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Depression and Anxiety symptoms are associated with White Blood Cell count and Red Cell Distribution Width: a sex-stratified analysis in a population-based study

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Running title: Association of Depression and Anxiety disorders with hematological inflammatory markers

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Abstract

Background: Depression and anxiety are two common mood disorders that are both linked to systemic inflammation. Increased white blood cell (WBC) count and red cell distribution width (RDW) are associated with negative clinical outcomes in a wide variety of pathological conditions. WBC is a non-specific inflammatory marker and RDW is also strongly related to other inflammatory markers. Therefore, we proposed that there might be an association between these hematological inflammatory markers and depression/anxiety symptoms.

Objective: The primary objective of this study was to perform a sex-stratified examination of the association between depression/anxiety symptoms and hematological inflammatory markers including WBC and RDW in a large population-based study.

Methods: Symptoms of depression and anxiety and a complete blood count (CBC) were measured in 9,274 participants (40% males and 60% females) aged 35-65 years, enrolled in a population-based cohort (MASHAD) study in north-eastern Iran. Symptoms of depression and anxiety were evaluated using the Beck Depression and Anxiety Inventories.

Results: The mean WBC count increased with increasing severity of symptoms of depression and anxiety among men. Male participants with severe depression had significantly higher values of RDW ($p < 0.001$); however, this relationship was less marked among women ($p = 0.004$). Also, men (but not women) with severe anxiety symptoms had significantly higher values of RDW ($p < 0.001$). Moreover, there was a negative association between red blood cell (RBC) and mean corpuscular hemoglobin (MCH) and symptoms of depression/anxiety.

Conclusion: Our results suggest that higher depression and anxiety scores are associated with an enhanced inflammatory state, as assessed by higher hematological inflammatory markers including WBC and RDW, even after adjusting for potential confounders.

K**eywords**: Depression; Anxiety; Hematological inflammatory markers; White blood cell count; Red cell distribution width.

1. Introduction

Depression is a common mental disorder and is estimated to affect around 350 million people worldwide (WHO, 2012). It is characterized by a range of symptoms including a depressed mood or a loss of interest in daily activities for more than two weeks (Rottenberg, 2005). It has been estimated that depressive disorders are an important cause of disease burden in men and women (Meyer, 2004; Ustun et al., 2004). Moreover, major depression was reported to be the second and tenth leading cause of disability-adjusted life years (DALYs) lost in women and men, respectively (Michaud et al., 2001). By 2020, has been estimated that depression will become the second leading cause of disability globally (after heart disease), and by 2030; it is expected to be the largest contributor to disease burden (WHO, 2012). Anxiety is another common, costly, and serious public health problem that may significantly affect the quality of life and may also predispose to psychiatric comorbidities such as depression (Freud, 2013; Olatunji et al., 2007). The global prevalence of anxiety disorders, adjusted for methodological differences, has been estimated to be 7.3% and ranged from 5.3% in African cultures to 10.4% in Euro/Anglo cultures (Baxter et al., 2013).

Several studies have found that depression is associated with higher levels of pro-inflammatory cytokines and acute phase proteins such as C-reactive protein (CRP) and Interleukin-6 (IL-6) (Baune et al., 2012; Danner et al., 2003; Elovainio et al., 2006; Gimeno et al., 2009a). There are also some reports of a positive association between anxiety and inflammation (Bankier et al., 2008; Duivis et al., 2013b). Moreover, we have previously shown that depression and anxiety both associate with serum level of hs-CRP as well as inflammation-linked conditions such as obesity and current smoking habit (Tayefi et al., 2017a). A heightened inflammatory state also positively associates with an enhanced cardiovascular risk (Kazemi-Bajestani et al., 2007; Ridker et al., 2000; Tayefi et al., 2017b).

