Nordic Journal of Psychiatry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipsc20

Associations between oxidative stress and perceived stress in patients with bipolar disorder and healthy control individuals

Ulla Knorr, Rasmus Ahrens Blom, Anja Hviid Simonsen, Henrik Enghusen Poulsen, Morten Akhøj, Julie Forman, Steen Gregers Hasselbalch & Lars Vedel Kessing

To cite this article: Ulla Knorr, Rasmus Ahrens Blom, Anja Hviid Simonsen, Henrik Enghusen Poulsen, Morten Akhøj, Julie Forman, Steen Gregers Hasselbalch & Lars Vedel Kessing (2021): Associations between oxidative stress and perceived stress in patients with bipolar disorder and healthy control individuals, Nordic Journal of Psychiatry, DOI: 10.1080/08039488.2021.1901987

To link to this article: https://doi.org/10.1080/08039488.2021.1901987

Published online: 29 Mar 2021.

Submit your article to this journal

Article views: 29

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ipsc20

NORDIC JOURNAL OF PSYCHIATRY
https://doi.org/10.1080/08039488.2021.1901987

Taylor & Francis
Taylor & Francis Group

ARTICLE

Check for updates

Associations between oxidative stress and perceived stress in patients with bipolar disorder and healthy control individuals

Ulla Knorr[a], Rasmus Ahrens Blom[a], Anja Hviid Simonsen[b], Henrik Enghusen Poulsen[c,d], Morten Akhøj[e], Julie Forman[e], Steen Gregers Hasselbalch[b] and Lars Vedel Kessing[a]

[a]Faculty of Health and Medical Sciences, Copenhagen Affective Disorder Research Center (CADIC), Psychiatric Center Copenhagen, University of Copenhagen, Copenhagen, Denmark; [b]Faculty of Health and Medical Sciences, Danish Dementia Research Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [c]Faculty of Health and Medical Sciences, Laboratory of Clinical Pharmacology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [d]Department of Clinical Pharmacology, Faculty of Health and Medical Sciences, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark; [e]Department of Public Health, Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Objective: Patients with neurodegenerative disorders, schizophrenia, and bipolar disorder present with increased oxidative stress markers. Not only is oxidative stress associated with development of disease, but also with increased disease progression and mortality. Oxidative stress reflects an increase in pro-oxidants, which subsequently leads to oxidative modifications of cellular components, such as RNA and DNA. Urinary excretion of 8-oxo-7,8-dihydroguanosine (8-oxoGuo) and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) is the valid marker of whole-body RNA and DNA damage, respectively. Recently, cerebrospinal fluid (CSF) oxidative stress markers of RNA damage (8-oxoGuo) have showed both state and trait dependence in patients with bipolar disorder. However, the relation to subjective measures of stress and quality of life (QoL) is unknown.

Materials and methods: This prospective, longitudinal 1-year follow-up case-control study investigated the association between the oxidative stress markers, 8-oxoGuo and 8-oxodG and, perceived stress and QoL in patients with bipolar disorder ($n = 86$, 51% female) and gender-and-age-matched healthy control (HC) individuals ($n = 44$, 44% female). Oxidative stress markers obtained in CSF and urine were analysed using ultra-performance liquid chromatography–tandem mass spectrometry. The subjective perception of stress was assessed using the Perceived Stress Scale. Subjective evaluation of QoL was assessed using the World Health Organization Quality of Life questionnaire.

Results and conclusion: We found that markers of oxidative stress in CSF and urine were not associated with perceived stress and QoL quality in patients with bipolar disorder. However, a putative association between urinary 8-oxoGuo oxidative stress marker for RNA damage and perceived stress in HC encourages further investigations.

ARTICLE HISTORY
Received 26 October 2020
Revised 22 February 2021
Accepted 4 March 2021

KEYWORDS
Bipolar disorder; oxidative stress; perceived stress; cerebrospinal fluid; case-control

Introduction

Bipolar disorder (BD) is a mental illness with lowered life expectancy of 8–12 years compared to the general population [1,2], higher suicidal risk [3], lifelong risk of recurrence of manic and depressive episodes, impaired psychosocial functioning [4], higher perceived stress [5], and lower quality of life (QoL) [6,7]. BD is often a progressive disorder with increasing risk of recurrence with every new episode and with the occurrence of stressful life events [8,9]. Functional recovery following a mood episode consistently lags symptomatic and syndromic recovery [10].

