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Elevated plasma F2-isoprostane levels in schizophrenia

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ABSTRACT

Background: Schizophrenia is one of the most disabling psychiatric disorders with increased morbidity and mortality. Both schizophrenia and oxidative stress have been associated with accelerated aging. Previous studies found increased oxidative stress in individuals with schizophrenia, though only one study measured F2-isoprostanes and did so in urine. To our knowledge, the present study is the first to assess plasma F2-isoprostane levels, the putative gold standard measure of systemic oxidative stress in vivo, in schizophrenia.
Methods: We compared plasma F2-isoprostane levels in 134 stable outpatients with schizophrenia and 120 age- and gender-matched healthy comparison (HC) subjects. Sociodemographic and clinical data were collected in both groups.
Results: Plasma F2-isoprostane levels were significantly higher in the schizophrenia group than in the HC group. Women had higher F2-isoprostane levels compared to men, and those with higher body mass index (BMI) had higher levels, within each group. F2-isoprostane levels correlated with BMI, physical functioning, and medical comorbidity but not with severity of psychopathology or executive function. Linear models showed significant effects of diagnosis, gender, and BMI on F2-isoprostane levels, but no interactions.
Discussion: Our finding of increased oxidative stress in schizophrenia is consistent with reports of increased morbidity and mortality as well as accelerated aging in schizophrenia. The significant associations between F2-isoprostane levels and both gender and BMI warrant further study.

1. Introduction

Schizophrenia is one of the top ten global causes of disability (WHO, 2001). In addition to its debilitating psychiatric symptoms, schizophrenia is also associated with many physical illnesses, especially metabolic and cardiovascular diseases, as well as higher mortality (Hennekens et al., 2005; Jeste et al., 2011; Meyer and Nasrallah, 2009; Nasrallah et al., 2015; Saha et al., 2007). The increased medical comorbidity and mortality in all age groups suggests that people with schizophrenia age at an accelerated rate (Kirkpatrick et al., 2008). The rapid aging in schizophrenia may be at least partly attributable to the effects of greater stress, higher incidence of smoking, antipsychotic medications, lower physical activity, and worse management of medical illnesses.

An important contributor to accelerated aging is believed to be oxidative stress, the unopposed and widespread free radical-mediated damage at a molecular level (Finkel and Holbrook, 2000; von Zglinicki, 2002). In the general population, oxidative stress is associated with higher body mass index (BMI) (Keaney et al., 2003; Vincent and Taylor, 2006), cigarette smoking (Bachi et al., 1996; Morrow et al., 1995), alcohol use (Meagher et al., 1999), and cardiovascular and metabolic diseases (Basu, 2008; Davies and Roberts, 2011; Stephens et al., 2009). In some studies, oxidative stress differed between men and women, with greater oxidative stress being found in women (Fukui et al., 2011; Khadir et al., 2015; Peskind et al., 2014; Wiener et al., 2014). Three of these studies found significant gender differences that persisted when controlling for BMI or abdominal adiposity (Fukui et al., 2011; Khadir et al., 2015; Peskind et al., 2014). One study reported that both gender and BMI seemed to be equally significant contributors to oxidative stress (Keaney et al., 2003).

F2-isoprostanes are prostaglandin-like compounds formed from free fatty acids, and have roles in vasoconstriction, immune activation, and specific disease mechanisms (Montuschi et al., 2004; Morrow and Roberts, 1997; Patrono and FitzGerald, 1997). Elevated F2-isoprostane levels are linked to lifestyle risk factors including smoking,

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hypercholesterolemia, diabetes mellitus, hyperhomocysteinemia, high fat diet, and higher BMI (Davi et al., 2004; Dietrich et al., 2002; Montuschi et al., 2004). Most, but not all, published studies have shown that F2-isoprostane levels appear to increase with age in normal humans and in mice (Li et al., 2014; Roberts and Reckelhoff, 2001). Some investigators consider F2-isoprostane levels as a gold standard marker of oxidative stress *in vivo*, due to their high sensitivity and specificity, stability, and detectability in a variety of body fluids (Milne et al., 2015; Milne et al., 2007; Morrow and Roberts, 1997, 2002).