The white blood cell (WBC) count, a non-specific inflammatory marker, is usually measured as part of the complete blood count (CBC) panel. Increased WBC count is associated with a wide variety of diseases such as hypertension, diabetes, and atherosclerotic cardiovascular disease (Nakanishi et al., 2002; Whitworth, 2004). Moreover, several studies have indicated that an elevated WBC count is significantly associated with all-cause cardiovascular and cancer mortality (Jee et al.,

2005). Red cell distribution width (RDW), a quantitative measure of anisocytosis, is an easy, inexpensive, routinely reported parameter as a part of the CBC test (McPherson and Pincus, 2016). It has been reported that increased RDW is associated with negative clinical outcomes in patients with cardiovascular diseases (i.e. heart failure, previous myocardial infarction, and stable coronary artery disease) independent of hemoglobin values (Cavusoglu et al., 2010; Felker et al., 2007). The strong correlation between RDW and inflammatory markers, hs-CRP and erythrocyte sedimentation rate, observed in previous studies (Lappe et al., 2011; Lippi et al., 2009), suggests that increased RDW may arise from an underlying inflammatory state which is associated with adverse outcomes (Kalay et al., 2011).

These findings prompted us to hypothesize that more severe depression/anxiety symptoms are associated with higher levels of inflammatory markers, presumably due to higher inflammatory state in depressed and anxious individuals. Several initial studies were conducted some decades ago regarding the association of WBC subtypes and affective disorders (Cosentino et al., 1996; Diebold, 1975; Maes et al., 1992a; Maes et al., 1992b). Moreover, there have been a limited number of studies that have aimed to determine the association between hematological inflammatory markers and mood disorders such as depression and anxiety (Demircan et al., 2015; Peng et al., 2016; Pitsavos et al., 2006). Demircan and colleagues found that some hematological inflammatory markers such as RDW and neutrophil/lymphocyte ratio (NLR) levels are significantly higher in patients with major depressive disorder (MDD) compared to the control group (Demircan et al., 2015). Similarly, Peng et al. observed elevated RDW and NLR values in patients with MDD, which was suggested to support the role of inflammation in the etiology of MDD (Peng et al., 2016). Shim et al. reported that patients with depressive disorders who are categorized in moderate-severe to severe anxious distress groups tend to have higher CRP and monocyte levels compared with the mild to moderate group (Shim et al., 2016). Another study in cardiovascular disease-free individuals showed that anxiety score was positively correlated with WBC count in women, but not in men (Pitsavos et al., 2006).

Despite these observations, few studies have evaluated the association between depression and anxiety symptoms with hematological inflammatory markers such as WBC and RDW. Since we

previously observed that the association of depression/anxiety symptoms with serum level of hs-CRP is more marked among men (Tayefi et al., 2017a), the primary objective of this study was to perform a sex-stratified examination of the association between depression/anxiety symptoms and hematological inflammatory markers such as WBC and RDW in a large population-based study.

2. Materials and Methods

2.1 Study Population

A total of 9,274 subjects [3719 (40%) males and 5555 (60%) females], were recruited as part of the Mashhad Stroke and Heart Atherosclerotic Disorders (MASHAD) cohort study as described previously (Ghayour-Mobarhan et al., 2015). The MASHAD study is a 10-year cohort study that aims to evaluate the impact of various genetic, psychosocial, nutritional, and environmental risk factors on the incidence of cardiovascular events among a general urban population aged 35-65 years in northeastern Iran (Ghayour-Mobarhan et al., 2015). The first phase of the MASHAD cohort study was completed in 2010 and it will continue until 2020. Participants were drawn from three regions in Mashhad using a stratified cluster random sampling technique. The overall inclusion and exclusion criteria of MASHAD study and the general characteristics of the sample population such as job status, marriage status, education level, comorbid conditions, biochemical and anthropometric measurements have been reported earlier (Ghayour-Mobarhan et al., 2015). Of the original, 9908 individuals recruited, 634 participants were excluded (19 with missing data of depression and anxiety, 559 with missing data of hematological indices, and 56 taking medication for anxiety/depression). The mean age of men and women were 48.90±8.5 y and 47.63±8.1 y, respectively. All participants gave informed, written consent to contribute in the survey, which was reviewed and approved by the ethics committee of Mashhad University of Medical Sciences (MUMS).

