

Changes in Oxidative Stress Biomarkers in the First-Episode Psychosis: A Systematic Review And Meta-Analysis

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Abstract

The literature has shown that oxidative stress markers can indicate the degree of disease severity in untreated patients with schizophrenia. There is evidence that the excessive production of free radicals or the installation of oxidative stress can be evidenced at the time of the first-episode psychosis (FEP). We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses Guidelines to conduct a systematic literature search to detect studies comparing oxidative stress markers in FEP patients and healthy controls (HC). Twenty-one studies were obtained for inclusion in this systematic review, comprising an overall sample of 415 FEP and 392 HC for CAT (6 studies), 1293 FEP and 1279 HC for SOD (15 studies), 500 FEP and 529 HC for GPx (9 studies), 218 FEP and 228 HC for GSH (5 studies), and 814 FEP and 852 HC for lipid peroxidation (12 studies). By analyzing the standardized mean differences, no significant differences were found between FEP and HC groups in any of the antioxidant defense system parameters assessed, despite favoring a decrease in activity of both the antioxidant and non-enzymatic enzyme systems. Lipid peroxidation levels showed a significant increase for the FEP group compared to the HC group ($p < 0.0001$). Heterogeneity among studies was high, with I^2 values $> 90\%$. Sensitivity analyzes were performed to obtain more homogeneous results. Significant differences were obtained for serum/plasma SOD ($p < 0.0001$) and lipid peroxidation ($p < 0.0001$) in the FEP group compared to the HC group, but still containing high heterogeneity. These results suggest that the oxidative stress biomarkers could be used to indicate the degree for the severity of the disease in untreated patients with schizophrenia.

Keywords: schizophrenia, first-episode psychosis, biomarker, oxidative stress, meta-analysis.

Introduction

Schizophrenia is a chronic psychiatric disorder with a neuroprogressive course. Its etiology is multifactorial, with important genetic components and starts in late adolescence or early adulthood and includes symptoms that are positive, negative, affective and cognitive, affecting at least 0.7% of the population^{1,2}. The diagnostic criteria are based on descriptive phenomenology of clinical symptoms and clinical course due to the lack of reliable and specific biomarkers³. The neuroprogression theory of schizophrenia postulates that changes in the immune system are accompanied by increased inflammatory markers, tryptophan catabolites and reactive oxygen species (ROS) affecting the growth and function of neuronal circuits since the intra-uterine period⁴. There is also an accumulating evidence that oxidative stress plays a role in the etiopathogenesis of mental disorders, particularly schizophrenia and bipolar disorder⁵, which commonly start at early ages^{6,7} with a first-episode psychosis (FEP). Some authors^{8,9}, but not all^{10,11}, suggest that oxidative injury occurs at the onset of psychosis and they also propose that oxidative stress is a feature of the disease process itself. Redox state is a regulatory system of posttranslational modifications that controls cellular signaling in response to oxidants and free radicals. Oxidative stress is defined as an imbalance between prooxidants and

antioxidants, which results in macromolecular damages (lipid peroxidation, protein carbonylation, and DNA oxidation) and in dysregulation of the redox system¹². Abnormalities induced by oxidative imbalance may contribute to compromised function of neurotransmitters and development of clinically significant consequences in schizophrenia, such as severity of psychopathology and extrapyramidal symptoms¹³. Heightened oxidative stress in schizophrenia may be due to genetic factors leading to decreased capacity to synthesize antioxidant compounds¹⁴ and/or early developmental insults that can increase generation of reactive oxygen species (ROS) in the brain¹⁵.

This imbalance may be attributable to a malfunctioning antioxidant system and/or high levels of ROS including superoxide anion radicals ($O_2^{\cdot-}$), hydroxyl radicals (HO^{\cdot}), peroxy radicals (HOO^{\cdot}), hydrogen peroxide (H_2O_2), nitric oxide, and reactive nitrogen species (RNS)¹⁶. $O_2^{\cdot-}$ is central to the formation of ROS; superoxide dismutases (SOD) can transform $O_2^{\cdot-}$ into the more stable H_2O_2 . H_2O_2 can subsequently form highly reactive HO^{\cdot} radicals through the Fenton reaction using Fe^{2+} as a catalyst. These HO^{\cdot} radicals are among the most cytotoxic and reactive ROS. Conversely, H_2O_2 may be decomposed to H_2O and O_2 by catalase (CAT) and peroxidases, as well as by the glutathione system. The glutathione peroxidase (GPx) utilizes reduced glutathione as a hydrogen donor for the removal of peroxides. Thus, it is crucial to maintain the glutathione levels (GSH) at adequate concentrations for normal cell functioning^{17,18,19}. However, by modifying lipids, proteins, nucleic acids, and other molecules, excess ROS can be damaging. In particular, increased ROS may lead to lipid peroxidation, which damages cells and organelle membranes¹³. The brain has comparatively greater vulnerability to oxidative damage as a result of the relatively low levels of antioxidants, high levels of polyunsaturated fatty acids and increased need of oxygen²⁰. Ciobica and collaborators²¹ showed studies where patients with schizophrenia have generally suggested the presence of a compromised antioxidant system, but this is not always consistent with specific observed parameters, which on the whole, showed evidences of dysregulation.

