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The association between major depressive disorder and generalized anxiety disorder with hematological indices in the Rafsanjan youth cohort study

Zahra Jamali[1,2], Reza Hosseiniara[3], Parvin Khalili[4], Mohammadreza Mirazaei[5], Sadegh Zarei[6], Mostafa Habibi[7] & Mojgan Noroozi Karimabad[5]✉

Depression and anxiety disorders appear to be associated with alterations in hematological indices, as well as increased systemic inflammation. This study aimed to investigate the association between major depressive disorder (MDD) and generalized anxiety disorder (GAD) with hematological indices in the youth population of Rafsanjan, Iran. This cross-sectional study involved a sample of 3006 urban and rural youth aged 15 to 35 who participated in the initial phase of the Rafsanjan youth cohort study ((RYCS), with relevant data available in the cohort database. The presence of MDD and GAD was confirmed and recorded using the composite international diagnostic interview version 2.1 tool. Data were collected on age, sex, education level, body mass index, history of smoking, opium or alcohol use, intensity of physical activity, and history of diabetes or hypertension. Hematological indices result, including RBC, WBC, HGB, HCT, MCV, MCH, MCHC, PLT, RDW, MO, GR, LY, PDW, and MPV, were extracted from the cohort system. The associations between hematological indices and MDD and GAD were evaluated using crude and adjusted models in linear regression analysis. A total of 2,939 young adults with a mean age of 25.77 ± 6.04 (55.97% females) were evaluated. The prevalence of MDD was found to be 14.9%, while the prevalence of GAD was 7.49%. In linear regression analysis, a negative association was observed between RDW (β=−0.1, [−0.18, −0.01], p = 0.022) and a positive association between NLR (β = 0.097, [0.01, 0.18], p = 0.031) with MDD in males; however, no significant associations were found between hematological indices and MDD in females. Conversely, RDW (β = −0.15, [−0.28, −0.02], p = 0.029) exhibited a negative association and MPV (β = 0.1, [0.003, 0.201], p = 0.046) and HCT (β = 0.494, [0.114, 0.974], P = 0.044) positive associations with GAD in females. In males, NLR (β = 0.22, [−0.09,−0.034], p = 0.001) showed a positive association and the percentage of lymphocytes (β=−2.71, [−5.39, −0.136], p = 0.029) a negative association with GAD. The findings indicate that RDW and NLR values are significantly related to MDD in males, while HCT, RDW and MPV values are significantly related to GAD in females. Additionally, NLR values and the percentage of lymphocytes are significantly related to GAD in males. To verify these associations, further studies with longitudinal design are needed.

Keywords Depression, Anxiety, MDD, GAD, Youth, Rafsanjan cohort study (RCS), Hematological indices

[1]Non-Communicable Diseases Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. [2]Clinical Research Development Unit (CRDU), Niknafs Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. [3]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, Iran. [4]Department of Epidemiology and Biostatistics, School of Health, Social Determinants of Health Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. [5]Molecular Medicine Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. [6]Department of Clinical Biochemistry, Faculty of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. [7]Clinical Research Development Unit (CRDU), Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran. ✉email: mojgan.noroozi@yahoo.com

Depression and anxiety are among the most prevalent mental health disorders worldwide. These conditions often co-occur, significantly diminishing individuals' quality of life and imposing substantial occupational and economic burdens on society, resulting in considerable indirect costs. Both disorders are multifactorial, influenced by a complex interplay of genetic, environmental, and psychosocial factors. Environmental stressors such as trauma, chronic stress, and life adversities play a critical role in the onset and exacerbation of depression and anxiety. Neurobiological factors, including dysregulation of neurotransmitter systems (e.g., serotonin, dopamine), alterations in brain structure and function, and neuroinflammation, also contribute to the pathophysiology of these disorders[1,2].

Several studies have demonstrated a association between depression and anxiety and alterations in blood parameters. Elevated white blood cell counts, increased levels of pro-inflammatory cytokines (such as interleukin-6 and tumor necrosis factor-alpha), and abnormal coagulation profiles have been observed in individuals with these conditions. Additionally, changes in red blood cell indices, such as mean corpuscular volume (MCV) and hemoglobin levels, have been reported in subjects with mood and anxiety disorders[3,4].

Chronic stress, a common feature of both depression and anxiety, contributes to systemic inflammation and alterations in blood parameters. This chronic stress can also affect the thyroid gland, leading to reduced secretion of thyroid hormones and diminished conversion of thyroxine (T4) to its active form, triiodothyronine (T3). Thyroid hormones play a crucial role in stimulating hematopoiesis through various mechanisms and are vital for erythropoietin stimulation. Furthermore, chronic stress activates several physiological axes in the body, including the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system. Activation of these pathways results in increased levels of hormones such as cortisol and catecholamines (epinephrine and norepinephrine), which can impact immune system functioning[5]. For instance, a sharp rise in cortisol and epinephrine can lead to a decrease in white blood cell counts. Additionally, elevated cortisol and epinephrine levels can reduce the proliferation of lymphocytes and natural killer cells[6,7].

Simultaneously, depression and anxiety can influence steroid hormone levels, leading to decreased hematopoietin synthesis and resulting in anemia[8]. Furthermore, these mental health conditions may contribute to gastrointestinal issues such as ulcers, which can lead to malnutrition. This malnutrition may result in malabsorption of essential nutrients like iron, further complicating hematopoiesis and contributing to anemia[9].

In recent studies, hematological parameters have garnered attention as potential biomarkers for assessing the severity and prognosis of depression and anxiety. Inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate, have been proposed as indicators of immune dysregulation in individuals with these mental health conditions. Additionally, alterations in platelet function and coagulation factors have been implicated in the pathophysiology of mood and anxiety disorders, suggesting their potential utility as biomarkers for risk stratification and therapeutic response[10,11].

However, some studies have reported no significant association between hematological parameters and depression or anxiety. For instance, Lever-van Milligen et al. demonstrated that there was no independent association between depressive and/or anxiety disorders and hemoglobin levels or anemia status[12]. Similarly, Vulser et al. found no significant correlation between depressive symptoms and neutrophil counts[13]. In the study by Pitsavos et al., while anxiety scores were positively correlated with white blood cell (WBC) counts in women, this association was not observed in men[14].

