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Basal low antioxidant capacity correlates with cognitive deficits in early onset psychosis. A 2-year follow-up study

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ABSTRACT

The objective of the study is to examine the association of baseline total antioxidant status (TAS) and glutathione (GSH) levels with short- and long-term cognitive functioning in patients with early onset first-episode psychosis, comparing affective and non-affective psychoses.

We analysed 105 patients with an early onset-first episode psychosis (age 9–17 years) and 97 healthy controls. Blood samples were taken at admission for measurement of TAS and GSH, and cognitive performance was assessed at baseline and at 2 years of follow-up. Regression analysis was used to assess the relationship between TAS/GSH levels at baseline and cognitive performance at both time points, controlling for confounders.

Baseline TAS and GSH levels were significantly lower in patients than healthy controls. In patients, baseline TAS was positively associated with the global cognition score at baseline ($p = 0.048$) and two years later ($p = 0.005$), while TAS was not associated with cognitive functioning in healthy controls. Further, baseline TAS in patients was specifically associated with the memory domain at baseline and with the memory and attention domains two years later. Stratifying by affective and non-affective psychoses, significant associations were only found between TAS and cognition in the non-affective psychosis group. Baseline GSH levels were not associated with cognitive functioning at either time point in either group.

The antioxidant defence capacity in early onset first-episode psychotic patients is directly correlated with global cognition at baseline and at 2 years of follow-up, especially in non-affective psychosis.

1. Introduction

An imbalance between pro-oxidant and antioxidant mechanisms in cells is thought to play a role in the pathophysiology of many diseases of the central nervous system, such as schizophrenia (Fendri et al., 2006; Bitanihirwe and Woo, 2011). As this imbalance is a potential cause of oxidative stress and damage to key brain circuits (van Os et al., 2010; Andreazza, 2012; Anderson et al., 2013) the accumulation of pro-oxidant molecules (i.e., reactive oxygen species) and/or impaired anti-oxidant defence mechanisms (both enzymatic and non-enzymatic) have become targets for study in psychotic disorders. The interest in and the evidence to justify these studies come from previous research

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Table 1
Neuropsychological tests and variables grouped by cognitive domain.

Cognitive domain	Neuropsychological variable
Attention	WAIS-III[a] Digits Forward
	Time to complete TMT-A[b]
	Number of correct items, Stroop 1 words
	Number of correct items, Stroop 2 colours
	Number of correct responses, CPT[c]
	Average reaction time, CPT
Working memory	WAIS-III Digits Backward
	WAIS-III Number–Letter Sequencing
Learning and memory	TAVEC[d] Total Learning
	TAVEC Short Term Free Recall
	TAVEC Long Term Free Recall
	TAVEC Discrimination
Executive functions	Time to complete TMTB[e]
	Number of words, FAS[f]
	Number of words, COWAT[g]
	Stroop Interference score
	WCST[h] number of perseverative errors
	WCST number of errors
	WCST conceptual level responses

[a] WAIS-III: Wechsler Adult Intelligence Scale, 3rd edition (Wechsler, 1997).
[b] TMT-A: Trail Making Test, part A (Spreen and Strauss, 1998).
[c] CPT: Conners' Continuous Performance Test (Conners, 2000).
[d] TAVEC: Spanish version (Benedet et al., 2001) of the California Verbal Learning Test (Delis et al., 1994).
[e] TMTB: Trail Making Test, part B = (time to complete TMT-B − time to complete TMT-A) / time to complete TMT-A (Spreen and Strauss, 1998).
[f] FAS: Verbal fluency test (Spreen and Strauss, 1998).
[g] COWAT: Control Oral Word Association Test. Semantic category "animals" (Benton, 1994).
[h] WCST: Wisconsin Card Sorting Test (Heaton, 1981; Spreen and Strauss, 1998).

in both adults (Anderson et al., 2013), children (Micó et al., 2011), and their siblings (Ben Othmen et al., 2008).

In the search for biomarkers of functional or structural damage in psychiatric disorders, early studies have suggested that total antioxidant status (TAS) should be systematically measured given its association with the pathophysiology of schizophrenia spectrum disorders (Ustundag et al., 2006). TAS reflects the cumulative effects of all antioxidants present in the plasma and other body fluids. Studies measuring TAS have found lower levels of antioxidants in patients with neuropsychiatric diseases (such as schizophrenia and bipolar disorder) than in healthy controls (Micó et al., 2011), as well as a dysfunctional balance of oxidative and pro/anti-inflammatory pathways in first-episode psychosis (FEP) (García-Bueno et al., 2013). It is especially important to study the disease at its outset as it is possible to find pathophysiological clues uncontaminated by chronicity or drug effect (Bernardo et al., 2013).

