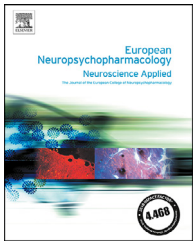
European Neuropsychopharmacology (2020) 000, 1–14

www.elsevier.com/locate/euroneuro



Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts

Patricia Martínez-Botía[a,b,1], Angela Velasco[a,c,d,1], Valeria Rolle[a], Luis Jiménez-Trevino[a,c,d,e], Lorena De la Fuente-Tomás[a,c,d], Ángel Bernardo[a,f], Tamara Arias[a,g], María del Carmen Muñoz-Turrillas[a,g], Leticia García-Alvarez[a,d], Leticia González-Blanco[a,c,d,e], Julia Rodríguez-Revuelta[a,c,e], Maria Paz Garcia-Portilla[a,c,d,e], Philippe Courtet[h,i], Julio Bobes[a,c,d,e], Laura Gutiérrez[a,b,*], Pilar Alejandra Sáiz[a,c,d,e,*]

[a] *Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain*
[b] *Department of Medicine, Universidad de Oviedo, Spain*
[c] *Department of Psychiatry, Universidad de Oviedo, Spain*
[d] *Biomedical Research Networking Centre in Mental Health (CIBERSAM), Oviedo, Spain*
[e] *Servicio de Salud del Principado de Asturias (SESPA), Oviedo, Spain*
[f] *Hospital Universitario Central de Asturias, Laboratorio de Diagnóstico Clínico Hematología, Oviedo, Spain*
[g] *Centro Comunitario de Sangre y Tejidos de Asturias, Oviedo, Spain*
[h] *Department of Emergency Psychiatry & Post-Acute Care, Lapeyronie Hospital, CHU Montpellier - Inserm U1061, University of Montpellier, Montpellier, France*
[i] *Fondation FondaMental, Créteil, France*

Received 19 December 2019; received in revised form 8 May 2020; accepted 9 June 2020
Available online xxx

* Corresponding authors at: Instituto de Investigación Sanitaria del Principado de Asturias (ISPA) and Universidad de Oviedo, Oviedo, Spain.
E-mail addresses: gutierrezglaura@uniovi.es (L. Gutiérrez), frank@uniovi.es (P.A. Sáiz).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.euroneuro.2020.06.006

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

KEYWORDS
Major depressive episode;
Haematopoiesis;
Suicide;
Inflammation;
Sex;
LTE

Abstract
Suicide is the leading cause of non-natural death worldwide, and major depressive disorder (MDD) is the mood disorder with the highest prevalence among individuals with suicidal behaviour (SB). The role of inflammation and immunomodulation in mood disorders has raised interest in recent years, as inflammation biomarkers have been reported to be increased in mood disorder patients, suggesting a role of inflammation in their pathogenesis. The influence of inflammation on the haematopoietic production is well known; however, a comprehensive study of the haematopoietic production in patients with major depressive episodes (MDE) is lacking. We examined global haematopoietic parameters from complete blood counts (CBC) of patients with MDE, in search of prognostic patterns. MDE patients presented differences in several CBC parameters, differences that were clearly pronounced and/or significant in concurrence with suicide attempts (SA). Red and white blood cell lineage parameters were affected, suggesting general haematopoietic modulation or imbalance. We observed distinct haematological parameter changes in women versus men, with men presenting milder alterations than women. Interestingly, we found that the List of Threatening Experiences (LTE) score, but not the Childhood Trauma Questionnaire (CTQ), was associated with the haematopoietic alterations observed exclusively in women and, more importantly, served as a parameter to stratify female MDE patients based on concurrence or non-concurrence with SA. In conclusion, grades of haematopoietic modulation in MDE patients are associated with absence or presence of SA. Haematopoietic manifestations differ between men and women and, in the latter, are markedly influenced by late, and not early, traumatic events.

1. Introduction

Suicide is the leading cause of non-natural death worldwide and the second leading cause of mortality in individuals aged 15–29 years (World Health Organization, 2018), psychiatric disorders and substance abuse being the acknowledged risk factors. Major depressive disorder (MDD) is the most prevalent mood disorder in individuals with suicidal behaviour (SB), depression itself being associated with a 20-fold increase in suicide mortality rate (Osby et al., 2001). Stressors in childhood and adulthood have been associated with suicide attempts (SA), and there is ongoing debate whether early events have a stronger association with SB in comparison with late or recent events (Liu et al., 2017; Ludwig and Dwivedi, 2018). Importantly, individuals who have attempted suicide are at higher risk for future attempts, and a large proportion of them experience self-inflicted injuries or long-term disability, requiring medical attention and follow-up. It is therefore of interest to health systems to develop and rely on more precise personalised algorithms and biomarkers to better predict and prevent SA (Barrigon and Baca-Garcia, 2018). In this direction, efforts have been made to identify different novel biomarkers using high-throughput technologies (GWAS, metabolomics), highlighting the importance of transversal or multidisciplinary approaches to understand mood disorders.

The role of inflammation and immunomodulation in different conditions or pathologies, including mood disorders, has raised interest recently (Pariante, 2017). Inflammation-related biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) (Ekinci and Ekinci, 2017; Ivkovic et al., 2016; Velasco et al., 2020) and C-reactive protein (CRP) (Courtet et al., 2015; Gibbs et al., 2016), have been reported to be increased in mood disorder patients, suggesting a role of inflammation in their pathogenesis and a potential use for these biomarkers as predictors of SB. More recently, NLR and mean platelet volume (MPV) have been related to the severity of SA (Orum et al., 2018). Inflammatory and infectious diseases, including allergy, asthma, and toxoplasmosis, have been associated with SB (Postolache et al., 2008; Zhang et al., 2012). Furthermore, an association has been established between SA, inflammation, and increased risk of morbidity and mortality from natural (cardiometabolic) causes (Bergen et al., 2012). Interestingly, patients treated with pro-inflammatory cytokines demonstrated increased risk of suicidal ideation or SA (Fragoso et al., 2010).

A comprehensive model focusing on the influence of the immune system in the pathophysiology of SB has been proposed (Courtet et al., 2016), where childhood abuse, sleep disturbance, infections, and other stressors induce a chronic inflammatory state causing dysregulation of the hypothalamic-pituitary-adrenal axis, increasing cortisol levels and indolamine 2,3-dioxygenase activation, which results in increased N-methyl-D-aspartate (NMDA) agonist and decreased serotonin levels. All these mechanisms may lead to psychological vulnerability and SB. However, the cause-consequence relationship between psychiatric disorders, SB, and systemic inflammation response and feedback is still largely unknown.

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

Haematopoiesis occurs in an inter-lineage equilibrium, where production of the different haematopoietic cell types that circulate in the blood is tightly regulated, as they need to be constantly replenished due to their short lifespan. A complete blood count (CBC) test measures a number of variables related to the different circulating blood cell-types, and is a *bona fide* portrait of an individual's health status. Hence, complete blood count (CBC) variables follow a given correlation in healthy individuals. When haematopoietic distress, imbalance, or modulation occurs, those correlations are disrupted, because the haematopoietic output shifts depending on the underlying physiological demand. It is well known that in response to external cues (e.g. cytokines during inflammation), the steady state output of the different types of blood cells shifts, usually towards producing higher numbers of innate immune cells (e.g. basophils, neutrophils, etc.), at the expense of erythropoiesis, megakaryopoiesis, and lymphopoiesis (Zhao and Baltimore, 2015). For example, anaemia of inflammation occurs when the body feels a need to increase white blood cell (WBC) production in response to infection, at the expense of red blood cell (RBC) production; in this case, the anaemia is caused by a rise in IL-6 and hepcidin levels, with subsequent inhibition of iron absorption, ultimately resulting in hampered erythropoiesis (Nemeth and Ganz, 2014). In a transgenic mouse model of anaemia of chronic disease, characterised by enhanced CD27-mediated co-stimulation and a strong increase in the production of IFN-γ-producing effector T cells, progressive anaemia is due to inhibition of erythropoiesis through the IRF-1-dependent activation of PU.1 transcription factor in haematopoietic precursors (Libregts et al., 2011). This exemplifies how this balance is self-regulated through transcriptional reprogramming of haematopoietic precursors. Contrariwise, recurrent infections are typical of chronic anaemia patients, as, in these cases, the necessity to increase RBC production negatively influences the commitment and differentiation of lymphoid precursors (Jonker et al., 2017). It has been reported that inflammation influences haematopoiesis at the haematopoietic stem cell level (King and Goodell, 2011). Hence, it is plausible that the sub-clinical inflammation (Köhler et al., 2017) reported in patients with MDE may be accompanied by other alterations in the haematopoietic production, which, we hypothesise, will manifest at different levels depending on SA co-occurrence, sex, and early or late stressors.

In the present study, we examine global haematopoietic parameters from CBCs of MDE patients, with or without SA, and evaluate potential haematopoietic imbalance based on SA co-occurrence, sex, and early or late stressors, with the objective of defining clinical patterns that would contribute to a better prognosis and SB management in these patients.