Increasing evidence suggests an association between multiple markers of oxidative stress and psychiatric disorders, such as BD, major depressive disorder, schizophrenia, and also metabolic and neurodegenerative disorders [11–14]. Not only is oxidative stress associated with development of disease, but also with increased disease progression and mortality [11–13]. Oxidative stress reflects an oxidant/antioxidant imbalance causing cell signalling disruption and molecular damage [11]. The oxidative stress markers 8-oxo-7,8-dihydroguanosine (8-oxoGuo) and 8-oxo-7,8-dihydro-2idative stress m (8-oxodG), markers of RNA and DNA oxidation, respectively, can be quantified in cerebrospinal fluid (CSF) and urine using ultra-performance liquid chromatography–-tandem mass spectrometry [15].

Psychosocial stress and low QoL have been associated with higher DNA oxidation and higher mortality, respectively, in population studies [16,17]. We have previously found that oxidative stress markers and perceived stress scores were higher in patients with BD compared to healthy control (HC) individuals [4,13]. However, the effect of subjective perception of both high stress load and lowered QoL on damage to RNA and DNA by oxidation in patients with BD and HC remains undetermined. Therefore, our group investigated, as

CONTACT Ulla Knorr ulla.knorr@regionh.dk Copenhagen Affective Disorder Research Center, Psychiatric Center Copenhagen, Section 6233, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark; Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

© 2021 The Nordic Psychiatric Association

the first, possible associations between repeated measures of CSF and urinary markers of oxidative stress AND perceived stress and QoL in BD and HC during a one-year prospective, longitudinal follow-up study. We tested the hypotheses that levels of CSF and urinary markers of oxidative stress 8-oxoGuo and 8-oxodG are associated with scores on the Perceived Stress Scale (PSS) and WHO Quality of life scale (WHOQoL), respectively, in all participants and separately in patients with BD and HC.

Methods

This longitudinal case-control study investigated if biomarkers of oxidative stress could be associated with scores of PSS and QoL.

The study was conducted at the Copenhagen Affective Disorder Research Center between April 2014 and April 2017. Patients with BD were recruited from Copenhagen Affective Disorder Clinic, that receives patients from the capital region of Denmark covering 1.6 million people. We included patients with BD in euthymia, aged 18–60. Exclusion criteria were significant physical illness, pregnancy or planned pregnancy within a year, substance abuse, expected non-compliance with the protocol, no informed consent, and practical reasons as scheduling hazards.

Furthermore, we included age-and-gender-matched HC with no personal or familial history of psychiatric disorders, among blood donors affiliated at the Blood Bank at Frederiksberg Hospital, Copenhagen. The exclusion criteria for HC were the same as for the patients with BD.

Information of the study was given to patients with BD and HC and followed up by phone or email. After giving informed consent, the participants were examined at baseline. Patients with BD and HC were evaluated using the semi-structured Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview [18]. The severity of affective symptoms of depression and mania was assessed by using the 17-item Hamilton Depression Rating Scale (HAMD) [19] and the Young Mania Rating Scale (YMRS) [20], respectively. Clinical characteristics were assessed including weight, height, current medication, alcohol consumption, smoking habits, duration of illness from first hypomanic episode, and history of psychoses. Severity of illness was assessed using the Global Clinical Impression Scale, details described elsewhere [13]. Finally, all patients with BD in euthymia and HC were assessed after one year at follow-up.

During follow-up, all patients self-monitored mood, sleep, alcohol, and medicine intake and were weekly in contact with psychiatrist (Ulla Knorr) via phone, SMS or email.

The study was reported according to the STROBE Statement [21].

Biological stress markers

All CSF, blood and urine samples from patients with BD and HC individuals were collected at the Danish Dementia Research Centre, Rigshospitalet, at baseline and follow-up, between 08:00 and 10:00 in the morning after an overnight fasting. CSF was collected by lumbar puncture by specialists of neurology, details have been described elsewhere [13]. Blood samples were collected and analysed regarding standard screening biochemical parameters at the Clinical Biochemical Laboratory at Rigshospitalet, Denmark. Freshly voided urine samples were collected, and the samples stored at −80 °C pending analyses.

