Addictive Behaviors Reports 7 (2018) 90–95

Contents lists available at ScienceDirect

Addictive Behaviors Reports

journal homepage: www.elsevier.com/locate/abrep

Depressed female smokers have higher levels of soluble tumor necrosis factor receptor 1

Mauro Porcu[b,c,*], Regina Célia Bueno Rezende Machado[b,c], Mariana Urbano[c,e], Waldiceu A. Verri Jr[c,d], Ana Carolina Rossaneis[c], Heber Odebrecht Vargas[a,b], Sandra Odebrecht Vargas Nunes[a,b,c]

[a] Department of Clinical Medicine, Londrina State University (UEL), Health Sciences Centre, Londrina, Paraná, Brazil
[b] Center of Approach and Treatment for Smokers, University Hospital, Londrina State University, Campus Universitário, Londrina, Paraná, Brazil
[c] Health Sciences Graduation Program, Health Sciences Center, State University of Londrina, Londrina, Paraná, Brazil
[d] Department of Pathology, Biological Sciences Center, Londrina State University, Brazil
[e] Department of Statistics, Center of Exact Sciences, Londrina State University, Londrina, Brazil

ARTICLE INFO

Keywords:
Tobacco use disorder
Depression
Inflammation
Metabolism
Child abuse

ABSTRACT

Aim: To examine clinical and biomarkers in depressed female smokers, in order to better clarify the process that link mood disorders, childhood trauma and smoking in women.
Methods: The clinical sample comprised women with unipolar or bipolar depression, divided into subgroups of smokers and never-smoker. The control groups comprised two subgroups non-depressed women, separated into smokers and never-smokers. A structured questionnaire was used to assess socio-demographic and clinical data. The following scales were used: 17-item version Hamilton Depression Rating Scale, Hamilton Anxiety Rating scale (HAM-A), Sheehan disability scale, the Child Trauma Questionnaire. The following biomarkers were investigated: lipid profile, including total cholesterol, high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol, triglycerides the Castelli's Risk indexes I and II; and cytokines, including interleukins (IL)-1β, IL-6, IL-10, IL-12, soluble tumor necrosis factor receptor 1 (sTNF-R1).
Results: Depressed female smokers showed a number of significant positive correlations: emotional neglect and sTNF-R1 ($p = 0.02$); waist circumference and sTNF-R1 ($p = 0.001$); body mass index and sTNF-R1 ($p < 0.01$); HAM-A and sTNF-R1 ($p = 0.03$); IL-1β and sTNF-R1 ($p < 0.01$); IL-10 and sTNF-R1 ($p = 0.001$); IL-12 and sTNF-R1 ($p < 0.01$);Castelli index I and sTNF-R1 ($p < 0.01$); Castelli index II and sTNF-R1 ($p < 0.01$); and a significantly negative correlation between HDLc and sTNF-R1($p = 0.014$).
Conclusion: This study suggests that depressed female smokers who experienced more childhood trauma and had more anxiety symptoms are associated with the activation of inflammatory processes and alterations in components of lipid profile.

1. Introduction

Unipolar and bipolar depression, as well as tobacco use disorder (TUD) have a significant global burden arising from heightened levels of chronicity, progressive disability and premature death. These disorders represent the leading causes of disability-adjusted life years (GBD 2015 Tobacco Collaborators et al., 2017; Murray et al., 2012; Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2015). The most common tobacco-related diseases are cardiovascular illnesses, chronic obstructive pulmonary disease and cancer (Ezzati & Lopez, 2003). Neoplasia, cardiovascular and respiratory diseases also affect bipolar disorder (BD) patients (Kupfer, 2005; Leboyer et al., 2012; McIntyre et al., 2006). TUD associates with a wide array of medical conditions as a consequence of chronic inflammatory process (Yanbaeva, Dentener, Creutzberg, Wesseling, & Wouters, 2007).

Despite the raised awareness of tobacco–related diseases, rates of tobacco use are increasing in young females (Mamudu, Hammond, & Glantz, 2008). There is a relationship between smoking and depression, which may be of particular relevence in women, given that women have higher rates of depression and anxiety (Roehr, 2013). Women who quit smoking exhibit similar levels of depressive symptomatology as current smokers (Pomerleau, Zucker, & Stewart, 2003). TUD is a vulnerability factor for the development of severe depressive and anxiety symptoms (Jamal, Willem Van der Does, Cuijpers, & Penninx, 2012).

* Corresponding author at: Center of Approach and Treatment for Smokers, Psychiatry Unit, Maringá State University, Paraná, Brazil.
E-mail address: mporcu@uol.com.br (M. Porcu).

https://doi.org/10.1016/j.abrep.2018.03.004
Received 8 January 2018; Received in revised form 22 March 2018; Accepted 23 March 2018
Available online 28 March 2018

Furthermore, a history of mood disorders increases the risk of early onset cigarette smoking, as well as to progression from daily smoking to nicotine dependence (Breslau, Novak, & Kessler, 2004). Childhood abuse may affect risks of diabetes and cardiovascular disease later in life (Bertone-Johnson, Whitcomb, Missmer, Karlson, & Rich-Edwards, 2012).

TUD is highly comorbid with mood disorders, including (BD) and major depressive disorder (MDD). In the National Comorbidity Survey nearly 61.3% of people with a lifetime history of panic disorder and 68.4% with generalized anxiety disorders were current or past smokers, whilst only 39% of smokers showed no evidence of a psychiatric disorder. In major depressive disorder, TUD prevalence ranges from 40% to 64% across studies. Nicotine-dependent smokers are twice as likely as non-smokers to have a history of depression (Lasser et al., 2016; Ziedonis et al., 2008). Such studies indicate an intimate interaction of TUD and mood dysregulation.