Since the mid-1950s, researchers have noted a strong association between oxidative stress and schizophrenia (Hoffer et al., 1954), and abnormalities in oxidative stress markers have been demonstrated in schizophrenia (Akyol et al., 2002; Ng et al., 2008; Wu et al., 2012; Yanik et al., 2003). Greater oxidative stress has also been linked to clinically more severe schizophrenia illness – i.e., with longer duration, earlier age of onset, and more severe symptoms as well as greater side effects of antipsychotic medications (Herken et al., 2001; Mukerjee et al., 1996; Pazvantoglu et al., 2009).

While certain gender differences in schizophrenia (i.e., later age of onset of schizophrenia in women) have been well-established (Aleman et al., 2003; Eranti et al., 2013; Hafner, 2003; Lindamer et al., 1999), gender differences in oxidative stress markers have not been adequately studied in people with schizophrenia. An interaction between gender and oxidative stress in schizophrenia has been shown in only two studies, where women had increased oxidative stress (Abdalla et al., 1986; Akyol et al., 2002), while other studies have not found significant gender differences (Herken et al., 2001; Kaiya et al., 1989; Padurariu et al., 2010; Reddy et al., 1991; Zhang et al., 2009; Zhang et al., 2003).

Different measures of oxidative stress (including superoxide dismutase activity, catalase activity, glutathione, nitric oxide and its metabolites) have been assessed in individual studies in schizophrenia. The limited literature on prostaglandin markers in schizophrenia is conflicting, with both positive (Kaiya et al., 1989; Mathe et al., 1980) and negative findings (Gerner and Merrill, 1983; Kaiya, 1984; Linnoila et al., 1983). To our knowledge, only one study examined F2-isoprostane levels by immunoassay in patients with schizophrenia and healthy comparison subjects (HCs), and found elevated isoprostane levels in urine in the schizophrenia group (Dietrich-Muszalska and Olas, 2009). The studied population was relatively young (ages ranging from 26 to 36 years) and the HCs were non-smokers. We did not find any studies of plasma F2-isoprostanes in people with schizophrenia.

The present investigation focused on evaluating oxidative stress in age- and gender-matched groups of people with versus without schizophrenia, using plasma levels of F2-isoprostanes. Previously we had reported a finding of significantly higher levels of high-sensitivity C-reactive protein (hs-CRP) in a smaller sample of patients with schizophrenia than in HCs from the same cohort (Joseph et al., 2015). In the present report, we hypothesized that the group with schizophrenia would have elevated F2-isoprostane levels compared to the HC group. We also hypothesized that there would be a gender difference in F2-isoprostane levels, with higher levels among women. We examined the relationship of age, gender, and group (schizophrenia vs. HC) and their interactions to better understand observed differences. We also explored the possible role of smoking and BMI, given their known associations with oxidative stress. Finally, within the schizophrenia group, we examined the relationship of F2-isoprostane levels to symptom severity, illness duration, and antipsychotic medication use.

2. Experimental/materials and methods

2.1. Study participants

We studied 134 adult outpatients with schizophrenia ($n = 80$) or schizoaffective disorder ($n = 54$), and 120 HCs with no history of major neuropsychiatric illness, matched by age group (26–35, 36–45, 46–55, and 56–65 years), in whom data on F2-isoprostanes were available. All the subjects were English-speaking and recruited from the greater San Diego community. The diagnoses of schizophrenia and schizoaffective disorder were based on the Structured Clinical Interview for the DSM-IV-TR (SCID) (First et al., 2002). Several papers have demonstrated similarities between schizoaffective disorder and schizophrenia (Amann et al., 2016; Evans et al., 1999). Over 90% of individuals with schizophrenia were treated with antipsychotic medications. HCs completed the Mini-International Neuropsychiatric Interview (MINI) to rule out a history of major neuropsychiatric illnesses (Sheehan et al., 1998). Exclusion criteria were: 1) other current DSM-IV-TR Axis I diagnoses; 2) alcohol or other substance (other than tobacco) abuse or dependence within 3 months prior to enrollment; 3) diagnosis of dementia, intellectual disability disorder, or a major neurological disorder; 4) any medical disability that interfered with a subject's ability to complete the study procedures. The protocol was reviewed and approved by the UC San Diego Human Research Protections Program. All study participants gave written informed consent to participate.

