross-sectional; studies; 1 case-control study | 2447 | 1484 | Free of medication: 11/29 (37.9%)<br><br>Taking medication: 13/29 (44.8%)<br><br>NR: 5/29 (17.2%) | 13 studies 24.1±11.88 (n=:669) | 20 studies<br><br>MDD: 36,77± 10.89 (n=1035) HC: 38.04±12. 89 (n=680) | 24 studies<br><br>MDD: 66.19% (n=2213) HC: 58.2% (n=930) | 5 studies<br><br>6.21 ± 5.74 (n=257) | Previously taking AD medication: SSRI 4 studies; SNRI 4 studies; TCA 4 studies; NRI 1 study; | 8 Studies with data RBC: N=4 Plasma: N=4 Serum: N=2 | 4 studies with data Serum: N=3 Plasma: N=1 | 6 Studies with data RBC: N=4 Plasma: N=1 Serum: N=1 Whole Blood: N=1 | 11 Studies with data RBC: N=5 Serum: N=6 | 3 Studies with data RBC: N=2 Serum: N=1 | 3 Studies with data Plama: N=2 Serum: N=1 | 13 studies with data Plasma N=2 Serum: N=9 |

Footnote:
AD, antidepressant; AC, anticonvulsants; AP, antipsychotic; CD, cerebrovascular diseases; CES-D scale, Center for Epidemiologic Studies Depression Scale; CES-D-K, Center for Epidemiologic Studies Depression Scale Korea; CVD, cardiovascular diseases; d/o, disorder; FE, first episode; FH, familiar history; GDS, Geriatric depression Scale; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; Long., longitudinal; MDARS, Montgomery-Asberg

Depression Scale; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; MS, mood stabilizers NR, not reported; NRI, (selective) norepinephrine reuptake inhibitor; PH, personal; Random., randomized; RE, relapsing and remitting; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant;

**Supplementary Table 2**. Quality Assessment Based on Guidelines from the STROBE Statement

| Study | Clear Description of Participant Eligibility and Sources / Methods of Participant Selection | Clearly Defined Exposure Ascertainment: Depression | Clearly Defined Outcome Ascertainment: Oxidative Stress / Antioxidant | Clear Description of Handling of Depression and Oxidative Stress in the Analyses | Control for Potential Confounders by Exclusion or Statistical Adjustment |
|---|---|---|---|---|---|
| Amani 2010[42] | X | X | X | X | X |
| Baek and Park 2013[43] | X | X | X | X | X |
| Bilici 2001[30] | | | X | X | |
| Chaudhari 2010[44] | X | X | X | X | |
| Chrapko 2006[45] | X | X | X | X | X |
| Crayton 2007[46] | X | | X | X | |
| Galecki 2009[77] | X | X | X | X | |
| Grieger 2009[47] | X | X | X | X | |
| Herken 2007[48] | X | | X | X | |
| Khanzode 2003[35] | | X | X | X | |
| Kotan 2011[36] | X | X | X | X | X |
| Maes 1994[49] | X | X | X | X | X |
| Maes 1997[50] | X | X | X | X | X |
| Maes 1999[51] | X | X | X | X | X |
| Maes 2011[17] | X | | X | X | |
| McLoughlin and Hodge 1990[53] | X | X | X | | |
| Narang 1991[54] | X | X | X | | |
| Nguyen 2009[55] | X | X | X | X | X |
| Rybka 2013[56] | X | | X | X | X |
| Russo 2010[57] | | | | X | |
| Salimi 2008[58] | | | X | X | |
| Salustri 2010[59] | X | X | X | X | X |
| Sarandol 2010[37] | X | X | X | X | |
| Stanley 2002[60] | X | X | X | | |
| Stefanescu 2012[61] | X | X | X | X | |
| Szuster-Ciesielska 2008[62] | X | X | X | X | |

| | | | | | |
|---|---|---|---|---|---|
| Vargas 2013[63] | X | X | X | X | X |
| Wen 2012[64] | X | X | X | X | X |
| Wiener 2013[65] | X | | X | X | X |
| Total | 25/29 (86.2%) | 21/29 (72.4%) | 28/29 (96.6%) | 26/29 (89.7%) | 13/29 (44.8 %) |

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology.

**Supplementary Table 3.** Studies of Oxidative Stress Marker and Antioxidant Levels in Patients with Depression Before and After Antidepressant Treatment