2. Experimental procedures

2.1. Study sample

We performed a cross-sectional study, including 172 Caucasian participants aged $\geq$ 18 years recruited in the area of Oviedo, Spain, from April 2016 to September 2018. All participants gave informed consent. The study was conducted according to the Declaration of Helsinki (World Medical Association, 2013).

The cohort consisted of 79 patients recruited at the Mental Health Services of Oviedo, diagnosed with MDE according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). The exclusion criteria were comorbid psychiatric diagnoses, acute infection, active or chronic inflammatory or autoimmune diseases, smoking $\geq$ 20 cigarettes/day, obesity (BMI $>$ 30 kg/m^2), current treatment with anti-inflammatory or immunosuppressant drugs, acute coronary syndrome, history of chronic renal, hepatic, or cerebrovascular disease, and reported haematological disorders.

Our control population consisted of 93 healthy active blood donors approved by the regional blood bank (Centro Comunitario de Sangre y Tejidos de Asturias, CCSTA).

2.2. Clinical assessment

Patients were assessed by well-trained interviewers using an *ad hoc* protocol for sociodemographic and clinical data. Psychometric evaluation included the Spanish versions of different scales and questionnaires. We employed the Hamilton Depression Rating Scale (HDRS) (Bobes et al., 2003) to determine severity of depression; the Childhood Trauma Questionnaire-Short Form (CTQ-SF) (Hernandez et al., 2013), a self-report questionnaire, to detect early life stressors (emotional, physical and sexual abuse, and emotional and physical neglect); the List of Threatening Experiences (LTE) to detect twelve stressful life events in the six months prior to the evaluation (Motrico et al., 2013), and the Medical Damage Scale (MDS) (Beck et al., 1975) to score medical damage due to SA, ranging from 0 (none) to 8 (dead).

SA was defined as a "self-initiated sequence of behaviours by an individual who, at the time of initiation, expected that the set of actions would lead to his or her own death" (American Psychiatric Association, 2013).

For every patient, seven days prior to assessment, mean daily antidepressant doses were calculated and standardised to fluoxetine equivalents (Hayasaka et al., 2015).

2.3. CBC analysis

Fasting blood samples were collected in the morning in EDTA tubes. CBCs were performed the same day using a Sysmex XN-10/XN-20 haematology analyser.

2.4. Statistical analysis

Descriptive parameters were shown as mean and standard deviation. In addition, normal distribution was assessed by the Shapiro-Wilk test. A Chi-square test was used for comparison of categorical variables, whereas an unpaired Mann-Whitney *U* test or a Kruskal-Wallis test were used to compare continuous variables among two or more groups, respectively. False discovery rate (FDR) correction was applied to account for multiple comparisons. Correlation analyses were performed by Spearman correlation, followed by FDR correction. Statistical significance was considered p (or q value in the case of FDR correction) $<$ 0.05. All data were analysed using R version 3.6 (R Core Team, 2019), and figures were produced using the ggplot2 package (Wickham, 2009). Principal component analysis (PCA) was performed after scale-to-interval normalisation of variable values using Perseus Software version 1.5.2.6.

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

3. Results

3.1. Patient cohort: socio-demographics and psychiatric evaluation

The study population consisted of 79 MDE patients [mean age (SD): 52.28 (10.56) years; females: 46 (58.2%)], most with MDD [$n = 71$ (89.9%)]. MDE patients were stratified into two major groups based on history of SA (MDE SA) [$n = 48$ (60.8%)] or absence of SA (MDE noSA) [$n = 31$ (39.2%)]. The control group consisted of 93 healthy active blood donors [mean age (SD): 48.22 (11.44) years; females: 40 (43.0%)]. No significant differences between patient groups were identified with regard to sociodemographic characteristics or sex. Age differed considerably between patient and control groups, although *post-hoc* pairwise analysis (Duncan) revealed significant differences only in the MDE noSA group compared with the control group (Table 1 and Supplementary Table 1).

3.2. CBC of MDE patients: grades of haematopoietic modulation associated with SA

The CBCs of all patients were within normal range for all variables analysed, including WBC and differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), RBC count, mean corpuscular volume (MCV), red cell distribution width (RDW), haematocrit (HCT), and haemoglobin-related variables (haemoglobin (Hb), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC)), and platelets and mean platelet volume (PLT, MPV). From these data, the neutrophil-to-lymphocyte (NLR), monocyte-to-lymphocyte (MLR), and platelet-to-lymphocyte (PLR) ratios were calculated (Table 2 and Supplementary Table 1).

Principal component analysis (PCA) was performed on the CBC variables as presented in Supplementary Table 1 (taking into consideration only the WBC differential counts and not the percentages) in order to visualise the clustering of the patients in the different groups and the controls. This analysis revealed that while the clusters of MDE patients without SA (MDE noSA) and the controls overlapped to a large extent, the cluster of MDE patients with SA (MDE SA) presented only a partial overlap with the cluster of controls, with a number of MDE SA patients located very distant from the nucleus (or centre) of the control cluster (Fig. 1). Of note, the MDE SA patients who clearly separated from the control cluster nucleus were females. This data suggests differential clustering of MDE patients, in concurrence with or without SA, based on their CBC measurements.

To identify the variables responsible for this differential clustering, we next compared potential haematological differences in blood samples between the two major subgroups of MDE patients (SA and noSA) and controls. Descriptive analysis revealed significant changes in RBC lineage-related parameters, e.g. RBC count (reduced), MCV (increased), RDW (reduced), MCH (increased), and MCHC (reduced), with no Hb or HCT changes, suggesting signs of stress erythropoiesis in MDE patients. There were no significant changes in WBC counts; however, there was a significant reduction in monocytes and an increase in eosinophils and basophils, suggestive of systemic inflammation. Platelet-related parameters showed a tendency toward thrombocytosis (not significant) with a significant reduction in MPV in MDE patients versus controls. The difference in these variables was significant and/or greater in MDE patients in concurrence with SA, supporting the PCA results. Furthermore, a tendency toward increased NLR and significantly reduced MLR were observed in MDE SA patients (Tables 2 and 3 and Fig. 2).

3.3. Disruption of haematopoietic equilibrium in MDE patients

We next evaluated the haematological equilibrium of CBC variables by studying their correlations in MDE patients versus controls, with the hypothesis that the identified differences and differential clustering observed in the PCA analysis could be explained by the loss of canonical or appearance of *de novo* correlations, supporting the notion of haematopoietic distress or production imbalance.

In fact, the significant correlations identified in the control group, and thus, the normal equilibrium of haematopoietic production, were gradually disrupted in MDE patients, with increasing severity associated with concurrence of SA (Fig. 3). Interestingly, we observed new significant correlations of haematopoietic variables that would indicate an imbalance of haematopoiesis not present in the control group. This imbalance would suggest an incipient shift favouring WBC lineage at the expense of RBC lineage production (Fig. 3).

3.4. Sex and haematopoietic modulation in MDE

It is well known that some haematological parameters from a CBC depend on age and sex (Cheng et al., 2004; Qiao et al., 2014); therefore we performed multiple regression analyses, which allowed us to identify the haematological parameters dependent on or influenced by these variables in our cohort of patients and controls (Table 2). As is already known, females presented slightly reduced RBC count, Hb, HCT, and MCH compared with males. Contrariwise, females displayed significantly higher platelet numbers. This also explains the differential clustering of male and female individuals in the PCA (Fig. 1). Additionally, we observed age-related differences that, although small, were still significant; i.e. the RDW % was higher in older individuals while the opposite was true for lymphocyte counts (Table 2).

It was therefore important to study whether the haematopoietic imbalance observed in our cohort was maintained when the sexes were studied separately and whether it would impact males and females equally. Therefore, we next performed the same comparative analysis after stratification of our cohort based on sex. Of note, the difference observed in age in the global population (MDE noSA vs controls) disappeared in women after stratifying our cohort, but persisted in men (data not shown).

We observed increased SA-associated haematopoietic imbalance both in men and women; however, both sexes presented particularities and separate haematopoietic modulation profiles. While females experienced the most evi-

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

Table 1 Sociodemographic and clinical data. SD: Standard deviation; HDRS: Hamilton Depression Rating Scale; MDE: Major Depressive Episode; SA: Suicide attempt; noSA: No suicide attempt; MDS: Medical Damage Score; LTE: List of Threatening Experiences; CTQ: Childhood Trauma Questionnaire; SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; NDRI: Norepinephrine Dopamine Reuptake Inhibitor;[1] Statistically different (Post-hoc Duncan test).