It is also of relevance to psychosis that oxidative stress can promote macro and microglial damage, including axonal demyelination (Qin et al., 2008; rev. in Adibhatla and Hatcher, 2010). Indeed, it has recently been shown that lower baseline plasma levels of the main cellular antioxidant, glutathione (GSH) at the time of a first psychotic episode are associated with greater decreases in cortical grey matter two years later in patients with early onset psychosis (Fraguas et al., 2012), suggesting a role for oxidative damage in the pathophysiology of this disease.

The relationship between oxidative stress and cognition has been explored in some studies. In a previous study of adults with FEP, we found that plasma GSH levels were positively associated with executive functioning (Martinez-Cengotitabengoa et al., 2012). A recent study found that higher activity of plasma manganese superoxide dismutase (a mitochondrial enzyme that detoxifies superoxide radicals to hydrogen peroxide) was significantly correlated with the degree of cognitive impairments in patients with schizophrenia (Zhang et al., 2013). Although these findings support an association between oxidative stress and cognitive deficits, both studies were cross-sectional in design and, to our knowledge, there have been no longitudinal studies.

The objective of this study was to explore the long-term effects of low baseline TAS and GSH levels on the cognitive functioning of patients with early onset psychosis. We hypothesized that the antioxidant status of patients during an early first psychotic episode would be inversely associated with their cognitive performance at baseline and two years after the acute episode. Further, for this analysis, we stratified patients into those with affective and non-affective psychoses.

2. Methods

2.1. Subjects

The original Child and Adolescent First-Episode Psychosis Study (CAFEPS) was a case–control study that included 110 FEP patients aged 9–17 years at the time of first evaluation. A first episode of psychosis was defined as the presence of positive psychotic symptoms of delusions or hallucinations for a period of less than 6 months. This short duration of symptomatology was used to obtain a more homogenous patient sample. Patients were recruited from Child and Adolescent Psychiatry Units at six university hospitals in Spain. Sample recruitment and patient characteristics have been described elsewhere (Castro-Fornieles et al., 2007). Exclusion criteria were: the presence of any other Axis I disorder that might account for the psychotic symptoms (such as substance abuse, autistic spectrum disorders, post-traumatic stress disorder, and acute stress disorder); mental retardation according to DSM-IV criteria, including not only an intelligence quotient of less than 70, but also impaired functioning; pervasive developmental disorder; neurological disorders; a history of head trauma with loss of consciousness; and pregnancy. Patients were not excluded for occasional substance use if positive symptoms persisted for more than two weeks after a negative urine drug test.

The study also included 98 healthy control subjects who were selected from the same catchment area and matched to the patients by age and gender. They were selected from publicly-funded schools with similar characteristics to those attended by patients through advertisements and from children who were seen for routine paediatric visits at our hospitals. The control subjects had no history of Axis I psychiatric disorders, neurological disorders, mental retardation, or head trauma, and were not pregnant, and there was no history of psychiatric disorders in their first-degree relatives.

Baseline blood samples for measuring oxidative stress were available for 105 patients and 97 controls of the original sample and these individuals were included in the present analysis. The study was approved by the Ethics and Clinical Research Boards of all the hospitals involved in the study. Parents or legal guardians gave written informed consent and patients assented to participate in the study.

2.2. Design and clinical assessment

In this prospective study, we assessed the antioxidant status of FEP patients at baseline and evaluated their cognitive functioning at baseline and two years later.

All patients met the DSM-IV criteria for a FEP (American Psychiatric Association, 1994), assessed using the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). Clinical assessments on admission and two years later were performed by an experienced child psychiatrist with specific training in the K-SADS-PL semi-structured interview. Socioeconomic status was estimated using the Hollingshead and Redlich scale (Hollingshead and Redlich, 1958), administered to the parents by the same clinician.

2.3. Oxidative stress evaluation

Based on preliminary data (Micó et al., 2011), we focused the present analyses on the following oxidative variables: TAS as a global measure of

Table 2
Baseline characteristics of healthy controls and all first-episode psychosis patients, and by patient diagnostic group at 2 years' follow-up.