This common co-occurrence of TUD and mood disorders has generated a number of theoretical explanations, including: cigarette smoking has anti-depressant effects, being a form of self-medication; TUD, BD and MDD share common environmental or genetic risk factors; BD and MDD are a consequence of brain dysfunction, which is worsened by TUD (Dome, Lazary, Kalapos, & Rihmer, 2010).

Both bipolar depression and MDD show evidence of heightened levels of pro-inflammatory and anti-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), soluble tumor necrosis factor receptor 1(sTNF-R1), interleukin -1β (IL-1β); IL-6, IL-8, IL-10, and IL-1 receptor antagonist (IL1RA), as well as acute phase proteins, such as C-reactive protein (CRP)(Barbosa et al., 2012; Brietzke et al., 2009; Doganavsargil-Baysal et al., 2013; Dowlati et al., 2010; Hope et al., 2015; Modabbernia, Taslimi, Brietzke, & Ashrafi, 2013; Munkholm, Braüner, Kessing, & Vinberg, 2013; Myint et al., 2007; Young, Bruno, & Pomara, 2014). The levels of hs-CRP, TNF-α, sTNF-R1 and sTNF-R2 are also elevated in current smokers with cardiovascular disease and chronic obstructive pulmonary disease (Asthana et al., 2010).

Mood disorders, when coupled to TUD, show higher levels of pro-inflammatory cytokines, versus non-depressed smokers, including TNF-α, IL-6, and CRP (Nunes et al., 2012). The shared activated immune-inflammatory and oxidative and nitrosative stress pathways by which TUD may increase the risk for development of depressive disorders are, in part, mediated by increased levels of pro-inflammatory cytokines, diverse neurotransmitter systems, hypothalamic–pituitary–adrenal (HPA) axis activation, and microglial activation, as well as increased levels of endogenous oxidative stress and decreased levels of endogenous antioxidants (Nunes et al., 2013).

The present study evaluated the clinical and biomarker differences between females with mood disorders, either bipolar depression or MDD, when either comorbid, or not, with TUD.

2. Method

This study included non-depressed female and never-smokers ($n = 28$), non-depressed smokers female ($n = 24$), depressed never-smokers female ($n = 38$), and depressed smokers female ($n = 69$). Female smokers were outpatients recruited from the Cigarette Smoking Cessation Service Center, State University of Londrina (UEL). Depressed female were patients with BD or MDD, who were recruited from the outpatients Psychiatric Ambulatory Clinic (UEL). Control participants were regarded as non-depressed and never-smokers if they reported never having smoked a cigarette or have smoked < 100 cigarettes in their lifetime, coupled to no previous experience of a mood disorder. Controls were recruited from the staff at the same institution.

All participants were women aged 18–65 years. Exclusion criteria were: a) another medical condition or medication-induced BD and MDD; b) participants with a diagnosis of mental retardation, schizophrenia, psycho-organic syndromes or any condition that would compromise the understanding of the study terms and c) pregnancy. All participants gave written informed consent to participate in the study after the approval of this research by the local Ethics Research Committee (number CAAE 34935814.2.0000.5231).

All participants completed a questionnaire, which comprised socio-demographic data (education, occupation, marital status years of education), and clinical data (hospitalizations, ability to work, smoking status, suicidal ideation and suicide attempts, as well as number of lifetime depressions).

Trained psychiatrists carried out the clinical assessments. Diagnoses were based on the Structured Clinical Interview for DSM-IV, Axis I (SCID-I), clinical version, translated and validated for the Portuguese language (Del-Ben et al., 2001) and on the 10th edition of the International Classification of Diseases (ICD-10) (World Health Organization., 1993).

Anxiety severity was assessed through Hamilton Anxiety Rating Scale (HAM-A) (HAMILTON, 1959).

Severity of depression was assessed through 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) (HAMILTON, 1960). $HDRS_{17}$ was translated and adapted for the Brazilian population (Moreno & Moreno, 1998).

Quality of life was evaluated using the World Health Organization Quality of Life Instrument, abbreviated version (WHOQOL-BREF), comprised by 26 items, measuring the following broad domains: physical health, psychological health, social relationships and environment. This instrument was translated and adapted to Portuguese (Fleck et al., 2000).

The Childhood Trauma Questionnaire (CTQ) is a self-administered instrument used to document a history of childhood maltreatment in 5 domains: sexual abuse, physical abuse, emotional abuse, emotional neglect and physical neglect (Bernstein et al., 2003). The 28 item-version of CTQ was validated in the Portuguese language (Grassi-Oliveira, Stein, & Pezzi, 2006).

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein (LDL-c) and triglycerides levels were determined by an automated method, namely the Dimension® RXL (Siemens Healthcare Diagnostics Inc., Newark, DE, USA). HDL-c levels were measured directly, without the necessity of sample pretreatment or specialized centrifugation steps. LDL-c was calculated by Friedewald's equation. Serum triglycerides were measured using an enzymatic procedure employing combinations of enzymes. We computed the Castelli risk index1 [TC/HDL-c] and Castelli risk index 2 [LDL-c/HDL-c].

The luminex kit was utilized to measure the cytokines, IL-1β, IL-1RA, IL-6, IL10, IL-12, and sTNF-R1.

Statistical analyses were performed to examine the relationship between socio-demographic, clinical and laboratory measurements. ANOVA was used for quantitative comparisons among groups (mood disorder smokers; mood disorder never-smokers; non-mood disorder smokers; non-mood disorder, never-smokers), followed by the Tukey test when the assumptions were attended (homogeneity of variances and normality of the residuals). If these criteria were not met, the Kruskal-Wallis test was used, followed by a post hoc test.