	MDE	MDE SA	MDE noSA	Healthy controls	MDE	MDE + Controls
	$n = 79$	$n = 48$	$n = 31$	$n = 93$	X^2 */T test (p)	X^2 */ANOVA (p)
Sex [n (%)]						
Males	33 (41.8%)	18 (37.5%)	15 (48.4%)	53 (57.0%)	0.918* (0.338)	4.849* (0.089)
Females	46 (58.2%)	30 (62.5%)	16 (51.6%)	40 (43.0%)	1.414 (0.162)	**3.810 (0.024)**
Age [Mean (SD)]	52.28 (10.56)	50.94 (9.71)	54.35 (11.61) [1]	48.22 (11.44)[1]		
Diagnosis [n (%)]						
Major Depressive Disorder	71 (89.9%)	43 (89.6%)	28 (90.3%)		0.011* (0.915)	
Bipolar Disorder	8 (10.1%)	5 (10.4%)	3 (9.7%)			
HDRS [Mean (SD)]	21.15 (4.21)	21.04 (4.56)	21.32 (3.67)		0.288 (0.774)	
Number of SA [Mean (SD)]	-	2.58 (2.53)	-		-	
Age of 1st SA [Mean (SD)]	-	39.71 (13.64)	-		-	
MDS [Mean (SD)]	-	3.17(1.45)	-		-	
LTE [Mean (SD)]	2.99 (2.44)	3.25 (2.99)	2.58 (1.12)		−1.193 (0.237)	
CTQ Total Score [Mean (SD)]	51.09 (17.90)	53.94 (19.93)	46.77 (13.45)		−1.894 (0.062)	
CTQ Physical Abuse [Mean (SD)]	6.64 (3.39)	7.13 (4.07)	5.90 (1.78)		−1.817 (0.074)	
CTQ Sexual Abuse [Mean (SD)]	6.82 (4.34)	7.32 (4.81)	6.06 (3.42)		−1.344 (0.183)	
CTQ Emotional Abuse [Mean (SD)]	8.88 (4.62)	9.45 (4.86)	8.03 (4.16)		−1.331 (0.187)	
CTQ Physical Neglect [Mean (SD)]	8.41 (3.83)	8.85 (3.71)	7.74 (3.98)		−1.256 (0.213)	
CTQ Emotional Neglect [Mean (SD)]	11.03 (5.40)	11.64 (5.48)	10.10 (5.21)		−1.239 (0.219)	
Pharmacological Treatment [n (%)]	74 (93.7%)	46 (95.8%)	28 (90.3%)		0.965* (0.326)	
Antidepressant equivalent to fluoxetine 40 mg/day [Mean (SD)]	45.21 (19.08)	45.74 (20.71)	44.36 (16.41)		−0.316 (0.766)	
SSRI [n (%)]	26 (32.9%)	17 (35.4%)	9 (29.0%)		0.348* (0.555)	
SNRI [n (%)]	36 (45.6%)	21 (43.6%)	15 (48.4%)		0.163* (0.686)	
NDRI [n (%)]	7 (8.9%)	4 (8.3%)	3 (9.7%)		0.042* (0.837)	
Others [n (%)]	36 (45.6%)	23 (47.9%)	13 (41.9%)		0.272* (0.602)	
Mood Stabilisers [n (%)]	10 (12.7%)	7 (14.6%)	3 (9.7%)		0.410* (0.522)	
Antipsychotics [n (%)]	32 (40.5%)	23 (47.9%)	9 (29.0%)		2.787* (0.095)	
Benzodiazepines [n (%)]	67 (84.8%)	43 (89.6%)	24 (77.4%)		2.163* (0.141)	
Others [n (%)]	12 (15.18%)	6 (12.5%)	6 (19.4%)		0.687* (0.407)	
Tobacco consumption [n (%)]						
Yes	36 (45.6%)	20 (41.7%)	16 (51.6%)		0.751* (0.386)	
No	43 (54.4%)	28 (58.3%)	15 (48.4%)			
No. of cigarettes/day [Mean (SD)]	15.19 (9.56)	13.35 (5.76)	17.50 (12.70)		1.307 (0.200)	

dent changes, these were not always significantly altered in males (Table 3). Regarding RBC lineage, a significant increase in RBC count with no change in RDW was observed in MDE females; however, in males, the MCV and RDW changes were significant only in concurrence with SA (Fig. 4). RDW is affected by age, as our analysis showed (Table 2), but since age was different in the MDE noSA group and the significant difference was detected in the MDE SA group, we consider our results valid. These data suggest that females with MDE are more prone to experience haematological imbalance, affecting both the RBC and WBC lineages, while men present overall milder alterations.

3.5. CTQ and LTE scores and haematopoietic modulation in MDE

Further analyses were conducted to evaluate the associations between stressors during childhood and adulthood, as assessed using CTQ and LTE scores, respectively, and the

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

Table 2 Complete blood parameters in the patient and control groups. Variables are summarised as mean (standard deviation). Differences between the MDE SA and MDE noSA groups and the healthy controls were assessed by one-way Kruskal-Wallis test. Variables with significant differences ($p < 0.05$) are highlighted in bold. MDE: Major Depressive Episode; SA: Suicide attempt; noSA: No suicide attempt; WBC: white blood cell count; RBC: red blood cell count; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; RDW: red cell distribution width; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio.

	MDE $N = 79$	MDE SA $N = 48$	MDE noSA $N = 31$	Healthy controls $N = 93$	One-way Kruskal-Wallis p	Sex adjusted p	Age adjusted p
WBC ($10^3/\mu L$)	7.47 (2.25)	7.82 (2.38)	6.93 (1.94)	7.11 (1.66)	0.205	1	1
RBC ($10^6/\mu L$)	4.73 (0.46)	4.69 (0.43)	4.79 (0.49)	4.90 (0.38)	**0.017**	**< 0.001**	1
Haemoglobin (g/dL)	14.31 (1.54)	14.17 (1.60)	14.51 (1.44)	14.56 (1.11)	0.460	**< 0.001**	1
Haematocrit (%)	42.49 (4.03)	42.25 (4.12)	42.86 (3.93)	42.34 (2.79)	0.945	**< 0.001**	1
MCV (fL)	89.76 (5.22)	89.87(6.35)	89.59 (2.75)	86.52 (3.94)	**< 0.001**	1	1
MCH (pg)	31.83 (9.84)	32.80 (12.54)	30.33 (1.29)	29.73 (1.50)	**0.006**	**< 0.001**	1
MCHC (g/dL)	33.73 (1.29)	33.65 (1.45)	33.85 (1.00)	34.37 (1.00)	**0.003**	1	1
RDW (%)	13.39 (1.24)	13.41 (1.41)	13.36 (0.96)	13.70 (1.01)	**0.022**	1	**< 0.001**
Neutrophils ($10^3/\mu L$)	4.23 (1.84)	4.54 (2.02)	3.74 (1.39)	3.95 (1.29)	0.109	1	1
Lymphocytes ($10^3/\mu L$)	2.38 (0.84)	2.41 (0.87)	2.35 (0.81)	2.31 (0.78)	0.835	1	**< 0.001**
Monocytes ($10^3/\mu L$)	0.56 (0.17)	0.57 (0.16)	0.55 (0.19)	0.64 (0.18)	**0.012**	1	1
Eosinophils ($10^3/\mu L$)	0.24 (0.15)	0.25 (0.15)	0.21 (0.14)	0.19 (0.12)	0.043	1	1
Basophils ($10^3/\mu L$)	0.05 (0.02)	0.06 (0.02)	0.05 (0.02)	0.03 (0.01)	**< 0.001**	1	1
Platelets ($10^3/\mu L$)	252.16 (68.97)	260.08 (80.56)	239.90 (44.09)	244.25 (60.63)	0.540	**< 0.001**	1
MPV (fL)	10.83 (0.80)	10.80 (0.81)	10.89 (0.78)	11.29 (0.94)	**0.008**	1	1
NLR	1.97 (1.35)	2.17 (1.66)	1.68 (0.57)	1.87 (0.80)	0.510	1	1
PLR	117.26 (53.49)	122.39 (64.51)	109.30 (28.50)	117.99 (54.77)	0.952	1	1
MLR	0.26 (0.11)	0.26 (0.12)	0.25 (0.08)	0.30 (0.13)	**0.017**	1	1