2.2. Sociodemographic and clinical characteristics

Sociodemographic and clinical characteristics for the study sample were ascertained through participant interview and review of available research and medical records, with the appropriate HIPAA authorization from the study participants. Subjects completed several assessments of cognition (Delis-Kaplan Executive Function System), mental health (Patient Health Questionnaire-9, Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms, Short Form Health Survey - Mental), and physical health (Cumulative Illness Rating, Short Form Health Survey - Physical) (Andreasen and Olsen, 1982; Delis et al., 2001; Kroenke et al., 2001; van den Berg et al., 2012; Ware and Sherbourne, 1992). Medical comorbidity was measured with the total score from the Cumulative Illness Rating Scale (CIRS), which combines the presence and severity of common medical comorbidities (Linn et al., 1968). BMI was based on assessment of participant height and weight (kg/m^2). Assessments were performed by study staff members who underwent rigorous training and inter-rater reliability certification. Staff was trained in the administration of standardized assessments – shadowing senior raters and then being observed while performing assessments.

2.3. Plasma F2-isoprostane assays

The lab assays were conducted at the Eicosanoid Laboratory at Vanderbilt University, using gas chromatography/negative ion chemical ionization mass spectrometry (GC/NICI-MS) methodology as described by Milne et al. (2007) and Morrow and Roberts (2002). Advantages of this method include high sensitivity and specificity, more accurate than the urine immunoassay which does not detect the glucoronidated F2-isoprostanes in the urine, up to 50% of the total F2-isoprostanes (Callewaert and Sloan, 2010). Normal plasma levels for this assay in healthy adults are 0.035 ± 0.006 ng/mL.

2.4. Statistical analyses

All study variables were scrutinized for violation of distribution assumptions required for parametric analyses, and appropriate transformations were made. A number of variables including F2-isoprostane levels were log-transformed for all analyses.

Independent *t*-tests or chi-square tests were performed to determine differences in sociodemographic, clinical, and physical health measures between schizophrenia and HC groups. F2-isoprostane levels were compared by diagnostic group and gender. Unequal variances were assumed in the calculation of the *t*-statistics. Pearson bivariate correlations between F2-isoprostane levels and BMI and smoking variables were examined separately in the two groups. Pearson correlations between F2-isoprostane levels (log-transformed) and several clinical

variables (i.e., duration of illness, severity of positive, negative, and depression symptoms, and daily antipsychotic dose) were also examined within the schizophrenia group.

To explore the associations of F2-isoprostane levels with age, gender, and group (schizophrenia vs. HC) along with any potential interactions, we conducted multiple linear regression analysis. These demographic variables were chosen because they are unmodifiable characteristics that might affect the interpretation of group differences observed in the univariate analyses. Also, our large samples that were matched on both age and gender and stratified well across these variables provided an opportunity to examine the role of these key variables.

After examining univariate correlations in the schizophrenia and healthy groups, we discovered that BMI was related to F2-isoprostanes levels, which raised the possibility that group differences in F2-isoprostanes levels might be driven by group differences in BMI. Thus, we further explored the effects of adding BMI and all relevant interactions to the model including group, age and gender, with a focus on changes in effect size for group relative to the univariate test.

Effect sizes are presented for all tests along with p-values. We interpreted results as meaningful when the effect sizes are medium or larger (i.e., Cohen's d ≥ 0.45).

3. Results

3.1. Schizophrenia and healthy comparison (HC) sample characteristics

There were no significant differences between the participants with schizophrenia compared with those with schizoaffective disorder on mean age, duration or severity of mental illness, lifestyle factors (smoking, substance use), physical health (BMI, medical comorbidity) or cognition. We also looked at F2-isoprostane levels between the two groups and found no significant difference between the two groups ($t(132) = -0.66$, $p = 0.51$). Therefore, subsequent analyses combined these two groups. The sociodemographic and clinical characteristics of the schizophrenia and HC groups are summarized in Table 1. As expected, the two groups did not differ in age or gender distribution. Consistent with the psychopathology of schizophrenia, the schizophrenia group had a history of greater substance use and alcohol abuse, and worse psychotic symptoms as well as mental and physical wellness scores. As has been described in other studies (Goff et al., 1992; Hughes et al., 1986), the schizophrenia group had a more extensive smoking history and smoked more cigarettes currently. The schizophrenia group also had a significantly higher mean BMI; although the mean BMI values in both groups were in the overweight-obese range.