The diagnosis performed in the FEP has important therapeutic and prognostic implications, considering that patients with mood disorder and those with schizophrenia spectrum disorders are likely to require different medical and psychosocial treatment. Furthermore, FEP patients should be diagnosed and treated urgently, as prolongation of the untreated period results in a poorer prognosis²². Thus, the present systematic review and the meta-analyses were derived from studies containing oxidative (lipid peroxidation, including dosages of plasma/serum thiobarbituric acid reactive substances - TBARS and malondialdehydes - MDA), enzymatic antioxidants (CAT, GPx and SOD) and non-enzymatic antioxidant (GSH) parameters in subjects who manifested FEP compared to healthy controls (HC). In this study we tested the hypothesis that the FEP is related to the intensification of the oxidative stress condition. If so, there is the possibility that some pro-oxidative and antioxidant markers can be used for the early clinical identification of schizophrenia.

Methods

Search strategy

A systematic search was conducted on PubMed, Web of Science e Scopus with the last update on April 19, 2021. The search included combined terms to match first-episode psychosis (or “FEP” or “early onset psychosis” or “EOP” or “early onset schizophrenia” or “first-episode schizophrenia” or “early psychosis” or “early schizophrenia”) with oxidative stress (or “oxidants” or “antioxidants” or “reactive oxygen species” or “catalase” or “superoxide dismutase” or “glutathione peroxidase” or “glutathione” or “malondialdehyde” or “thiobarbituric acid reactive substances”).

The flowchart of study selection is detailed in Figure 1. We included studies showing effects of first-episode psychosis oxidative stress (FEP) and healthy control group (HC) on blood concentration of CAT, SOD, GPx, GSH and lipid peroxidation in adults >21 years of age. Studies were excluded if they met any of the following hierarchical exclusion criteria: (1) they were not published as original peer-reviewed articles; (2) they did not include a healthy control group; (3) they did not include a FEP group (to consider this group as ‘first episode’, all patients included in the study should be experiencing a first episode of psychosis according to DSM-III R, DSM-IV ou PANNS criteria and should be 21 years old at the onset of psychosis; including brief psychotic disorder, psychotic disorder not otherwise specified, schizophreniform disorder, schizophrenia, mania with psychotic symptoms, and depression with psychotic symptoms; none of the reviewed studies included patients with substance-induced psychosis); and (4) they did not report results or data that could reach the mean and standard deviation values of the oxidative stress markers, as well as data on the statistical comparison between patients with FEP and controls. After

the overall screening, four studies were not included in the meta-analysis due to the presence of conflicting criteria for the characterization of FEP and adolescents in both the experimental and control groups.

Two independent reviewers selected studies and extracted data. Among the 21 studies selected, 06 assessed CAT^{10, 23-27}, 15 SOD^{10,22-35}, 9 GPx^{10,22-24,27,28,31,36,37}, 5 GSH^{10,20,23,37,38} and 12 lipid peroxidation^{20,22,24,25,27,31,33,35,36,38-40}. Lipid peroxidation data included experiments analyzing TBARS and malondialdehyde levels. From these studies emerged the data from the meta-analyses seen in Table 2. Mean, standard deviation (SD) and sample number (n) were used for analysis. Standard error (SE) was converted to SD by the equation $SD=SE * (\sqrt{n})$, if SD was not provided in the original study. Furthermore, median and interquartile range (IQR) was replaced by median and SD ($SD=[IQR / 1.35]$)⁴². To identify the heterogeneity of the findings, sensitivity analyzes were applied in order to verify whether the type of sample (erythrocyte or serum/plasma) used in the experiments would generate subgroups.