2.2 Data collection and measurements

For all individuals, height (cm), weight (kg), and body mass index (BMI; kg/m^2) were measured based on standard protocols. Biochemical parameters including high sensitivity C-reactive protein (hs-CRP) and total cholesterol (TC) were measured as described previously (Emamian et al., 2017; Kazemi-Bajestani et al., 2017). A CBC including red blood cell (RBC), hemoglobin (HGB),

hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), platelet (PLT), platelet distribution width (PDW), mean platelet volume (MPV), RDW, and WBC was previously evaluated for each individual.

2.3 Measurement of depression

In this study the Beck Depression Inventory (BDI) was used for assessing the symptoms of depression (Dozois et al., 1998). This questionnaire contains 21 items each assessed on a 0 (lack of depressive symptoms) to 3 (severe depressive symptoms) scale. Each item represents a single symptom associated with depression including sadness, crying, feelings of hopelessness, feelings of guilt, fear and loss of appetite, and sleep disturbance over the past 2 weeks (Scogin et al., 1988). Scores are classified as the following: 0-13 minimal or no depression, 14-19 mild depression, 20-28 moderate depression and 29-63 severe depression (Scogin et al., 1988). Ghassemzadeh et al. (2005) have validated this questionnaire in its Persian translation, with an acceptable internal consistency (Cronbach's alpha = 0.87) and test-retest reliability (r = 0.74) (Ghassemzadeh et al., 2005).

2.4 Measurement of anxiety

To measure anxiety, the Beck Anxiety Inventory (BAI) was used (Beck et al., 1988). This questionnaire also contains 21 items and each assessed on a 0 (lack of anxiety symptoms) to 3 (severe anxiety symptoms) scale. Thus, the total score of the questionnaire ranges from 0 to 63. In general, a score of 0–7 indicates no or minimal anxiety, 8–15 mild anxiety, 16–25 moderate anxiety and over 26 severe anxiety (Beck et al., 1988). Kaviani and Mousavi showed that the Persian version of BAI has good reliability ($r = 0.83$, $P < 0.001$), validity ($r = 0.72$, $P < 0.001$), and an appropriate internal consistency (Alpha = 0.92) (Kaviani and Mousavi, 2008).

2.5 Statistical analysis

Data analysis was carried out using SPSS-18 software (SPSS Inc., IL, USA). The normality of data was evaluated using Kolmogorov–Smirnov test. Descriptive statistics including mean, frequency, and standard deviation (SD) were determined for all variables and expressed as mean ± SD for normally distributed variables and as median and interquartile range (IQR) for non-normally distributed variables. Chi-square tests were used to compare the qualitative variables. For normally distributed variables, analysis of variance (ANOVA) was performed. The Mann-Whitney U test was

used for serum hs-CRP since it was found to be a continuous non-normal variable even after logarithmically transformed. All the analyses were two-sided and p-value <0.05 was considered as significant. Depression and anxiety scores were divided into categories according to their severity and participants in the first group (no or minimal depression or anxiety) were considered as a reference group. Multivariate analyses were used to estimate the risk, as approximated by the odds ratio (OR). The odds ratios, with 95% confidence intervals (CI), were obtained using multivariate logistic regression, in order to determine the influence of potential confounding factors, e.g. age, education level, current smoking, BMI, TC, and hs-CRP.