	Healthy controls (N = 97)	Patients (N = 105)	Statistic	p-Value	Patient diagnostic group at 2 years			Statistic	p-Value
					Non-affective psychosis (n = 50)	Affective psychosis (n = 30)	Data missing (n = 25)		
Gender, male, n (%)	63 (64.9)	71 (67.6)	$\chi^2 = 0.161$	0.688	36 (72.0)	19 (63.3)	16 (64.0)	$\chi^2 = 0.839$	0.657
Age, years, mean (SD)	15.2 (1.9)	15.5 (1.8)	U = 5689.5	0.138	15.4 (2.0)	15.9 (1.1)	15.4 (2.0)	H = 0.303	0.859
Tobacco abuse or dependence[a], n (%)	6 (6.2)	32 (30.5)	$\chi^2 = 19.479$	**<0.001**	12 (24.0)	13 (43.3)	7 (28.0)	$\chi^2 = 3.403$	0.182
Socioeconomic status, n (%)			$\chi^2 = 12.539$	**0.014**				$\chi^2 = 8.727$	0.366
5 (lowest)	10 (10.3)	22 (21.0)			8	6	8		
4	23 (23.7)	35 (33.3)			15	13	7		
3	26 (26.8)	23 (21.9)			13	7	3		
2	10 (10.3)	12 (11.4)			7	3	2		
1 (highest)	28 (28.9)	13 (12.4)			7	1	5		
Antipsychotic treatment, n (%)	NA	101 (96.2)			48 (96.0)	30 (100.0)	23 (92.0)	$\chi^2 = 2.391$	0.303
Antioxidant parameters at baseline, mean (SD)									
TAS (mM)	1.3 (0.5)	1.0 (0.4)	U = 2764.5	**<0.001**	1.0 (0.4)	0.85 (0.2)	1.0 (0.3)	H = 3.398	0.183
GSH (μM)	387.8 (158.8)	326.9 (127.3)	U = 3138	**0.007**	318.8 (144.0)	325.8 (109.1)	343.4 (120.9)	H = 1.177	0.555

NA: not applicable; TAS: total antioxidant status; GSH: glutathione.
Significant difference in bold (p-values ≤0.05).
[a] Tobacco abuse or dependence according to DSM-IV criteria.

antioxidant capacity, and the level of glutathione (GSH) as the main cellular antioxidant. These variables were determined as follows. Blood samples were taken from each patient at the time of admission and from the healthy controls. Following centrifugation, the erythrocytes and plasma were separated and stored frozen at −80 °C until analysis. All samples were analysed at the same time. TAS was determined by standardised spectrophotometric assays (Bioxytech, Beverly Hills, USA) in plasma. Briefly, the TAS assay relies on the ability of antioxidants present in plasma to inhibit the oxidation of 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid), monitored by measuring the absorbance at 600 nm. Total GSH levels were determined by standardised spectrophotometric assays (Bioxytech) of erythrocyte haemolysates. The assay is based on the formation of a chromophoric thione, with the absorbance measured at 420 nm being directly proportional to the GSH concentration.

2.4. Neurocognitive assessment

Cognitive assessments were carried out four to eight weeks after admission to allow time for acute symptoms to stabilize, and at two years after illness onset. The battery of neurocognitive tests was designed to assess four cognitive domains (attention, working memory, learning and memory, and executive functioning) by combining selected individual measures from different tests (Table 1). The selection of measures for each domain was based on the MATRICS battery (Green et al., 2004), as well as on the psychometric characteristics of the tests (Lezak, 1995; Strauss et al., 2006) and on previous studies using similar procedures (Heinrichs and Zakzanis, 1998; Addington et al., 2003; de Mello Ayres et al., 2010; Zabala et al., 2010). All tests were administered and scored according to standardised instructions by psychologists trained in the use of the instruments. The intra-class correlation coefficient (ICC), calculated as a measure of the inter-rater reliability, was between 0.95 and 0.99.

Raw test scores were converted to z-scores (mean = 0; SD = 1) based on the performance of the healthy control group, to obtain an overall score for each cognitive domain. For these, a higher score indicates a better performance. z-Scores were truncated at −4.0 to exclude extremely deviant scores. Mean summary scores were then calculated as the arithmetic means of the individual scores obtained for each cognitive domain (i.e., means of the aforementioned z-scores). The global cognitive score was calculated as the arithmetic mean of the scores for the four cognitive domains.