This study focuses on identifying potential associations between MDD or GAD and hematological indices in a youth cohort, providing preliminary insights that may inform future longitudinal or mechanistic studies. Given the limited research in this field within Iran, this study aims to investigate the association between MDD, GAD, and hematological indices in a large sample of young people in Rafsanjan in the Southeast of Iran.

Methods

This cross-sectional study involved participants aged 15 to 35 years who participated in Rafsanjan Youth Cohort Study (RYCS), as part of Rafsanjan Cohort Study (RCS) conducted in Rafsanjan city in the Southeast of Iran[15]. In total, 3006 young individuals within this age range took part, all of whom had data recorded in the cohort database.

Eligible participants for the RYCS, were selected using a random cluster sampling method, based on specific inclusion and exclusion criteria. Participants were recruited from both urban and rural areas served by four health centers in Rafsanjan city (Iran).

Inclusion criteria

- Age between 15 and 35 years.
- Iranian nationality or legal residence in Iran.

Exclusion criteria

- Inability to understand the Persian language.
- Presence of severe physical or mental disorders that could interfere with the interview process.

In the current cross-sectional study, additional exclusion criteria were applied:

- History of heart or cerebrovascular disease, liver or kidney failure, or chronic obstructive pulmonary disease (COPD).
- Diagnosis of malignancies.

Ultimately, the study population comprised 2939 individuals.

Data collection tool

The data collection tool consisted of completed questionnaires from the RYCS. These questionnaires were developed as part of a software program, and face-to-face interviews were conducted by trained interviewers. Participants' responses and results from hematological tests were directly entered into the computer system. Additionally, psychological assessment data, including measures of MDD and GAD were gathered using the composite international diagnostic interview version 2.1. The validity and reliability of these psychological questionnaires have been confirmed in the Iranian population[16].

Information extracted from the RYCS:

- Demographic data (age, sex, education level, body mass index).
- History of smoking, opiate use, or alcohol consumption.
- Level of physical activity.
- Medical history of diabetes and hypertension.
- Depression and anxiety status.

Anxiety and depression questionnaire

Trained interviewers conducted face-to-face interviews with participants from the RYCS, recording their responses in the system. The questionnaires were subsequently scored by a psychologist or psychiatrist. The assessment utilized the Composite International Diagnostic Interview Version 2.1, specifically sections D and E for measuring anxiety and depression, respectively[17]. Those patients who met the criteria for diagnosis of Major Depressive Disorder and Generalized Anxiety Disorder were considered as MDD and GAD[17].

Blood parameters

Key hematological indices were evaluated using fasting peripheral blood samples collected from all young participants in the RYCS. These samples were analyzed with automated hematology analyzers to measure several important indices, including red blood cells (RBC), white blood cells (WBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets (PLT), red cell distribution width (RDW), monocytes (MO), granulocytes (GR), lymphocytes (LY), platelet distribution width (PDW), and mean platelet volume (MPV). The immune cells were quantified as relative percentages, which provide a useful snapshot of the immune profile but can be affected by variations in the parent cell types.

Assessment of physical activity

A two-question questionnaire was utilized to assess physical activity among youth cohort participants. One question inquired about the number of days in the past week that participants engaged in at least 10 min of moderate to vigorous physical activity; the other asked about the duration of such activities. Moderate to vigorous physical activity is defined as activities that elevate breathing rates. These questions were derived from the short form of the international physical activity questionnaire (IPAQ)[18].

Anthropometric assessment

Anthropometric measurements were conducted by a trained investigator in the morning while participants were still fasting to minimize potential bias. Key measurements included height (in cm) and weight (in kg), following the protocols established by the US National Institutes of Health[19]. Participants were weighed with minimal clothing and without shoes, using a digital scale (SECA Digital Scale, Germany). Height was measured with a stadiometer that provides precision to 0.5 cm (SECA Stadiometer, Germany). Body mass index (BMI) was calculated by dividing weight (in kg) by height squared (in m^2). The BMI values were categorized into three groups: under 25, between 25 and 30, and over 30[20].

Individual habits

The history of smoking, alcohol, and opium consumption was assessed using the following questions:

- Smoking: History of daily smoking in the past 12 months.
- Alcohol consumption: History of alcohol consumption in the past 12 months.
- Opium use: History of opium use in the past 12 months.

Data gathering

After obtaining the necessary permits and coordinating with relevant officials, we accessed the cohort center. Subsequently, patient information available in the cohort database was extracted from the cohort system.

Statistical analysis

Data analysis was conducted using STATA version 14 software. Qualitative data were described using frequency and percentage, while quantitative data were summarized with mean and standard deviation. To examine the associations between qualitative variables, the chi-square test was employed, provided that the assumptions were met. Independent t-tests were used to compare the means of quantitative variables across different categories.

The associations between hematological indices and MDD and GAD were evaluated using crude and two adjusted models in linear regression analysis. Confounders were identified using a causal diagram (Supplementary file 1: Figure S1) based on subject matter knowledge and the relevant epidemiological literature. Model 1

included age, education, physical activity, BMI and histories of arteritis rheumatoid, diabetes and hypertension. Adjusted model 2 included all variables in model 1 and additionally included smoking, alcohol consumption and opium use, as these were hypothesized to be potential intermediates on the causal pathways that could explain association between MDD and GAD and hematological indicator. Prior to investigating associations using linear regression models, we assessed the normality of the distribution of hematological indicators through normal probability charts (histograms) and skewness and kurtosis indices. The relevant assumptions were maintained throughout all analyses.

In the linear regression models, collinearity among variables was examined by calculating the variance inflation factor using multiple linear regression analysis. Data were presented as unstandardized regression coefficients along with 95% confidence intervals. All analyses were conducted in State V.12. All p-values. All p-values were two-sided, with p-values < 0.05 considered statistically significant.

Ethical considerations

The study was carried out after obtaining the required approvals from the ethics committee at Rafsanjan University of Medical Sciences, which issued the ethical code IR.RUMS.REC.1400.249. Prior to their participation, individuals signed a written informed consent form, thereby adhering to the guidelines established in the Declaration of Helsinki.

Patient consent

Informed consent was obtained from all participants included in the study. For participants aged 15, informed consent was also obtained from their parents and/or their legal guardian(s).