Results

Among the 9,274 individuals, the average age was 48.1±8.3 years, with 60% being female. Participants were stratified for their depression and anxiety status based on their depression and anxiety scores. Clinical and biochemical characteristics of the study population are presented in Table 1. The percentage of females, illiterate subjects and current smokers increased with increasing severity of depression and symptoms of anxiety. Moreover, subjects with no or minimal symptoms of depression and anxiety had significantly lower BMI and serum hs-CRP levels when compared with individuals with high depression and anxiety scores. There were no significant differences in age and TC between different categories of depression/anxiety symptoms (Table 1).

With respect to depression, male participants with severe depressive symptoms had significantly higher levels of WBC counts when compared with other individuals who had no, low or moderate depressive symptoms (Table 2). However, there was no significant difference among women (p=0.2). As reported in Table 2, RBC and HGB fell significantly with increasing severity of depressive symptoms among men (p=0.002 and p=0.001, respectively); however, there were no significant differences among women. Among both sexes, patients with severe depressive symptoms had significantly lower MCHC when compared with non-depressed subjects. Moreover, there was a positive association between RDW and the severity of depressive symptoms; however, this association was much stronger among men (Table 2). With regards to anxiety, only WBC and RDW

significantly increased with increasing the severity of anxiety symptoms among men ($p=0.02$ and $p<0.001$, respectively).

In all our multivariate analyses, the group who had normal scores for depression, or anxiety, served as a reference group. Multivariate analysis showed that in the mild, moderate and severely affected groups compared with the reference group, WBC, RBC, MCH, and RDW were the strongest determinants for the severity of depressive symptoms among men but not women (Table 3). However, only WBC and RDW were amongst the determinants for the severity of anxiety symptoms among men but not women.

Even after adjusting for potential confounders (i.e. age, education level, current smoking, BMI, TC, and hs-CRP), several hematological parameters (WBC, RBC, MCH and RDW) were significantly associated with the severity of depressive symptoms (Table 4). Interestingly, after adjusting for potential confounders RBC and RDW became significant among women, as well. Moreover, after adjusting for potential confounders only RDW remained significantly associated with the severity of symptoms of anxiety.

Discussion

Our results suggest that higher depression and anxiety scores are associated with an enhanced inflammatory state, as assessed by higher hematological inflammatory markers including WBC and RDW. However, in the case of WBC, this association was only present in men. Higher depression scores were also associated with lower RBC and MCH.

Several studies have found elevated WBC count among depressed and anxious individuals (Aydin Sunbul et al., 2016; Duivis et al., 2013a; Kobrosly and van Wijngaarden, 2010; Maes et al., 1992b; Pitsavos et al., 2006; Seidel et al., 1996). Duivis et al. showed that participants with recurrent depressive symptoms have higher WBC counts after 5 years of follow-up (Duivis et al., 2013a). Consistent with our results, Surtees and colleagues reported that following adjustment for age and cigarette smoking, there is still an association between major depressive disorder and leukocyte counts for men, but not for women (Surtees et al., 2003). In contrast, Vulser et al. observed no significant association between depressive symptoms and neutrophil count, after adjustment for a

semiquantitative measure of smoking (Vulser et al., 2015). Moreover, in a study on cardiovascular disease-free people, Pitsavos et al. observed that anxiety score is positively correlated with WBC count in women, but not in men (Pitsavos et al., 2006). Beydoun et al. also reported that WBC count and related markers are linked to depressive symptoms, mostly among women (Beydoun et al., 2016). Darko and colleagues found a relative lymphopenia, absolute neutrophilia and leukocytosis in depressed patients. However, the authors suggested that leukocytosis and neutrophilia may be secondary to medication use (Darko et al., 1988). Similarly, Garcia-Rizo et al. observed lower lymphocyte count in newly diagnosed antidepressant-naïve patients when compared with control subjects (Garcia-Rizo et al., 2013).