The PEDro scale assessed quality of the studies⁴². Thus, scores on PEDro scale ranged from 0 (very low methodological quality) to 9 (high methodological quality). The quality of the studies was used for qualitative assessment, and it was not an exclusion criteria. Egger's tests were performed to check the risk of publication bias in each of the meta-analyses.

Data extracted from eligible studies seen in Table 1 included: first author; year of the study; age (mean and SD); number of FEP patients and HC controls; gender (as number of men/women); diagnosis criteria; tobacco users (as total number); mean and SD for each oxidative stress marker (for both FEP patients and controls); antipsychotic use (yes/no), name of oxidative stress marker included.

Statistical Analysis

The five meta-analyses were performed using *Review Manager* Software version versão 5.4.1. The effect size was calculated based on standard mean difference (SMD: difference between the changes within FEP and control groups) and its 95% CIs were calculated for every individual marker. Based on the known heterogeneity of markers, we expected that the estimates would also vary substantially between studies. Random-effects models assume that the true effect size varies from one study to the next and, accordingly, are more conservative than fixed effect models. Therefore, random effects models were used.

Statistical heterogeneity was assessed through visual inspection of forest plots and using the Q statistic (a magnitude of heterogeneity) and the I² statistic (a measure of the proportion of variance in summary effect size attributable to heterogeneity). It was decided to analyze separately the experiments performed on erythrocytes and plasma/serum samples.

Figure 1. Flowchart of studies selection.

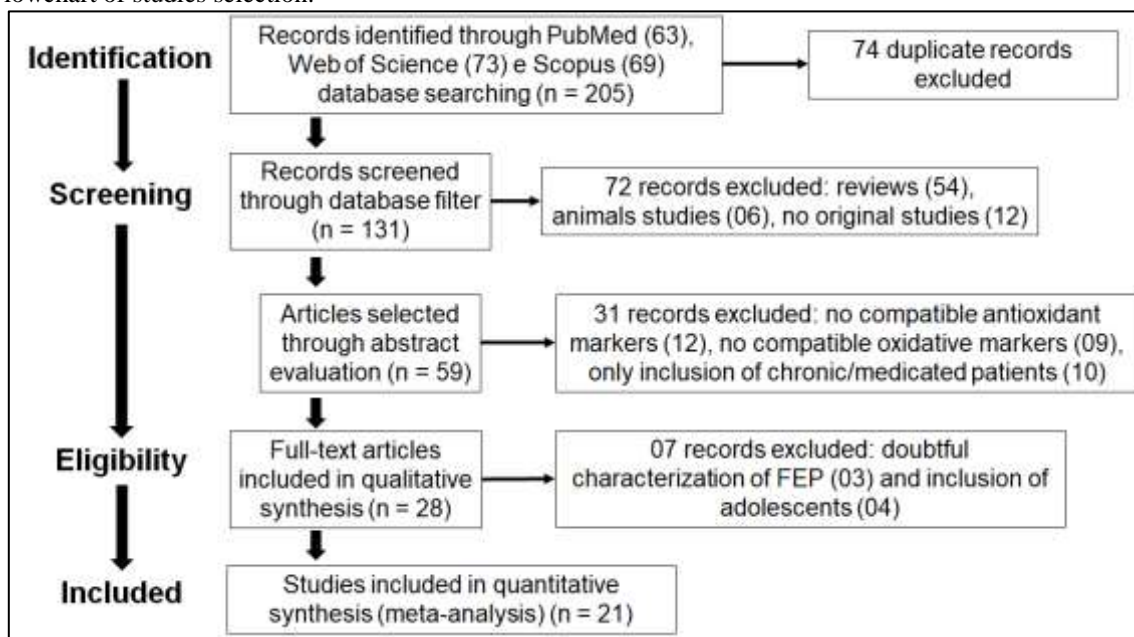


Table 1. Characteristics of studies included in the meta-analyses (n = 21).