Results

In this study, a total of 2,939 young adults with mean age of 25.77 ± 6.04 were evaluated, comprising 55.97% females and 44.03% males. According to the established criteria, 438 individuals (14.9%) were diagnosed with MDD, including 159 males (12.29% of males) and 279 females (16.96% of females).

Among the females with MDD, there was a significantly higher prevalence of alcohol consumption ($p < 0.001$), smoking ($p = 0.022$), and opium use ($p = 0.033$). The associations between other parameters and MDD were not statistically significant (Table 1). Males with MDD exhibited a significantly higher level of education ($p = 0.039$), more smoking ($p < 0.001$), more opium use ($p = 0.017$), and reported higher levels of physical activity ($p = 0.028$) (Table 1).

According to the established criteria, 220 individuals (7.49%) were diagnosed with GAD, including 80 males (6.22% of males) and 140 females (8.56% of females). In females, GAD was significantly related with older age ($p = 0.032$) and a history of diabetes ($p = 0.009$). In males, GAD was significantly related to older age ($p = 0.005$), history of hypertension ($p = 0.018$), more smoking ($p < 0.001$), and more drug use ($p = 0.001$) (Table 2).

Comparing the mean hematological indices between young individuals with and without MDD, according to sex, revealed NLR was significantly higher in males with MDD compared to those without ($p = 0.022$) (Table 1S).

The comparison of hematological indices between youth with and without GAD showed the NLR and N were significantly higher in males with GAD ($p = 0.001$, $P = 0.04$). Additionally, the percentage of blood lymphocytes was significantly lower in males with GAD ($p = 0.031$). Conversely, MPV was significantly higher in females with GAD ($p = 0.038$) (Table 2S).

Table 3 shows the association between hematological indices and MDD using the linear regression analysis in crude and adjusted models. In the crude model, the associations between RDW (β=−0.09, $p = 0.04$) and NLR ($\beta = 0.1$, $p = 0.02$) with MDD in males were significant.

Model 1 adjusted for age, education, physical activity, BMI and histories of arteritit rhomatoid, diabetes and hypertension showed that the associations between RDW and NLR with MDD in males remained significant. Adjusted model 2 included all variables considered in adjusted model 1, plus smoking, alcohol consumption and opium use, as these were hypothesized to be potential intermediates in the causal pathways that could explain association between MDD and GAD and hematological indicator. However, the obtained results showed the associations between RDW (β = −0.1, [−0.18, −0.01], $p = 0.022$) and NLR ($\beta = 0.097$, [0.01, 0.18], $p = 0.031$) with MDD in males remained significant. There were a negative association between RDW and MDD and a positive association between NLR and MDD.

Other parameters did not show significant associations with depression in either females or males ($p > 0.05$).

Table 4 shows the association between hematological indices and GAD using the linear regression analysis in crude and adjusted models. In the crude model, significant associations were found between NLR ($\beta = 0.22$, $p < 0.001$), neutrophil count (N) ($\beta = 2.79$, $p = 0.04$), and lymphocyte count (L) (β = −2.79, $p = 0.03$) with GAD in males, as well as a significant association between MPV ($\beta = 0.1$, $p = 0.04$) and GAD in females. Adjusted model 1 showed that the associations between NLR with GAD in males and MPV with GAD in females remained significant, while association between lymphocyte count with GAD in males disappeared. Also, in adjusted model 1, significant associations were found between HCT and RDW with GAD in females. Adjusted model 2 showed that the associations between HCT ($\beta = 0.494$, [0.114, 0.974], $P = 0.044$), RDW (β = −0.15, [−0.28, −0.02], $p = 0.029$), and MPV ($\beta = 0.102$, [0.003, 0.201], $p = 0.045$) with GAD in females were significant. Additionally, the associations of lymphocyte count (β = −2.71, [−5.39, −0.136], $p = 0.029$) and NLR (β: 0.22(0.09, 0.001) with GAD in males were significant. Other hematological indices did not demonstrate significant associations with GAD ($p > 0.05$) (Table 4).

In addition to adjusting for history of diseases in adjusted model 1, we performed a sensitivity analysis and excluded subjects with history of arteritis rheumatoid, diabetes and hypertension. Table 3S shows the associations between MDD and GAD with hematological indices using the linear regression analysis in a fully

Variables	Females			Males		
	No Major depressive disorder ($N=1366$)	Major depressive disorder ($N=279$)	*P*-value	No major depressive disorder ($N=1135$)	Major depressive disorder ($N=159$)	*P*-value
Age, years, n (%)						
≤ 20	333 (24.38%)	63 (22.58%)	0.589	310 (27.31%)	32 (20.13%)	0.109
21–30	596 (43.63%)	131 (46.95%)		501 (44.14%)	82 (51.57%)	
≥ 31	437 (31.99%)	85 (30.47%)		324 (28.55%)	45 (28.30%)	
Years of education, n (%)						
≤ Median	825 (60.44%)	176 (63.08%)	0.41	728 (64.14%)	88 (55.70%)	0.039
> Median	540 (39.56%)	103 (36.92%)		407 (35.86%)	70 (44.30%)	
Body mass index (BMI), n (%)						
≤ 24.999	750 (55.03%)	160 (57.35%)	0.687	641 (56.73%)	85 (53.80%)	0.694
25–29.999	396 (29.05%)	74 (26.52%)		314 (27.79%)	49 (31.01%)	
≥ 30	217 (15.92%)	45 (16.13%)		175 (15.49%)	24 (15.19%)	
History of hypertension, n (%)						
No	1328 (97.15%)	269 (96.42%)	0.512	1123 (98.94%)	157 (98.74%)	0.819
Yes	39 (2.85%)	10 (3.58%)		12 (1.06%)	2 (1.26%)	
History of diabetes, n (%)						
No	1269 (92.83%)	265 (94.98%)	0.194	1124 (99.03%)	158 (99.37%)	0.675
Yes	98 (7.17%)	14 (5.02%)		11 (0.97%)	1 (0.63%)	
Alcohol consumption in past 12 months, n (%)						
No	1348 (98.61%)	263 (94.27%)	< 0.001	777 (68.46%)	97 (61.01 5)	0.06
Yes	19 (1.39%)	16 (5.73%)		358 (31.54%)	62 (38.99%)	
Cigarette smoking, n (%)						
No	1366 (99.93%)	277 (99.28%)	0.022	1021 (89.96%)	128 (80.50%)	< 0.001
Yes	1 (0.07%)	2 (0.72%)		114 (10.04%)	31 (19.50%)	
Opium consumption in past 12 months, n (%)						
No	1317 (96.34%)	261 (93.55%)	0.033	998 (87.93%)	129 (81.13%)	0.017
Yes	50 (3.66%)	18 (6.45%)		137 (12.07%)	30 (18.87%)	
Physical activity, Minutes per week. n (%)						
No	854 (62.52%)	181 (64.87%)	0.729	527 (46.43%)	59 (37.11%)	0.028
≤ Median	311 (22.77%)	58 (20.79%)		252 (22.20%)	49 (30.82%)	
> Median	201 (14.71%)	40 (14.34%)		356 (31.37%)	51 (32.08%)	