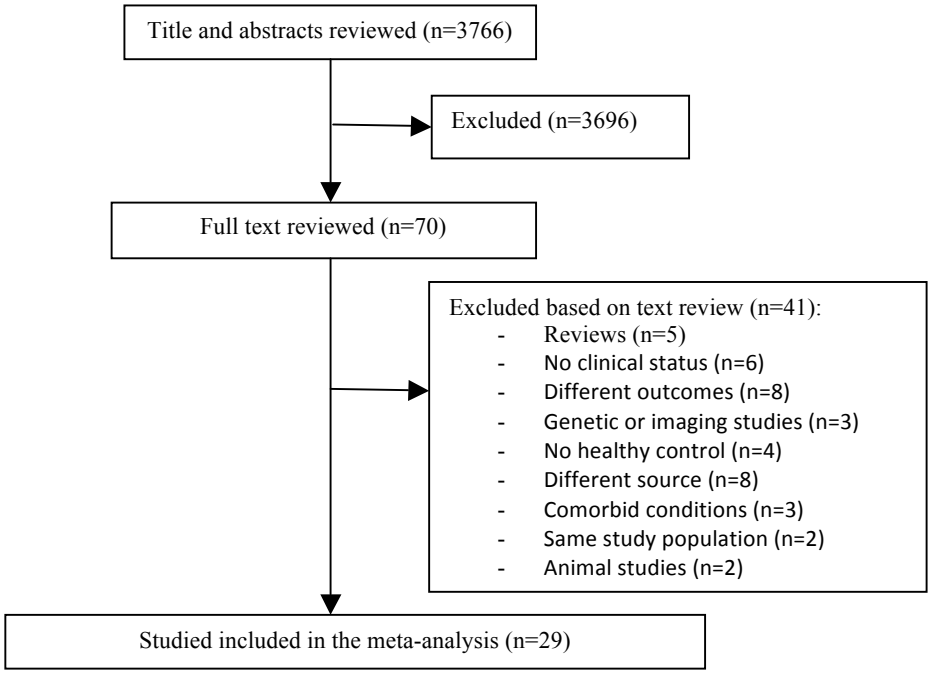
| Study (Country) | Design | Dura-tion (weeks) | N Patients with Depression | Population | Mean Baseline Depression Rating Scale Score ± SD | Mean Endpoint Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness Duration (Years) | Anti-depressant Treatment | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Bilici et al. 2001**[30] *(Turkey)* | Cohort Long. | 12 | 30 | MDD (DSM-IV), AD free during index episode, free of medical illness (including infection, inflammation or allergic reaction) HC: free of any medication ≥2 months. No drinkers or heavy smorkers. No PH and FH of psychiatric d/o | HDRS-17: 24.12±3.61 | HDRS-17: 14.32±5.57 | 40.3±7.0 | 70 | 6.5±2.4 | SSRI | *Plasma* BL: 4.32±1.6 F/U: 2.93±0.42 *RBC* BL:149.8 ±32.2 F/U:110.8 ±36.7 | | *Plasma* BL: 115.1± 29.3 F/U: 108.3± 27.9 *RBC* BL: 6.6±1.2 F/U: 6.9±2.3 | *RBC* BL: 1250± 153 F/U: 1170± 171 | *RBC* BL: 283.9± 46.8 F/U: 285.5± 39.8 | | |
| **Chaudhari et al. 2010**[44] **(***India)* | Random parallel group | 12 | 36 | MDD (DSM-IV), No other psychiatric diagnoses, no medical illness. Vegetarian diet HC: >50kg body weight, good diet (vegetarian), non-smoker, non-alcoholic, medication free ≥1month. No PH of psychiatric d/o | HDRS-21: 25.33±2.29 | HDRS-21: 16.99±1.23 | (18-65) | NR | NR | SSRI: fluoxetine 20 mg (n=20) vs. citalopram 20 mg (n=20) | | *Serum* BL: 3.765± 0.79 F/U: 4.82± 0.36 | | | | | |
| **Chrapko et al. 2006**[45] *(Canada)* | Cohort long. study | 8 | 17 | MDD (DSM-IV), comorbid with anxiety disorder. Free of psychotropic medication for at least 1 year. No current or past or FH of early cerebrocardiovascular illness | HDRS-21: 20.71±4.25 BDI: 25.18±4.08 | NR | 34.5±2.08 | 64.7 | NR | SSRI: Paroxetine 20 mg (n=17) | | | | | | Plasma: BL: 4.41±5.04 F/U: 12.53±7.52 | |
| **Galecki et al. 2009**[77] **(***Poland)* | Cohort study, long. | 12 | 50 | MDD (DSM-IV) medication free ≥3 weeks, free of medical illness (including infection, inflammation or allergic reaction) HC: free of any medication ≥2 months. No drinkers or heavy smokers. No PH and FH of psychiatric d/o | HDRS-21: 32.3±2.9 | | 36.7±5.2 | 56 | NR | SSRI: Fluoxetine 20 mg | *RBC* BL:0.739 ±0.164 F/U: 0.607±0.136 | | *RBC* BL: 74.2±13.5 F/U: 70.2±15.5 | *RBC* BL: 2078±199 F/U: 2028±124 | *RBC* BL: 17.4±3.1 F/U: 17.6±3.2 | | |
| **Herken et al. 2007**[48] *(Turkey)* | Cohort study, long. | 8 | 32 | MDD (DSM-IV) medication ceased ≥2 weeks before. No axis I cormobidity. No medical illness or substance use HC: free of medication ≥6 weeks before. No drinkers or heavy smokers or drug consumers. No PH and FH of psychiatric d/o | HDRS: NR | NR | (17-62) | 52.7 | 2.7±4.7 | SSRI: fluoxetine 20 mg (n=11), citalopram 20mg (n=10), sertraline 50 mg (n=8), fluvoxamine 150 mg (n=7) | | | | *Serum* BL: 8.3±1.6 F/U: 9.5±0.8 | | Serum: BL: 64.7±17.9 F/U: 54.5±17.0 | |
| **Khanzode et al. 2003**[35] **(***India)* | Random. paralle | 12 | 62 | MDD (DSM-IV) medication stopped ≥2 weeks. No axis I or II comorbidity. No medical illness which can affect free radical status HC: free of any medication ≥1 month. No drinkers or heavy smokers or drug consumers.PH and FH of psychiatric d/o | HDRS-21: 24.28±4.62 | HDRS-21: 17.29±4.56 | 43.8±12.9 | 55 | NR | SSRI: fluoxetine 20 mg (n=32) vs citalopram 20 mg(n=30) | *Serum* BL: 6.45±0.94 F/U: 3.84±0.76 | | | *Serum* BL:7.807±2.67 F/U: 3.694±1.521 | | | |