CSF and urinary were analysed at Laboratory of Clinical Pharmacology Rigshospitalet using ultra-performance liquid chromatography–tandem mass spectrometry, a method of high specificity, regarding oxidative stress markers 8-oxoGuo and 8-oxodG [15]. The analysed oxidative markers were normalised against urinary creatinine concentration.

Subjective stress markers

Subjective stress was assessed by using Cohen's PSS [22], a 10-item self-report questionnaire. PSS is widely used, designed to measure the perception of stress, by querying to which degree how stressful and unpredictable, uncontrollable, and overloaded the respondents find their lives within the last month. Each item is scored from 0 to 4, with a total PSS range of 0–40. A higher score indicates higher levels of perceived stress.

QoL was assessed using the World Health Organization's Quality of Life Instrument – Short Version (WHOQoL-BREF) scale [23], a 26-item self-report questionnaire. QoL consists of two items concerning overall QoL and general health and 24 items concerning four domains: physical health (raw score range: 7–35), psychological health (raw score range: 6–30), social relationships (raw score range: 3–15) and environment (raw score range: 8–40). All items score from 1 to 5, and when calculated, for reverse negatively phrased items, total WHOQoL scores range from 26 to 130. A higher score indicates higher QoL.

PSS and WHOQoL-BREF were assessed at baseline and at 12-month follow-up of the study.

Statistical analyses

All data were analysed according to a preestablished statistical analysis plan. Statistical analyses were conducted with SAS software version 9.4 (Copyright 2013, SAS Institute Inc., Cary, NC). All biological biomarkers were transformed by the natural logarithm prior to the analyses.

Demographic and clinical data at baseline and follow-up were compared between BD and HC using either Fisher's exact test, Welch' *t*-test or the Mann–Whitney *U* test, whichever was most appropriate (Table 1).

The association between each of the oxidative stress biomarkers (CSF 8-oxoGuo, CSF 8-oxodG, urine 8-oxoGuo, urine 8-oxodG) AND the outcomes PSS and WHOQoL were evaluated in a linear mixed model with the biomarker as fixed effect and with an unstructured covariance pattern to account for repeated measurements on each subject. The analyses were performed for the entire study period including data at baseline and at 12 months follow-up, and for the

Table 1. Clinical characteristics of patients with bipolar disorder and healthy control individuals.

	BD baseline	HC baseline	*p* Value	BD follow-up	HC follow-up	*p* Value
N (% female)	86 (51)	44 (54)	.581[a]	73 (52)	41 (53)	.846[a]
Age, media (Q1;Q3)	33 (25;42)	31 (24;41)	.526[b]	35 (26;42)	30 (24;40)	.352[b]
Bipolar type I, *N* (%)	49 (57)			43 (58)		
Bipolar type II, *N* (%)	37 (43)			31 (42)		
Clinical global impression, mean (SD)	4.6 (0.6)			4.8 (0.6)		
Duration of illness, *N* years, mean (SD)	12.4 (9.8)					
Prior psychosis, *N* (%)	36 (41)			31 (42)		
First and second-degree family members with affective disorder, *N* (mean)	2.25 (1.9)	0				
Young Mania Rating Scale, median (Q1;Q3)	1 (0;2)	0 (0;0)	<.001	0 (0;1)	0 (0;0)	<.001
Hamilton Depression Rating Scale 17 items	3 (1;5)	0 (0;0)	<.001	2 (0;4)	0 (0;0)	<.001
Daily alcohol consumption, median (Q1;Q3)	0.2 (0;1)	0.5 (0;1)	.375[b]	0.3 (0.1;1)	1 (0.3;1.2)	.015[c]
Smokers, *N* (%) daily cigarettes, median (min; max)	28 (34)	8 (18)	.096[a]	25 (34)	8 (20)	.132[a]
	14.5 (0.2;20)	3.5 (0.5;30)	.026[b]	12 (0.5;35)	2.5 (0.1;20)	.032[b]
BMI, mean (SD)	25.3 (4.9)	24.9 (3.4)	.659	25.6 (5.2)	25.6 (3.7)	.973
Lithium, *N* (%)	44 (51)			40 (54)		
Antipsychotics, *N* (%)	33 (38)			25 (34)		
Anticonvulsants, *N* (%)	43 (50)			37 (50)		
Antidepressants, *N* (%)	2 (2)			4 (5)		
Benzodiazepines, *N* (%)	6 (7)			9 (12)		
CSF 8-oxoGuo (pmol/L), median (Q1;Q3)	54.8 (47.3;68)	48.1 (39.3;56.4)	<.001	61.5 (54.6;72.4)	51.8 (41.2;58.8)	<.001
Urine 8-oxoGuo (nmol/mmol creatinine), median (Q1;Q3)	1.8 (1.5;2.1)	1.5 (1.3;1.8)	<.001	1.6 (1.4;2)	1.2 (1.1;1.5)	<.001
CSF 8-oxodG (pmol/L), median (Q1;Q3)	6.5 (4.6;8.9)	5.4 (3.1;7)	.016	6.9 (5.8;8.2)	5.9 (4.5;7.3)	.196
Urine 8-oxodG (nmol/mmol creatinine), median (Q1;Q3)	1.4 (1.1;1.7)	1.3 (1;1.4)	.069	1.3 (1.1;1.6)	1.1 (0.9;1.3)	<.001
PSS, mean (SD)	13.33	7.3 (0.9)	<.001	10.85	5.9 (0.9)	<.001
WHOQoL, mean (SD)	88.71	99.9 (1.6)	<.001	92.70	100.8 (1.5)	<.001