First author, year	Schizophrenia Manifestation (FEP)						Healthy Control (HC)				Markers included
	FEP (n)	Age (m ± SD)	Diagnostic criteria	Gender (M/W)	Smoker (n, %)	Drug naïve	HC (n)	Age (m ± SD)	Gender (h/m)	Smoker (n)	
Mukherjee et al. (1996) ²⁸	14	22.82 ± 4.2	DSM-III R	11/3	n/a	yes	10	28.61 ± 7.3	6/4	n/a	SOD
Mahadik et al. (1998) ³⁸	26	23.3 ± 4.6	DSM-III R	20/6	n/a	yes	10	27.9 ± 8.3	6/4	n/a	TBARS
Kartalci et al. (2011) ²⁰	28	30.3 ± 7.6	DSM-IV	15/13	13	yes	20	29.5 ± 9.7	10/10	9	MDA, GSH
Raffa et al. (2011) ²³	23	29.3 ± 7.5	DSM-IV	20/3	13	yes	45	29.6 ± 6.2	36/9	11	SOD, GPx, CAT, GSH
Khan et al. (2012) ³⁹	22	22.40 ± 4.8	DSM-IV	18/4	n/a	yes	16	24 ± 5.6	14/2	n/a	TBARS
Martínez-Cengotitabengoa et al. (2012) ¹⁰	28	27.68 ± 9.18	DSM-IV	21/7	n/a	yes	28	27.95 ± 7.50	21/7	n/a	CAT, SOD, GPx, GSH
Wu et al. (2012) ²⁹	78	29.4 ± 9.1	DSM-IV	42/36	27	yes	100	29.9 ± 10.9	65/35	32	SOD
Ozornina et al. (2013) ²⁴	66	24.5 ± 05	ICD-10 PANSS	34/22	n/a	yes	20	24.5 ± 05	11/9	n/a	SOD, CAT, GPx, TBARS
Noto et al. (2015) ⁴⁰	51	25.4 ± 7.5	DSM-IV	36/15	10	yes	61	26 ± 7.3	32/29	0	LOOH
Sarandol et al. (2015) ²²	26	25.6 ± 7	DSM-IV	10/16	19	yes	25	23.5 ± 9.2	10/15	19	MDA, SOD, GPx
Camkurt et al. (2016) ²⁵	50	36.4 ± 12.4	DSM-IV	16/34	n/a	yes	50	33.84 ± 10.7	22/28	n/a	MDA, CAT, SOD
Bai et al. (2018) ³⁰	40	27.13 ± 1.06	PANSS	16/24	n/a	yes	80	27.48 ± 0.069	44/36	n/a	GPx, SOD, MDA
Jordan et al. (2018) ³¹	22	30 ± 2.62	PANSS	13/9	16	yes	43	35 ± 4.45	26/17	15	MDA, SOD, TSG
Langbein et al. (2017) ³⁶	27	25.3 ± 3.52	PANSS	13/14	11	yes	31	25.12 ± 4.68	18/13	12	TBARS, GSHt, GPx,
Miljević et al. (2018) ²⁶	19	24.2 ± 1.4	ICD-10	n/a	13	yes	20	27 ± 2	n.e.	10	SOD, CAT, GPx
Reyes-Madrigal et al. (2019) ³⁷	10	22.30 ± 4.42	DSM-IV	5/5	1	yes	9	22.56 ± 2.35	5/4	0	GSH
Lang et al. (2020) ³²	166	25.8 ± 9.1	DSM-IV	98/67	40	yes	133	27.7 ± 7.6	70/63	39	SOD
Wang et al. (2020) ³⁴	163	26 ± 9.2	DSM-IV	96/67	38	yes	133	27.75 ± 7.5	70/63	39	SOD
Xiu et al. (2020) ³³	327	26.9 ± 9.4	DSM-IV	160/118	28.3%	yes	391	27.7 ± 7.4	208/18	33%	SOD, MDA
Zhu et al. (2020) ²⁷	119	29.07 ± 7.71	DSM-IV	76/43	12	yes	135	29.38 ± 7.21	80/55	9	SOD, GPx, CAT, MDA
Reyazuddin et al. (2021) ³⁵	50	28.33 ± 10.9	ICD-10 PANSS	10/40	n/a	yes	50	29.54 ± 11.90	12/38	n/a	GPx, SOD, MDA

Abbreviations: FEP = first episode psychosis; HC = healthy control; n/a = not available; n = number; m = mean; SD = standard deviation; M = men; W = women; CAT = catalase; SOD = superoxide dismutase; GPx = glutathione peroxidase; GSH = glutathione; TBARS = thiobarbituric acid reactive substances; MDA = malondialdehydes; LOOH = lipid hydroperoxides; TSG = total shulphydryl groups; GSHt = total glutathione; DSM = Diagnostic and Statistical Manual of Mental Disorders; PANSS = Pretrained Audio Neural Networks; ICD-10 = International Classification of Diseases, Tenth Revision.