| Study (Country) | Design | Dura-tion (weeks) | N Patients with Depression | Population | Mean Baseline Depression Rating Scale Score ± SD | Mean Endpoint Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness Duration (Years) | Anti-depressant Treatment | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Kotan et al. 2011**[36] **(***Turkey)* | Cohort study, long. | 24 | 50 | MDD (DSM-IV). No other axis I or II diagnosis, no alcohol/drug consumption, no physical disease or syndrome, no CVD in first-degree relatives, pregnancy. No BMI ≥30, no regular treatment or heavy smokers (>15 cigarettes/day)<br><br>HC: same characteristics as MDD | HDRS-17: 30.4±3 | NR | 33.1±10 | 78 | NR | SNRI, SSRI MAOI, TCA: venlafaxine 125±43.3 mg (n=21), paroxetine 25±7.6 mg (n=8), escitalopram 16.3±5.2 mg (n=8), sertraline 80±27.4 mg (n=5), citalopram 33.3±11.5 mg (n=3), milnacipran 100 mg (n=2), fluoxetine 20 mg (n=1), tianeptin 37.5 mg (n=1), moclobemid 600 mg (n=1) | *Plasma* BL: 1.93±1.41 F/U:1±0.75 | *Plasma* BL: 3.6± 0.9 F/U: 3.7± 1.2 | *RBC* BL: 12.4±5.5 F/U: 13.8±5.6 | *RBC* BL: 2331±1201 F/U: 1878±614 | | | |
| **McLoughlin and Hodge 1990**[53] *(United Kingdom)* | Cohort study long. | NR (until point of discharge) | 9 | MDD. No recent myocardial infaction, abnormal renal function, severe infection, evidence of clinical dehydratation or pregnancy | BDI: 23±5.5 | 9±4.5 | 56.8±16.7 | 78.57 | NR | 57.14 % AD (n=8); 7.14% carbamazepine (n=1); 7.14% night sedation | | | | | | | *Plasma:* BL: 12.5±1.7<br><br>F/U: 14.3±3.2 |
| **Narang et al. 1991**[54] *(India)* | Cohort study long. | NR (until recovery) | 35 | MDD | NR | NR | NR | 40 | NR | NR | | | | | | | *Plasma:* BL: 107.62±21.94<br><br>F/U: 125.68±18.24 |
| **Stanley et al. 2002**[60] *(Nigeria)* | Cohort study long. | 7 | 21 | MDD (ICD-10) | NR | NR | 16-50 | NR | NR | TCA: amitryptiline 75 mg AP: Chlorpromzine 100 mg | | | | | | | *Serum:* BL: 11.9±3.96<br><br>F/U: 20±3.59 |

| Study (Country) | Design | Dura-tion (weeks) | N Patients with Depression | Population | Mean Baseline Depression Rating Scale Score ± SD | Mean Endpoint Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness Duration (Years) | Anti-depressant Treatment | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Wen et al., 2012**[64] **(*China)*** | Cohort study, Long., | 5 | 124 | Depression: MDD or moderate depression (DSM-IV). Exclusion criteria: treatment with drugs that could increase or affect uric acid | HAMD-24: 34.56±15.23 | NR | 41. 8 (16-78) | 69 | 5.4±3.6 | AD | | *Serum* BL: 271.97±77.5 F/U:312.28± 63.94 | | | | | |
| **Total (means, SDs and percentages are weighted with n values)** | 11Studies: 9 cohort studies 2 open randomized parall. | 10.38 | 466 | In 7 studies MDD patients were free of medication before the study started. | 6 studies: 27.06±5.12 (n=245) | 3 studies: 16.51±3.86 (n=116) | 6 studies: 39.04±11.55 (n=216) | 62.74 (n=409) | 3 studies: 5.1±3.6 (n=186) | | 4 studies with data RBC: N=-2 Plasma: N=. Serum: N=1 | 3 studies with data Serum: N=2 Plasma: N=1 | 3 studies with data RBC: N=3 Plasma: N=1 | 5 studies with data RBC: N=3 Serum: N=2 | 2 studies with data RBC: N=2 | 2 studies with data: Serum: N=1 Plasma: N=1 | 3 studies with data: Serum: N=1 Plasma: N=2 |

Footnote:
AD, antidepressant; AP, antipsychotic; BDI, Beck inventory depression; d/o, disorder; FH, family history; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; Long., longitudinal; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; NR, not reported; NRI, (selective) norepinephrine reuptake inhibitor; PH: personal history; Random parallel, randomized parallel; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant

**Supplementary eFigure 1.** Flow chart of study selection process



**Supplementary Table 1.** Studies of Oxidative Stress Marker and Antioxidant Levels in Patients with Depression vs. Healthy Controls

| Study (Country) | Design | N Patients with Depression | N Healthy Controls (variables matched on) | Population | Mean baseline Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness duration (Years) | Antidepressant Treatment duration | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Amani et al. (2010)**[42] *(Iran)* | Cross-sectional study | 23 | 23 (sex, age) | Students with moderate to severe depression (Beck´s questionnaire>19) | BDI: 47.2±17.3 | MDD: 20.7±1.6<br>HC: 20.2±0.9 | MDD: 100<br>HC: 100 | NR | No reported AD medication | | | | | | | *Serum:*<br>MDD: 79.6±30.7<br>HC: 111.6±21.9 |
| **Baek and Park (2013)**[43] (South Korea) | Cross-sectional study | 80 | 80 (sex, age) | MDD (DSM-IV) | CES-D-K: 35.41±0.78 | MDD: 44.85±1.77<br>HC: 44.47±1.63 | MDD: 73.75<br>HC: 65 | NR | NR | | | | *Serum:*<br>MDD: 11.06±3<br>HC: 9.37±3 | | | |
| **Bilici et al. (2001)**[30] *(Turkey)* | Cohort 12-week long. study | 30 | 32 (sex, age) | MDD (DSM-IV), AD free during index episode, free of medical illness (including infection, inflammation or allergic reaction)<br>HC: free of any medication ≥2 months. No drinkers or heavy smokers. No PH and FH of psychiatric d/o | HDRS-17: 24.12±3.61 | MDD: 40.3±7<br>HC: 42.1±7 | MDD: 70<br>HC: 50 | 6.5±2.4 | SSRI | *Plasma*<br>MDD: 4.32±1.6<br>HC: 2.89±1.1<br>*RBC*<br>MDD:149.8±32.2<br>HC: 109.3±32.8 | | *Plasma*<br>MDD: 115.1±29.3<br>HC: 109.7±33.6<br>*RBC*<br>MDD: 6.6±1.2<br>HC: 5.5±1.6 | *RBC*<br>MDD: 1250±153<br>HC: 966±129 | *RBC*<br>MDD: 283.9±46.8<br>HC: 290.4±5.6 | | |
| **Chaudhari et al. (2010)**[44] **(***India)* | Random. parallel group, 12week long. study | 40 | 36 (sex, age,) | MDD (DSM-IV), No other psychiatric diagnoses, no medical illness. Vegetarian diet<br>HC: >50kg body weight, good diet (vegetarian), non-smoker, non-alcoholic, medication free ≥1month. No PH of psychiatric d/o | HDRS-21: 25.33±2.29 | (18-65) | NR | NR | SSRI: fluoxetine 20 mg (n=20) vs citalopram 20 mg (n=20) | | *Serum*<br>MDD 3.765±0.79<br>HC: 5.256±1.02 | | | | | |
| **Chrapko et al. (2006)** [45] *(Canada)* | Cohort 8-week long. study | 17 | 12 (sex, age) | MDD (DSM-IV), comorbid with anxiety disorder. Free of psychotropic medication for at least 1 year. No current or past or FH of early cerebrocardiovascular illness | HDRS-21: 20.71±4.25<br>BDI: 25.18±4.08 | MDD: 34.50±2.08<br>HC: 26.75±2.78 | MDD: 35.3<br>HC: 41.6 | NR | SSRI: Paroxetine 20 mg (n=17) | | | | | | *Plasma:*<br>MDD: 5.74±6.0<br>HC: 23.33±13.01 | |
| **Crayton et al. (2007)** [46] *(USA)* | Cross-sectional study | 485 | 28 (sex, age) | Clinical diagnosis and treated by primary care psysicians or psychiatrists. Excluded BPD or other psychiatric condition | NR | 30-60 | 100 | NR | NR | | | | | | | *NR:*<br>MDD: 73±15<br>HC: 77±12 |
| **Crayton et al. (2007)** [46] *(USA)* | Cross-sectional study | 328 | 26 (sex, age) | Clinical diagnosis and treated by primary care psysicians or psychiatrists. Excluded BPD or other psychiatric condition | NR | 30-60 | 0 | NR | NR | | | | | | | *NR:*<br>MDD: 78±14<br>HC: 78±15 |