Table 1. Demographic characteristics of females and males in the RYCS according to the presence or absence of major depressive disorder.

adjusted model after excluding histories of mentioned diseases. The results showed the same results on (Tables 3, 4 and 3S).

Since, MDD and GAD are highly comorbid conditions and there is an overlaping of symptoms/diagnosis of participants, we performed a sensitivity analysis and categorized subjects in to 4 groups: only MDD, GAD, MDD + GAD and no MDD or GAD. Table 5 shows the Association between hematological Indices and MDD and GAD and MDD + GAD compared to reference group (no MDD or GAD). In adjusted model, the associations between RDW with MDD in males (β= −0.111, [−0.205, −0.017], $P=0.044$) and NLR with GAD in females (β: −0.107[−0.235, 0.021], $P=0.01$) were significant. Additionally, the associations of neutrophil count ($\beta=4.468$ [0.639, 8.298], $p=0.022$), NLR ($\beta=0.457$[0.283, 0.632], $p<0.001$) and lymphocyte count (β=−4.51[−8.082, −0.935], $p=0.013$) with MDD + GAD in males were significant.

Discussion

In the young population from the Rafsanjan youth cohort database, the prevalence of MDD was found to be 14.9%, while the prevalence of GAD was 7.49%. Notably, both disorders affected females more than males. These findings align with previous research indicating that females are more vulnerable to depression and anxiety than their male counterparts[21,22]. This sex disparity may be attributed to various factors, including hormonal fluctuations, social pressures, and differences in coping mechanisms. Furthermore, the higher prevalence of depression and anxiety among females highlights the urgent need for targeted interventions and support systems to address the unique mental health challenges faced by this demographic[23].

In this study, specific factors significantly contributed to MDD and GAD in both sexes. For females, alcohol consumption, smoking, and opium use were noteworthy contributors to MDD. In contrast, males' MDD was significantly related to educational level, increased physical activity, as well as smoking and opium use. Regarding GAD, older age and a history of diabetes were significant factors for females, while older age, a history of hypertension, smoking, and opium use were significant factors for males. Previous studies have indicated that

Variables	Females			Males		
	No generalized anxiety disorder (*N* = 1496)	Generalized anxiety disorder (*N* = 140)	*P*-value	No generalized anxiety disorder (*N* = 1027)	Generalized anxiety disorder (*N* = 80)	*P*-value
Age, years, n (%)						
≤ 20	373 (24.95%)	22 (15.71%)	0.032	328 (27.17%)	13 (16.25%)	0.005
21–30	657 (43.95%)	64 (45.71%)		546 (45.24%)	32 (40.00%)	
≥ 31	465 (31.10%)	54 (38.57%)		333 (27.59%)	35 (43.75%)	
Years of education, n (%)						
≤ Median	905 (60.58%)	94 (67.14%)	0.127	765 (63.43%)	48 (60.00%)	0.537
> Median	589 (39.42%)	46 (32.86%)		441 (36.57%)	32 (40.00%)	
Body mass index (BMI), n (%)						
≤ 24.999	834 (55.90%)	71 (50.71%)	0.068	684 (56.91%)	40 (50.63%)	0.506
25–29.999	429 (28.75%)	37 (36.43%)		335 (27.87%)	24 (30.38%)	
≥ 30	229 (15.35%)	32 (22.86%)		183 (15.22%)	15 (18.99%)	
History of hypertension, n (%)						
No	1452 (97.06%)	135 (96.43%)	0.676	1196 (99.09%)	77 (96.25%)	0.018
Yes	44 (2.94%)	5 (3.57%)		11 (0.91%)	3 (3.75%)	
History of diabetes, n (%)						
No	1401 (93.65%)	123 (87.86%)	0.009	1195 (99.01%)	80 (100%)	0.370
Yes	95 (6.35%)	17 (12.14%)		11 (0.97%)	0 (0.00%)	
Alcohol consumption in past 12 months, n (%)						
No	1467 (98.06%)	135 (96.43%)	0.195	822 (68.10%)	48 (60.00 5)	0.134
Yes	29 (1.94%)	5 (3.57%)		385 (31.90%)	32 (40.00%)	
Cigarette smoking, n (%)						
No	1493 (99.80%)	140 (100%)	0.022	1083 (89.73%)	60 (75.00%)	< 0.001
Yes	3 (0.2%)	0 (0.00%)		114 (10.04%)	20 (25.00%)	
Opium consumption in past 12 months, n (%)						
No	1433 (95.79%)	135 (96.43%)	0.717	1061 (87.90%)	60 (75.00%)	0.001
Yes	63 (4.21%)	5 (3.57%)		137 (12.07%)	20 (25.00%)	
Physical activity, minutes per week. N (%)						
No	935 (62.54%)	90 (64.29%)	0.918	553 (45.82%)	30 (37.50%)	0.341
≤ Median	339 (22.68%)	30 (21.43%)		277 (22.95%)	22 (27.50%)	
> Median	221 (14.78%)	20 (14.29%)		377 (31.23%)	28 (35.00%)	

Table 2. Demographic characteristics of females and males in the RYCS according to the presence or absence of generalized anxiety disorder.

the prevalence of depression and anxiety disorders tends to increase significantly with age during childhood and adolescence[24,25]. Additionally, the presence of chronic underlying conditions can exacerbate treatment costs and lead to physical disabilities due to pain or other symptoms. This psychological and social burden is particularly pronounced among teenagers and young adults who are experiencing mood instability[26,27].