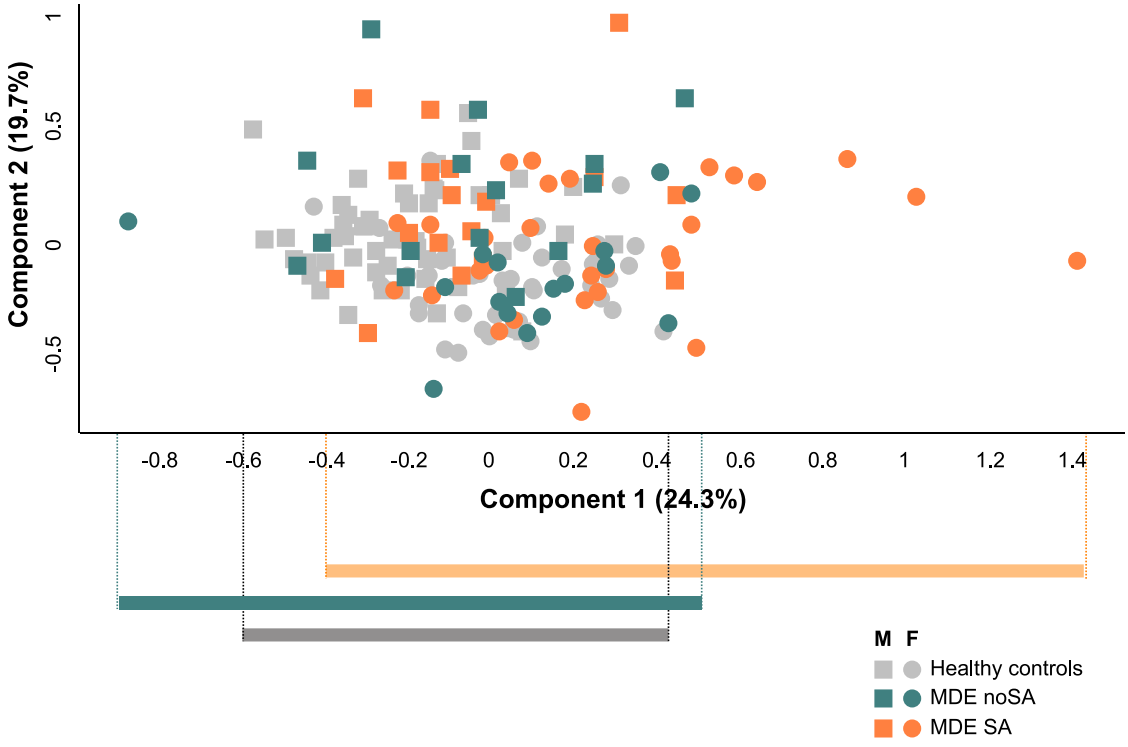


Fig. 1 Principal component analysis (PCA) of haematological parameters in MDE patients and healthy controls shows distinct clustering of samples depending on co-occurrence of SA.
PCA of haematological parameters performed on MDE patients (MDE noSA, MDE SA, and controls) is depicted.

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

Table 3 Differences between patient groups, stratified by severity of MDE (SA/noSA) and sex, and healthy controls were evaluated by the Mann-Whitney *U* test, and the False Discovery Rate (FDR, *q* value) is indicated. Variables with significant differences are highlighted in bold. Ratios show the relationship between the means of each patient group and the healthy controls for each haematological parameter. MDE: Major Depressive Episode; SA: Suicide attempt; noSA: No suicide attempt; WBC: white blood cell count; RBC: red blood cell count; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; RDW: red blood cell distribution width; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio.

	Global				Male				Female			
	MDE SA		MDE noSA		MDE SA		MDE noSA		MDE SA		MDE noSA	
	q	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio
WBC ($10^3/\mu L$)	0.236		0.722		0.687		0.811		0.726		0.134	**0.85**
RBC ($10^6/\mu L$)	**0.02**	**0.96**	0.218		0.638		0.811		0.190		0.309	
Haemoglobin (g/dL)	0.342		0.676		0.856		0.914		0.797		0.630	
Haematocrit (%)	0.884		0.947		0.687		0.811		0.698		0.576	
MCV (fL)	**< 0.001**	**1.04**	**< 0.001**	**1.04**	**0.04**	**1.03**	0.153		**0.005**	**1.04**	**0.003**	**1.04**
MCH (pg)	**0.02**	**1.10**	0.125		0.056		0.365		0.182		0.409	
MCHC (g/dL)	**0.02**	**0.98**	0.077		0.130		0.811		0.190		**0.02**	**0.98**
RDW (%)	**0.02**	**0.98**	0.218		**0.04**	**0.96**	0.351		0.660		0.630	
Neutrophils ($10^3/\mu L$)	0.193		0.558		0.587		0.811		0.726		0.128	
Lymphocytes ($10^3/\mu L$)	0.656		0.947		0.995		0.811		0.732		0.521	
Monocytes ($10^3/\mu L$)	**0.03**	**0.88**	0.089		0.587		0.860		0.153		**0.031**	**0.71**
Eosinophils ($10^3/\mu L$)	**0.03**	**1.34**	0.558		0.242		0.365		0.190		0.978	
Basophils ($10^3/\mu L$)	**< 0.001**	**2.05**	**< 0.001**	**1.81**	**0.001**	**1.87**	**0.009**	**1.88**	**< 0.001**	**2.27**	**0.031**	**1.78**
Platelets ($10^3/\mu L$)	0.386		0.993		0.812		0.994		0.726		0.921	
MPV (fL)	**0.020**	**0.96**	0.111		0.242		0.145		0.153		0.693	
NLR	0.545		0.676		0.812		0.811		0.855		0.309	
PLR	0.998		0.917		0.964		0.811		0.883		0.921	
MLR	**0.02**	**0.88**	0.218		0.638		0.990		0.112		0.128	

haematopoietic modulation observed in MDE patients, with or without stratification based on sex.

First, we studied the distribution of CTQ and LTE scores in our patient cohort. Although there was a tendency towards a progressive increase in those scores from lower in MDE noSA patients to higher in MDE SA patients, there were no significant changes in CTQ nor LTE scores (data not shown). In order to analyse the association of CTQ and LTE scores with the haematopoietic imbalance observed in MDE patient subgroups, we generated new ratio variables calculated as "haematopoietic parameter value vs CTQ or LTE score" per patient (Table 4) in the global MDE cohort and after stratification based on sex. This analysis showed that LTE (and not CTQ) was associated with the haematological alterations observed in females only, and that the ratios calculated with all the RBC lineage parameters and those calculated with lymphocytes and monocytes as part of the WBC differential clearly separated SA from noSA in females (Fig. 5). These results suggest that females are more susceptible to developing signs of haematopoietic distress, that this imbalance is more severe in concurrence with SA, and that the correlation of all RBC lineage parameters and some of the WBC parameters with the LTE score clearly separates SA from noSA in female patients with MDE.

4. Discussion

We examined global haematological parameters from CBCs of MDE patients, with or without SA, and evaluated potential haematopoietic modulation, imbalance or distress due to co-occurrence of SA, and how sex and early or late stressors may influence potential haematopoietic modulation manifestations in MDE patients.

We suggest that the haematopoietic imbalance observed in these patients goes beyond the inflammatory status previously reported by others (Courtet et al., 2016, 2015; Ekinci and Ekinci, 2017; Gibbs et al., 2016; Glaus et al., 2018a, b; Ivkovic et al., 2016; Kayhan et al., 2017; Liu et al., 2012; Mazza et al., 2019; Miller and Raison, 2016; Orum et al., 2018). Haematopoietic imbalance, modulation, or distress refers to the physiological response of the haematopoietic system to a certain stimulus, which causes loss of the haematopoietic production equilibrium. This loss of equilibrium may not affect single variables (as the normal ranges for some of them are considerably wide), and hence, CBCs as such may be within the normal range. However, since the haematopoietic production is so tightly regulated, correlations amongst variables start to be lost even when shifts of variables are still present within the normal range, but deviate from the values and correlations measured in a given individual under healthy conditions. A simple cold, which is transitory, will induce such distress. Furthermore, studying a given variable, like the red blood cell count, in a certain patient cohort, such as the one as we present in this manuscript, may show a skewed distribution towards a minimum threshold -still within the normal range-, while in healthy donors, the distribution is evenly dispersed within the top and bottom limits. While it is important to ac-