BD: patients with bipolar disorder; HC: healthy control individuals.
Summary statistics are *N* (%) for categorical data, mean (SD) for normally distributed continuous data and median (lower quartile; upper quartile) for non-normally distributed continuous data.
[a]Fisher's exact test.
[b]Data log-transformed, *p* values are *t*-tests of medians are the same.
[c]'Wilcoxon rank' test. Note that three patients were not treated with any psychotropic medication at inclusion.

Table 2a. Association between levels of CSF and urine oxidative stress markers 8-oxoGuo and 8-oxodG AND PSS and WHOQoL with all participants pooled as one group.

Outcome	Predictor	Coefficient	*p* Val. (adj.)	Lower	Upper
Perceived stress	Urine-8-oxoGuo	0.68	.36 (0.69)[a]	−0.79	2.15
Perceived stress	Urine-8-oxodG	0.22	.81 (0.87)[a]	−1.55	1.99
Perceived stress	CSF-8-oxoGuo	0.01	.69 (1)[b]	−0.06	0.09
Perceived stress	CSF-8-oxodG	−0.18	.29 (0.69)[a]	−0.52	0.16
WHOQoL	Urine-8-oxoGuo	−0.61	.58 (0.83)[a]	−2.80	1.57
WHOQoL	Urine-8-oxodG	0.58	.67 (0.84)[a]	−2.09	3.24
WHOQoL	CSF-8-oxoGuo	−0.09	.12 (0.61)[a]	−0.20	0.02
WHOQoL	CSF-8-oxodG	0.24	.38 (0.69)[a]	−0.30	0.79

[a]Adjusted using the Benjamin and Hochbergs correction.
[b]Adjusted using the Bonferroni correction for multiple familywise analyses.

BD and HC groups jointly (Table 2a, eight analyses) and separately (Table 2b, 16 analyses).

p Values concerning the association between PSS and CSF 8-oxoGuo (the primary end point) were adjusted for multiple testing by the Bonferroni correction. *p* Values concerning the remaining exploratory end points were adjusted for multiple testing using the method of Benjamin and Hochberg which controls the false discovery rate. An adjusted *p* value <.05 was considered statistically significant.

Patients with BD and HC individuals were well matched except regarding smoking and alcohol consumption. As previously reported, we found no effect of smoking, alcohol consumption, BMI and duration of illness on neither CSF 8-oxoGUO, CSF 8-oxodG, urine 8-oxoGUO nor urine 8-oxodG [13]. Thus, these parameters were not included in the analyses.

Due to the explorative nature of the study, a priori power analysis was not conducted to determine if the study was adequately powered in terms of sample size to find an effect. Regarding sample size and power, the numbers of participants in this present study, including 86 patients with BD and 44 HC individuals are like the largest prior case-control studies, regarding peripheral oxidative stress markers in BD [14,24,25].

Results

A total of 86 patients with BD and 44 age-and-gender-matched HC individuals were included in the study, details has been described elsewhere [13]. Demographics, clinical characteristics, and psychotropic medication of the participants of the study are presented in Table 1.

A total of 24 participants (BD = 15, HC = 9) received medical treatment for a stabilised physical disorder or as hormone anticonception: hypertension (BD = 1), diabetes mellitus type II (BD = 1), hypothyroidism (BD = 3, HC = 1), and hormonal contraceptives (BD = 10, HC = 9). A total of 36 patients with BD developed an affective episode during follow-up [13].