In the linear regression analysis conducted in this study, NLR values were positively correlated with MDD and GAD in males; however, no significant association was observed in females. These findings are consistent with reports from Demircan et al.[28] Sunbul et al.[29] and Peng et al.[30] which documented a positive association between NLR and the severity of depression and neuropsychiatric disorders. According to Sunbul et al., an NLR greater than 1.57 serves as an independent predictor of severe or very severe depression[29]. Additionally, Demircan et al. demonstrated that treatment with serotonin reuptake inhibitors in 100 patients with depression resulted in a decrease in NLR values, further supporting its association with depression[28]. NLR provides valuable insights not only into systemic inflammation but also into the patient's stress response. Elevated neutrophil counts primarily reflect inflammation, while reduced lymphocyte counts indicate poor general health and physiological stress[31]. An increased NLR is also linked to oxidative stress and heightened cytokine production- findings that have been reported in relation to depressive disorders[32]. NLR appears to be a simple and cost-effective method for assessing the severity of depression in individuals with major depressive disorder, making it suitable for use in outpatient settings. For patients with elevated NLR levels, particularly males, more comprehensive follow-up regarding depression and anxiety may be warranted. Velasco et al. recently identified NLR as a potential environmental biomarker for predicting suicidal behavior tendencies in major depression, further highlighting the significance of this parameter[33]. However, a study by Vulser et al., which involved 44,806 participants, found no significant association between depressive symptoms and neutrophil count[13].

Our findings indicate a negative correlation between the percentage of lymphocytes and GAD, but this association was observed exclusively in males. Lymphocytes are essential components of the acquired immune system; they enable specific responses to pathogens, contribute to immune memory, and help maintain immune

Variables		Major depressive disorder					
		Crude model	P-value	Adjusted model 1	P-value	Adjusted model 2	P-value
WBC	Males	−0.009(−0.255, 0.274)	0.946	−0.051(−0.319, 0.217)	0.71	−0.095(−0.036, 0.174)	0.489
	Females	0.079(−0.03, 0.141)	0.483	−0.059(−0.257, 0.157)	0.593	−0.08(−0.30, 0.14)	0.425
RBC	Males	−0.05(−0.0121, 0.023)	0.179	−0.051(−0.123, 0.021)	0.166	−0.042(−0.114, 0.03)	0.251
	Females	−0.004(−0.056, 0.047)	0.88	0.005(−0.056, 0.047)	0.861	−0.007(0.059, −0.045)	0.792
HGB	Males	−0.07(−0.25, 0.11)	0.46	−0.07(−0.26, 0.11)	0.429	−0.07(−0.248, 0.115)	0.472
	Females	0.02(0.15, −0.12)	0.80	0.023(−0.111, 0.157)	0.741	−0.005(−0.14, 0.13)	0.943
HCT	Males	−0.21(−0.69, 0.28)	0.40	−0.25(−0.73, 0.238)	0.318	−0.21(−0.69, 0.27)	0.399
	Females	0.08(0.44, −0.28)	0.67	0.086(−0.273, 0.446)	0.637	0.015(−0.347, 0.378)	0.934
MCV	Males	0.37(−0.46, 1.19)	0.38	0.32(−0.51, 1.15)	0.449	0.26(−0.58, 1.09)	0.543
	Females	0.16(−0.58, 0.90)	0.67	0.186(−0.55, 0.92)	0.622	0.093(−0.065, 0.839)	0.807
MCH	Males	0.13(−0.21, 0.48)	0.44	0.13(−0.21, 0.48)	0.446	0.102(−0.24, 0.45)	0.563
	Females	0.03(−0.27, 0.33)	0.85	0.043(−0.255, 0.34)	0.778	0.006(−0.295, 0.306)	0.971
MCHC	Males	0.02(0.12, 0.15)	0.78	0.04(−0.10, 0.17)	0.604	0.022(−0.114, 0.155)	0.754
	Females	−0.03(−0.13, 0.08)	0.61	−0.02(−0.12, 0.08)	0.688	−0.03(−0.13, 0.07)	0.572
RDW	Males	**−0.09(−0.17, −0.003)**	**0.04**	**−0.10(−0.18, −0.12)**	**0.025**	**−0.1(−0.18, −0.01)**	**0.022**
	Females	−0.04(−0.14, 0.06)	0.45	0.05(−0.15, 0.05)	0.34	−0.04(−0.14, 0.06)	0.462
PLT	Males	0.73(−6.65, 8.12)	0.85	1.63(−5.76, 9.02)	0.665	2.04(−5.40, 9.48)	0.59
	Females	2.57(−3.99, 9.13)	0.44	2.47(−4.05, 8.989)	0.458	2.42(−4.18, 9.02)	0.472
N/L(NLR)	Males	**0.10(0.01, 0.19)**	**0.02**	**0.09(−0.002, 0.177)**	**0.046**	**0.097(0.009, 0.18)**	**0.031**
	Females	−0.005(−0.07, 0.07)	0.90	−0.0002(−0.07, 0.07)	0.996	0.005(−0.065, 0.075)	0.895
N	Males	0.12(−1.78, 2.02)	0.90	−0.35(−2.26, 1.56)	0.72	−0.19(−2.11, 1.73)	0.846
	Females	−0.21(−1.71, 1.29)	0.78	0.10(−1.58, 1.38)	0.894	−0.17(−1.5, 1.48)	0.982
L	Males	−0.19(−1.97, 1.58)	0.83	0.21(−1.57, 1.99)	0.815	0.037(−1.75, 1.83)	0.967
	Females	0.14(−1.25, 1.54)	0.84	0.05(−1.33, 1.44)	0.941	−0.015(−1.42, 1.39)	0.984
M	Males	0.015(−0.255, 0.285)	0.913	0.066(−0.205, 0.34)	0.632	0.08(−0.19, 0.35)	0.561
	Females	0.088(−0.0177, 0.284)	0.38	0.07(−0.12, 0.27)	0.458	0.05(−0.14, 0.25)	0.605
MPV	Males	−0.01(0.08, −0.10)	0.79	−0.01(−0.1, 0.08)	0.824	−0.012(−0.11, 0.08)	0.804
	Females	−0.002(0.07, −0.08)	0.96	0.0005(−0.7, 0.7)	0.99	−0.003(−0.08, 0.07)	0.932
PCT	Males	0.00002(−0.08, 0.006)	0.99	0.001(−0.005, 0.006)	0.787	0.001(−0.005, 0.007)	0.71
	Females	0.002(−0.003, 0.007)	0.49	0.002(−0.003, 0.007)	0.501	0.002(−0.003, 0.007)	0.515
PDW	Males	−0.03(−0.15, 0.08)	0.60	−0.03(−0.15, 0.08)	0.578	−0.04(−0.15, 0.08)	0.552
	Females	−0.04(−0.13, 0.05)	0.39	−0.03(−0.12, 0.06)	0.493	−0.04(−0.13, 0.05)	0.424