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

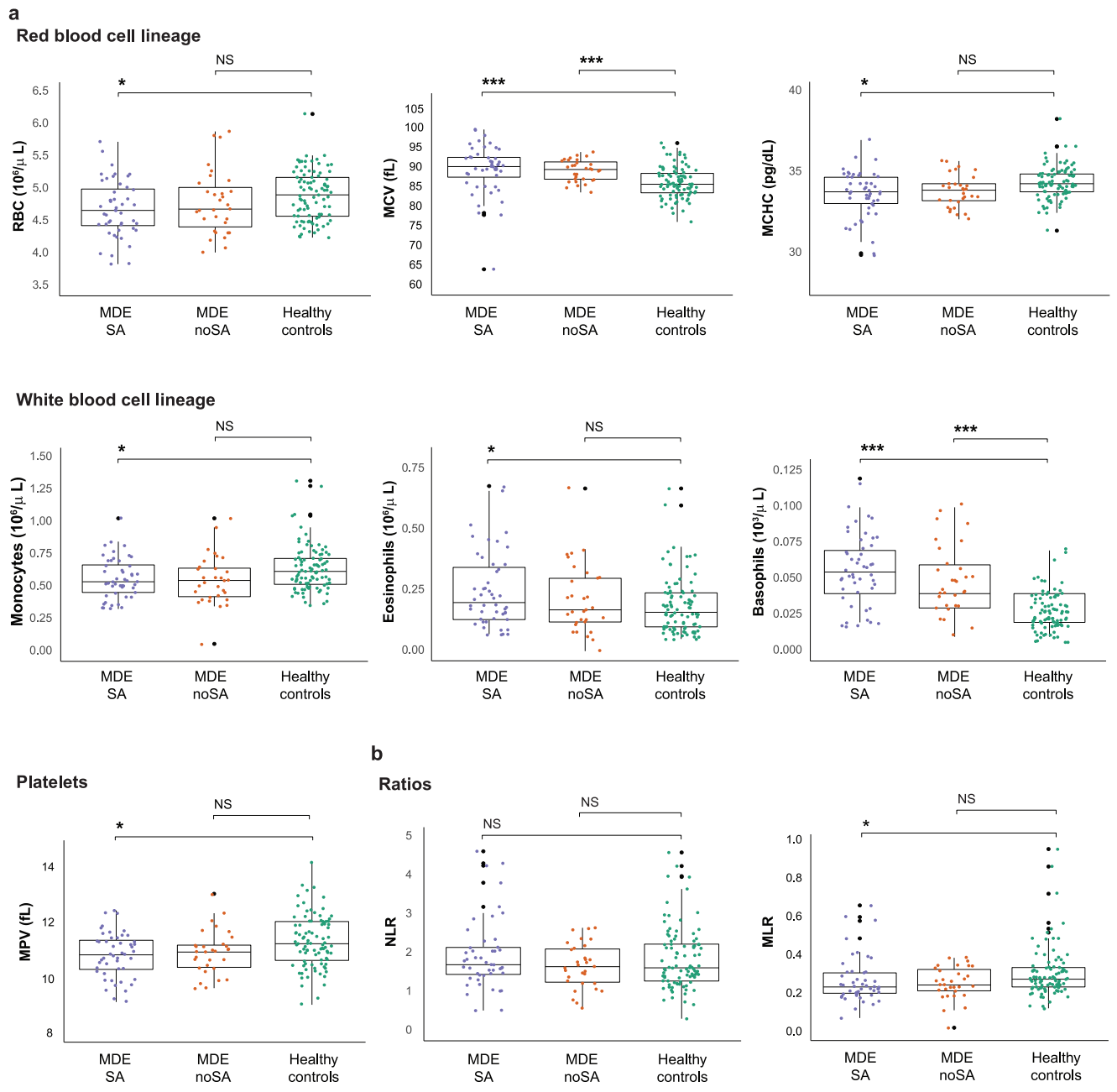


Fig. 2 Haematological parameters are affected in MDE patients and changes are more pronounced in co-occurrence with SA. (a) Box plots of selected haematological parameters from the CBCs of MDE patients (SA and noSA) and healthy controls. Top row depicts some parameters of the RBC lineage. Middle row depicts some parameters of the WBC lineage differential. Lower row depicts the mean platelet volume. (b) Box plots of calculated ratios. RBC, red blood cell; MCV, mean corpuscular volume; MCHC, mean corpuscular haemoglobin concentration; MPV, mean platelet volume; NLR, neutrophil-lymphocyte ratio; and MLR, monocyte-lymphocyte ratio. $^{*}p < 0.05$ and *** $p < 0.001$. NS: not significant.

knowledge that CBCs of all patients were within the normal range, we observed clear signs of stress erythropoiesis (reduced RBC and RDW with increased MCV) accompanying inflammation (decreased monocytes and increased basophils and eosinophils). The tendency toward increased platelet counts, although not significant, along with reduced MPV, are suggestive of reactive thrombocytosis and platelet vesiculation, which is normally present in acute phase response or systemic inflammation. All these changes were more pronounced or significant in MDE patients in co-occurrence with SA. Furthermore, the equilibrium of the haematopoietic production, as exemplified by haematological variable correlation matrixes, showed a disappearance of many correlations and the appearance of *de novo* correlations in MDE patients versus controls. These data, taken together, suggest increasing grades of haematopoietic modulation/distress in MDE patients (associated with SA), indicative of inflammation (as previously reported), but also

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

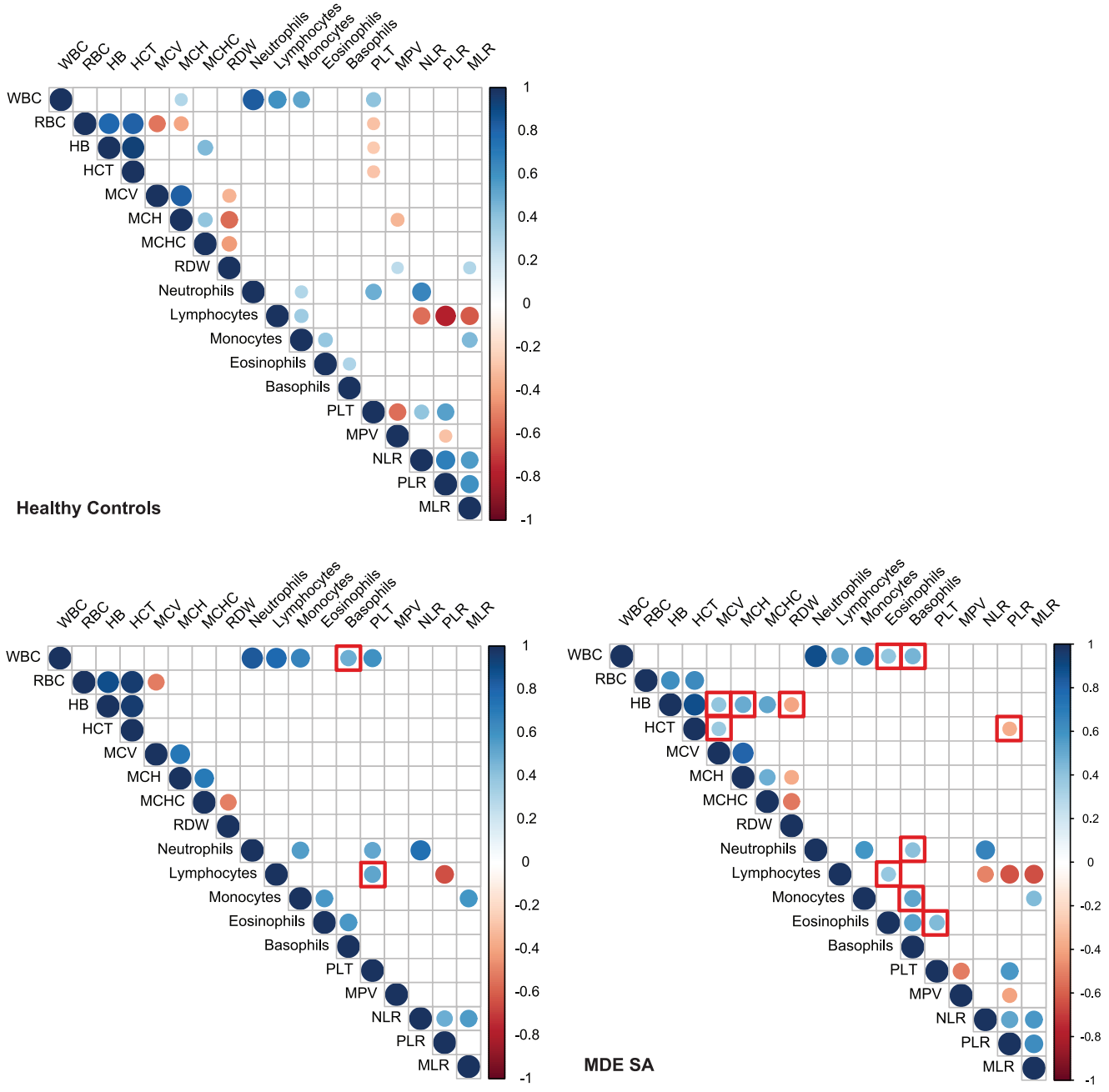


Fig. 3 Correlation of haematological parameters is disturbed in MDE patients.
Correlation matrixes of haematological parameters in MDE patients (noSA and SA) and healthy controls are depicted. Significant correlations are shown by different sized circles, indicating the strength of the slope. Direct correlations are coloured blue, while negative correlations are coloured red. Note that many correlations identified in the healthy control group disappear in MDE patients. *De novo* correlations are framed in a red-line square. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

indicative of underlying or onset of stress erythropoiesis. Changes in haematological parameters in mood disorders have been previously reported, including the appearance of specific correlations as we report in this study (Wysokinski and Szczepocka, 2016, 2018). In some reports, the tendencies observed are the opposite (increased RDW vs decreased RDW as we observed) (Demircan et al., 2016). Heterogeneity among study cohorts (probably due to sociodemographic and environmental factors) and sample size may condition this discrepancy, separating inflammation-associated erythroid stress due to iron deficiency (or malabsorption) from other types of dyserythropoiesis. Furthermore, the variables affected by sex (i.e. RBC, HB, HCT, MCH, and PLT) or by age (RDW and lymphocyte count) suggest that correction or