Many studies have reported a positive association between depression and inflammation (Gimeno et al., 2009b; Pasco et al., 2010; Vetter et al., 2013), and some of them have also proposed that depression is an inflammatory disease (Berk et al., 2013; Maes, 2011). Since WBC count is an independent predictor of atherosclerosis and cardiovascular diseases (Loimaala et al., 2006; Madjid et al., 2004), it could be hypothesized that higher cardiac events observed in depressed patients (Blumenthal, 2008; Musselman et al., 1998) may be partly explained by a higher WBC count, or the associated inflammatory state.

In agreement with our results regarding the positive association between depression/anxiety symptoms and RDW, Demircan et al. reported significantly higher RDW and Neutrophil/Lymphocyte Ratio (NLR) levels in patients with major depressive disorder (MDD) compared to the control group. However, this significant difference between the levels of RDW and NLR in patients with MDD and the control group was dissolved after selective serotonin reuptake inhibitor (SSRI) treatment (Demircan et al., 2015). Similarly, Peng et al. conducted a study on 167 MDD patients and 180 healthy controls and observed that RDW and NLR are associated with MDD independently of hemoglobin (Peng et al., 2016). May and colleagues also reported an association between increasing levels of RDW and a follow-up depression diagnosis, which persisted despite adjustment by risk factors, medications, and indicators of other disease states (May et al., 2013). In another study, MCV, MCH, MCHC, and RDW were not found to be significantly different between major depressed

subjects and normal controls. However, this inconsistency can be due to the small sample size and consequent low power of the study (Maes et al., 1996).

RDW is a strong predictor of mortality and has association with a variety of cardiovascular and thrombotic disorders (Montagnana et al., 2012; Patel et al., 2009). Therefore, higher levels of RDW among depressed and anxious individuals may predict greater risk of developing cardiovascular diseases in these patients. In support of this hypothesis, it has been shown that patients with major depression are at greater risk for cardiovascular diseases (Blumenthal, 2008; Musselman et al., 1998).

Maes et al. found significantly lower level of RBC, HCT and HGB in subjects with major depression compared with normal controls (Maes et al., 1996). Moreover, strong associations between higher number of depressive symptoms and lower HGB level was also reported in a sample of 1875 participates (Stewart and Hirani, 2012). A case-control study on cancerous patients showed that individuals with a hemoglobin level lower than 11 g/dl had higher scores of depression but not anxiety when compared to those with higher HGB levels (Glaus and Müller, 2000). The same results were observed by Skarstein et al. who reported a positive association between low HGB levels and depression, but not anxiety, even after adjustment for covariates (Skarstein et al., 2005).

Despite the strengths of this study (e.g., large sample size, population-based study and using a stratified-cluster method), there are several limitations. First, the WBC count was not further characterized by a differential white cell count. Second, the evaluation of severity of depression and anxiety symptoms were based on self-administered tools instead of more accurate face-to-face interviews. Third, the cross-sectional design does not allow an insight into causality. The MASHAD study is a longitudinal cohort and will be continued for at least a decade. We therefore intend to analyze the relationship between aggravation of depression/anxiety symptoms and baseline hematological inflammatory parameters.

In conclusion, this study showed a positive association between depression/anxiety symptoms and levels of hematological inflammatory markers including WBC and RDW, which persisted despite adjustment by potential confounders.

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Table Legends

Table 1. Values are expressed as mean±SD for variables with normal distribution, and median and interquartile range for hs-CRP as a non-normally distributed variable. BMI: body mass index; TC: total cholesterol; hs-CRP: high sensitivity C-reactive protein. *P<0.05; **P<0.01; ***P<0.001.

Table 2. Values are expressed as mean±SD. WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width. *P<0.05; **P<0.01; ***P<0.001.

Table 3. Odds ratios with 95% confidence intervals (95% CI) obtained from multiple logistic regression tests. WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width. *P<0.05; **P<0.01; ***P<0.001.