Table 3. Linear regression analysis in crude and adjusted models investigating the association between hematological indices and major depressive disorder according to sex. The Crud model was not adjusted. Model 1 included age, education, physical activity, body mass index (BMI), histories of arteritis rheumatoid, diabetes and hypertension. Adjusted model 2 included all variables in model 1 and additionally included smoking, alcohol consumption, opium use. Significant values are in bold.

balance[34]. A decline in lymphocyte levels often signals overall poor health and increased physiological stress[35]. Additionally, research has shown that heightened stress levels, a common experience among students, are associated with a reduction in CD19 + B lymphocytes and an altered cortisol awakening response. Hierarchical linear regression analyses suggest that changes in cortisol awakening response may mediate the decrease in CD19 + B lymphocytes. These findings imply that chronic stress, as evidenced by emotional distress and irregular cortisol patterns, is associated with significant immunological changes, particularly a reduction in B lymphocyte counts[36]. Together with the rise in NLR among individuals suffering from depression or anxiety, these findings suggest a significant role for the innate immune system in the increased susceptibility to mood and mental disorders. Additionally, acquired immune cells may be partially reprogrammed by stress to promote neuroplasticity; a study found that mice receiving lymph node transplants devoid of mature lymphocyte cells exhibited anti-inflammatory tendencies[37]. Previous studies have also reported an increase in neutrophils without a corresponding change in lymphocyte counts in animals experiencing long-term stress and in patients with severe depression[38,39].

In the current study, RDW values were negatively associated with MDD in males and GAD disorders in females. This finding contrasts with the results of studies by Shafiee et al.[40] Demircan et al.[28] May et al.[41] and Peng et al.[30] which reported a positive correlation between RDW and mood disorders (depression and anxiety). Kriegmair et al.[42] observed that there was no notable difference in red cell distribution width (RDW) between individuals with depression and healthy controls, nor was there a correlation between RDW levels and the severity of depression. However, they found that elevated RDW values were linked to increased overall symptom

Variables		Generalized anxiety disorder					
		Crude model	P-value	Adjusted model 1	P-value	Adjusted model 2	P-value
WBC	Males	0.17(−0.21, 0.55)	0.38	0.135(−0.251, 0.522)	0.492	0.11(−0.276, 0.496)	0.577
	Females	−0.21(−0.51, 0.08)	0.16	−0.203(−0.493, 0.087)	0.17	−0.20(−0.49, 0.09)	0.18
RBC	Males	−0.03(−0.13, 0.08)	0.60	−0.004(−0.107, 0.1)	0.212	0.01(−0.09, 0.14)	0.844
	Females	0.03(−0.04. 0.10)	0.42	0.04(−0.26, 0.112)	0.211	0.041(−0.028, 0.114)	0.24
HGB	Males	−0.04(−0.22, 0.31)	0.74	0.116(−0.247, 0.279)	0.906	0.03(−0.24, 0.303)	0.751
	Females	0.10(− 0.08, 0.28)	0.26	0.148(− 0.31, 0.327)	0.104	0.15(− 0.03, 0.32)	0.11
HCT	Males	−0.04(−0.74, 0.65)	0.90	0.117(−0.583, 0.816)	0.744	0.25(−0.473, 0.903)	0.547
	Females	0.38(−0.87,0.10)	0.118	**0.504(0.24, 0.985)**	**0.04**	**0.494(0.114, 0.974)**	**0.044**
MCV	Males	0.32(−0.87, 1.50)	0.60	0.269(−0.929, 1.466)	0.66	0.231(−0.97, 1.42)	0.706
	Females	0.32(−0.67, 1.31)	0.52	0.33(−0.66, 1.32)	0.513	0.34(−0.651, 1.33)	0.501
MCH	Males	0.06(−0.43, 0.05)	0.82	0.031(−0.468, 0.53)	0.902	−0.033(−0.51, 0.49)	0.902
	Females	0.07(−0.33, 0.46)	0.75	0.078(−0.321, 0497)	0.691	−0.08(−0.32, 0.48)	0.69
MCHC	Males	−0.05(−0.24, 0.15)	0.63	−0.33(−0.229, 0.162)	0.737	−0.047(−0.25, 0.15)	0.664
	Females	−0.05(−0.19, 0.09)	0.47	00.039(−0.197, 1.099)	0.584	−0.038(−0.018, 0.099)	0.584
RDW	Males	0.001(−0.12, 0.12)	0.98	−0.015(−0.133, 0.106)	0.807	−0.01(−0.13, 0.106)	0.854
	Females	−0.13(−0.26, 0.003)	0.06	**−0.143(−0.274, −0.012)**	**0.032**	**−0.15(−0.277, −0.015)**	**0.029**
PLT	Males	4.83(−5.77, 15.43)	0.37	6.794(−3.742, 17.452)	0.211	6.86(−3.86, 17.58)	0.198
	Females	1.03(−7.75, 9.82)	0.82	2.267(−0.493, 11.027)	0.612	2.29(−6.492, 11.072)	0.609
N/L(NLR)	Males	**0.22(0.09, 0.34)**	**0.001**	**0.208(0.282, 0.334)**	**0.001**	**0.22(0.09, 0.34)**	**0.001**
	Females	−0.06(−0.15, 0.04)	0.23	−0.81(−0.184, 0.012)	0.086	−0.08(−0.17, 0.01)	0.1
N	Males	**2.79(0.07, 5.51)**	**0.04**	2.35(−0.451, 5.102)	0.094	2.69(−0.08, 5.46)	0.06
	Females	−0.82(−2.82, 1.19)	0.42	−1.313(−3.431, 0.575)	0.164	−1.34(−3.36, 0.652)	0.187
L	Males	**−2.79(−5.33, −0.26)**	**0.03**	−2.454(−5.22, 0.114)	0.061	**−2.71(−5.39, −0.136)**	**0.039**
	Females	0.81(−1.06, 2.68)	0.40	1.357(−0.498, 3.212)	0.152	1.292(−0.54, 3.18)	0.173
M	Males	−0.03(−0.41, 0.36)	0.89	0.062(−0.327, 0.451)	0.753	0.067(−0.324, 0.45)	0.737
	Females	0.07(−0.20, 0.33)	0.62	0.122(−0.137, 0.381)	0.357	0.15(−0.14, 0.38)	0.386
MPV	Males	−0.01(−0.14, 0.12)	0.88	−0.024(−0.184, 0.11)	0.726	−0.02(−0.15, 0.0111)	0.726
	Females	**0.1 (0.006, 0.20)**	**0.045**	**0.101(0.002, 0.095)**	**0.045**	**0.102(0.003, 0.201)**	**0.045**
PCT	Males	0.004(−0.004, 0.01)	0.39	0.005(−0.003, 0.013)	0.246	0.005(−0.003, 0.013)	0.23
	Females	0.004(−0.003, 0.01)	0.27	0.005(−0.002, 0.011)	0.171	0.005(−0.002, 0.011)	0.16
PDW	Males	−0.03(−0.003, 0.05)	0.38	−0.197(−0.276, 0.006)	0.212	−0.103(−0.27, 0.07)	0.234
	Females	−0.06(−0.18, 0.07)	0.37	−0.065(−0.187, 0.057)	0.296	−0.06 (−0.18, 0.058)	0.303