3.2. F2-isoprostane levels

Plasma F2-isoprostane levels were significantly higher in the schizophrenia group compared to the HCs, with a medium effect size (Cohen's $d = -0.43$).

3.3. Correlates of F2-isoprostane levels

Univariate Pearson correlation analysis showed that age and cigarette use were not significantly correlated with F2-Isoprostane levels in either group (Table 2). F2-isoprostane levels were significantly related to gender, being higher in women than in men, in both diagnostic groups. F2-isoprostane levels were significantly positively correlated with BMI in both groups. F2-isoprostane levels also correlated with physical functioning (SF-36 Physical Composite Score), and medical comorbidity (CIRS total score) but not with severity of psychopathology or executive function in schizophrenia.

F2-isoprostane levels were significantly correlated with hs-CRP levels in the schizophrenia and HC groups. Within the schizophrenia group, F2-isoprostane levels were not significantly related to duration

Table 1
Comparison of study participants with and without schizophrenia.

	Healthy comparison (HC)			Schizophrenia			*t*	df	p	Cohen's d
	N	Mean	Std dev	N	Mean	Std dev				
Sociodemographic factors										
Age (years)	120	48.6	11.6	134	48.1	10.1	0.34	237.4	0.731	0.044
Gender (% women)	54%			45%			2.23[a]	1	0.167	1.49[b]
Education (years)	120	14.5	2.2	134	12.4	2.0	8.00	243.4	<0.001	
Current packs of cigarettes per day	120	0.02	0.08	134	0.38	0.48	−8.5	142.4	<0.001	−1.04
Number of years smoked	120	5.4	10.6	133	16.3	14.7	−6.83	239.2	<0.001	−0.84
Substance abuse (yes)	19	15%		55	41%		19.85[a]	1	<0.001	4.45[b]
Clinical factors										
Duration of illness (years)				133	25.1	11.2				
Antipsychotic dose[c]				134	1.8	1.5				
PHQ-9 score	116	2.0	2.9	130	7.6	6.6	−8.72	182.0	<0.001	−1.29
Positive symptoms[d]	119	0.3	0.7	134	6.5	4.3	−16.63	141.4	<0.001	−2.80
Negative symptoms[e]	118	1.4	2.3	134	7.4	4.4	−13.93	203.6	<0.001	−1.95
SF-36 mental composite score	117	54.6	5.8	132	43.4	11.3	9.97	201.7	<0.001	1.40
Executive function	120	0.4	0.6	134	−0.5	0.7	11.63	249.9	<0.001	1.47
Physical factors										
SF-36 Physical Composite Score	117	51.5	8.8	132	43.2	10.1	6.99	247.0	<0.001	0.89
CIRS total score	101	3.2	3.2	116	6.8	4.9	−6.45	200.3	<0.001	−0.91
BMI (kg/m^2)	117	27.7	7.0	132	32.2	7.4	−4.90	245.7	<0.001	−0.63
hs-CRP (mg/L)	116	2.18	3.5	131	5.08	8.8	−3.47	174.7	0.001	−0.53
Plasma F2-isoprostanes (ng/mL)	120	0.032	0.015	134	0.040	0.021	−3.31	243.4	0.001	−0.43

PHQ-9 = patient health questionnaire.
SF = Short Form Health Survey.
CIRS = Cumulative Illness Rating.
BMI = body mass index.
hs-CRP = high sensitivity C-reactive protein.
[a] χ^2 value.
[b] *r* value.
[c] Antipsychotic medication daily dosages were converted to WHO average daily doses based on published standards (WHO, 2009, 2010).
[d] Scale for the Assessment of Positive Symptoms (SAPS) total score.
[e] Scale for the Assessment of Negative Symptoms (SANS) total score.

Table 2
Pearson correlations between key demographic and clinical variables and F2-isoprostane levels in study participants with and without schizophrenia.