For the qualitative variables, the Chi-square test or Fisher exact test was used, followed by the z-test, to compare the percentages among the groups. The statistical significance level used was 0.05 and when the p-value is < 0.05, the means (for the quantitative variables) or the percentages (for the qualitative variables) are followed by letters. The same letters for the same variable indicate that there are no differences between the means or percentages among the groups and different letters for the same variable indicate that there are differences between the means or the percentages among the groups.

Following these univariate comparisons Pearson correlation coefficients were utilized to compare some pairs of clinical and physiological data.

All the analyses were performed in software R (R foundation, 2018).

Table 1
Clinical and demographic characteristics of the four study groups.

p-Value*	Femalenon-smokers, non-mood disorders (n = 28)	Femalesmokers,non mood disorders (n = 24)	FemaleBipolar/Unipolar never-smokers (n = 38)	FemaleBipolar/Unipolar smokers (n = 69)	Variable
Age (years); mean (SD)	39.21 (13.19)	43.54 (11.85)	41.08 (13.61)	46.07 (10.58)	0.07
Years of education; mean (SD)	16.64 (4.25) a	9.13 (5.23) b	10.73 (4.93) b	9.18 (4.65) b	< 0.01
WHOQoL - physical health; mean (SD)	29.71 (3.51) a	26.88 (4.46) a	22.00 (4.75) b	21.97 (5.18) b	< 0.01
WHOQoL -psychological health; mean (SD)	24.57 (2.68) a	21.69 (3.97) a	17.39 (4.13) b	17.06 (4.55) b	< 0.01
WHOQoL - Social relationship; mean (SD)	12.86 (1.41) a	10.31 (2.59) b	9.18 (2.75) bc	8.28 (2.54) c	< 0.01
WHOQoL – environment; mean (SD)	32.64 (3.18) a	27.96 (4.28) b	26.38 (4.51) b	25.36 (5.79) b	< 0.01
WHOQoL - total score; mean (SD)	99.79 (8.96) a	87.46 (10.53) b	75.16 (13.04) c	72.16 (14.69) c	< 0.01
HAM-D; mean (SD)	2.32 (2.55) a	2.95 (4.02) a	9.37 (6.61) b	11.59 (7.74) b	< 0.01
HAM-A; mean (SD)	4.54 (6.02) a	7.96 (7.03) a	16.62 (12.06) b	17.60 (11.47) b	< 0.01
BMI; mean (SD)	24.73 (3.47) a	28.18 (6.05) ab	29.34 (6.63) b	26.49 (5.07) ab	0.01
Sheehan work; mean (SD)	0.43 (1.23) a	2.25 (2.99) a	5.05 (3.33) b	5.59 (3.62) b	< 0.01
Sheehan social life; mean (SD)	0.36 (0.99) a	2.63 (3.22) a	5.63 (3.47) b	5.91 (3.75) b	< 0.01
Sheehan Home responsabilities; mean (SD)	0.10 (0.31) a	2.21 (3.67) ac	4.82 (3.57) bc	5.92 (3.60) b	< 0.01
Work absences (last 30 days); mean (SD)	0.00 (0.00) a	0.00 (0.00) a	5.76 (10.57) b	4.45 (9.12) b	< 0.01
Unproductive days (last 30 days); mean (SD)	0.32 (1.06) a	1.54 (6.13) ab	8.21 (11.74) b	6.94 (10.80) ab	< 0.01
Sexual abuse; mean (SD)	5.35 (1.10) a	5.67 (2.62) ab	8.68 (4.86) b	7.35 (4.78) ab	< 0.01
Physical abuse; mean (SD)	6.29 (2.59) a	8.04 (4.56) ab	9.54 (4.66) b	10.02 (4.54) b	< 0.01
Emotional abuse; mean (SD)	6.14 (1.24) a	9.42 (4.96) ab	12.22 (5.38) cb	13.22 (6.08) c	< 0.01
Emotional neglect; mean (SD)	10.64 (6.84)	11.25 (6.93)	14.86 (7.26)	13.52 (5.80)	0.06
Physical neglect; mean (SD)	8.25 (4.69) ab	7.63 (3.08) b	10.73 (4.46) a	9.92 (4.37) ab	0.02

Abbreviations: $HDRS_{17}$: 17-item Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; BMI: Body mass index; SDS: Sheehan Disability Scale; CTQ Childhood Trauma Questionnaire, WHOQOL-bref: World Health Organization Quality of Life.
**p*-Value obtained by ANOVA or Kruskall-Wallis test. The same letters for the same variable indicate that there are no differences between the means among the groups and different letters for the same variable indicate that there are differences between the means among the groups.

3. Results

The demographic and clinical data of all groups are shown in Table 1. Groups did not differ with respect to age. Comparing non-depressed/never-smokers versus the other groups, we may conclude that the average for years of educations and quality of life had the best results, i.e. more years of education and better quality of life scores on the WHOQOL-BREF in all domains ($p < 0.01$).

Depressed, smokers and never smokers versus non-depressed never-smokers experienced more childhood trauma, including emotional abuse, and physical abuse ($p < 0.001$). Only depressed non-smokers, versus non-depressed never-smokers had significant difference for childhood sexual abuse ($p < 0.01$).

Depressed, versus non-depressed, smokers and never-smokers scored higher for depressed symptoms on the $HDRS_{17}$ and also for anxiety symptoms, as indicated on the HAM-A scale ($p < 0.01$). Higher body mass index is likely to be associated with depressed never-smokers compared to non-depressed never smokers ($p < 0.01$). Irrespective of TUD, patients with mood disorders also had more functional impairment on subscale of work, social life, work absences on Sheehan disability scale ($p < 0.01$). Unipolar or bipolar depressed smokers had significantly lower levels of domestic care routines on Sheehan disability scale than non-depressed never smokers ($p < 0.01$).