Table 4. Linear regression analysis in crude and adjusted models investigating the association between hematological indices and generalized anxiety disorder according to sex. The Crud model was not adjusted. Model 1 included age, education, physical activity, body mass index (BMI). histories of arteritis rheumatoid, diabetes and hypertension. Adjusted model 2 included all variables in model 1 and additionally included smoking, alcohol consumption, opium use. Significant values are in bold.

severity. However, some studies found no significant association between RDW values and the likelihood of depression[39]. Therefore, we recommend that future studies specifically investigate changes in RDW in relation to anxiety disorders.

In the present study, MPV was positively correlated with GAD exclusively in females, while no association was observed between MPV and MDD in either sex. This finding aligns with the research conducted by Chen et al., which noted that MPV increases in neuropsychiatric disorders, particularly mood disorders[43]. Additionally, it is consistent with the study by Fábián et al., which reported a significant positive correlation between MPV and anxiety disorders[44]. Similarly, Ataoglu et al. found that MPV was significantly elevated in patients with mood disorders, returning to normal levels with appropriate treatment[45]. It is well established that individuals with depression or anxiety exhibit higher sympathetic activity, catecholamine levels, and cortisol secretion. Furthermore, increased catecholamines and sympathetic nervous system activity have been linked to heightened platelet activation[46,47]. In a study involving chronically stressed caregivers, elevated levels of depressive and anxiety symptoms were associated with increased and prolonged platelet activity[48]. However, the precise mechanisms underlying the association between changes in platelet parameters and mood disorders remain unclear, necessitating further research to elucidate these effects.

In our study, a positive correlation between HCT and GAD in females suggests that individuals with higher HCT may experience greater physiological stress or inflammation, a factor often exacerbated by anxiety disorders. This finding is consistent with previous research by Ransing et al.[49] suggesting that altered red blood cell indices, including increased HCT in patients with panic disorder, can reflect systemic responses to chronic