In relation to drinking and smoking, the HC individuals had higher alcohol consumption; however, the patients with BD had a higher use of cigarettes.

The completion rates from baseline to follow-up regarding assessment of CSF and urine for patients with BD and HC

Table 2b. Association between levels of CSF and urine oxidative stress markers 8-oxoGuo and 8-oxodG AND PSS and WHOQoL in patients with BD and HC.

Outcome	Predictor	Group	Coefficient	*p* Val. (adj.)	Lower	Upper
Perceived stress	Urine-8-oxoGuo	HC	2.96	.04 (0.61)[a]	0.14	5.79
Perceived stress	Urine-8-oxoGuo	BD	−0.94	.31 (0.69)[a]	−2.74	0.87
Perceived stress	Urine-8-oxodG	HC	3.00	.08 (0.61)[a]	−0.42	6.42
Perceived stress	Urine-8-oxodG	BD	−1.47	.17 (0.64)[a]	−3.56	0.63
Perceived stress	CSF-8-oxoGuo	HC	−0.03	.68 (1)[b]	−0.15	0.10
Perceived stress	CSF-8-oxoGuo	BD	−0.03	.51 (1)[b]	−0.13	0.06
Perceived stress	CSF-8-oxodG	HC	−0.43	.13 (0.61)[a]	−0.99	0.14
Perceived stress	CSF-8-oxodG	BD	−0.26	.23 (0.69)[a]	−0.69	0.17
WHOQoL	Urine-8-oxoGuo	HC	−3.29	.14 (0.61)[a]	−7.65	1.08
WHOQoL	Urine-8-oxoGuo	BD	1.17	.38 (0.69)[a]	−1.46	3.81
WHOQoL	Urine-8-oxodG	HC	−2.30	.4 (0.69)[a]	−7.66	3.06
WHOQoL	Urine-8-oxodG	BD	2.59	.1 (0.61)[a]	−0.54	5.73
WHOQoL	CSF-8-oxoGuo	HC	−0.11	.23 (0.69)[a]	−0.29	0.07
WHOQoL	CSF-8-oxoGuo	BD	0.00	1 (1)[a]	−0.14	0.14
WHOQoL	CSF-8-oxodG	HC	0.24	.59 (0.83)[a]	−0.64	1.12
WHOQoL	CSF-8-oxodG	BD	0.50	.14 (0.61)[a]	−0.17	1.17

BD: bipolar disorder; 8-oxoGuo: 8-oxo-7,8-dihydroguanosine; 8-oxodG: 8-oxo-7,8-dihydro-2-deoxyguanosine; CSF: cerebrospinal fluid; PS: perceived stress; QoL: quality of life; HC: healthy control individuals; PSS: Perceived Stress Scale; WHOQoL: World Health Organizations Quality of Life scale; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; HAMD: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale.
[a]Adjusted using the Benjamin and Hochbergs correction.
[b]Adjusted using the Bonferroni correction for multiple familywise analyses.

individuals were 65% versus 86%, and 70% versus 93%, respectively. A total of 62 patients with BD and 40 HC individuals provided samples of both CSF and urine at baseline.

The biomarkers of oxidative stress CSF 8-oxoGuo and urine 8-oxoGuo were statistically significantly higher in patients with BD compared to HC individuals both at baseline and at follow-up as the same was the case for urine 8-oxodG, but this association was only statistically significant at follow-up. The biomarker of CSF 8-oxodG was higher in patients with BD compared to HC individuals, but not statistically significantly.

The overall wellbeing, measured as low PSS and high QoL, was significantly higher among HC individuals compared to patients with BD both at baseline and at follow-up.

Associations between levels of CSF and urinary oxidative stress marker and PSS and WHOQoL scores

There were no statistically significant association between any CSF or urinary oxidative stress markers and PSS nor WHOQoL scores, in the mixed model analyses (Table 2a).

Furthermore, in the separate analyses of BD and HC, we found no statistically significant associations between any CSF or urinary oxidative stress markers and PSS or WHOQoL (Table 2b).

It is noted that data showed an association between perceived stress and urinary 8-oxoGuo (2.96; *p* value=.04 (adjusted *p* value .61), confidence interval: 0.14–5.79) in HC (Table 2b).