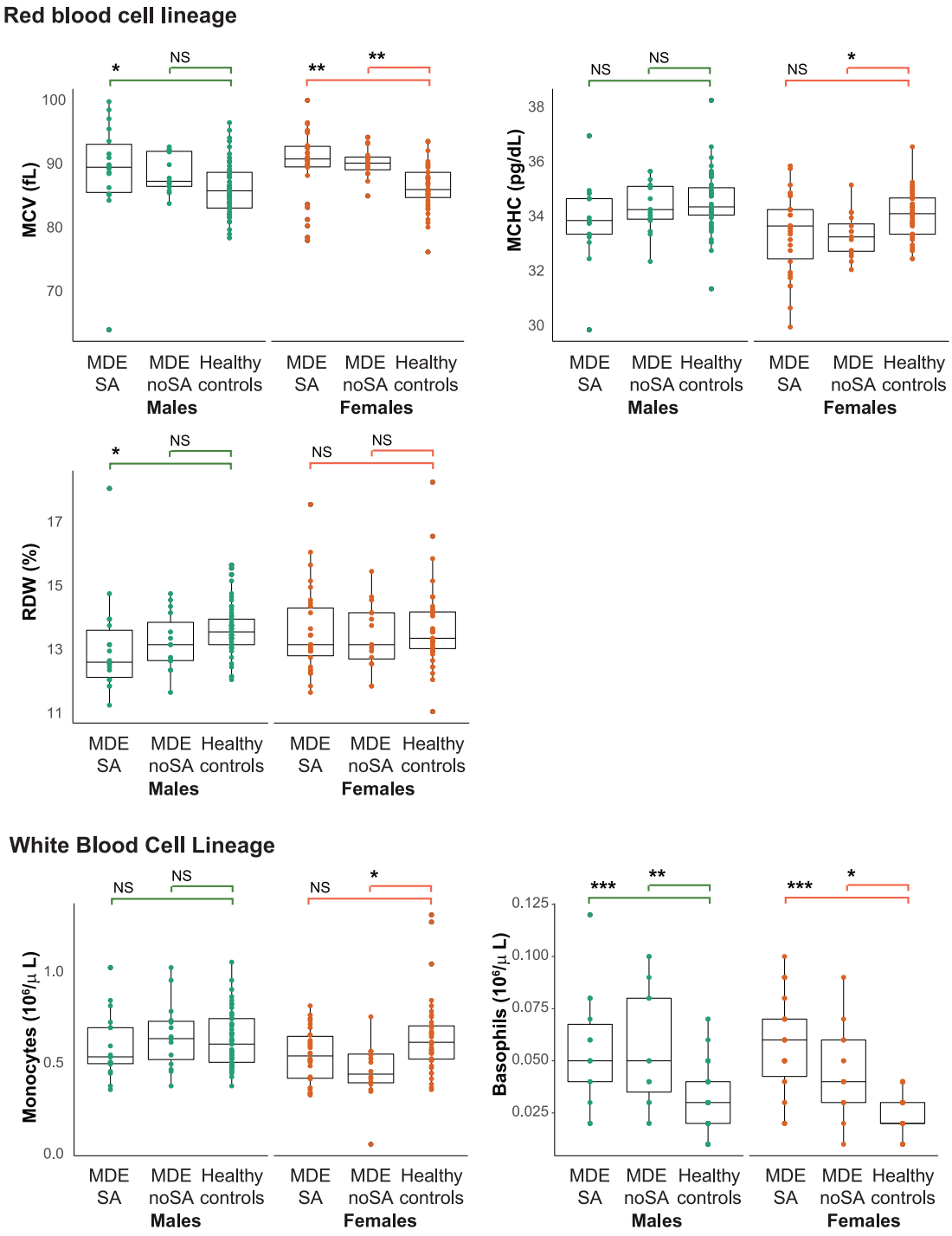


Fig. 4 Sex associates with a distinct haematopoietic modulation response in MDE patients.
Box plots depicting MCV (mean corpuscular volume), MCHC (mean corpuscular haemoglobin concentration), RDW (red cell distribution width), and monocyte and basophil counts in MDE patients with or without SA (SA and noSA, respectively) compared with healthy controls, stratified by sex. $^{*}p < 0.05$, $^{**}p < 0.005$ and $^{***}p < 0.001$. NS, not significant.

stratification should be done to study the haematological component rigorously.

Our data highlight reduced monocytes and reduced MLR as potential markers that separate SA from noSA MDE. A possible explanation of the reduced peripheral blood monocyte counts and percentages in our cohort is the recruitment of activated monocytes to the central nervous system, becoming active players in the described neuro-inflammation of mood disorders (Weber et al., 2017).

We next assessed whether sex may condition a distinct response regarding the identified haematopoietic modulation in MDE patients. This is relevant, since many of the

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

Table 4 Differences between the CBC vs CTQ/LTE ratios of patient groups, stratified by severity of MDE (SA/noSA) and sex, and healthy controls were evaluated by the Mann-Whitney *U* test, and the False Discovery Rate (FDR, *q* value) is indicated. Variables with significant differences are highlighted in bold. Ratios show the relationship between the means of each patient group and the healthy controls for each haematological parameter. MDE: Major Depressive Episode; SA: Suicide attempt; noSA: No suicide attempt; WBC: white blood cell count; RBC: red blood cell count; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; RDW: red blood cell distribution width; MPV: mean platelet volume; NLR; neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio.

	Global				Male				Female			
	CTQ		LTE		CTQ		LTE		CTQ		LTE	
	q	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio
WBC ($10^3/\mu L$)	0.943		0.288		0.841		1		0.802		0.305	
RBC ($10^6/\mu L$)	0.460		0.108		0.740		1		0.802		**0.022**	**0.631**
Haemoglobin (g/dL)	0.460		0.108		0.662		1		0.802		**0.026**	**0.630**
Haematocrit (%)	0.460		0.108		0.662		1		0.802		**0.022**	**0.633**
MCV (fL)	0.460		0.117		0.662		1		0.802		**0.022**	**0.642**
MCH (pg)	0.623		0.136		0.797		1		0.802		**0.022**	**0.644**
MCHC (g/dL)	0.460		0.127		0.662		1		0.802		**0.022**	**0.645**
RDW (%)	0.491		0.108		0.662		1		0.802		**0.024**	**0.641**
Neutrophils ($10^3/\mu L$)	0.623		0.219		0.797		1		0.802		0.118	
Lymphocytes ($10^3/\mu L$)	0.460		0.063		0.662		1		0.802		**0.011**	**0.565**
Monocytes ($10^3/\mu L$)	0.219		0.063		0.662		1		0.802		**0.011**	**0.587**
Eosinophils ($10^3/\mu L$)	0.797		0.621		0.810		1		0.872		0.591	
Basophils ($10^3/\mu L$)	0.623		0.244		0.797		1		0.802		0.157	
Platelets ($10^3/\mu L$)	0.797		0.621		0.882		1		0.802		0.592	
MPV (fL)	0.623		0.127		0.662		1		0.915		0.090	
NLR	0.623		0.159		0.662		1		0.991		0.283	
PLR	0.943		0.987		0.797		1		0.802		0.831	
MLR	0.943		0.521		0.797		1		0.872		0.540	

symptoms associated with mood disorders suggest an autoimmune background, and women have a higher prevalence of autoimmune disorders (Rainville and Hodes, 2019). Sex-related differences in levels of inflammation markers have been previously reported (Majd et al., 2018). Indeed, we observed that changes were more pronounced in women versus men, and some of the variables followed a different pattern. Our analyses suggest that MDE females are prone to develop a cumulative increase in haematological changes, which indicate or are associated with systemic inflammation. The increase in MCV could be a reflection of haematopoietic imbalance due to a consolidated systemic immune response, which induces haematopoietic production compensation shifts at the expense of RBC production. On the other hand, our data suggest that MDE males have reduced haematopoietic alterations compared to MDE females, with signs of mild ineffective erythroid production (extrapolated from RDW values) and mild signs of systemic inflammation in association with SA.

Next, we evaluated whether the identified haematopoietic imbalance in MDE associates with early or late stressors, as there is a long-standing debate about how traumatic events in childhood may confer vulnerability to SB in MDE patients (Liu et al., 2017; Nelson et al., 2017). Interestingly, despite not finding an association of CTQ or LTE with MDE regardless of the presence of SA, we observed an association of alterations in haematopoietic parameters with the LTE score in females only. All these results suggest that stressors during adulthood seem to be a major factor contributing to the severity of the haematopoietic modulation observed in MDE patients, which associates with SA in females.