Variables		Major depressive disorder	*P*-value	Generalized anxiety disorder	*P*-value	Major depressive disorder + generalized anxiety disorder	*P*-value
WBC	Males	−0.223(−0.553, 0.077)	0.145	−0.163(−0.699, 0.374)	0.552	0.328(−0.207, 0.864)	0.230
	Females	−0.013(−0.263, 0.235)	0.916	−0.083(−0.486, 0.312)	0.685	−0.319(−0.724, 0.079)	0.115
RBC	Males	−0.063(−0.143, 0.18)	0.126	−0.022(−0.165, 0.122)	0.768	0.026(−0.118, 0.17)	0.719
	Females	−0.021(−0.08, 0.038)	0.484	0.036(−0.058, 0.131)	0.451	0.042(−0.054, 0.127)	0.395
HGB	Males	−0.307(−0.845, 0.23)	0.262	0.158(−0.803, 1.12)	0.747	0.171(−0.788, 1.131)	0.726
	Females	−0.069(−0.233, 0.85)	0.381	0.078(−0.169, 0.324)	0.526	0.197(−0.54, 0.447)	0.965
HCT	Males	−0.307(−0.845, 0.23)	0.262	0.165(−0.803, 1.119)	0.747	0.171(−0.788, 1.133)	0.726
	Females	0.19(−0.602, 0.222)	0.367	0.274(−0.387, 0.935)	0.416	0.669(−0.002, 1.34)	0.051
MCV	Males	0.389(−0544, 1.322)	0.414	0.629(−1.041, 2.298)	0.46	−0.093(−1.76, 1.57)	0.913
	Females	−0.097(−0.947, 0.754)	0.824	0.03(−1.36, 1.37)	0.997	0.644(−0.739, 2.026)	0.361
MCH	Males	0.169(−0.217, 0.557)	0.392	0.197(−0.496, 0.891)	0.577	−0.01(−0.792, 0.593)	0.778
	Females	−0.05(−0.399, 0.292)	0.772	−0.016(−0.564, 0.533)	0.956	0.165(−0.391, 0.722)	0.56
MCHC	Males	0.047(−0.105, 0.199)	0.543	−0.013(−0.286, 0.259)	0.924	−0.069(−0.341, 0.203)	0.618
	Females	−0.021(−0.14, 0.098)	0.727	−0.018(−0.209, 0.172)	0.85	−0.06(−0.253, 0.130)	0.544
RDW	Males	**−0.111(−0.205, −0.017)**	**0.021**	0.012(−0.156, 0.181)	0.885	−0.054(−0.222, 0.1114)	0.529
	Females	−0.014(0.127, 0.99)	0.809	−0.157(−0.338, 0.023)	0.088	−0.138(−0.321, 0.045)	0.141
PLT	Males	1.675(−6.639, 9.988)	0.693	9.354(−0.521, 24.23)	0.218	4.837(−10.017, 19.69)	0.523
	Females	2.741(−4.777, 10.259)	0.475	3.218(−8.834, 15.27)	0.601	2.179(−10.048, 14.406)	0.727
N/L(NLR)	Males	−00.008(−0.0105, 0.09)	0.878	−0.0025(−0.199, 0.149)	0.778	**0.457(0.283, 0.632)**	**0.000**
	Females	0.013(−0.066, 0.093)	0.741	**−0.107(−0.235, 0.021)**	**0.1**	−0.043(−0.173, 0.087)	0.513
N	Males	−1.508(−3.650.656)	0.168	0.315(−3.054, 4.15)	0.772	**4.468(0.639, 8.298)**	**0.022**
	Females	0.071(−1.639, 1.78)	0.936	−1.96(−4.7, 0.785)	0.162	−686(−3.467, 2.094)	0.628
L	Males	1.313(−0.687, 3.313)	0.198	−0.052(−4.01, 0.59)	0.776	**−4.51(−8.082, −0.935)**	**0.013**
	Females	0.068(−1.663, 1.527)	0.933	1.98(−0.577, 4.427)	0.129	0.554(−2.035, 3.153)	0.673
M	Males	−0.136(−0.169, 0.441)	0.383	0.246(−0.298, 0.781)	0.375	−0.07(−0.613, 0.472)	0.8
	Females	0.002(−0.222, 0.225)	0.988	0.035(−0.321, 0.392)	0.202	0.202(−0.154, 0.564)	0.273
MPV	Males	0.01(−0.103, 0.106)	0.979	−0.005(−0.0183, 0.192)	0.961	−0.0057(−0.244, 0.129)	0.447
	Females	−0.020(−0.11, 0.065)	0.641	0.125(−0.011, 0.261)	0.072	0.072(−0.066, 0.212)	0.304
PCT	Males	0.001(−0.005, 0.007)	0.726	0.008(−0.004, 0.019)	0.177	0.002(−0.009, 0.013)	0.713
	Females	0.001(−0.004, 0.007)	0.651	0.006(−0.003, 0.015)	0.205	0.004(−0.005, 0.013)	0.408
PDW	Males	−0.033(−0.165, 0.098)	0.62	−0.146(−0.381, 0.089)	0.224	−0.068(−0.302, 0.167)	0.572
	Females	−0.038(−0.143, 0.066)	0.471	−0.084(−0.0252, 0.084)	0.327	−0.059(−0.223, 0.118)	0.546

Table 5. Linear regression analysis in adjusted models investigating the association between hematological indices and major depressive disorder and generalized anxiety disorder and major depressive disorder + generalized anxiety disorder according to sex. Adjusted model included age, education, physical activity, body mass index (BMI), histories of arteritis rheumatoid, diabetes and hypertension, smoking, alcohol consumption and opium use. Significant values are in bold.

stress. The association between HCT and GAD could be attributed to several factors. Stress, particularly chronic psychological stress as seen in anxiety disorders, can induce physiological changes such as increased sympathetic nervous system activity and altered cortisol secretion, which in turn can affect hematological parameters. Research by Mischler et al.[50] supports this notion, demonstrating that stress-related hormonal imbalances, including elevated cortisol, influence erythropoiesis and could lead to changes in HCT levels. In general, while our findings contribute to the growing body of literature suggesting an association between elevated HCT and GAD in females, additional studies are needed to confirm the causal pathways and to explore the physiological mechanisms that underpin these associations. Longitudinal research would be particularly valuable in determining whether changes in HCT levels precede the onset of anxiety symptoms or are a consequence of long-term anxiety.

Limitations

One of the key limitations of this study is its cross-sectional design, which focused on youth without follow-up assessments to evaluate the long-term effects of depression and anxiety disorders on the variables in question. Additionally, the study's geographical scope is limited, as all participants were drawn from the same city, leading to similarities in demographic and behavioral characteristics. The measurement of physical activity relied on a brief two-question self-report questionnaire, which may not fully capture the complexity of participants' activity levels. Furthermore, immune cells were assessed as relative percentages; this method can be influenced by variations in the parent cell type, making it a less comprehensive representation of the overall immune

landscape. Given that we conducted multiple statistical tests without adjusting for these comparisons, there is an increased risk of false positives.

On the positive side, this study benefits from a population-based design with a large sample size, and all hematological indices were analyzed in a single laboratory, enhancing the reliability of our findings. Importantly, this research contributes valuable new data to future meta-analyses, particularly by offering insights from a non-Western population.

Suggestions

Future studies should expand on the dimensions of the current research by investigating individuals with significant behavioral and cultural differences. Longitudinal follow-up of these individuals regarding changes in disorder severity and subsequent alterations in hematological indices would enhance our understanding of this association.

Conclusion

Our study identified a significant association between hematological indices and mental health outcomes in youths. Specifically, we found that RDW and NLR were associated with MDD in males, while HCT, RDW and MPV were linked to GAD in females. Additionally, NLR values and lymphocyte percentages were associated with GAD in males. Further research is needed to clarify the underlying mechanisms driving these associations and to explore their clinical implications for early detection and intervention strategies in this vulnerable population.

Data availability

The data used in this study are available from the corresponding author on request.

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Author contributions

ZJ and NMK designed the study, RH, PK, MM, SZ, and MH collected data, ZJ, MH, MNK and PK analyzed data, and RH and SZ wrote the manuscript. All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and Institutional Review Board approval has been obtained (IR.RUMS.REC.1400.249). Informed consent was obtained from all participants included in the study. For those participants who were 15 years old, consent was also obtained from their parents and/or legal guardians.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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Correspondence and requests for materials should be addressed to M.N.K.