Discussion

This is the first study to examine the relation between oxidative stress and subjective stress in patients with BD and HC individuals. We did not find any relationship between high levels of CSF or urinary oxidative stress markers and, high PSS or low QoL in patients with BD. Similarly, in the HC individuals, we found no statistically significant relationship between any oxidative stress marker and PSS and QoL. Thus, the overall conclusion was that oxidative stress markers were not associated with PSS and QoL in patients with BD or HC individuals.

A strength of this study is the number of participants that was similar to or larger than previous studies [14]. All procedures were carried out at the Copenhagen Psychiatric Centre and the Danish Dementia Research Centre, Rigshospitalet, ensuring minimal variation compared with multicentre studies.

As a limitation the patients who experienced an affective episode during the follow-up period had fewer repeated CSF samples than urine samples. We have previously found that perceived stress scores were significantly higher among those patients with BD with versus without an affective episode during follow-up [4]. However, we did not investigate whether an affective episode during follow-up interacted with the association between oxidative stress markers and PSS and QoL.

All together, we believe that our results reflect valid findings. As oxidative stress and PSS both are associated with the pathology of BD [9,13], these associations may be independent of one another.

The underlying mechanism of both RNA and DNA oxidation is controlled by an extensive network of regulatory systems and pathways in multiple cellular compartments of the cell [12], and is not yet fully understood. Thus, the relationship between RNA and DNA oxidation and PSS could be a subject for future investigation. We believe this study to be of importance, since many different oxidative stress markers as well as PSS in numerous studies have been associated with disease progression and mortality [9,11–13,17]. Nevertheless, no prior study has investigated associations between oxidative stress markers and PSS in relation to BD. Our findings of no associations between oxidative stress markers and subjective wellbeing measured with PSS or QoL

are surprising since higher PSS and lower QoL are both subjective and could be reflective of the illness burden inherent in BD. Moreover, PSS/QoL are closely related to current mood symptoms. Increased oxidation and inflammation may be a link between ageing and psychopathology. A prior case-only study of 49 women diagnosed with anxiety found that higher levels of perceived stress had worse immune functionality and higher oxidative and inflammatory stress compared to women with low perception of stress [26]. Although these potential mechanisms linking perceived stress and oxidative stress are compelling our data suggest that oxidative stress markers and PSS may be independently associated with BD. We suspect that PSS could be a possible confounder to be adjusted in future studies on oxidative stress markers. Furthermore, oxidative stress and PSS could therefore also be independent targets for future medical and psychological treatment.

Finally, with the results from this study, it is less likely that the treatment of one target, PSS, would have effect on the other, oxidative stress.

The finding of an association between perceived stress and urinary 8-oxoGuo in HC in unadjusted analyses may be a coincidence. Especially, since it is the only finding with a *p* value beneath .05. However, the finding may encourage future studies with a protocol that prespecifies the association between perceived stress and urinary 8-oxo-Guo in a larger sample of HC.

In conclusion, this study is the first to explore the association between oxidative stress markers and subjective stress measures in a relatively large sample and reports preliminary null findings for an association between oxidative stress and perceived stress among adults with BD.

Acknowledgements

Ethical approval: The study was approved by the Local Ethical Committee (H-6-2014-006) and the Danish Data Protection Agency, Capital Region of Copenhagen. The study complied with the latest Declaration of Helsinki.

Disclosure statement

Authors UK, RAB, AHS, SGH, HEP, MA, and JF reported no biomedical financial interests or potential conflicts of interest. LVK reported having been a consultant for Lundbeck within the preceding three years.

Funding

The study was supported by The Mental Health Services of Capital of Denmark Research Foundation, AP Møller Foundation for Promotion of Medical Science, The Beckett Foundation, The King Christian 10th Foundation and the Max and Oda Wørzner Foundation (recipient author UK). The Danish Dementia Research Centre is supported by grants from the Danish Ministry of Health (J No. 2007-12143-112, project 59506/J No. 0901110, project 34501) and the Danish Health Foundation (J No. 2007B004).

Notes on contributor

Contributors UK, RAS, HEP, JF, MA and LVK conceived the study and authored the protocol. All authors helped implement the study. All authors contributed to, and approved the final version of the manuscript.