The study was performed in Caucasians, which limits the extrapolation of our observations to other ethnicities. However, our MDE cohort excluded individuals with severe chronic illness and those treated with anti-inflammatory drugs, to prevent confounders in the analysis. In addition, we performed the analysis on MDE patients and evaluated the impact of changes and correlations of haematological parameters versus a healthy control group, which adds power to the clinical significance of the haematopoietic modulation of interest. However, this study is of exploratory nature, and the cross-sectional design and reduced N of the cohort may compromise our conclusions. Along this line, we did not see a significant increase in the NLR in MDE SA patients (although there was a tendency), while the MLR was significantly reduced in concurrence with SA. We recently postulated NLR as a biomarker of suicidal behaviour, however in a much larger cohort (Velasco et al., 2020).

We conclude from our observations that grades of haematopoietic modulation in MDE patients associate with co-occurrence of suicide attempts. Interestingly, haematopoietic manifestations differed between men and women and were markedly influenced by late but not early

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

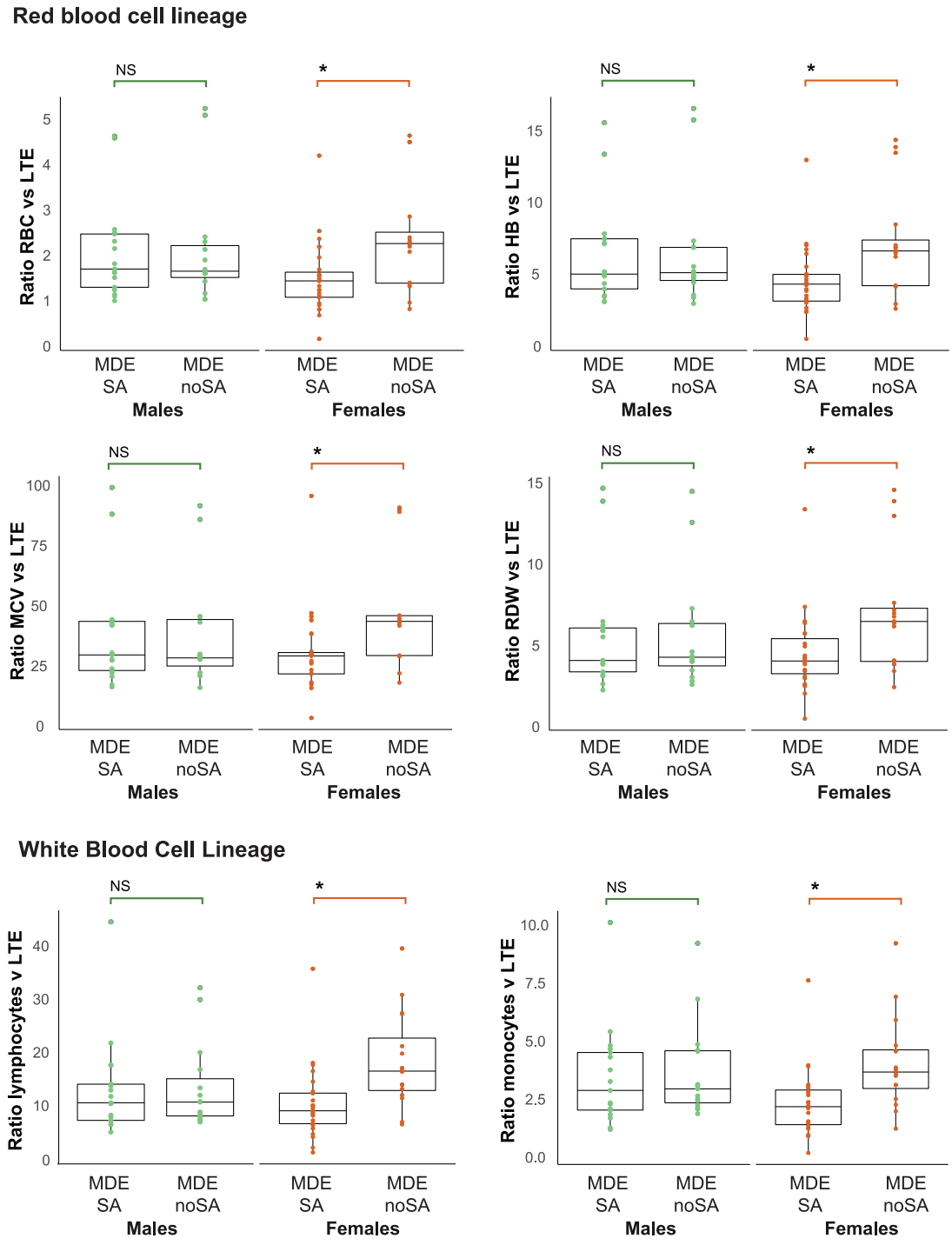


Fig. 5 Stressors and sex association with haematopoietic modulation in MDE patients.
Box plots depicting ratios of CBC parameters vs LTE scores are depicted, stratified by sex. In the upper half of the figure, the ratios calculated with red blood cell lineage parameters are depicted, and in the bottom, those calculated with white blood cell parameters are depicted. $^{*}p < 0.05$. NS, not significant.

traumatic events exclusively in females. We hypothesise that haematopoietic imbalance could be an underlying basis for systemic changes, including those affecting the immune response and inflammation. How these haematological arms regulate each other in the context of mood disorders remains to be elucidated, a question that we will pursue by studying larger independent cohorts and implementing a mathematical model of CBC variables, in combination with molecular and cell biology studies.

Conflict of interest

All authors declare no conflict of interest relative to this study.

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006

Role of funding source

This research was partially supported by grants FIS PI14/02029 and PI17/01433 (PI: P. A. S.) of the Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness, and Fondos Europeos de Desarrollo Regional (FEDER), by the Government of the Principality of Asturias PCTI-2018-2022 IDI/2018/235, by an RYC fellowship (RYC-2013-12587) to L.G., and an I+D 2017 grant (SAF2017-85489-P) to L. G. and P. M.-B. Finally, L. F.-T, A. V., and P. M.-B. received a Severo Ochoa grant (PA-17-PF-B16-179, PA-18-PF-BP17-177, and PA-20-PF-BP19-014, respectively) supported by the Principado de Asturias government. La Fundación para la Investigación e Innovación Biosanitaria del Principado de Asturias (FINBA) partially supported this study. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Contributors

PMB, AV, and VR analysed and interpreted the data and wrote the manuscript; AV, LJT, LFT, LGA, LGB, JRR, MPGP, JB, and PAS followed up patients and performed/assisted in evaluations; AB, TA, and MCMT performed CBC counts of blood samples and assessed the haematological analysis and data interpretation of the study; LG and PAS designed the study, analysed data, contributed to data interpretation, and wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank Lorena Rodríguez Lorenzo and Begoña García Méndez for their technical support and Sharon Grevet for her assistance with English editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2020.06.006.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Publishing, Arlington, VA.

Barrigon, M.L., Baca-Garcia, E., 2018. Current challenges in research in suicide. Rev. Psiquiatr. Salud Ment. 11, 1–3.

Beck, A.T., Beck, R., Kovacs, M., 1975. Classification of suicidal behaviors: I. Quantifying intent and medical lethality. Am. J. Psychiatry 132, 285–287.

Bergen, H., Hawton, K., Waters, K., Ness, J., Cooper, J., Steeg, S., Kapur, N., 2012. Premature death after self-harm: a multicentre cohort study. Lancet 380, 1568–1574.

Bobes, J., Bulbena, A., Luque, A., Dal-Re, R., Ballesteros, J., Ibarra, N.Grupo de Validacion en Espanol de Escalas, P., 2003. [A comparative psychometric study of the Spanish versions with 6, 17, and 21 items of the Hamilton depression rating scale]. Med. Clin. Barc 120, 693–700.

Cheng, C.K., Chan, J., Cembrowski, G.S., van Assendelft, O.W., 2004. Complete blood count reference interval diagrams derived from NHANES III: stratification by age, sex, and race. Lab. Hematol. 10, 42–53.

Courtet, P., Giner, L., Seneque, M., Guillaume, S., Olie, E., Ducasse, D., 2016. Neuroinflammation in suicide: toward a comprehensive model. World J. Biol. Psychiatry 17, 564–586.

Courtet, P., Jaussent, I., Genty, C., Dupuy, A.M., Guillaume, S., Ducasse, D., Olie, E., 2015. Increased CRP levels may be a trait marker of suicidal attempt. Eur. Neuropsychopharmacol. 25, 1824–1831.

Demircan, F., Gozel, N., Kilinc, F., Ulu, R., Atmaca, M., 2016. The impact of red blood cell distribution width and neutrophil/lymphocyte ratio on the diagnosis of major depressive disorder. Neurol. Ther. 5, 27–33.

Ekinci, O., Ekinci, A., 2017. The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. Nord. J. Psychiatry 71, 574–580.

Fragoso, Y.D., Frota, E.R., Lopes, J.S., Noal, J.S., Giacomo, M.C., Gomes, S., Goncalves, M.V., da Gama, P.D., Finkelsztejn, A., 2010. Severe depression, suicide attempts, and ideation during the use of interferon beta by patients with multiple sclerosis. Clin. Neuropharmacol. 33, 312–316.