Table 4. Odds ratios with 95% confidence intervals (95% CI) obtained from multiple logistic regression tests adjusted for potential confounders (i.e. age, education level, current smoking habit, BMI, TC, and hs-CRP). WBC: white blood cell; RBC: red blood cell; MCH: mean corpuscular hemoglobin; RDW: red cell distribution width. *P<0.05; **P<0.01; ***P<0.001.

Table 1. Demographic and biochemical characteristics of individuals in groups of Depression and Anxiety.

	Depression severity score				**Anxiety severity score**			
	No or minimal N=6029	**Low** N=1502	**Moderate** N=1145	**Severe** N=598	**No or minimal** N=4815	**Low** N=2341	**Moderate** N=1293	**Severe** N=825
Sex (Female) n(%)	3331 (55.2)	975 (64.9)	791 (69.1)	458 (76.6)***	2502 (52.0)	1512 (64.6)	926 (71.6)	615 (74.5)***
Education level (Illiterate) n(%)	763 (12.7)	213 (14.3)	171 (15.0)	103 (17.3)***	590 (12.3)	322 (13.8)	194 (15.1)	144 (17.6)***
Current smoking n(%)	1157 (19.2)	347 (23.1)	307 (26.8)	189 (31.6)***	925 (19.2)	527 (22.5)	321 (24.8)	227 (27.5)***
Age (year)	48.0±8.2	48.4±8.1	47.8±8.5	48.3±8.0	48.2±8.2	48.0±8.2	48.3±8.3	47.5±8.3
BMI (kg/m^2)	27.6±4.6	28.3±4.7	28.3±5.1	28.7±5.3***	27.4±4.5	28.0±4.7	28.6±5.0	28.8±5.0***
TC (mg/dL)	191.7±39.3	192.0±38.0	190.5±38.5	193.5±41.3	191.2±38.9	192.2±38.8	193.3±40.7	190.9±39.1
Serum hs-CRP (mg/L)	1.57 (0.99-3.26)	1.81 (1.03-3.90)	1.79 (1.05-4.40)	1.97 (1.06-4.80)***	1.53 (0.97-3.14)	1.78 (1.03-3.90)	1.77 (1.06-3.99)	2.02 (1.09-4.88)***

Table 2. Hematological parameters in groups of Depression and Anxiety.

		Depression severity				Anxiety severity			
		No or minimal N=6029	**Low** N=1502	**Moderate** N=1145	**Severe** N=598	**No or minimal** N=4815	**Low** N=2341	**Moderate** N=1293	**Severe** N=825
WBC (10^9/L)	Male	6.16±1.58	6.35±1.74	6.33±1.84	6.90±2.24***	6.17±1.6	6.27±1.7	6.30±1.7	6.52±1.8*
	Female	5.94±1.47	6.04±1.51	6.05±1.46	6.03±1.47	5.98±1.4	5.99±1.5	5.94±1.4	6.07±1.5
RBC (10^{12}/L)	Male	5.15±0.46	5.15±0.42	5.08±0.44	5.07±0.52**	5.15±0.46	5.13±0.43	5.15±0.48	5.08±0.52
	Female	4.66±0.39	4.67±0.41	4.67±0.44	4.63±0.40	4.64±0.38	4.67±0.43	4.67±0.40	4.68±0.42
HGB (g/dl)	Male	14.83±1.3	14.81±1.2	14.63±1.2	14.49±1.5**	14.81±1.3	14.82±1.2	14.78±1.5	14.60±1.3
	Female	13.02±1.8	13.10±1.1	12.98±1.5	12.91±1.3	12.98±1.3	13.01±1.3	13.13±2.9	13.03±1.3
HCT (%)	Male	43.94±3.4	44.14±3.0	43.56±2.9	43.53±4.1	43.89±3.3	43.99±3.1	44.09±3.7	43.64±3.5
	Female	39.41±5.8	39.60±3.1	39.47±4.1	39.31±5.1	39.24±3.4	39.61±8.0	39.59±3.3	39.63±3.8
MCV (fl)	Male	85.32±5.7	85.85±4.6	85.93±5.1	85.68±6.8	85.24±5.8	85.86±5.3	85.64±5.1	86.11±5.0
	Female	84.42±6.1	84.91±5.8	84.38±6.7	84.78±6.5	84.48±6.1	84.50±6.3	84.67±6.5	84.57±5.7
MCH (pg/cell)	Male	28.89±2.7	28.84±2.0	28.88±2.2	28.62±2.1	28.87±2.7	28.96±2.1	28.75±2.3	28.80±2.1
	Female	27.98±2.7	28.11±2.4	27.85±2.7	27.88±2.6	27.99±2.6	27.96±2.7	28.03±2.8	27.86±2.5
MCHC (g/dl)	Male	33.69±1.9	33.53±1.6	33.59±1.2	33.26±1.4*	33.67±2.0	33.68±1.2	33.47±1.9	33.43±1.3
	Female	33.03±1.5	33.02±1.3	32.88±1.5	32.77±1.5**	33.04±1.4	32.97±1.6	32.91±1.5	32.90±1.5