2.5. Data analyses

All statistical analyses were performed using PASW Statistics version 18 and differences were considered significant when $p < 0.05$. The baseline characteristics of patients and healthy controls were summarised using descriptive statistics: means and standard deviations (SD) for continuous variables and frequencies for categorical variables. Comparisons were made between the patient and control groups using the chi-square test (categorical variables) or Mann–Whitney U test (continuous variables). Multiple linear regression models were used to assess the influence of oxidative stress on cognitive functioning and the results are presented as Beta coefficients with p-values after establishing the lack of multicollinearity and independence of errors. As oxidative stress has also been associated with tobacco consumption (Zhang et al., 2006, 2007) and antipsychotic treatment (Lepping et al., 2011), we controlled for these variables in the model, using the number of chlorpromazine equivalent doses in the case of antipsychotic treatment. We also controlled for baseline differences in socioeconomic status.

3. Results

3.1. Sample characteristics

Table 2 summarises the characteristics of the patients and healthy controls at baseline. Group comparisons identified significant differences

Table 3
Cognitive functioning (z-scores) at baseline and at 2 years' follow-up in healthy controls and all patients, and by patient diagnostic group at 2 years.

	Healthy controls (N = 97)	Patients (N = 105)	Statistic	p-Value	Patient diagnostic group at 2 years			Statistic	p-Value
					Non-affective psychosis (n = 50)	Affective psychosis (n = 30)	Data missing (n = 25)		
Cognition at baseline, mean (SD)									
Global score	−0.00 (0.53)	−1.28 (0.73)	U = 853.0	**<0.001**	−1.30 (0.65)	−1.33 (0.78)	−1.16 (0.85)	H = 0.624	0.732
Attention	0.03 (0.66)	−1.25 (0.79)	U = 1118.0	**<0.001**	−1.31 (0.71)	−1.21 (0.86)	−1.18 (0.89)	H = 0.531	0.767
Working memory	−0.00 (0.84)	−0.92 (1.01)	U = 2127.5	**<0.001**	−0.96 (0.90)	0.89 (1.16)	−0.88 (1.06)	H = 0.617	0.734
Memory	−0.01 (0.83)	−1.91 (1.33)	U = 1197.0	**<0.001**	−1.92 (1.25)	−2.07 (1.27)	−1.71 (1.57)	H = 0.458	0.795
Executive functions	0.01 (0.64)	−1.07 (0.83)	U = 1549.0	**<0.001**	−1.07 (0.84)	−1.16 (0.89)	−0.92 (0.73)	H = 1.055	0.590
Cognition after 2 years, mean (SD)									
Global score	0.27 (0.53)	−0.94 (0.75)	U = 500.0	**<0.001**	−0.84 (0.73)	−1.09 (0.76)	NA	U = 430.0	0.069
Attention	0.24 (0.72)	−0.81 (0.85)	U = 942.0	**<0.001**	−0.75 (0.86)	−0.91 (0.83)	NA	U = 506.0	0.297
Working memory	0.20 (0.89)	−0.93 (0.85)	U = 915.0	**<0.001**	−0.86 (0.78)	−1.05 (0.96)	NA	U = 443.5	0.098
Memory	0.24 (0.80)	−1.58 (1.43)	U = 776.0	**<0.001**	−1.44 (1.42)	−1.80 (1.44)	NA	U = 488.0	0.264
Executive functions	0.23 (0.55)	−0.54 (0.78)	U = 1175.0	**<0.001**	−0.43 (0.76)	−0.72 (0.80)	NA	U = 460.0	0.086

NA = No data available at 2 year assessment.
U = Mann–Whitney U.
H = Kruskal–Wallis H. Items in bold indicate statistical significance.

between the patient and control groups for tobacco abuse or dependence ($p < 0.001$) and socioeconomic status ($p = 0.014$). The baseline antioxidant status also differed between these groups, with the patients having significantly lower levels of antioxidants ($p < 0.001$) and GSH ($p = 0.007$). Table 2 also presents the baseline characteristics of the patients by their diagnostic category at the two-year follow-up assessment (using DSM-IV criteria). Of the 80 patients who completed the assessment both at baseline and two years later, 50 had non-affective psychosis and 30 had affective psychosis at the two-year follow-up. The non-affective psychosis group comprised patients with schizophrenia (38) and psychotic disorder not otherwise specified (12), while the affective psychosis group consisted of patients with a diagnosis of bipolar disorder (19), psychotic depression (4) or schizoaffective disorder (7). Among these different diagnostic groups of patients, there were no significant differences in tobacco use, socioeconomic status or baseline antioxidant status (Table 2).