| Study (Country) | Design | N Patients with Depression | N Healthy Controls (variables matched on) | Population | Mean baseline Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness duration (Years) | Antidepressant Treatment duration | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Galecki et al. (2009)** [77] **(***Poland)* | Cohort 12-week long. study | 50 | 30 (sex, age) | MDD (DSM-IV) medication free ≥3 weeks, free of medical illness (including infection, inflammation or allergic reaction) HC: free of any medication ≥2 months. No drinkers or heavy smokers. No PH and FH of psychiatric d/o | HDRS-21: 32.3±2.9 | MDD: 36.7±5.2 HC: 32.1±4.3 | MDD: 56 HC: 53 | NR | SSRI: fluoxetine 20 mg | *RBC* MDD: 0.739± 0.164 HC: 0.549± 0.224 | | *RBC* MDD: 74.2±13.5 HC: 68.7±16.7 | *RBC* MDD: 2078± 199 HC: 1978± 196 | *RBC* MDD:17.4±3.1 HC:14.2± 3.5 | | |
| **Grieger et al. (2009)** [47] *(Australia)* | Cross-sectional study | 28 | 43 (NR) | MDD | GDS: 8.1±2.12 | 80.2±10.6 | NR | NR | NR | | | | | | | *Serum:* MDD: 10.1±2.12 HC: 11.9±3.28 |
| **Herken et al. (2007)** [48] *(Turkey)* | Cohort 8-week long. study | 36 | 20 (sex, age, smoking) | MDD (DSM-IV) medication ceased ≥2 weeks before. No axis I cormobidity. No medical illness or substance use HC: free of medication ≥6 weeks before. No drinkers or heavy smokers or drug consumers. No PH and FH of psychiatric disorder | HDRS (no results given) | (17-62) | MDD: 52.7 | 2.7±4.7 | SSRI: fluoxetine 20 mg (n=11), citalopram 20 mg (n=10), sertraline 50 mg (n=8), fluvoxamine 150 mg (n=7) | | | | *Serum* MDD: 7.7±1.8 HC: 9.2±0.5 | | *Serum:* MDD: 66.4±21.3 HC:61.6± 9.0 | |
| **Khanzode et al. (2003)** [35] **(***India)* | Random. Parallel group, 12–week long. study | 62 | 40 (NR) | MDD (DSM-IV) medication ceased ≥2 weeks before. No axis I or II comorbidity. No medical illness which can affect free radical status HC: free of any medication ≥1 month. No drinkers, heavy smokers or drug consumers. No PH and FH of psychiatric d/o | HDRS-21: 24.28±4.62 | MDD: 43.8± 12.9 HC: 40.8±10.2 | MDD: 55 HC: 45 | NR | SSRI: fluoxetine 20 mg (n=32) vs. citalopram 20 mg(n=30) | *Serum* MDD: 6.45±0.94 HC: 1.74±0.64 | | | *Serum* MDD: 7.80± 2.64 HC: 2±0.87 | | | |
| **Kotan et al. (2011)** [36] **(***Turkey)* | Cohort 24-week long. study | 50 | 44 (sex, age, BMI, smoking) | MDD (DSM-IV). No other axis I or II diagnosis, no alcohol/drug consumption, No physical disease or syndrome, no CVD in first-degree relatives, pregnancy. No BMI ≥30, no regular treatment or heavy smokers (>15 cigarettes/day) HC: same characteristics as MDD. | HDRS-17: 30.4±3 | MDD: 33.1±10 HC: 33.2±7.9 | MDD: 78 HC: 77 | NR | SNRI, SSRI, MAOI, TCA: venlafaxine 125±43.3 mg (n=21); paroxetine 25±7.6 mg (n=8); escitalopram 16.3±5.2 mg (n=8); sertraline 80±27.4 mg (n=5); citalopram 33.3±11.5 mg (n=3); milnacipran 100 mg (n=2); fluoxetine 20 mg (n=1); tianeptin 37.5 mg (n=1); moclobemid 600 mg (n=1) | *Plasma* MDD: 1.93±1.41 HC: 1.08±0.58 | *Plasma* MDD: 3.6± 0.9 HC: 4.1± 1.3 | *RBC* MDD: 12.4±5.5 HC: 13.2±5 | *RBC* MDD: 2331± 1201 HC:1 771±477 | | | |
| **Maes et al. (1994)** [49] *(USA)* | Cross-sectional study | 48 | 32 (sex, age) | MDD (DSM-III). No other axis I; no treatment with antionulsants or high dosages of neuroleptics during the previous year; Clinical or laboratory test, ECG, EGG, chest X-ray without | HDRS-17: 19.18±6.0 | MDD: 49.64±11.27 HC: 43.8±15.3 | NR | NR | Low-dosage of benzodiazepines (n=23) if severe anxiety, agitation or sleep disturbances. | | | | | | | *Serum*: MDD: 1.81±0.28 HC: 2.02±0.2 |