RDW (fl)	Male	41.38±3.2	41.93±3.4	42.04±2.9	42.63±3.6***	41.40±3.1	41.76±3.3	41.70±3.2	42.44±3.9***
	Female	41.65±3.2	41.60±3.0	41.80±3.1	42.18±3.4**	41.60±3.2	41.77±3.0	41.85±3.0	41.75±3.4

Table 3. The odds ratio of having mild, moderate or severe depression or anxiety symptoms associated with hematological parameters among men and women.

		Depression severity			**Anxiety severity**		
		Reference group and mildly affected group	Reference group and moderately affected group	Reference group and severely affected group	Reference group and mildly affected group	Reference group and moderately affected group	Reference group and severely affected group
WBC (10^9/L)	Males	1.06 (1.005-1.1)*	1.06 (0.99-1.1)	1.20 (1.1-1.3)***	1.026 (0.97-1.07)	1.037 (0.97-1.10)	1.097 (1.02-1.17)*
	Females	1.03 (0.98-1.08)	1.05 (0.99-1.1)	1.04 (0.97-1.1)	0.99 (0.95-1.04)	0.97 (0.92-1.02)	1.02 (0.96-1.08)
RBC (10^{12}/L)	Males	1.34 (0.44-4.0)	1.16 (0.99-1.1)	0.15 (0.03-0.65)*	0.66 (0.27-1.59)	0.44 (0.13-1.54)	0.80 (0.13-4.76)
	Females	1.49 (0.94-2.3)	1.03 (0.76-1.3)	0.96 (0.64-1.4)	1.65 (0.92-2.96)	1.06 (0.58-1.96)	0.86 (0.43-1.74)
HGB (g/dl)	Males	0.87 (0.67-1.1)	0.82 (0.62-1.1)	0.87 (0.59-1.2)	0.92 (0.72-1.18)	0.96 (0.71-1.30)	0.88 (0.65-1.21)
	Females	0.99 (0.90-1.08)	0.99 (0.93-1.06)	0.99 (0.91-1.07)	0.84 (0.66-1.08)	1.16 (0.91-1.49)	1.11 (0.86-1.44)
HCT (%)	Males	1.02 (0.9-1.1)	1.007 (0.8-1.2)	1.26 (0.9-1.5)	1.07 (0.96-1.20)	1.31 (0.97-1.31)	1.04 (0.84-1.28)
	Females	0.97 (0.92-1.02)	1.00 (0.98-1.01)	0.99 (0.96-1.02)	1.02 (0.97-1.06)	0.98 (0.93-1.04)	1.01 (0.97-1.06)
MCV (fl)	Males	1.06 (0.98-1.1)	1.05 (0.96-1.1)	0.99 (0.95-1.03)	1.02 (0.98-1.06)	1.03 (0.96-1.1)	1.08 (0.95-1.22)
	Females	1.02 (0.99-1.06)	1.00 (0.97-1.02)	1.01 (0.97-1.04)	0.99 (0.97-1.01)	0.98 (0.96-1.00)	1.01 (0.97-1.06)
MCH (pg/cell)	Males	0.92 (0.78-1.08)	0.90 (0.73-1.1)	0.74 (0.57-0.95)*	0.91 (0.79-1.05)	0.83 (0.69-0.99)	0.80 (0.62-1.03)
	Females	1.05 (0.96-1.1)	1.02 (0.94-1.1)	1.04 (0.93-1.1)	1.09 (0.98-1.21)	1.11 (0.99-1.23)	0.93 (0.79-1.1)
MCHC (g/dl)	Males	1.02 (0.93-1.1)	1.09 (0.91-1.3)	1.07 (0.86-1.3)	1.07 (0.95-1.19)	0.99 (0.91-1.07)	1.07 (0.86-1.34)
	Females	0.91 (0.82-1.00)	0.90 (0.81-1.00)	0.84 (0.74-0.96)	0.95 (0.85-1.05)	0.77 (0.68-0.87)***	0.90 (0.77-1.06)