	F2-Isoprostanes in healthy comparison group			F2-Isoprostanes in schizophrenia group		
	N	*r*	d	N	*r*	d
Sociodemographic factors						
Age (years)	120	0.07	0.14	134	0.06	0.12
Gender	120	−0.29**	−0.61	134	−0.36***	−0.77
Education (years)	120	−0.06	−0.12	134	−0.03	
Current packs of cigarettes per day	120	0.06	0.12	134	−0.12	−0.24
Number of years smoked	120	0.09	0.18	133	−0.00	0.01
Substance abuse (yes)	120	0.08	0.16	133	−0.10	
Clinical factors						
Duration of illness (years)	–	–	–	133	0.16	0.33
Antipsychotic dose	–	–	–	134	−0.07	−0.14
PHQ-9 score	116	0.02	0.04	130	0.14	0.28
Positive symptoms[a]	–	–	–	134	0.06	0.12
Negative symptoms[b]	–	–	–	134	0.05	0.10
SF-36 mental composite score	117	−0.06	−0.12	132	−0.13	−0.26
Executive function	120	0.06	0.12	134	−0.16	−0.33
Physical factors						
SF-36 Physical Composite Score	117	−0.18	−0.37	132	−0.24**	−0.49
CIRS total score	101	0.17	0.34	116	0.24**	0.49
BMI (kg/m^2)	117	0.23*	0.47	132	0.24**	0.49
hs-CRP (mg/L)	116	0.19*	0.39	131	0.27**	0.56

PHQ-9 = patient health questionnaire.
SF = Short Form Health Survey.
CIRS = Cumulative Illness Rating.
BMI = body mass index.
hs-CRP = high sensitivity C-reactive protein.
***, **, and *: significant 2-tailed correlation coefficients at the 0.001, 0.01 and 0.05 levels, respectively.
[a] Scale for the Assessment of Positive Symptoms (SAPS) total score.
[b] Scale for the Assessment of Negative Symptoms (SANS) total score.

of illness, severity of positive symptoms, negative symptoms, depressive symptoms, or current daily antipsychotic dose.

3.4. Age, gender, and group relationships with F2-isoprostane levels

A general linear model that included age, gender, and group, and all interactions was significant with good model fit ($F = 6.5$, $p < 0.001$, $R^2 = 0.16$), and revealed a main effect of group ($F(1, 246) = 17.4$, $p < 0.001$, Cohen's $d = 0.53$) with levels being higher in the schizophrenia group, and a main effect of gender ($F(1,246) = 29.7$, $p < 0.001$, Cohen's $d = 0.70$) with levels being higher in women (see Fig. 1). There was no main effect of age, and no meaningful two-way or three-way interactions (all p's > 0.32, all Cohen's d's < 0.13).

3.5. Age, gender, group, and BMI relationships with F2-isoprostane levels

When we added BMI to the previous model containing age, gender, and group, along with all possible 2-, 3-, and 4-way interactions, the model was again significant and fit well ($F = 4.4$, $p \leq 0.001$, $R^2 = 0.22$). The main effect of group (schizophrenia > HC) remained