3.2. Relationship between oxidative stress and cognition

Baseline TAS differed between tobacco abusers or dependants and others (patients + controls) ($U = 2247.0$; $p = 0.029$), being higher in the non-smoker group, while baseline GSH levels in these groups were not significantly different ($U = 1897.5$; $p = 0.236$). Within the patient group, no significant differences were found in the levels of TAS and GSH between smokers and non-smokers ($U = 980.0$, $p = 0.439$; $U = 625.0$, $p = 0.245$).

Table 3 presents the mean z-scores for each of the four cognitive domains and the global cognition scores in the patient and control groups. Compared with the healthy control group, the FEP patients had a poorer cognitive performance both at baseline and two years of follow-up ($p < 0.001$ for all four domains). However, there was no difference in cognitive functioning between the affective psychosis group and the non-affective psychosis group at either time point (Table 3).

Fig. 1 shows that in FEP patients baseline TAS levels were significantly positively associated with the global cognition score at baseline ($B = 0.405$; $p = 0.048$) and two years later ($B = 0.708$; $p = 0.005$), after controlling for confounding variables, while in the control group there was no significant association between baseline TAS and cognition at either time point. In contrast, there were no significant associations between baseline GSH levels and global cognitive functioning at either time point in either group (data not shown).

Table 4 summarises the associations between baseline TAS and cognitive functioning at baseline and at two years of follow-up in the patient and control groups, after controlling for confounding variables. In the patient group, there was a significant positive association between baseline TAS and memory both at baseline and two years later. In addition, in this group a higher TAS level at baseline was associated with better attention at two-years of follow-up (Table 4).

Among the diagnostic subgroups of patients, in those with non-affective psychosis at two years there was a direct relationship between baseline TAS and attention, working memory and global cognition at baseline, as well as a positive association between baseline TAS and attention, memory, executive function and global cognition at two years of follow-up (Table 4). In the group with affective psychosis, however, we found no significant associations between baseline TAS and cognitive functioning.

4. Discussion

In our sample of early onset psychotic patients, plasma total antioxidant status at the onset of the illness was positively associated with global cognitive performance both at baseline and at two years of follow-up, after controlling for tobacco use, antipsychotic exposure at baseline and socioeconomic status.

These findings are in line with studies, in vitro and in vivo, demonstrating that the accumulation of oxidative and nitrosative mediators

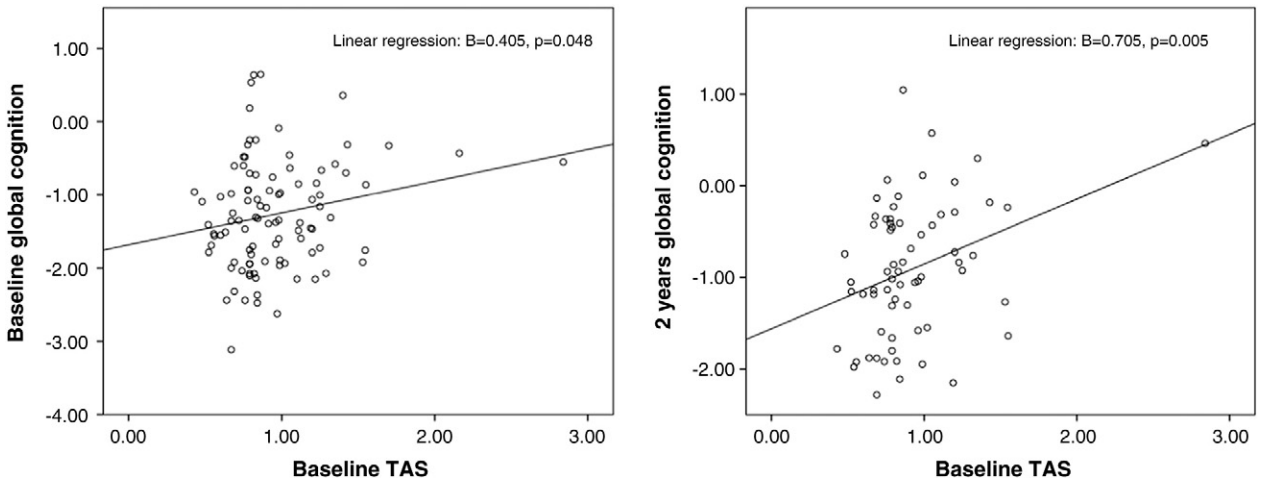

Fig. 1. Association between baseline total antioxidant status (TAS) and global cognition score at (a) baseline and (b) after 2 years of follow-up.