Results

Table 2 presents the selected markers for the meta-analyses of the enzymatic (CAT^{10, 23-27}, SOD^{10,22-35}, and GPx^{10,22-24,27,28,31,36,37}) and non-enzymatic (GSH^{10,20,23,37,38}) antioxidant systems, such as the oxidative attack marker, the lipid peroxidation^{20,22,24,25,27,31,33,35,36,38-40}.

Table 2. Effect size between FEP and HC groups for markers evaluated in meta-analyses.

Random Model				Effect Size			Heterogeneity			
Marker	Studies (n)	FEP (n)	HC (n)	SMD (95% CI)	Z	P	Q	P(Q)	I ²	Tau ²
CAT	06	415	392	-0.42 (-0.91, 0.07)	1.69	0.09	59.82	0.00001	90%	0.37
SOD	15	1293	1279	-0.30 (-0.90, 0.30)	0.99	0.32	630.88	0.00001	98%	1.42
GPx	9	500	529	-1.39 (-2.64, -0.15)	2.19	0.03	563.51	0.00001	98%	3.94
GSH	5	218	228	-0.91 (-2.57, 0.76)	1.07	0.29	248.88	0.00001	98%	4.24
LP	12	814	852	+1.75 (0.93, 2.57)	4.18	< 0.0001	483.32	0.00001	98%	1.99

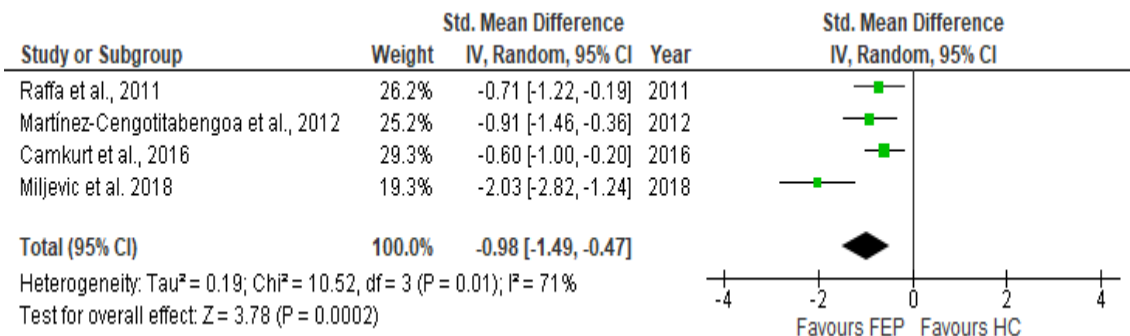
Abbreviations: FEP = first_episode psychosis; HC = healthy control; n = number; SMD = standardized mean difference; 95% CI = 95% confidence interval considering mean value (maximum value, minimum value); CAT = catalase; SOD = superoxide dismutase; GPx = glutathione peroxidase; GSH = glutathione; LP = lipid peroxidation.

A total of 5 markers were addressed by 6 or more studies: CAT, SOD, GPx, GSH, and lipid peroxidation. Therefore, 5 meta-analyses were performed assessing these oxidative markers from 21 studies, as shown in **Table 2**, comprising an overall sample of 415 FEP and 392 HC for CAT (6 studies), 1293 FEP and 1279 HC for SOD (15 studies), 500 FEP and 529 HC for GPx (9 studies), 218 FEP and 228 HC for GSH (5 studies), and 814 FEP and 852 HC for lipid peroxidation (12 studies). No significant differences were found between FEP and HC groups in any of the antioxidant defense system parameters (CAT, SOD, GPx, and GSH) assessed, despite favoring a decrease in activity of both the antioxidant and non-enzymatic enzyme systems (seen in the mean values for SMD in Table 2). Lipid peroxidation levels showed a significant increase for the FEP group compared to the HC group ($p < 0.0001$). Heterogeneity among studies was high, with I^2 values $> 90\%$.