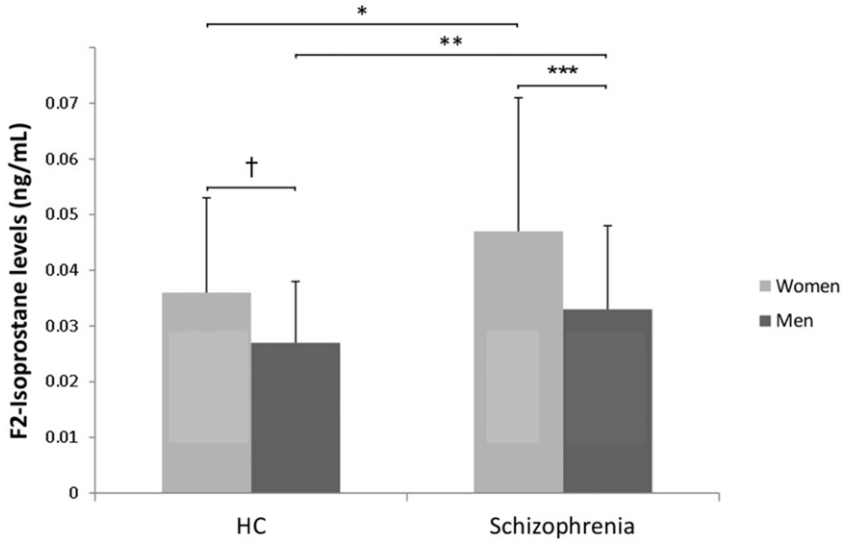

Fig. 1. F2-Isoprostane levels by diagnostic group and gender. Bar graph depicting the mean levels of F2-isoprostanes (in ng/mL) in women (gray) and men (black) in the healthy comparison (HC) and schizophrenia group. Error bars depict the standard deviation around the mean. * $t = -3.01$, df = 104.3, $p = 0.003$, ** $t = -2.36$, df = 126.0, $p = 0.02$, *** $t = 4.06$, df = 91.9, $p < 0.001$, † $t = 3.35$, df = 112.5, $p = 0.001$.

significant ($F(1,233) = 9.1$, $p = 0.003$, Cohen's $d = 0.40$), although the magnitude of the effect size was slightly smaller than in the model without BMI ($d = 0.40$ versus $d = 0.53$). Gender was still highly related to F2-isoprostane levels in the model containing BMI ($F(1,233) = 28.3$, $p < 0.001$, Cohen's $d = 0.70$), with women having higher levels than men. As suggested by the correlation analyses, BMI was significantly associated with F2-isoprostane levels in this model ($F(1,233) = 6.8$, $p = 0.01$, Cohen's $d = 0.34$), but with a somewhat lower effect size than in the univariate correlation analysis ($d = 0.34$ versus $d = 0.47$). Age was not strongly related to F2-isoprostane level ($F(1,233) = 1.2$, $p = 0.27$, Cohen's $d = 0.14$), nor were there any meaningful two-, three-, or four-way interactions (all p's > 0.07, all Cohen's d's < 0.23). Thus, we did not find evidence that BMI was differentially related to F2-isoprostane levels in individuals with schizophrenia compared to HCs, or in men relative to women.

4. Discussion

Consistent with our hypothesis, people with schizophrenia had higher levels of plasma F2-isoprostanes, indicating higher oxidative stress compared to HCs. Our exploratory analysis showed that F2-isoprostane levels were higher in women than in men and associated with higher BMI in both groups. Smoking was not significantly associated with F2-isoprostane levels in either group. The medium-sized effect of group persisted in models that accounted for age, gender, and BMI. F2-isoprostane levels did not correlate significantly with illness duration, symptom severity, or antipsychotic dose in the schizophrenia group.

This report of elevated F2-isoprostane levels in the schizophrenia group is consistent with several previous studies of oxidative stress. However, the literature is inconsistent and heterogeneous, with varied study populations and different markers of oxidative stress. Our use of F2-isoprostanes assayed by GC/NICI-MS is believed to provide an accurate measure of *in vivo* oxidative stress, and our results are consistent with the one other study of F2-isoprostanes in schizophrenia using a different assay and different body fluid – i.e., urine (Dietrich-Muszalska and Olas, 2009). Our larger age range allowed us to test for age associations (none were found), although the upper age limit was 65 years. Thus, this study broadens the generalizability of F2-isoprostane abnormalities to include young and middle-aged adults with schizophrenia.

We found, consistent with some previous studies (Fukui et al., 2011; Khadir et al., 2015; Peskind et al., 2014; Wiener et al., 2014), that women had higher levels of F2-isoprostanes. Antioxidant effects of estrogen have been demonstrated in cardiovascular and metabolic diseases, which might possibly account for the gender variance (Arias-Loza et al., 2013; Vassalle et al., 2012). The gender differences may also be related to differences in adiposity and inflammation (Joseph et al., 2015; Rossi et al., 2012).

We also found that individuals with higher BMI had more oxidative stress. This has been observed by other investigators in cross-sectional studies (Keaney et al., 2003; Sankhla et al., 2012; Vincent and Taylor, 2006), but the direction of causality is not clear. Obesity may place physiological stress on the body which engenders oxidative stress, or higher oxidative stress levels may promote weight gain. Interestingly, we did not see any evidence that relationships of F2-isoprostanes to gender and BMI were different in the two groups. Gender and BMI did not appear to interact, either, suggesting independent mechanisms of association with oxidative stress.