| Study (Country) | Design | N Patients with Depression | N Healthy Controls (variables matched on) | Population | Mean baseline Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness duration (Years) | Antidepressant<br><br>Treatment duration | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | alterations. Free of drugs or illness (known to affect immune or endocrines system or zinc metabolism). No allergic or infectious reactions 2 weeks prior to blood test. | | | | | | | | | | | | |
| **Maes et al. (1997)** [50] *(Belgium)* | Cross-sectional study | 36 | 15 (sex, age) | MDD (DSM-III). No other axis I; no treatment with fluoxetine or trazodone during the index episode; free of medical illnesses and free of acute infections and inflammatory or allergic reactions for at least 2 weeks prior to the study. | 24.4±3.9 | MDD: 50.9±14.2 HC: 47.5±15.0 | MDD: 50 HC: 33.3 | 11.5±9.4 | Trazodone 100mg (n=7); trazodone 100 mg + pindolol 7.5 mg (n=8); trazodone 100 mg + fluoxetine 20 mg (n=11) | | | | | | | *Serum* MDD: 95±12 HC:114±13 |
| **Maes et al. (1999)** [51] *(Belgium)* | Cross sectional study | 34 | 14 (sex, age) | MDD (DSM-III-R). No other axis I; no axis-II diagnosis; free of abnormal radiograph or heart/lungs/EGG; no treatment with fluoxetine, trazodone, MAOIs, antipsychotic drugs, antivonvulsants, lithium or ECT the year previous; free of acute or chronic and acute infections or allergic reactions for at least 2 weeks prior to the study; free of low fat diet or cholesterol-lowering drugs; no mediction that affect fatty acid metabolism or endocrine and immune functions; BMI inside normal limits; no heavy smokers; consuming Belgian diet | HDRS-17: | MDD: 52.2±13.6 HC: 48.3±15.2 | MDD: 47.01 HC: 35.71 | NR | No treatment | | | | | | | *Serum:* MDD: 96.4±10.4 HC: 113.6±12.1 |
| **Maes et al. (2011)** [17] *(Thailand)* | Cross-sectional study | 39 | 24 (sex, age) | MDD (DSM-IV) and HC exclusion criteria: 1) medical illnesses; 2) abnormal blood test; 3) inflammatory or allergic reactions last 2 months; 4) treated with AP, AC, MS; 5) dietary supplements | HDRS: (no results given) | MDD: 44.6±12 HC: 45.5±9.9 | MDD: 56 HC: 29 | NR | NR | | | *Whole Blood* MDD:35.1±10.7 HC: 42.4±17.5 | | | | |
| **McLoughlin and Hodge (1990)** [53] *(United Kingdom)* | Cohort long. study | 14 | 14 (sex, age) | MDD. No recent myocardial infaction, abnormal renal function, severe infection, evidence of clinical dehydratation or pregnancy | BDI: 21±6.3<br><br>HDRS-17: 21±2 | MDD: 56.8±16.7<br><br>HC: 56.2±15.6 | MDD: 78.57 | NR | 57.14 % AD (n=8); 7.14% carbamazepine (n=1); 7.14% night sedation | | | | | | | *Plasma:* MDD: 12.3±1.64<br><br>HC: 14.1±1.46 |
| **Narang et al. (1991)** [54] *(India)* | Cohort long. study | 35 | 35 (sex, age) | MDD | HDRS (no results given) | NR | MDD: 40 | NR | NR | | | | | | | *Plasma:* MDD: 107.62±21.94<br><br>HC: 115.8±24.88 |
| **Nguyenet al. (2009)** [55] | Cross sectional study | 182 | 187 (sex, age) | CES-D>16; Women were not admitted if :1) pregnancy; 2) lactation (child within the last | CES-D (no results given) | MDD: 32.8±9.3 | 100 | | NR | | | | | | | *Serum:* MDD: 10.6±2.0 |