RDW (fl)	Males	1.03 (0.99-1.07)	1.04 (0.99-1.08)	1.09 (1.02-1.1)**	1.01 (0.98-1.04)	0.99 (0.94-1.03)	1.06 (1.007-1.1)*
	Females	0.97 (0.94-1.00)	0.99 (0.97-1.03)	1.02 (0.98-1.05)	1.01 (0.98-1.03)	0.99 (0.96-1.02)	0.99 (0.96-1.03)

Table 4. The odds ratio of having mild, moderate or severe Depression or Anxiety associated with hematological parameters among men and women adjusted for potential confounders.

		Depression severity			**Anxiety severity**		
		Reference group and mildly affected group	Reference group and moderately affected group	Reference group and severely affected group	Reference group and mildly affected group	Reference group and moderately affected group	Reference group and severely affected group
WBC (10^9/L)	Males	1.028 (0.97-1.09)	1.026 (0.95-1.09)	1.13 (1.04-1.22)**	1.015 (0.96-1.06)	1.007 (0.94-1.08)	1.063 (0.98-1.15)
	Females	1.019 (0.97-1.07)	1.021 (0.96-1.07)	1.015 (0.97-1.1)	0.97 (0.93-1.02)	0.94 (0.89-0.99)	0.98 (0.92-1.05)
RBC (10^{12}/L)	Males	1.04 (0.81-1.31)	0.75 (0.57-0.98)*	0.67 (0.46-0.96)*	0.94 (0.77-1.14)	0.98 (0.74-1.30)	0.78 (0.56-1.08)
	Females	1.1 (0.89-1.34)	0.93 (0.75-1.16)	0.76 (0.58-0.99)*	1.17 (0.99-1.41)	1.22 (0.99-1.52)	1.14 (0.89-1.46)
MCH (pg/cell)	Males	0.98 (0.93-1.03)	0.95 (0.90-1.01)	0.89 (0.82-0.96)**	1.002 (0.96-1.04)	0.97 (0.92-1.03)	0.93 (0.87-1.00)
	Females	1.03 (0.99-1.06)	0.98 (0.95-1.01)	0.97 (0.93-1.01)	1.004 (0.97-1.03)	1.02 (0.99-1.05)	0.99 (0.96-1.04)
RDW (fl)	Males	1.05 (1.02-1.08)**	1.04 (1.003-1.08)*	1.1 (1.04-1.15)***	1.025 (0.99-1.05)	1.025 (0.98-1.06)	1.08 (1.03-1.1)**
	Females	0.99 (0.97-1.02)	1.01 (0.98-1.04)	1.04 (1.01-1.08)**	1.02 (0.99-1.04)	1.025 (1.00-1.05)	1.015 (0.98-1.04)