Although the schizophrenia group had a higher mean BMI than the HC group, this does not appear to entirely account for the findings of elevated F2-isoprostane levels in schizophrenia. The magnitude of the group difference was only slightly reduced (from Cohen's $d = 0.5$ to $d = 0.4$) in the model also containing age, gender, BMI, and all possible interactions. Thus, oxidative stress level alterations in schizophrenia, while related to BMI, are not completely explained by this factor. Anti-oxidant treatments such as vitamin C, vitamin E, and dehydroepiandrosterone have been tried without much improvement in symptoms of schizophrenia, though longer trials with broader outcomes including measures of relapse and functioning are needed (Magalhaes et al., 2016).

Cigarette use (either current or duration) was not significantly correlated with F2-isoprostane levels in either group. Cigarette use and oxidative stress have been associated in the general population (Bachi et al., 1996; Morrow et al., 1995). There were relatively low rates of smoking among our HCs, which may be reflective of the geographic location of the study sample (California boasts one of the lowest smoking rates in the US). However, our finding of a lack of association between smoking and increased F2-isoprostane levels in schizophrenia patients is similar to that of several other studies which reported no significant association in persons with schizophrenia (Yao et al., 2006; Yao et al., 2004; Yao et al., 2000). Some studies have found elevated oxidative stress in the schizophrenia group despite being matched for smoking with the HC group (Al-Asmari and Khan, 2014; Jorgensen et al., 2013; Padurariu et al., 2010; Sarandol et al., 2007; Yanik et al., 2003; Zhang et al., 2003).

Unlike previous studies using other markers of oxidative stress such as total antioxidant potentials, malondialdehyde, or superoxide dismutase (Mukerjee et al., 1996; Padurariu et al., 2010; Pazvantoglu et al., 2009; Wu et al., 2012), we did not find correlations of F2-isoprostane levels within the schizophrenia group with clinical variables such as illness duration, symptom severity, and antipsychotic dose. Longitudinal studies would be helpful to determine if fluctuations in severity of psychopathology or antipsychotic dose affect F2-isoprostane levels.

F2-isoprostane levels were significantly correlated with hs-CRP levels in both groups. This finding suggests that inflammation and oxidative stress are closely associated.

Several limitations of this study may affect the interpretation of these results. The cross-sectional study data cannot prove causality between oxidative stress and variables such as cigarette smoking and BMI. These findings are based on a sample of relatively stable outpatients with schizophrenia having mild to moderate level of psychopathology, and may not apply to inpatients or more acutely ill people with schizophrenia, treatment-resistant, or treatment-naïve patients. Another limitation was the possibility of Type I error due to multiple comparisons and correlations.

Future work should examine how oxidative stress levels in plasma relate to those in the CSF or brain. Examining hormone levels may clarify the source of gender differences seen in F2-isoprostane levels. Longitudinal studies are warranted, as trajectories of change with age in oxidative stress may differ in those with and without schizophrenia, despite lack of cross-sectional interactions with age. Further investigation into the dysregulated oxidative stress system may provide novel targets for intervention. The association between obesity and cigarette use to oxidative stress underlines the clinical importance of lifestyle factors to the physical health of people with schizophrenia (McEvoy et al., 2005). Clinicians should focus on reducing BMI, modifying a sedentary lifestyle and utilizing a smoking cessation program to improve the health of patients with schizophrenia.

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Contributors

Ellen E. Lee conducted literature reviews, data interpretation, and manuscript preparation.

Lisa T. Eyler conducted data analyses, data interpretation, and manuscript preparation.

Owen Wolkowitz was involved with study design and manuscript preparation.

Averria Sirkin Martin was involved in data collection and manuscript preparation.

Chase Reuter was involved in data analyses and data interpretation.

Helena Kraemer was involved in data analyses and data interpretation.

Dilip V. Jeste designed the study and was involved in manuscript preparation.

Conflicts of interest

The authors declare no relevant conflicts of interest.

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