| Study (Country) | Design | N Patients with Depression | N Healthy Controls (variables matched on) | Population | Mean baseline Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness duration (Years) | Antidepressant<br><br>Treatment duration | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 3 mo); 3) supplements consumption; 4) chronic diseases; 5) severe anemia | | HC: 29.5±9.2 | | | | | | | | | | HC: 10.5±2.2 |
| **Rybka et al. (2013)** [56] **(***Poland)* | Cross-sectional study | 15 | 19 (sex, age) | Recurrent depressive disorder (ICD-10). No other psychiatric diagnosis (axis I or axis II) or medical illness. All patients and HC were on their usual medication | BDI (no results given) | MDD: 62.3±2.8 HC: 62.3± 2.84 | NR | NR | SSRI (60%), SNRI (35%), TCA (15%) | *RBC* MDD: 0.169± 0.0743 HC: 0.088± 0.0148 | | *RBC* MDD: 12.23± 5.39 HC: 19.01± 4.24 | *RBC* MDD: 2269.9± 643.81 HC: 2637.1± 282.00 | | | |
| **Russo (2010)** [57] *(United States)* | Cohort long. study | 36 | 18 (sex, age) | MDD; HC: no documented mental illness | HDRS (no results given) | MDD: 35.2 HC: 41.7 | MDD: 61.5 HC: 73.7 | NR | NR AD medication; Antioxidant therapy | | | | *Serum* MDD:0.695±0.479 HC:0.326± 0.14 | | | |
| **Salimi et al. (2008)** [58] *(Iran)* | Cross sectional study | 161 | 144 (sex, age) | MDD; No taking psychotropic drugs | NR | MDD: 35.37±10.13 HC: 38.53±10.4 | MDD: 57.76 HC: 58.3 | NR | No treatment | | | | | | | *Serum:* MDD: 64.94±13.9 HC: 69.67±11.29 |
| **Salustri et al. (2010)** [59] *(Italy)* | Cross-sectional study | 13 | 13 (sex, age) | MDD (DSM-IV). No alcoholism, psychotropic drugs abuse and mental retardation. | MADRS HDRS-17 (no results given) | MDD: 54.2±13.5 HC: 55.9±19.3 | MDD: 85 HC: 85 | NR | Immediately after admission started a therapy. | | | | | | | *Serum:* MDD: 107.59±54.85 HC: 86.05±7.22 |
| **Sarandol et al. (2007)** [37] *(Turkey)* | Cross-sectional study | 96 | 54 (sex, age, smoking status) | MDD (DSM-IV) No other axis I or axis II disorder; no known major health problems HC: free of any medication, free of medication ≥3 weeks | HDRS-17: 15-23 | MDD: 40.0±11 HC: 37±9 | MDD: 75 HC: 74 | NR | SNRI, NRI: venlafaxine 150 mg, reboxetine 8 mg, sertraline 50 mg | *Plasma* MDD: 0.88±0.44 HC: 0.64±0.26 *RBC* MDD: 108±30 HC: 84±20 | Whole blood: MDD: 4.2±2.0 HC: 4.1±1.3 | Whole blood: MDD: 4554±2030 HC: 5225±1414 | *RBC* MDD:266.67± 177.78 HC: 100±83.3 | | | |
| **Stanley et al. (2002)** [60] *(Nigeria)* | Cohort long. 7-weeks study | 21 | 20 (NR) | MDD (ICD-10) | NR | 16-50 | NR | NR | TCA: amitryptiline 75 mg AP: Chlorpromzine 100 mg | | | | | | | *Serum:* MDD: 11.9±3.96 HC: 20.1±3.46 |
| **Stefanescu et al. (2012)** [61] **(***Romania)* | Cross-sectional study | 31 | 20 (sex, age) | MDD (DSM-IV): first episode and recurrent episodes. No CVD, CD, hepatic/renal diseases, DM, hypothyroidism, malignancies, alcohol (>30mg/day), supplementation. HC: no PH of psychiatric disorder. Free of medication | HDRS: 21.6±5.6 | MDD: 47.6±8.5 HC: 46.3±7.8 | MDD: 64.5 HC: 65 | 7.1±6.1 | SSRI, SNRI, TCA: FE: mirtazapine 30 mg (n=8); venlafaxine 75 mg (n=7); RR: tianeptine 37.5 mg (n=16); escitalopram 10 mg (n=5); venlafaxine 150 mg (n=5) | *Serum* MDD: 76.66±27.8 HC: 63.33± 16.97 | | *Serum* MDD: 0.084± 0.022 HC: 0.092± 0.04 | *Serum* MDD: 0.34± 0.22 HC: 0.46±0.2 | | | |

| Study (Country) | Design | N Patients with Depression | N Healthy Controls (variables matched on) | Population | Mean baseline Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness duration (Years) | Antidepressant Treatment duration | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Szuster-Ciesielska et al. (2008)** [62] *(Poland)* | Cross-sectional study | 29 | 30 (sex, age) | MDD (DSM-IV): No other axis I disorder, free of medical illness, no regular drinker or drug consumer. HC: free of medication ≥1month, free of medical illness, no regular drinker or drug consumer | HDRS-17: 30.4±3.5 | MDD: 48.2±11 HC: 41.3±4.4 | MDD: 51.7 HC: 50 | NR | TCA, AP and different combination of amitriptyline 100-200 mg, sulpiride 100-200 mg, clomipramine 75-150 mg, perazine 25-125 mg, levopromazine 150 mg, imipramine 25 mg | | | | *Serum* MDD: 0.169± 0.03 HC: 0.15± 0.02 | *Serum* MDD: 39.4± 18.6 HC: 10.4±7.6 | | |
| **Vargas et al. (2013)** [63] **(***Brazil)* | Cross-sectional study | 140 | 201 (sex, age, smoking status) | | HDRS: 10.76±9.5 | (18-60) | MDD: 75.8 HC: 58.45 | NR | NR | *Plasma* MDD: 15.62±6.38 HC: 16±5.4 | | | | | *Plasma:* MDD: 3.92±2.18 HC: 4.07±2.4 | |
| **Wen et al. (2012)** [64] **(***China)* | Cohort,. 5-week long. study | 124 | 42 (NR) | Depression: MDD or moderate depression (DSM-IV). Exclusion criteria: treatment with drugs that could increase or affect uric acid | HDRS -24: 34.56±15.23 | MDD: 41. 8 (16-78) HC: 31 (17-66) | MDD: 69 HC: 30 | 5.4±3.6 | AD treatment | | *Serum* MDD: 271.97±77.5 HC: 315.76±87.5 | | | | | |
| **Wiener et al. (2013)** [65] *(Brazil)* | Case-control study | 82 | 94 (sex, age) | MDD: current or euthymic (DSM-IV). HC: exclusion criteria are medical cormobidities and abnormal blood values | HDRS (no results given) | (18-24) | MDD: 76.8 HC: 57.4 | NR | 9 patients were taking psychiatric medications | | *Serum* MDD: 4.004± 3.44 (Eu-thymia: 3.846±-3.0) HC: 4.135±-3.82 | | | | | |
| **Total (means, SDs and percentages are weighted with n values)** | 30 studies: 12 cohort studies; 17 cross-sectional; studies; 1 case-control study | 2447 | 1484 | Free of medication: 11/29 (37.9%) Taking medication: 13/29 (44.8%) NR: 5/29 (17.2%) | 13 studies 24.1±11.88 (n=:669) | 20 studies MDD: 36,77± 10.89 (n=1035) HC: 38.04±12. 89 (n=680) | 24 studies MDD: 66.19 % (n=2213) HC: 58.2% (n=930) | 5 studies 6.21 ± 5.74 (n=257) | Previously taking AD medication: SSRI 4 studies; SNRI 4 studies; TCA 4 studies; NRI 1 study; | 8 Studies with data RBC: N=4 Plasma: N=4 Serum: N=2 | 4 studies with data Serum: N=3 Plasma: N=1 | 6 Studies with data RBC: N=4 Plasma: N=1 Serum: N=1 Whole Blood: N=1 | 11 Studies with data RBC: N=5 Serum: N=6 | 3 Studies with data RBC: N=2 Serum: N=1 | 3 Studies with data Plasma: N=2 Serum: N=1 | 13 studies with data Plasma N=2 Serum: N=9 |