ORCID

Henrik Enghusen Poulsen http://orcid.org/0000-0003-4242-9924

Data availability statement

The data that support the findings of this study are available from the corresponding author (UK) upon reasonable request.

References

[1] Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry. 2001;58(9):844–850.

[2] Ösby U, Westman J, Hällgren J, et al. Mortality trends in cardiovascular causes in schizophrenia, bipolar and unipolar mood disorder in Sweden 1987–2010. Eur J Public Health. 2016;26(5):867–871.

[3] Hällgren J, Ösby U, Westman J, et al. Mortality trends in external causes of death in people with mental health disorders in Sweden, 1987–2010. Scand J Public Health. 2019;47(2):121–126.

[4] Pech J, Akhøj M, Forman J, et al. The impact of a new affective episode on psychosocial functioning, quality of life and perceived stress in newly diagnosed patients with bipolar disorder: a prospective one-year case-control study. J Affect Disord. 2020;277:486–494.

[5] Faurholt-Jepsen M, Frost M, Busk J, et al. Is smartphone-based mood instability associated with stress, quality of life, and functioning in bipolar disorder? Bipolar Disord. 2019;21(7):611–620.

[6] Pascual-Sánchez A, Jenaro C, Montes-Rodríguez JM. Quality of life in euthymic bipolar patients: a systematic review and meta-analysis. J Affect Disord. 2019;255:105–115.

[7] Morton E, Murray G, Michalak EE, et al. Quality of life in bipolar disorder: towards a dynamic understanding. Psychol Med. 2018;48(7):1111–1118.

[8] Kessing LV, Vradi E, Andersen PK. Life expectancy in bipolar disorder. Bipolar Disord. 2015;17(5):543–548.

[9] Prior A, Vestergaard M, Davydow DS, et al. Perceived stress, multimorbidity, and risk for hospitalizations for ambulatory care-sensitive conditions: a population-based cohort study. Med Care. 2017;55(2):131–139.

[10] Gitlin MJ, Miklowitz DJ. The difficult lives of individuals with bipolar disorder: a review of functional outcomes and their implications for treatment. J Affect Disord. 2017;209:147–154.

[11] Poulsen HE, Specht E, Broedbaek K, et al. RNA modifications by oxidation: a novel disease mechanism? Free Radic Biol Med. 2012;52(8):1353–1361.

[12] Morris G, Walder KR, Berk M, et al. The interplay between oxidative stress and bioenergetic failure in neuropsychiatric illnesses: can we explain it and can we treat it? Mol Biol Rep. 2020;47(7):5587–5620.

[13] Knorr U, Simonsen AH, Roos P, et al. Cerebrospinal fluid oxidative stress metabolites in patients with bipolar disorder and healthy controls: a longitudinal case-control study. Transl Psychiatry. 2019;9(1):325.

[14] Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. Psychiatry Res. 2014;218(1–2):61–68.

[15] Weimann A, Simonsen AH, Poulsen HE. Measurement of 8-oxo-7,8-dihydro-2′-deoxyguanosine and 8-oxo-7,8-dihydro-guanosine in cerebrospinal fluid by ultra performance liquid chromatography–tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2018;1073:110–117.

[16] Netuveli G, Pikhart H, Bobak M, et al. Generic quality of life predicts all-cause mortality in the short term: evidence from British

Household Panel Survey. J Epidemiol Community Health. 2012; 66(10):962–966.
[17] Shimanoe C, Hara M, Nishida Y, et al. Perceived stress, depressive symptoms, and oxidative DNA damage. Psychosom Med. 2018; 80(1):28–33.
[18] Wing JK, Babor T, Brugha T, et al. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry. 1990;47(6): 589–593.
[19] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.
[20] Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133: 429–435.
[21] von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495–1499.
[22] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385–396.
[23] Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med. 1998;28:551–558.
[24] Jacoby AS, Vinberg M, Poulsen HE, et al. Increased DNA and RNA damage by oxidation in patients with bipolar I disorder. Transl Psychiatry. 2016;6(8):e867.
[25] Munkholm K, Poulsen HE, Kessing LV, et al. Elevated levels of urinary markers of oxidatively generated DNA and RNA damage in bipolar disorder. Bipolar Disord. 2015;17(3):257–268.
[26] Martínez de Toda I, Miguélez L, Siboni L, et al. High perceived stress in women is linked to oxidation, inflammation and immunosenescence. Biogerontology. 2019;20(6):823–835.