leads to oxidative stress when antioxidant systems are unable to detoxify these harmful compounds in the central nervous system (Aksenova et al., 2005; Fernández-Checa et al., 2010). Data from animal models suggest that antioxidant depletion in the brain can cause cognitive impairment (Dean et al., 2009) due to cellular lack of resilience and damage that, if not repaired, can lead to altered physiology and cognitive dysfunction (Pedrini et al., 2012). These findings reinforce the need to evaluate patients at the prodromal phase and all those in ultra-high risk groups, in order to avoid the deleterious consequences of the oxidative stress of the first psychotic episode.

Our results support the view that oxidative stress, in patients with early psychosis, but not in healthy controls, may alter some neuroprotective factors that are essential for cognitive tasks (Cabungcal et al., 2013; Dodd et al., 2013). The reduced capacity to protect against free radicals found in our sample of early onset patients (Mico et al., 2011) could lead to membrane dysfunction and DNA damage contributing to and explaining the specific symptoms of these patients, such as cognitive dysfunction (Martinez-Cengotitabengoa et al., 2012). On the other hand, previous studies have highlighted the role of NMDA-receptors in memory functioning (Morris et al., 2013). It seems as if a lower level of antioxidant protection could influence the normal functioning of NMDA receptors, causing abnormal functioning of memory processes (Kantrowitz and Javitt, 2010; Javitt et al., 2012).

The analysis of diagnostic subgroups yielded an interesting finding. Namely, the insult of oxidative stress at baseline affects affective and non-affective psychotic patients in a different manner both at baseline and follow-up. Specifically, baseline TAS is related to cognition in non-affective psychosis, but not in affective psychosis. The different relationship between TAS and cognition at baseline and two years after onset in the two types of psychosis could be related not only to a different aetiology for the cognitive deficit, but also to a different capacity of modulating damage in affective disorders, at least in the earlier stages of the illness. We cannot exclude the impact of some factors that were not measured, such as antioxidant status during follow-up. In addition, we cannot conclude that there is no type II error in the subsample of patients with affective disorder.

To date, it has been shown that there is a relationship between oxidative stress and clinical severity both in bipolar disorder during a depressive or a manic episode (Raffa et al., 2012; Kulak et al., 2013), and in major depression (Tobe, 2013). A relationship between cognition and oxidative stress has also been observed in chronic bipolar patients (Vieta et al., 2013) but there are no previous studies analysing the relationships between TAS and cognition in the medium term. Although these results need confirmation by new research, they suggest that the inability of the systemic antioxidant defences to control activated pro-oxidant pathways, that may underlie the insult produced by an early psychotic episode, persists and may contribute to cognitive outcome two years after the initial episode. Our work also indicates the potential predictive value of TAS as a peripheral biomarker of cognitive impairments, as it reflects overall antioxidant capacity including the

Table 4
Association between baseline total antioxidant status (TAS) and cognitive functioning at baseline and at 2 years of follow-up: results of regression models controlled for tobacco use, antipsychotic treatment and socioeconomic status.

	Cognitive domain								Global cognition	
	Attention		Working memory		Memory		Executive function			
	B	p-Value	B	p-Value	B	p-Value	B	p-Value	B	p-Value
At baseline										
Healthy controls (N = 97)	−0.016	0.915	−0.236	0.199	0.019	0.919	0.007	0.958	−0.059	0.601
Patients (N = 105)	0.381	0.088	0.462	0.109	0.905	**0.019**	0.148	0.502	0.405	**0.048**
Non-affective psychosis (n = 50)	0.516	**0.042**	0.653	**0.037**	0.760	0.097	0.450	0.089	0.514	**0.028**
Affective psychosis (n = 30)	0.084	0.913	0.641	0.544	0.904	0.431	−0.790	0.320	0.170	0.814
Data missing (n = 25)	−0.169	0.775	−0.069	0.919	0.653	0.484	−0.378	0.349	0.019	0.971
At 2 years of follow-up										
Healthy controls (N = 97)	−0.155	0.322	−0.105	0.601	0.139	0.432	−0.031	0.795	−0.057	0.584
Patients (N = 105)	0.705	**0.015**	0.517	0.079	1.241	**0.012**	0.419	0.090	0.708	**0.005**
Non-affective psychosis (n = 50)	0.704	**0.032**	0.393	0.189	1.124	**0.040**	0.504	**0.043**	0.663	**0.013**
Affective psychosis (n = 30)	0.651	0.387	0.772	0.337	0.972	0.449	−0.529	0.452	0.352	0.606
Data missing (n = 25)	NA			NA		NA				NA