Gibbs, H.M., Davis, L., Han, X., Clothier, J., Eads, L.A., Caceda, R., 2016. Association between C-reactive protein and suicidal behavior in an adult inpatient population. J. Psychiatr. Res. 79, 28–33.

Glaus, J., von Kanel, R., Lasserre, A.M., Strippoli, M.F., Vandeleur, C.L., Castelao, E., Gholam-Rezaee, M., Marangoni, C., Wagner, E.N., Marques-Vidal, P., Waeber, G., Vollenweider, P., Preisig, M., Merikangas, K.R., 2018a. The bidirectional relationship between anxiety disorders and circulating levels of inflammatory markers: results from a large longitudinal population-based study. Depress. Anxiety 35, 360–371.

Glaus, J., von Kanel, R., Lasserre, A.M., Strippoli, M.F., Vandeleur, C.L., Castelao, E., Gholam-Rezaee, M., Marangoni, C., Wagner, E.N., Marques-Vidal, P., Waeber, G., Vollenweider, P., Preisig, M., Merikangas, K.R., 2018b. Mood disorders and circulating levels of inflammatory markers in a longitudinal population-based study. Psychol. Med. 48, 961–973.

Hayasaka, Y., Purgato, M., Magni, L.R., Ogawa, Y., Takeshima, N., Cipriani, A., Barbui, C., Leucht, S., Furukawa, T.A., 2015. Dose equivalents of antidepressants: evidence-based recommendations from randomized controlled trials. J. Affect. Disord. 180, 179–184.

Hernandez, A., Gallardo-Pujol, D., Pereda, N., Arntz, A., Bernstein, D.P., Gaviria, A.M., Labad, A., Valero, J., Gutierrez-Zotes, J.A., 2013. Initial validation of the Spanish childhood trauma questionnaire-short form: factor structure, reliability and association with parenting. J. Interpers. Violence 28, 1498–1518.

Ivkovic, M., Pantovic-Stefanovic, M., Dunjic-Kostic, B., Jurisic, V., Lackovic, M., Totic-Poznanovic, S., Jovanovic, A.A., Damjanovic, A., 2016. Neutrophil-to-lymphocyte ratio predicting suicide risk in euthymic patients with bipolar disorder: moderatory effect of family history. Compr. Psychiatry 66, 87–95.

Jonker, F.A.M., Te Poel, E., Bates, I., Boele van Hensbroek, M., 2017. Anaemia, iron deficiency and susceptibility to infection in children in sub-Saharan Africa, guideline dilemmas. Br. J. Haematol. 177, 878–883.

Kayhan, F., Gunduz, S., Ersoy, S.A., Kandeger, A., Annagur, B.B., 2017. Relationships of neutrophil-lymphocyte and platelet-lymphocyte ratios with the severity of major depression. Psychiatry Res. 247, 332–335.

King, K.Y., Goodell, M.A., 2011. Inflammatory modulation of HSCs:

viewing the HSC as a foundation for the immune response. Nat. Rev. Immunol. 11, 685–692.
Köhler, C.A., Freitas, T.H., Maes, M., de Andrade, N.Q., Liu, C.S., Fernandes, B.S., Stubbs, B., Solmi, M., Veronese, N., Herrmann, N., Raison, C.L., Miller, B.J., Lanctôt, K.L., Carvalho, A.F., 2017. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr. Scand. 135, 373–387.
Libregts, S.F., Gutierrez, L., de Bruin, A.M., Wensveen, F.M., Papadopoulos, P., van Ijcken, W., Ozgur, Z., Philipsen, S., Nolte, M.A., 2011. Chronic IFN-gamma production in mice induces anemia by reducing erythrocyte life span and inhibiting erythropoiesis through an IRF-1/PU.1 axis. Blood 118, 2578–2588.
Liu, J., Fang, Y., Gong, J., Cui, X., Meng, T., Xiao, B., He, Y., Shen, Y., Luo, X., 2017. Associations between suicidal behavior and childhood abuse and neglect: a meta-analysis. J. Affect. Disord. 220, 147–155.
Liu, Y., Ho, R.C., Mak, A., 2012. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J. Affect. Disord. 139, 230–239.
Ludwig, B., Dwivedi, Y., 2018. The concept of violent suicide, its underlying trait and neurobiology: a critical perspective. Eur. Neuropsychopharmacol. 28, 243–251.
Majd, M., Graham-Engeland, J.E., Smyth, J.M., Sliwinski, M.J., Lipton, R.B., Katz, M.J., Engeland, C.G., 2018. Distinct inflammatory response patterns are evident among men and women with higher depressive symptoms. Physiol. Behav. 184, 108–115.
Mazza, M.G., Tringali, A.G.M., Rossetti, A., Botti, R.E., Clerici, M., 2019. Cross-sectional study of neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in mood disorders. Gen. Hosp. Psychiatry 58, 7–12.
Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16, 22–34.
Motrico, E., Moreno-Kustner, B., de Dios Luna, J., Torres-Gonzalez, F., King, M., Nazareth, I., Monton-Franco, C., Gilde Gomez-Barragan, M.J., Sanchez-Celaya, M., Diaz-Barreiros, M.A., Vicens, C., Moreno-Peral, P., Bellon, J.A., 2013. Psychometric properties of the List of Threatening Experiences-LTE and its association with psychosocial factors and mental disorders according to different scoring methods. J. Affect. Disord. 150, 931–940.
Nelson, J., Klumparendt, A., Doebler, P., Ehring, T., 2017. Childhood maltreatment and characteristics of adult depression: meta-analysis. Br. J. Psychiatry 210, 96–104.
Nemeth, E., Ganz, T., 2014. Anemia of inflammation. Hematol. Oncol. Clin. N. Am. 28, 671–681 vi.
Orum, M.H., Kara, M.Z., Egilmez, O.B., 2018. Mean platelet volume and neutrophil to lymphocyte ratio as parameters to indicate the severity of suicide attempt. J. Immunoass. Immunochem. 39, 647–659.
Osby, U., Brandt, L., Correia, N., Ekbom, A., Sparén, P., 2001. Excess mortality in bipolar and unipolar disorder in Sweden. Arch. Gen. Psychiatry 58, 844–850.
Pariante, C.M., 2017. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. Eur. Neuropsychopharmacol. 27, 554–559.
Postolache, T.T., Komarow, H., Tonelli, L.H., 2008. Allergy: a risk factor for suicide? Curr. Treat. Options Neurol. 10, 363–376.
Qiao, R., Yang, S., Yao, B., Wang, H., Zhang, J., Shang, H., 2014. Complete blood count reference intervals and age- and sex-related trends of North China Han population. Clin. Chem. Lab. Med. 52, 1025–1032.
R. Core Team, 2019. R: A Language Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.
Rainville, J.R., Hodes, G.E., 2019. Inflaming sex differences in mood disorders. Neuropsychopharmacology 44, 184–199.
Velasco, Á., Rodríguez-Revuelta, J., Olié, E., Abad, I., Fernández-Peláez, A., Cazals, A., Guillaume, S., de la Fuente-Tomás, L., Jiménez-Treviño, L., Gutiérrez, L., García-Portilla, P., Bobes, J., Courtet, P., Sáiz, P.A., 2020. Neutrophil-to-lymphocyte ratio: a potential new peripheral biomarker of suicidal behavior. Eur. Psychiatry 63, e14.
Weber, M.D., Godbout, J.P., Sheridan, J.F., 2017. Repeated social defeat, neuroinflammation, and behavior: monocytes carry the signal. Neuropsychopharmacology 42, 46–61.
Wickham, H., 2009. Ggplot2: Elegant Graphics For Data Analysis. Springer, New York.
World Health Organization, 2018. Suicide Prevention: Toolkit For Engaging Communities, Switzerland.
World Medical Association, 2013. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310, 2191–2194.
Wysokinski, A., Szczepocka, E., 2016. Platelet parameters (PLT, MPV, P-LCR) in patients with schizophrenia, unipolar depression and bipolar disorder. Psychiatry Res. 237, 238–245.
Wysokinski, A., Szczepocka, E., 2018. Red blood cells parameters in patients with acute schizophrenia, unipolar depression and bipolar disorder. Psychiatr. Danub. 30, 323–330.
Zhang, Y., Traskman-Bendz, L., Janelidze, S., Langenberg, P., Saleh, A., Constantine, N., Okusaga, O., Bay-Richter, C., Brundin, L., Postolache, T.T., 2012. Toxoplasma gondii immunoglobulin G antibodies and nonfatal suicidal self-directed violence. J. Clin. Psychiatry 73, 1069–1076.
Zhao, J.L., Baltimore, D., 2015. Regulation of stress-induced hematopoiesis. Curr. Opin. Hematol. 22, 286–292.

Please cite this article as: P. Martínez-Botía, A. Velasco and V. Rolle et al., Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts, European Neuropsychopharmacology, https://doi.org/10.1016/j.euroneuro.2020.06.006