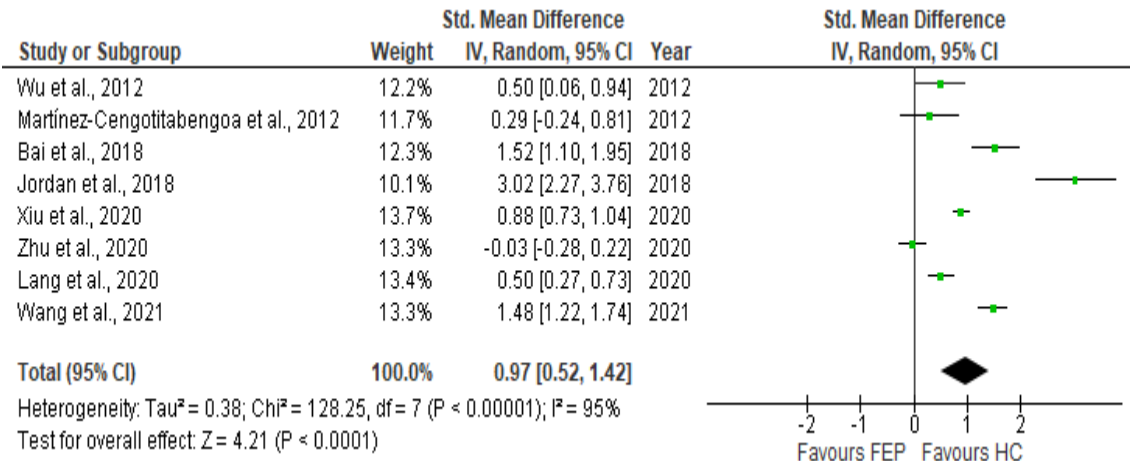
Sensitivity analyzes were performed to obtain more homogeneous results with this new form of analysis, by excluding studies identified as sources of heterogeneity. In the present study, we chose to analyze only data extracted from experiments performed with erythrocyte samples for CAT^{10,24,26,27} (Figure 2A), GPx^{10,24,25,27,36} (Figure 2C) and GSH^{10,24} (Figure 3) and plasma or serum for SOD^{10,28,30-35} (Figure 2B) and lipid peroxidation^{20,22,24,25,27,31,35,36,38-40} (Figure 4).

Figure 2. Forest plot of main results of the erythrocyte (CAT, GPx) and plasma/serum (SOD) antioxidant enzymatic system comparing FEP and HC groups.