Items in bold indicate statistical significance.
B = Beta coefficient.
NA = No data available at 2 year assessment.

function of a range of markers of oxidative stress. Glutathione was not associated with cognition in this research, although it has previously been associated with psychosis (Mico et al., 2011).

Our results also support the suggestion made by other authors of prescribing antioxidants to treat schizophrenia (Mahadik et al., 2006; Dean et al., 2011; Reddy et al., 2011) due to the involvement of oxidative stress in several processes occurring over the course of the illness including cognitive impairment. We underline that these antioxidants could be used in the very early stages, as a more benign form of treatment, attempting to delay the introduction of antipsychotic medication in early onset patients and, thereby, avoid the adverse events of such medications for as long as possible as suggested by some other authors (Francey et al., 2010), and also combining their effects with those of antipsychotic medication, ideally enabling lower doses to be used in children and adolescents. However, for this approach to be adopted in routine practice, further research is needed to demonstrate the usefulness of antioxidants in schizophrenia.

Lastly, our findings point to the possibility of using peripheral markers of oxidative and antioxidative balance in patients with first-episode psychosis, for prognostic and preventive purposes, taking into account the high sensitivity of the brain to oxidative damage (Ng et al., 2008) that is reflected in multiple stress-mediated responses such as cognitive dysfunction in individuals with impaired antioxidant defence.

This study has various limitations and strengths. It is a prospective naturalistic study but biochemical parameters (TAS and GSH levels) were only measured at baseline. A second limitation is that, though this is a multicentre study, the majority of participating centres were hospital units that had an inpatient facility and this may represent a bias towards the inclusion of more severe cases, making it difficult to generalize the results to less severe ones. On the other hand, nearly 70% of patients with early psychosis are hospitalized (Murphy et al., 2009). A third limitation is that we assume that changes in peripheral blood levels adequately reflect changes in the mental state of the brain. The last limitation to mention is that we cannot exclude completely that nutritional status or lifestyle could have had an effect on the results, although most of the patients had similar nutritional and lifestyle at the time of TAS assessment due to their inpatient status. One of the study strengths is the homogeneity of the sample and the existence of a control group. Further, a relevant strength is that compared with studies with similar design characteristics, our patient sample is the largest reported to date to detect predictive variables for a cohort in early psychosis.

In conclusion, our study shows that the antioxidant defence system in patients with early onset first-episode psychosis has an inverse correlation with global cognition at baseline and at two years of follow-up. Oxidative damage may contribute to the pathophysiology and account for a poor cognitive function in this early onset group. Future research should consider chronic stages stratifying by diagnostic subgroups to clarify the possible utility of TAS as a peripheral marker of oxidative stress and as a prognostic factor for each specific diagnosis.

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Contributors

The CAFEPS study was led by CA and CA, AG, JC, MG, MP and IB designed the study and wrote the protocol.

MM, AG and JAM designed the present study using data from the CAFEPS study.

MM , MPL and IZM undertook the statistical analysis.

MM, AG and JCL wrote the first version of the manuscript and all authors contributed to and have approved the final version.

Conflict of interest

Dr. Mónica Martínez-Cengotitabengoa reports no conflict of interest.

Dr. Micó reports no conflict of interest.

Dr. Arango. has been a consultant to or has received honoraria or grants from Abbot, AMGEN, AstraZeneca, Bristol-Myers Squibb, Caja Navarra, CIBERSAM, Fundación Alicia Koplowitz, Instituto de Salud Carlos III, Janssen Cilag, Lundbeck, Merck, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad, Mutua Madrileña, Otsuka, Pfizer, Roche, Servier, Shire, Takeda and Schering Plough.

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