Footnote:
AD, antidepressant; AC, anticonvulsants; AP, antipsychotic; CD, cerebrovascular diseases; CES-D scale, Center for Epidemiologic Studies Depression Scale; CES-D-K, Center for Epidemiologic Studies Depression Scale Korea; CVD, cardiovascular diseases; d/o, disorder; FE, first episode; FH, familiar history; GDS, Geriatric

depression Scale; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; Long., longitudinal; MDARS, Montgomery-Asberg Depression Scale; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; MS, mood stabilizers NR, not reported; NRI, (selective) norepinephrine reuptake inhibitor; PH, personal; Random., randomized; RE, relapsing and remitting; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant;

**Supplementary Table 2**. Quality Assessment Based on Guidelines from the STROBE Statement

| Study | Clear Description of Participant Eligibility and Sources / Methods of Participant Selection | Clearly Defined Exposure Ascertainment: Depression | Clearly Defined Outcome Ascertainment: Oxidative Stress / Antioxidant | Clear Description of Handling of Depression and Oxidative Stress in the Analyses | Control for Potential Confounders by Exclusion or Statistical Adjustment |
|---|---|---|---|---|---|
| Amani 2010[42] | X | X | X | X | X |
| Baek and Park 2013[43] | X | X | X | X | X |
| Bilici 2001[30] | | | X | X | |
| Chaudhari 2010[44] | X | X | X | X | |
| Chrapko 2006[45] | X | X | X | X | X |
| Crayton 2007[46] | X | | X | X | |
| Galecki 2009[77] | X | X | X | X | |
| Grieger 2009[47] | X | X | X | X | |
| Herken 2007[48] | X | | X | X | |
| Khanzode 2003[35] | | X | X | X | |
| Kotan 2011[36] | X | X | X | X | X |
| Maes 1994[49] | X | X | X | X | X |
| Maes 1997[50] | X | X | X | X | X |
| Maes 1999[51] | X | X | X | X | X |
| Maes 2011[17] | X | | X | X | |
| McLoughlin and Hodge 1990[53] | X | X | X | | |
| Narang 1991[54] | X | X | X | | |
| Nguyen 2009[55] | X | X | X | X | X |
| Rybka 2013[56] | X | | X | X | X |
| Russo 2010[57] | | | | X | |
| Salimi 2008[58] | | | X | X | |
| Salustri 2010[59] | X | X | X | X | X |
| Sarandol 2010[37] | X | X | X | X | |
| Stanley 2002[60] | X | X | X | | |
| Stefanescu 2012[61] | X | X | X | X | |
| Szuster-Ciesielska 2008[62] | X | X | X | X | |

| | | | | | |
|---|---|---|---|---|---|
| Vargas 2013[63] | X | X | X | X | X |
| Wen 2012[64] | X | X | X | X | X |
| Wiener 2013[65] | X | | X | X | X |
| Total | 25/29 (86.2%) | 21/29 (72.4%) | 28/29 (96.6%) | 26/29 (89.7%) | 13/29 (44.8 %) |

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology.

**Supplementary Table 3.** Studies of Oxidative Stress Marker and Antioxidant Levels in Patients with Depression Before and After Antidepressant Treatment

| Study (Country) | Design | Dura-tion (weeks) | N Patients with Depression | Population | Mean Baseline Depression Rating Scale Score ± SD | Mean Endpoint Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness Duration (Years) | Anti-depressant Treatment | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Bilici et al. 2001**[30] *(Turkey)* | Cohort Long. | 12 | 30 | MDD (DSM-IV), AD free during index episode, free of medical illness (including infection, inflammation or allergic reaction) HC: free of any medication ≥2 months. No drinkers or heavy smorkers. No PH and FH of psychiatric d/o | HDRS-17: 24.12±3.61 | HDRS-17: 14.32±5.57 | 40.3±7.0 | 70 | 6.5±2.4 | SSRI | *Plasma* BL: 4.32±1.6 F/U: 2.93±0.42 *RBC* BL:149.8 ±32.2 F/U:110.8 ±36.7 | | *Plasma* BL: 115.1± 29.3 F/U: 108.3± 27.9 *RBC* BL: 6.6±1.2 F/U: 6.9±2.3 | *RBC* BL: 1250± 153 F/U: 1170± 171 | *RBC* BL: 283.9± 46.8 F/U: 285.5± 39.8 | | |
| **Chaudhari et al. 2010**[44] **(***India)* | Random parallel group | 12 | 36 | MDD (DSM-IV), No other psychiatric diagnoses, no medical illness. Vegetarian diet HC: >50kg body weight, good diet (vegetarian), non-smoker, non-alcoholic, medication free ≥1month. No PH of psychiatric d/o | HDRS-21: 25.33±2.29 | HDRS-21: 16.99±1.23 | (18-65) | NR | NR | SSRI: fluoxetine 20 mg (n=20) vs. citalopram 20 mg (n=20) | | *Serum* BL: 3.765± 0.79 F/U: 4.82± 0.36 | | | | | |
| **Chrapko et al. 2006**[45] *(Canada)* | Cohort long. study | 8 | 17 | MDD (DSM-IV), comorbid with anxiety disorder. Free of psychotropic medication for at least 1 year. No current or past or FH of early cerebrocardiovascular illness | HDRS-21: 20.71±4.25 BDI: 25.18±4.08 | NR | 34.5±2.08 | 64.7 | NR | SSRI: Paroxetine 20 mg (n=17) | | | | | | Plasma: BL: 4.41±5.04 F/U: 12.53±7.52 | |
| **Galecki et al. 2009**[77] **(***Poland)* | Cohort study, long. | 12 | 50 | MDD (DSM-IV) medication free ≥3 weeks, free of medical illness (including infection, inflammation or allergic reaction) HC: free of any medication ≥2 months. No drinkers or heavy smokers. No PH and FH of psychiatric d/o | HDRS-21: 32.3±2.9 | | 36.7±5.2 | 56 | NR | SSRI: Fluoxetine 20 mg | *RBC* BL:0.739 ±0.164 F/U: 0.607±0.136 | | *RBC* BL: 74.2±13.5 F/U: 70.2±15.5 | *RBC* BL: 2078±199 F/U: 2028±124 | *RBC* BL: 17.4±3.1 F/U: 17.6±3.2 | | |
| **Herken et al. 2007**[48] *(Turkey)* | Cohort study, long. | 8 | 32 | MDD (DSM-IV) medication ceased ≥2 weeks before. No axis I cormobidity. No medical illness or substance use HC: free of medication ≥6 weeks before. No drinkers or heavy smokers or drug consumers. No PH and FH of psychiatric d/o | HDRS: NR | NR | (17-62) | 52.7 | 2.7±4.7 | SSRI: fluoxetine 20 mg (n=11), citalopram 20mg (n=10), sertraline 50 mg (n=8), fluvoxamine 150 mg (n=7) | | | | *Serum* BL: 8.3±1.6 F/U: 9.5±0.8 | | Serum: BL: 64.7±17.9 F/U: 54.5±17.0 | |
| **Khanzode et al. 2003**[35] **(***India)* | Random. paralle | 12 | 62 | MDD (DSM-IV) medication stopped ≥2 weeks. No axis I or II comorbidity. No medical illness which can affect free radical status HC: free of any medication ≥1 month. No drinkers or heavy smokers or drug consumers.PH and FH of psychiatric d/o | HDRS-21: 24.28±4.62 | HDRS-21: 17.29±4.56 | 43.8±12.9 | 55 | NR | SSRI: fluoxetine 20 mg (n=32) vs citalopram 20 mg(n=30) | *Serum* BL: 6.45±0.94 F/U: 3.84±0.76 | | | *Serum* BL:7.807±2.67 F/U: 3.694±1.521 | | | |