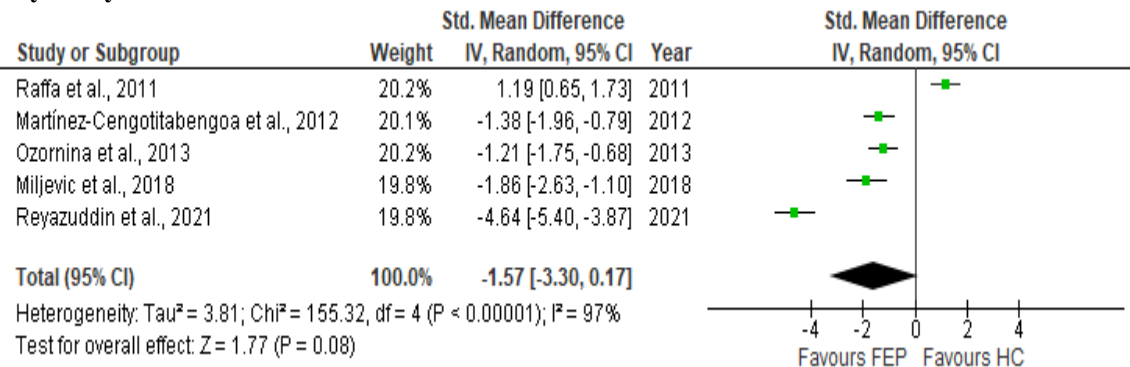
A) Erythrocyte CAT



B) Plasma/Serum SOD

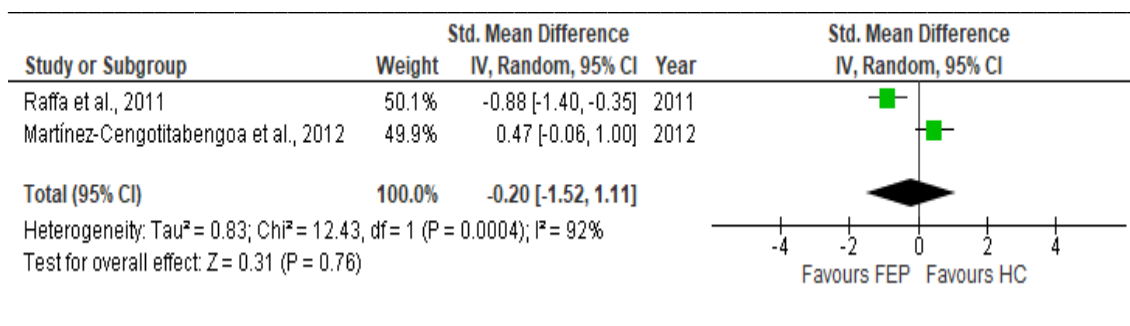


C) Erythrocyte GPx



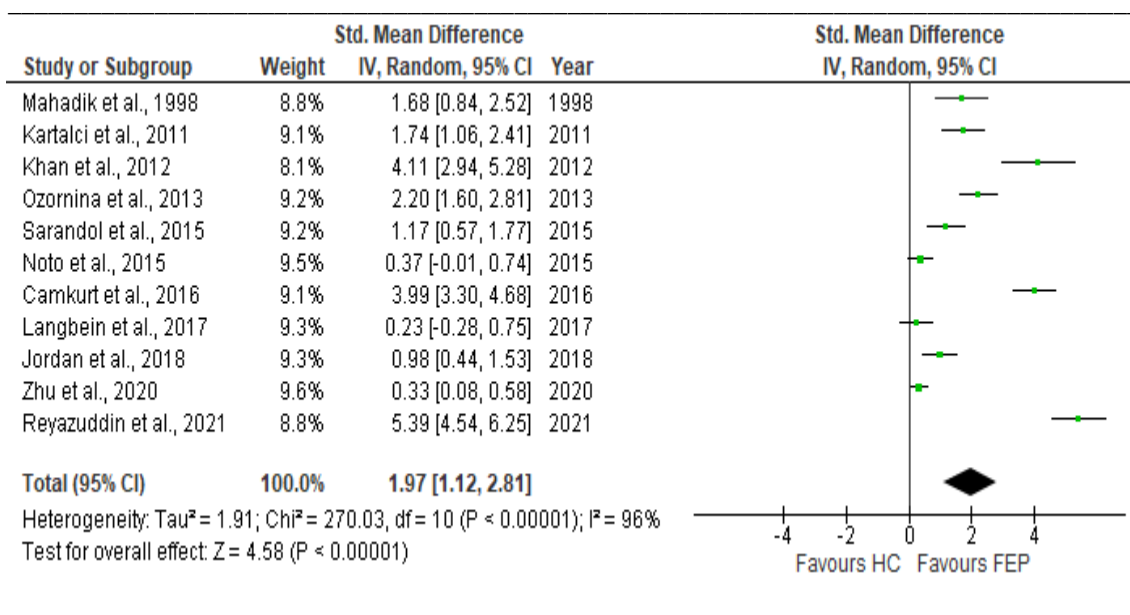
Abbreviations: FEP = first-episode psychosis; HC = healthy control; CAT = catalase; SOD = superoxide dismutase; GPx = glutathione peroxidase.

Figure 3. Forest plot of main results of the erythrocyte non-enzymatic antioxidant marker (GSH) comparing FEP and HC groups.



Abbreviations: FEP = first-episode psychosis; HC = healthy control; GSH = glutathione.

Figure 4. Forest plot of main results of plasma/serum lipid peroxidation marker comparing FEP and HC groups.



Abbreviations: FEP = first-episode psychosis; HC = healthy control.

The proposal above was to understand in these two subgroups (erythrocytes and serum/plasma) which is the best strategy to understand the effect of oxidative stress in FEP patients. Therefore, another 5 meta-analyses were performed assessing these oxidative markers from 21 studies, comprising an overall sample of 120 FEP patients and 143 HC for CAT^{10,24,26,27} (4 studies), 943 FEP and 970 HC for SOD^{10,28,30-35} (8 studies), 186 FEP and 163 HC for GPx^{10,24,25,27,36} (5 studies), 51 FEP and 73 HC for GSH^{10,24} (2 studies), and 487 FEP and 461 HC for lipid peroxidation^{20,22,24,25,27,31,35,36,38-40} (11 studies). We analyzed for each marker both types of samples, erythrocyte and plasma/serum, and the forest plots showed the most significant values obtained. Significant differences were obtained for serum/plasma SOD (p < 0.0001) and lipid peroxidation (p < 0.0001), but still containing high heterogeneity (p < 0.0001). Interestingly, there was an increase in SOD activity compared to the other two antioxidant enzymes, erythrocyte CAT and GPx, which showed a decrease in activity. The increased levels of serum/plasma lipid peroxidation support the hypothesis of oxidative stress in the etiology of FEP.

Discussion

A variety of methods have previously been employed to assess oxidative stress within schizophrenia. A large number of studies have assessed peripheral biomarkers of oxidative stress such as antioxidant levels⁴³. In the present study, meta-analyses of 5 antioxidants markers to FEP and HC groups did not show any significant results, with great heterogeneity among studies, and even opposite effects found for some markers in different studies, considering the results in Table 2. These contradictory findings may be due, to some extent, to large differences between samples, including different evaluations and analytical methods and clinical factors that can alter oxidative stress levels parameters. Also, most of the studies provided

insufficient information or not control for confounding factors such as body mass index, gender-based differences, disease development stage and substance or tobacco use^{44,45}. The family members' perception of what would be the FEP can also be a primary limiting factor.

We replicated the findings for antioxidant enzyme markers considering only one sample type (erythrocyte or plasma/serum) as experimental and sample procedures could affect an accurate analysis of antioxidant events, as shown in Figures 2A (CAT), 2B (SOD) and 2C (GPx). Despite the evidence of favoring the decrease of the antioxidant defense systems (enzymatic and non-enzymatic) in FEP, according to Table 2, in experiments with both erythrocyte and plasma/serum samples, a new condition emerged for analysis in plasma/serum in SOD (Figure 2B) when we found that there was an increase in the activity of this enzyme favoring the FEP group in relation to the HC group. The activity values for CAT and GPx were also closer to significance in studies involving only erythrocyte analysis (Figures 2A and 2B, respectively). The SOD metabolizes O_2^{\cdot} into H_2O_2 in an attempt to attenuate the formation of more offensive radical species, such as the HO^{\cdot} radicals. This may be the reason for the increase in SOD activity with the consequent decrease in CAT and GPx activities, which denotes an imbalance in the antioxidant enzymatic defense system and a modulation condition on the initial state of events that trigger FEP³⁰.

Although not significant, the decrease in GSH levels, shown both in Table 2 and Figure 3, can change the redox condition of antioxidant enzymes⁴⁶. Perhaps a small change in molecular markers, even without statistical significance, could alter the dynamics of antioxidant defense events and emerge as triggers in the process of oxidative stress in FEP. Finally, the oxidative stress condition is notorious when there is a significant increase in lipid peroxidation levels only in plasma/serum samples. Our meta-analyses collaborate with the finding that the oxidant and antioxidant defense systems indicators have shown that antioxidant defense system defects reflect early pathophysiologic changes in schizophrenics⁴⁴. But it should be noted that even performing sensitivity analyzes for all markers, it was not possible to reduce the heterogeneity of the results obtained. There is a need for more studies that only isolate the same experimental conditions, with a careful selection of subjects reported as FEP.

Estimating levels of reactive oxidative products provides a very useful strategy to determine the impact of oxidative stress. Lipid peroxidation is often assayed by measuring thiobarbituric acid reactive substances (TBARS). The end products of lipid peroxidation, such as MDA assessment, have been very widely used indexes of oxidative stress in clinical studies^{47,48,49}. Also, elevated levels of MDA have been shown in plasma, erythrocytes, leucocytes and platelets of patients with schizophrenia⁵⁰. The brain has comparatively greater vulnerability to oxidative damage as a result of the relatively low levels of antioxidants, high levels of polyunsaturated fatty acids and increased need of oxygen^{51,52}. There is increasing evidence suggesting the involvement of free radical-mediated neuronal dysfunction in schizophrenia^{53,54,55,56,57}, which might be the molecular key to the manifestation of FEP according to the results of the meta-analyses presented.

Conclusions

The meta-analyses showed a favoring of the decreases in CAT and GPx activities in erythrocyte samples, as well as a significant increase in SOD activity in serum/plasma in the FEP group compared to the HC group, it should be considered that there is a modulation strategy to contain the installation of the oxidative stress condition. This condition can be an initial event that signals the triggering of FEP. Evidence allows us to consider that the operating system activation key in the pathophysiology of schizophrenia has some level of relationship with the imbalance between pro-oxidant and antioxidant molecules within cells and tissues. Cellular damage, seen here by lipid peroxidation, in the intervention of this operating system, appears to be present in the early stages of schizophrenia and other psychoses. Thus, an initial diagnostic strategy by analyzing the oxidative stress markers analyzed here can aid clinical decision-making and help stop the progression and severity of the disorder.

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