Table 2 includes psychiatric comorbidities and family history. Irrespective of TUD, patients with mood disorders had a significantly stronger family history of BD. Irrespective of mood disorders; smokers had a statistically stronger family history of TUD.

Still in Table, we may note that the number of depressed episode is significantly greater for depressed female when compared with non-depressed female ($p < 0.01$). Irrespective of TUD, depressed smokers and never-smokers also had more lifetime and current suicide ideation, lifetime suicide attempts, more obsessive-compulsive disorder, and generalized anxiety disorder ($p < 0.01$). Depressed never-smokers had significantly more panic disorder than non-depressed smokers and never smokers.

The physiological biomarkers of all groups are shown in Table 3. Female depressed smokers and never-smokers, versus non-depressed never-smoker, had significantly lower HDL-c levels, higher triglycerides and Castelli indexes I and II. No significant differences on sTNF-R1 and sTNF-R2 levels in all groups.

Correlation Coefficient analysis was conducted to identify the relationship between two variables, including clinical and clinical, or clinical and biomarkers, or biomarkers and biomarkers in smokers with and without mood-disorders and never-smokers with and without mood disorders among women. These results were summarized in Table 4.

Depressed female smokers showed a significant positive correlation between emotional neglect and sTNF-R1 ($p = 0.02$), waist circumference and sTNF-R1 ($p = 0.001$), BMI and sTNF-R1 ($p < 0.001$), HAM-A and sTNF-R1($p = 0.03$); IL-1β and sTNF-R1($p < 0.001$), IL-6 and sTNF-R1($p < 0.001$), IL-10 and sTNF-R1($p < 0.001$), IL-12 and sTNF-R1($p < 0.001$), Castelli I and sTNF-R1($p < 0.001$), and the Castelli II and sTNF-R1 ($p = 0.002$), as well as a significant negative significant correlation between HDL-c and sTNF-R1($p = 0.014$).

4. Discussion

Our results indicate alterations in inflammatory processes in depressed smokers female, highlighting significant correlations between sTNF-R1 levels and other inflammatory and anti-inflammatory cytokines, components of metabolism, childhood trauma, and anxiety symptoms. A number of processes may have contributed to these results. Hypothalamic–pituitary–adrenal (HPA) axis, which increases microglia activation (Moylan, Maes, Wray, & Berk, 2013), may contribute to driving the increase in inflammatory cytokines that can contribute to mood dysregulation. Such alterations in microglia activity can be associated with excessive inflammation, astrocyte loss, and inappropriate glutamate receptor activation, thereby disrupting the balance of neuroprotective, versus neurotoxic, processes. Such alterations are likely to drive processes of neuroprogression, which increase the likelihood of neurodegeneration and decreased neurogenesis (Anderson & Maes, 2014). HPA axis dysregulation associates with reduced prefrontal cortex and hippocampal activity, amygdala hyperfunction, contributing to the defective glucocorticoid-negative feedback that has been reliably observed in BD patients with TUD (Daban, Vieta, Mackin, & Young, 2005) as well as in TUD (Rohleder & Kirschbaum, 2006). Corticotrophin-releasing factor may be relevant, in that it contributes to

Table 2
Psychiatric comorbidities among women in the four groups.

Variable	Female non-smokers, non-mood disorders (n = 28)	Female smokers, non-mood disorders (n = 24)	Female bipolar/ unipolar never-smokers (n = 38)	Female bipolar/ unipolar smokers (n = 69)	*p*-Value*
Number of depressive episodes; mean (SD)	0.00 (0.00) a	0.11 (0.32) a	6.14 (5.45) b	6.02 (10.71) b	< 0.01
Suicide attempt; mean (SD)	0.04 (0.19) a	0.21 (0.83) a	1.29 (2.54) bc	1.08 (2.97) ac	< 0.01
Lifetime suicide ideation	10.70% a	16.00% a	81.60% b	73.00% b	< 0.01
Current suicide ideation last month	3.60% a	4.20% a	26.30% ab	34.30% b	< 0.01
Suicide behavior last 30 days	0.00% a	0.00% a	15.80% b	4.80% ab	0.02
Panic disorder	10.70% ab	4.20% b	50.00% c	32.80% ac	< 0.01
Obsessive-compulsive disorder	3.60% a	0.00% a	21.60% b	8.80% ab	0.02
TAG	7.10% a	22.70% ab	43.20% b	42.60% b	< 0.01
Family history of TUD	57.10% a	88.50% b	60.50% a	81.00% b	< 0.01
Family history of BD	0.00% a	4.00% ab	42.10% c	28.10% bc	< 0.01

Abbreviations: TUD: Tobacco use disorder, TAG: Generalized anxiety disorder.
**p*-Value obtained by ANOVA or Kruskall-Wallis test for the quantitative variables, or Chi-square test or Fisher exact test for the qualitative variables. The same letters for the same variable indicate that there are no differences between the means or percentages among the groups and different letters for the same variable indicate that there are differences between the means or the percentages among the groups.

HPA axis and brain stress system regulation, and thereby of some importance in both depression and TUD (Bruijnzeel, 2012). Heightened pro-inflammatory cytokines increase the enzymatic activity of indolamine 2,3-dioxygenase (IDO), which decreases tryptophan availability for serotonin and melatonin synthesis by driving tryptophan to the production of neuroregulatory kynurenine pathway products (Rosenblat, Cha, Mansur, & McIntyre, 2014).

In addition, depressed, versus non-depressed, female smokers and never-smokers reported more childhood trauma, including sexual abuse, emotional abuse and physical abuse. Women with a history of moderate to severe childhood trauma, have a heightened risk of developing mood and substance use disorders (Blalock et al., 2013). Individuals who have experienced abuse or neglect in childhood are more likely to be diagnosed with MDD or anxiety in adulthood, in association with alterations in HPA axis activity (C Heim & Nemeroff, 2001; Christine Heim, Plotsky, & Nemeroff, 2004; Kendler et al., 2000). Individuals who have experienced early life stress have an earlier onset cigarette use, smoke more heavily and are more nicotine dependent (Anda et al., 1999; Blalock et al., 2013).

The current study shows depressed female smokers to score more highly on measures of depression and anxiety. TUD increases the risk of developing more severe depressive and anxiety symptoms, as well as have a slower clinical recovery (Jamal et al., 2012), which may be modulated by genetic susceptibilities, including variations in the brain derived neurotrophic factor Val (66) Met polymorphism (Jamal, Van der Does, & Penninx, 2015).

Irrespective of mood disorders, female smokers had a stronger

Table 4
Pearson correlations coefficients across the four groups.

Variable 1	Variable 2	Female non-smokers, non-mood disorders (n = 28)	Female smokers, non-mood disorders (n = 24)	Female bipolar/ unipolar never-smokers (n = 38)	Female bipolar/ unipolar smokers (n = 69)
sTNF-R1	Emotional neglect	−0.248	0.221	−0.072	0.344*
sTNF-R1	Waist circumference	0.228	−0.207	0.012	0.446**
sTNF-R1	BMI	0.173	−0.081	0.106	0.509**
sTNF-R1	HAM-A	−0.02	0.123	−0.100	0.302*
sTNF-R1	IL-1β	0.302	0.340	0.125	0.505**
sTNF-R1	IL-6	0.057	0.209	0.321	0.498*
s TNF-R1	IL-10	0.285	0.636**	0.159	0.783**
s TNF-R1	IL-12	0.266	−0.032	0.013	0.474**
s TNF-R1	HDL-c	−0.115	0.354	−0.008	−0.338*
s TNF-R1	Castelli I	0.175	−0.100	0.141	0.500**
s TNF-R1	Castelli II	0.083	−0.164	−0.024	0.419**

IL-1β: interleukin -1β; IL-6: interleukin-6; IL-10: interleukin-10; IL-12: interleukin-12. HDL-c: High-density lipoprotein cholesterol (mg/dL); LDL: Low-density lipoprotein cholesterol (mg/dL), Castelli's Risk indexes I and II (total cholesterol /HDLc and low density lipoprotein [LDL-c]/[HDL-c respectively], HAM-A: Hamilton Anxiety Rating Scale; BMI: Body mass index.
* indicate that the *p*-value is < 0.05, and when followed by ** indicate that the *p*-value is < 0.01.

Table 3
Biomarkers across groups.

Variable	Female non-smokers, non-mood disorders (n = 28)	Female smokers, non-mood disorders (n = 24)	Female bipolar/unipolar never-smokers (n = 38)	Female bipolar/unipolar smokers (n = 69)	*p*-Value*
Lipids (mg/dl)					
TC	187.15 (35.74)	193.13 (35.89)	190.91 (41.78)	197.50 (38.64)	0.69
LDL-c	105.93 (29.64)	127.58 (34.66)	113.26 (33.07)	122.32 (34.96)	0.07
HDL-c	60.67 (17.22) a	44.96 (10.73) b	49.51 (13.00) b	47.68 (13.68) b	< 0.01
TG	96.81 (47.24) a	100.75 (42.14) a	138.60 (77.76) b	134.02 (72.78) b	0.03
Castelli I	4.14 (4.66) a	4.56 (1.48) b	4.09 (1.29) ab	4.50 (1.56) b	< 0.01
Castelli II	1.88 (0.80) a	3.09 (1.32) b	2.45 (0.90) ab	2.78 (1.17) b	< 0.01
s TNF-R1(pg/mL)	423.72 (282.57)	397.32 (388.84)	519.67 (337.27)	406.69 (393.78)	0.24
s TNF-R2 (pg/mL)	8431.44 (5268.04)	7401.89 (4450.89)	8953.92 (6262.80)	6389.10 (4599.58)	0.20

HDL-c: High-density lipoprotein cholesterol (mg/dL); LDL: Low-density lipoprotein cholesterol (mg/dL), Castelli's Risk indexes I and II (total cholesterol /HDLc and low density lipoprotein [LDL-c]/[HDL-c respectively], sTNF-RI: soluble tumor necrosis factor receptor 1; sTNF-RII: soluble tumor necrosis factor receptor 2.
*p-Value obtained by ANOVA or Kruskall-Wallis test. The same letters for the same variable indicate that there are no differences between the means among the groups and different letters for the same variable indicate that there are differences between the means among thegroups

family history of TUD. This is supported by previous research indicating that a history of familial smoking increases TUD initiation in females only, with lower self-esteem associating with a significantly earlier onset (Sylvestre, Wellman, O'Loughlin, Dugas, & O'Loughlin, 2017). Irrespective of TUD, patients with mood disorders had a significantly stronger family history of BD. Mood disorders are highly familial independent of whether the parent's condition is unipolar or bipolar disorders (Oquendo et al., 2013).

This study has a number of limitations. Firstly, sample sizes lead to small numbers, especially for biomarker stratification. Secondly, the age of our sample was 18–65 years old and therefore results cannot be generalized to older or younger populations. Third, we selected individuals, who did not have inflammatory or immune abnormalities were accompanied by other medical conditions or induced by medication, including infections, cancer, autoimmune illness, cardiovascular disease, use of interferon. These conditions are known to involve in relationship between soluble tumor necrosis factor receptor 1 (sTNF-RI) and physical symptoms and the effects of depressive symptoms (Heo et al., 2014). Finally, some clinical and childhood trauma were retrospective data and could be subject to recall bias.

In conclusion, women showing comorbid TUD and depression in clinical practice are common. Depressed female smokers show significant differences in clinical and biomarker measures, including reported childhood trauma, anxiety and inflammatory biomarkers.

It will be important to identify subgroups of depressed female smokers exhibiting heightened levels of inflammatory biomarkers, as such subgroups may benefit from treatment with adjunctive anti-inflammatory agents (Miller & Raison, 2015; Rosenblat & McIntyre, 2016). Future research should target treatments in depressed female smokers that reduce inflammatory biomarkers, and thereby neuroregulatory kynurenines and glutamatergic activity.

Role of funding source

This study was supported by Health Sciences Postgraduate Program at Londrina State University, Paraná, Brazil (UEL), and Ministry for Science and Technology of Brazil (CNPq). CNPq number 470344/2013-0 and CNPq number 465928/2014-5 and FAEPE UEL N ° 01/2015.

Acknowledgements

The authors would like to thank the Center of Approach and Treatment for Smokers at UEL, the Clinical Laboratory of the University Hospital and the Laboratory of Research and Graduate College Hospital (LPG), Brazil.

Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contributions

MP, HOV, RCRM and SOVN initiated and conceived the study, analyzed the data and drafted the manuscript. RRM, MP, HOV SOVN collected the data and blood samples and were involved in planning the study. ACR and WPJ performed all blood sample analyses. MU performed statistical analyses. All the authors analyzed all data of the manuscript, read and approved the final manuscript.

Funding

This study was supported by Health Sciences Postgraduate Program at Londrina State University, Paraná, Brazil (UEL), and Ministry for Science and Technology of Brazil (CNPq). CNPq number 470344/2013-0 and CNPq number 465928/2014-5.

MM is supported by a CNPq - PVE fellowship at the Health Sciences Graduate Program fellowship, State University of Londrina.

Fundação Araucária (senior research fellowship to EGM).

Fundação Araucária (Senior professor to SOVN).

Acknowledgements

The authors wish to thank the Centre of Approach and Treatment for Smokers, Psychiatric Unit at UEL, Clinical Laboratory of the University Hospital and Laboratory of Research and Graduate College Hospital (LPG), Brazil.

References

Anda, R. F., Croft, J. B., Felitti, V. J., Nordenberg, D., Giles, W. H., Williamson, D. F., & Giovino, G. A. (1999). Adverse childhood experiences and smoking during adolescence and adulthood. *JAMA, 282*(17), 1652–1658. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10553792.

Anderson, G., & Maes, M. (2014). Oxidative/nitrosative stress and immuno-inflammatory pathways in depression: treatment implications. *Current Pharmaceutical Design, 20*(23), 3812–3847. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24180395.

Asthana, A., Johnson, H. M., Piper, M. E., Fiore, M. C., Baker, T. B., & Stein, J. H. (2010). Effects of smoking intensity and cessation on inflammatory markers in a large cohort of active smokers. *American Heart Journal, 160*(3), 458–463. http://dx.doi.org/10.1016/j.ahj.2010.06.006.

Barbosa, I. G., Rocha, N. P., Huguet, R. B., Ferreira, R. A., Salgado, J. V., Carvalho, L. A., & Teixeira, A. L. (2012). Executive dysfunction in euthymic bipolar disorder patients and its association with plasma biomarkers. *Journal of Affective Disorders, 137*(1–3), 151–155. http://dx.doi.org/10.1016/j.jad.2011.12.034.

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., & Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect, 27*(2), 169–190. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12615092.

Bertone-Johnson, E. R., Whitcomb, B. W., Missmer, S. A., Karlson, E. W., & Rich-Edwards, J. W. (2012). Inflammation and early-life abuse in women. *American Journal of Preventive Medicine, 43*(6), 611–620. http://dx.doi.org/10.1016/j.amepre.2012.08.014.

Blalock, J. A., Minnix, J. A., Mathew, A. R., Wetter, D. W., McCullough, J. P., & Cinciripini, P. M. (2013). Relationship of childhood trauma to depression and smoking outcomes in pregnant smokers. *Journal of Consulting and Clinical Psychology, 81*(5), 821–830. http://dx.doi.org/10.1037/a0033381.

Breslau, N., Novak, S. P., & Kessler, R. C. (2004). Psychiatric disorders and stages of smoking. *Biological Psychiatry, 55*(1), 69–76. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14706427.

Brietzke, E., Stertz, L., Fernandes, B. S., Kauer-Sant'anna, M., Mascarenhas, M., Escosteguy Vargas, A., & Kapczinski, F. (2009). Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *Journal of Affective Disorders, 116*(3), 214–217. http://dx.doi.org/10.1016/j.jad.2008.12.001.

Bruijnzeel, A. W. (2012). Tobacco addiction and the dysregulation of brain stress systems. *Neuroscience and Biobehavioral Reviews, 36*(5), 1418–1441.

Daban, C., Vieta, E., Mackin, P., & Young, A. H. (2005). Hypothalamic-pituitary-adrenal axis and bipolar disorder. *The Psychiatric Clinics of North America, 28*(2), 469–480.

Del-Ben, C. M., Antônio, J., Vilela, A., Alexandre, J., Crippa, D. S., Eduardo, J., & Labate, C. M. (2001). Confiabilidade da "Entrevista Clínica Estruturada para o DSM-IV – Versão Clínica" traduzida para o português Reliability of the Structured Clinical Interview for DSM-IV – Clinical Version translated into Portuguese. *Revista Brasileira Psiquiatrica*. http://dx.doi.org/10.1590/S1516-44462001000300008.

Doganavsargil-Baysal, O., Cinemre, B., Aksoy, U. M., Akbas, H., Metin, O., Fettahoglu, C., & Davran, F. (2013). Levels of TNF-α, soluble TNF receptors (sTNFR1, sTNFR2), and cognition in bipolar disorder. *Human Psychopharmacology, 28*(2), 160–167. http://dx.doi.org/10.1002/hup.2301.

Dome, P., Lazary, J., Kalapos, M. P., & Rihmer, Z. (2010). Smoking, nicotine and neuropsychiatric disorders. *Neuroscience and Biobehavioral Reviews, 34*(3), 295–342. http://dx.doi.org/10.1016/j.neubiorev.2009.07.013.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry, 67*(5), 446–457. http://dx.doi.org/10.1016/j.biopsych.2009.09.033.

Ezzati, M., & Lopez, A. D. (2003). Estimates of global mortality attributable to smoking in 2000. *The Lancet, 362*(9387), 847–852. http://dx.doi.org/10.1016/S0140-6736(03)14338-3.

Fleck, M. P., Louzada, S., Xavier, M., Chachamovich, E., Vieira, G., Santos, L., & Pinzon, V. (2000). Application of the Portuguese version of the abbreviated instrument of quality life WHOQOL-bref. *Revista de Saude Publica, 34*(2), 178–183. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10881154.

GBD 2015 Tobacco Collaborators, M. BFullman, N., Ng, M., Salama, J. S., Abajobir, A., Abate, K. H., ... Gakidou, E. . (2017). Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: A systematic analysis from the Global Burden of Disease Study 2015. *Lancet (London, England), 389*(10082), 1885–1906. http://dx.doi.org/10.1016/S0140-6736(17)30819-X.

Grassi-Oliveira, R., Stein, L. M., & Pezzi, J. C. (2006). Translation and content validation of the Childhood Trauma Questionnaire into Portuguese language. *Revista de Saude Publica, 40*(2), 249–255. https://doi.org//S0034-89102006000200010.

Hamilton, M. (1959). The assessment of anxiety states by rating. *The British Journal of Medical Psychology, 32*(1), 50–55. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/13638508.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23*, 56–62. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14399272.

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological Psychiatry, 49*(12), 1023–1039. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11430844.

Heim, C., Plotsky, P. M., & Nemeroff, C. B. (2004). Importance of studying the contributions of early adverse experience to neurobiological findings in depression. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 29*(4), 641–648. http://dx.doi.org/10.1038/sj.npp.1300397.

Heo, S., Moser, D. K., Pressler, S. J., Dunbar, S. B., Dekker, R. L., & Lennie, T. A. (2014). Depressive symptoms and the relationship of inflammation to physical signs and symptoms in heart failure patients. *American Journal of Critical Care, 23*(5), 404–413. http://dx.doi.org/10.4037/ajcc2014614.

Hope, S., Hoseth, E., Dieset, I., Mørch, R. H., Aas, M., Aukrust, P., ... Andreassen, O. A. (2015). Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls. *Schizophrenia Research, 165*(2–3), 188–194.

Jamal, M., Willem Van der Does, A. J., Cuijpers, P., & Penninx, B. W. J. H. (2012). Association of smoking and nicotine dependence with severity and course of symptoms in patients with depressive or anxiety disorder. *Drug and Alcohol Dependence, 126*(1–2), 138–146. http://dx.doi.org/10.1016/j.drugalcdep.2012.05.001.

Jamal, M., Van der Does, W., & Penninx, B. W. J. H. (2015). Effect of variation in BDNF Val66Met polymorphism, smoking, and nicotine dependence on symptom severity of depressive and anxiety disorders. *Drug and Alcohol Dependence, 148*, 150–157. http://dx.doi.org/10.1016/j.drugalcdep.2014.12.032.

Kendler, K. S., Bulik, C. M., Silberg, J., Hettema, J. M., Myers, J., & Prescott, C. A. (2000). Childhood sexual abuse and adult psychiatric and substance use disorders in women: an epidemiological and cotwin control analysis. *Archives of General Psychiatry, 57*(10), 953–959. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11015813.

Kupfer, D. J. (2005). The increasing medical burden in bipolar disorder. *JAMA, 293*(20), 2528–2530. http://dx.doi.org/10.1001/jama.293.20.2528.

Lasser, K., Boyd, J. W., Woolhandler, S., Himmelstein, D. U., McCormick, D., & Bor, D. H. (2016). Smoking and mental illness: A population-based prevalence study. *JAMA, 284*(20), 2606–2610.

Leboyer, M., Soreca, I., Scott, J., Frye, M., Henry, C., Tamouza, R., & Kupfer, D. J. (2012). Can bipolar disorder be viewed as a multi-system inflammatory disease? *Journal of Affective Disorders, 141*(1), 1–10.

Mamudu, H. M., Hammond, R., & Glantz, S. (2008). Tobacco industry attempts to counter the World Bank report curbing the epidemic and obstruct the WHO framework convention on tobacco control. *Social Science & Medicine, 67*(11), 1690–1699. http://dx.doi.org/10.1016/j.socscimed.2008.09.062.

McIntyre, R. S., Konarski, J. Z., Soczynska, J. K., Wilkins, K., Panjwani, G., Bouffard, B., & Kennedy, S. H. (2006). Medical comorbidity in bipolar disorder: Implications for functional outcomes and health service utilization. *Psychiatric Services (Washington, D.C.), 57*(8), 1140–1144.

Miller, A. H., & Raison, C. L. (2015). Are anti-inflammatory therapies viable treatments for psychiatric disorders?: Where the rubber meets the road. *JAMA Psychiatry, 72*(6), 527–528. http://dx.doi.org/10.1001/jamapsychiatry.2015.22.

Modabbernia, A., Taslimi, S., Brietzke, E., & Ashrafi, M. (2013). Cytokine alterations in bipolar disorder: A meta-analysis of 30 studies. *Biological Psychiatry, 74*(1), 15–25. http://dx.doi.org/10.1016/j.biopsych.2013.01.007.

Moreno, R. A., & Moreno, D. H. (1998). Escalas de depressao de Montgomery & Asberg (MADRS) e de Hamilton (HAM-D). *Rev. Psiquiatr. Clín. (São Paulo),* 262–272. Retrieved from http://saudepublica.bvs.br/pesquisa/resource/pt/lil-228053.

Moylan, S., Maes, M., Wray, N. R., & Berk, M. (2013). The neuroprogressive nature of major depressive disorder: Pathways to disease evolution and resistance, and therapeutic implications. *Molecular Psychiatry, 18*(5), 595–606.

Munkholm, K., Braüner, J. V., Kessing, L. V., & Vinberg, M. (2013). Cytokines in bipolar disorder vs. healthy control subjects: A systematic review and meta-analysis. *Journal of Psychiatric Research, 47*(9), 1119–1133. http://dx.doi.org/10.1016/j.jpsychires.2013.05.018.

Murray, C. J. L., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., & Lopez, A. D. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet (London, England), 380*(9859), 2197–2223.

Myint, A.-M., Kim, Y. K., Verkerk, R., Scharpé, S., Steinbusch, H., & Leonard, B. (2007). Kynurenine pathway in major depression: Evidence of impaired neuroprotection. *Journal of Affective Disorders, 98*(1–2), 143–151.

Nunes, S. O. V., Vargas, H. O., Brum, J., Prado, E., Vargas, M. M., de Castro, M. R. P., & Berk, M. (2012). A comparison of inflammatory markers in depressed and non-depressed smokers. *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco, 14*(5), 540–546. http://dx.doi.org/10.1093/ntr/ntr247.

Nunes, S. O. V., Vargas, H. O., Prado, E., Barbosa, D. S., de Melo, L. P., Moylan, S., & Berk, M. (2013). The shared role of oxidative stress and inflammation in major depressive disorder and nicotine dependence. *Neuroscience & Biobehavioral Reviews, 37*(8), 1336–1345.

Oquendo, M. A., Ellis, S. P., Chesin, M. S., Birmaher, B., Zelazny, J., Tin, A., & Brent, D. A. (2013). Familial transmission of parental mood disorders: Unipolar and bipolar disorders in offspring. *Bipolar Disorders, 15*(7), 764–773. http://dx.doi.org/10.1111/bdi.12107.

Pomerleau, C. S., Zucker, A. N., & Stewart, A. J. (2003). Patterns of depressive symptomatology in women smokers, ex-smokers, and never-smokers. *Addictive Behaviors.*. http://dx.doi.org/10.1016/S0306-4603(01)00257-X.

R foundation. (n.d.). R Core Team (2018). *R: A language and environment for statistical computing.* Vienna, Austria: R Foundation for Statistical Computing. https://www.R-project.org/.e.

Roehr, B. (2013). American Psychiatric Association explains DSM-5. *BMJ (Clinical Research Ed.), 346*, f3591. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23744600.

Rohleder, N., & Kirschbaum, C. (2006). The hypothalamic–pituitary–adrenal (HPA) axis in habitual smokers. *International Journal of Psychophysiology, 59*(3), 236–243.

Rosenblat, J. D., Cha, D. S., Mansur, R. B., & McIntyre, R. S. (2014). Inflamed moods: A review of the interactions between inflammation and mood disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 53*, 23–34. http://dx.doi.org/10.1016/j.pnpbp.2014.01.013.

Rosenblat, J. D., & McIntyre, R. S. (2016). Bipolar disorder and inflammation. *Psychiatric Clinics of North America, 39*(1), 125–137. http://dx.doi.org/10.1016/j.psc.2015.09.006.

Sylvestre, M.-P., Wellman, R. J., O'Loughlin, E. K., Dugas, E. N., & O'Loughlin, J. (2017). Gender differences in risk factors for cigarette smoking initiation in childhood. *Addictive Behaviors, 72*, 144–150. http://dx.doi.org/10.1016/j.addbeh.2017.04.004.

Whiteford, H. A., Ferrari, A. J., Degenhardt, L., Feigin, V., & Vos, T. (2015). The global burden of mental, neurological and substance use disorders: An analysis from the global burden of disease study 2010. *PLoS One, 10*(2), e0116820. http://dx.doi.org/10.1371/journal.pone.0116820.

World Health Organization (1993). *The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research.* World Health Organization. Retrieved from https://books.google.com.br/books?hl=pt-BR&lr=&id=cnU0DgAAQBAJ&oi=fnd&pg=PP1&dq=World+Health+Organization,+1993.+The+ICD-10+&ots=H9WZGVKoer&sig=N2Hox7pWTlkqOGeenh6rEQcenXI#v=onepage&q=World Health Organization%2C 1993. The ICD-10&f=false.

Yanbaeva, D. G., Dentener, M. A., Creutzberg, E. C., Wesseling, G., & Wouters, E. F. M. (2007). Systemic effects of smoking. *Chest, 131*(5), 1557–1566. http://dx.doi.org/10.1378/chest.06-2179.

Young, J. J., Bruno, D., & Pomara, N. (2014). A review of the relationship between proinflammatory cytokines and major depressive disorder. *Journal of Affective Disorders, 169*, 15–20. http://dx.doi.org/10.1016/j.jad.2014.07.032.

Ziedonis, D., Hitsman, B., Beckham, J. C., Zvolensky, M., Adler, L. E., Audrain-McGovern, J., & Riley, W. T. (2008). Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco, 10*(12), 1691–1715.