| Study (Country) | Design | Dura-tion (weeks) | N Patients with Depression | Population | Mean Baseline Depression Rating Scale Score ± SD | Mean Endpoint Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness Duration (Years) | Anti-depressant Treatment | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Kotan et al. 2011**[36] **(***Turkey)* | Cohort study, long. | 24 | 50 | MDD (DSM-IV). No other axis I or II diagnosis, no alcohol/drug consumption, no physical disease or syndrome, no CVD in first-degree relatives, pregnancy. No BMI ≥30, no regular treatment or heavy smokers (>15 cigarettes/day)<br><br>HC: same characteristics as MDD | HDRS-17: 30.4±3 | NR | 33.1±10 | 78 | NR | SNRI, SSRI MAOI, TCA: venlafaxine 125±43.3 mg (n=21), paroxetine 25±7.6 mg (n=8), escitalopram 16.3±5.2 mg (n=8), sertraline 80±27.4 mg (n=5), citalopram 33.3±11.5 mg (n=3), milnacipran 100 mg (n=2), fluoxetine 20 mg (n=1), tianeptin 37.5 mg (n=1), moclobemid 600 mg (n=1) | *Plasma* BL: 1.93±1.41 F/U:1±0.75 | *Plasma* BL: 3.6± 0.9 F/U: 3.7± 1.2 | *RBC* BL: 12.4±5.5 F/U: 13.8±5.6 | *RBC* BL: 2331±1201 F/U: 1878±614 | | | |
| **McLoughlin and Hodge 1990**[53] *(United Kingdom)* | Cohort study long. | NR (until point of discharge) | 9 | MDD. No recent myocardial infaction, abnormal renal function, severe infection, evidence of clinical dehydratation or pregnancy | BDI: 23±5.5 | 9±4.5 | 56.8±16.7 | 78.57 | NR | 57.14 % AD (n=8); 7.14% carbamazepine (n=1); 7.14% night sedation | | | | | | | *Plasma:* BL: 12.5±1.7<br><br>F/U: 14.3±3.2 |
| **Narang et al. 1991**[54] *(India)* | Cohort study long. | NR (until recovery) | 35 | MDD | NR | NR | NR | 40 | NR | NR | | | | | | | *Plasma:* BL: 107.62±21.94<br><br>F/U: 125.68±18.24 |
| **Stanley et al. 2002**[60] *(Nigeria)* | Cohort study long. | 7 | 21 | MDD (ICD-10) | NR | NR | 16-50 | NR | NR | TCA: amitryptiline 75 mg AP: Chlorpromzine 100 mg | | | | | | | *Serum:* BL: 11.9±3.96<br><br>F/U: 20±3.59 |

| Study (Country) | Design | Dura-tion (weeks) | N Patients with Depression | Population | Mean Baseline Depression Rating Scale Score ± SD | Mean Endpoint Depression Rating Scale Score ± SD | Mean Age ± SD (Range) | % Females | Illness Duration (Years) | Anti-depressant Treatment | Malonyl-dialdehyde | Uric acid | Glutathione Peroxidase | Superoxide Dismutase | Catalase | Total nitrite | Zinc |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Wen et al., 2012**[64] **(*China*)** | Cohort study, Long., | 5 | 124 | Depression: MDD or moderate depression (DSM-IV). Exclusion criteria: treatment with drugs that could increase or affect uric acid | HAMD-24: 34.56±15.23 | NR | 41. 8 (16-78) | 69 | 5.4±3.6 | AD | | *Serum* BL: 271.97±77.5 F/U:312.28± 63.94 | | | | | |
| **Total (means, SDs and percentages are weighted with n values)** | 11Studies: 9 cohort studies 2 open randomized parall. | 10.38 | 466 | In 7 studies MDD patients were free of medication before the study started. | 6 studies: 27.06±5.12 (n=245) | 3 studies: 16.51±3.86 (n=116) | 6 studies: 39.04±11.55 (n=216) | 62.74 (n=409) | 3 studies: 5.1±3.6 (n=186) | | 4 studies with data RBC: N=-2 Plasma: N=. Serum: N=1 | 3 studies with data Serum: N=2 Plasma: N=1 | 3 studies with data RBC: N=3 Plasma: N=1 | 5 studies with data RBC: N=3 Serum: N=2 | 2 studies with data RBC: N=2 | 2 studies with data: Serum: N=1 Plasma: N=1 | 3 studies with data: Serum: N=1 Plasma: N=2 |

Footnote:
AD, antidepressant; AP, antipsychotic; BDI, Beck inventory depression; d/o, disorder; FH, family history; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; Long., longitudinal; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; NR, not reported; NRI, (selective) norepinephrine reuptake inhibitor; PH: personal history; Random parallel, randomized parallel; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant