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Association between neutrophil to lymphocyte ratio and depressive symptoms among Chinese adults: A population study from the TCLSIH cohort study

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ABSTRACT

Background: The prevalence of depression in the general population has risen sharply over the past few decades and has become a major health problem throughout the world. Increasing evidence suggests that inflammation plays an important role in the pathogenesis of depression. To better understand the role of inflammation in the pathogenesis of depression we can use the neutrophil-to-lymphocyte ratio (NLR) because it is a simple and effective marker of inflammation and immunity.

Methods: This cross-sectional study was conducted among adults from the healthy general population in Tianjin, China. NLR was measured according to the complete blood count. Depressive symptoms were assessed using the Zung Self-Rating Depression Scale (SDS), and a cutoff score of 45 was used to indicate the presence of depressive symptoms in the study participants. The relationship between NLR and the prevalence of depressive symptoms was evaluated separately for men and women using the multiple logistic regression analysis.

Results: In the present study, the overall prevalence of depressive symptoms was 17.0% among all participants. In women, the multivariable-adjusted OR of having depressive symptoms was 1.28 (95% CI 1.10, 1.49; p for trend < 0.01) for the fifth compared with the first quintile of NLR, and was 1.22 (95% CI 1.07,1.39; $p < 0.01$) per unit increase of NLR. However, no significant association was found between NLR and depressive symptoms in men.

Conclusion: This study suggests that increased NLR levels are independently related to depressive symptoms in women, but not in men. Further research is required to investigate this relationship with longitudinal data to establish the temporal ordering between these variables.

1. Introduction

Depression is a common mental illness with an increasing prevalence during last two decades and is considered to be an important contributor to the total burden of disease (Compton et al., 2006; Ferrari et al., 2013). As with many other psychiatric disorders, depression has a profound impact on a person's cognitive faculties (Hammar and Ardal, 2009), social functions (Steger and Kashdan, 2009), quality of life (Brenes, 2007), and risk of suicide (Miret et al., 2013). Therefore, an urgent need exists to identify preventive strategies to reduce the burden of depression on both the individual and society.

Although there are several theories with at least some empirical support, the exact pathophysiology of depression is complex and incompletely understood. Previous studies have indicated that low-grade inflammation plays a critical role in the development of depression (Patel, 2013). Multiple studies have clearly shown that antidepressants can moderately improve depressive symptoms by reducing the levels of pro-inflammatory cytokines and increase the production of anti-

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inflammatory cytokines (Hannestad et al., 2011; Kenis and Maes, 2002). Inflammatory mediators have also been found to interact with key biological systems that are implicated in depression, including altering neurotransmitter metabolism, neuroendocrine function, neural plasticity, and reactive oxygen species (Irwin and Miller, 2007; Miller et al., 2009).

In recent years, the neutrophil to lymphocyte ratio (NLR) has emerged as a well-accepted biomarker for the assessment of overall inflammatory status (Imtiaz et al., 2012). NLR is a simple and cost-effective marker that can be easily derived from a white blood cell count differential (Arbel et al., 2012). Elevated levels of NLR were found to be interconnected with oxidative stress and increased cytokine productions in patients with depressive disorders (Kasama et al., 2005). Several studies conducted in animals have also reported an association between NLR and chronic stress (Puppe et al., 1997; Trevisi et al., 2009). These findings prompted us to hypothesize that higher NLR is associated with more severe depressive symptoms. A limited number of clinical studies have investigated the association between NLR and depression and have indicated that NLR was significantly higher in patients with major depressive disorder (MDD) than healthy controls (Cai et al., 2017; Demir et al., 2015; Demircan et al., 2016; Euteneuer et al., 2017). A hospital based cross-sectional study conducted among 256 patients diagnosed with depression in Turkey, reported that higher HAM-D scores were associated with higher levels of NLR (Aydin Sunbul et al., 2016). However, all of these studies were limited by relatively small sample sizes. In addition, several important confounding factors, such as gender, body mass index (BMI), lifestyle, and physical activity, were not taken into account in these studies.

With these considerations in mind, we performed a cross-sectional study to examine the association between NLR values and depressive symptoms in a large-scale Chinese population.

2. Material and methods

2.1. Participants

Participants were recruited as part of the Tianjin Chronic Low-grade Systemic Inflammation and Health (TCLSIH) Cohort Study, which is a large prospective dynamic cohort study focusing on the relationships between chronic low-grade systemic inflammation and the health status of a population living in Tianjin (Sun et al., 2014), a city in northern China with a population of over 15 million people. A detailed description of this cohort study has been published elsewhere (Gu et al., 2017). Briefly, participants were recruited from the general adult population (aged 18 years or older) and were selected randomly from health management centers and community management centers during annual health examinations. Moreover, detailed questionnaires covering demographic, medical, dietary, and lifestyle variables were administered to selected participants from this population since May 2013. The study was approved by the Institutional Review Board of Tianjin Medical University and all participants provided written informed consent.

TCLSIH data from 2013 to 2016 was used to perform a cross-sectional analysis in the present study. During the research period, a total of 28,657 participants had received health examination at least once. We excluded participants who did not complete the food frequency questionnaire or depression scale (n = 338), or those who did not undergo white blood cell (WBC) counts (n = 1315), or those with a history of cardiovascular disease (n = 27), cancer (n = 1342) or autoimmune diseases (n = 278). Following these exclusions, the final cross-sectional study population comprised 25,357 participants, including 13,679 men (mean ± standard deviation age: 42.1 ± 11.9 years) and 11,678 women (mean ± standard deviation age: 40.5 ± 11.6 years).

2.2. Measures

2.2.1. Assessment of depressive symptoms

The depressive symptoms of each subject were measured using the Chinese version of the Zung Self-Rating Depression Scale (SDS), a self-report questionnaire consisting of 10 symptom-positive items and 10 symptom-negative items. Participants were required to give a score from 1 to 4 for each item. A total score was calculated for each participant by summing up the scores of all positively-keyed items and the reversed scores of all the symptom-negative items (Zung, 1965). Previous studies have demonstrated its reliability and validity in adult Chinese populations (Wang, 1999). In this study, participants who scored 45 or above were considered to have present depressive symptoms (Fountoulakis et al., 2001).

2.2.2. Assessment of NLR

Venous blood samples were taken from subjects in the morning after an overnight fast of at least 12 h. WBC, neutrophil, and lymphocyte counts were measured using the automated hematology analyzer and expressed as $\times 1000$ cells/mm^3, and the NLR was calculated as the ratio of the neutrophil count to the lymphocyte count. In order to reveal the exact association between these hematological parameters and the presence of depressive symptoms, we treated them both as quartiles and as continuous variables so that we can use the available information more flexibly and efficiently.

2.2.3. Assessment of other variables

Anthropometric parameters, including height (cm), weight (kg), waist circumference (cm) were measured using standard procedures, and BMI was calculated as weight/height squared. After participants had rested for at least 5 min, systolic and diastolic blood pressure were measured twice in the right arm, using an automatic device (KD598; Andon). The mean value of two measurements was used for data analyses. Blood samples were collected in siliconized vacuum plastic tubes for the measurement of plasma glucose and lipids. Fasting blood sugar (FBS) level was measured by the glucose oxidase method, total cholesterol (TC) and triglycerides (TG) were determined by enzymatic methods, low density lipoprotein (LDL) cholesterol was measured using the polyvinyl sulfuric acid precipitation method, and high density lipoprotein (HDL) cholesterol was measured by chemical precipitation. All the above mention tests were performed on a Cobas 8000 analyzer (Roche, Mannheim, Germany). Metabolic syndrome was defined based on the criteria proposed by the American Heart Association's Scientific Statement in 2009 [21].

Social and demographic variables were also assessed, including gender, age, educational level, occupation, monthly household income, marital status, cohabitants, and frequency of visiting friends. Level of education was assessed by the following question: “what is the highest degree you earned?” and was categorized into 2 categories: < College graduate or ≥ College graduate. Income level was divided into two groups according the threshold of 10,000 yuan per month. Marital status was divided into married or unmarried. Living condition was defined as living alone or with others. Information about the frequency of contacts with friends, a question asked: “Do you often visit your friends and relatives?” Data on smoking status (current or former/never), alcohol drinking (current or former/never), history of physical illness and current medication use (yes or no) of the participants were collected using a standard questionnaire. Physical activity (PA)(h/week) was measured using a short version of the International Physical Activity Questionnaire (IPAQ), which provides information on the amount of minutes spent in vigorous-intensity activities, moderate-intensity activities, walking, and sitting during the past seven days (Craig et al., 2003). Metabolic equivalent (MET) hours per week (MET × hours/week) were calculated using corresponding MET coefficients (8.0, 4.0 and 3.3, respectively) according to the following formula: MET coefficient of activity × duration (hours) × frequency (days) (Craig

et al., 2003). The levels of total PA were computed by combining separate scores for different activities. A validated extensive self-administered food frequency questionnaire (FFQ) containing 100 food items was used to assess the usual dietary intake. By combining information obtained from the food frequency questionnaire with the Chinese food composition table (Yang et al. (2002), we were able to calculate the mean total energy intake for each subject.

2.3. Statistical analysis

For descriptive statistics, data are expressed as the mean ± standard deviation (95% confidence interval, CI) for continuous variables and percentages for categorical variables. For further analysis, the prevalence of depressive symptoms was used as a dependent variable, and NLR, leukocyte, neutrophil and lymphocyte counts (quartiles, continuous, and per unit change) were used as independent variables. Differences between groups classified by SDS scores were tested with an analysis of variance for continuous variables and logistic regression analyses for proportional variables. Multiple logistic regression analyses were performed in order to estimate the association between the quintiles of NLR and depressive symptoms initially, using the lowest quintile as the reference group. We also analyzed NLR levels as a continuous variable in all regression models. In model 1, crude odds ratios (ORs) were calculated with 95% confidence interval. In model 2, potential confounding variables including age and BMI were further adjusted for. In model 3, multivariate-adjusted OR were computed after adjustment for smoking and drinking habits, PA, marital status, total energy intake, household incomes, occupations, educational levels, visiting friends, living alone, MS, EPA and DHA intake, vegetable intake and fruit intake (by the forced entry method). Tests for linear trend across quintiles of NLR was examined by using the median value of each quintile as an ordinal variable in the linear regression models. The interactions between NLR levels and potential confounders were also tested by adding the cross-product term to the final regression model. All the statistical tests were two-tailed and P values < 0.05 were considered as statistically significant. Data analysis was done using Statistical Analysis System version 9.3 for Windows (SAS Institute Inc., Cary, NC).

3. Results

3.1. Characteristics of study subjects

In the present study, the prevalence of depressive symptoms was 16.0% and 18.2% among men and women when the recommended cut-off point of 45 was used. The characteristics of the subjects by SDS scores are presented in Table 1. In men, participants with depressive symptoms status tended to have a lower level of BMI ($P < 0.01$), education, physical activity, employ as Managers, household income, and visiting to friends ($P < 0.0001$), but had a higher level of EPA and DHA intake ($P < 0.01$). In addition, they were more likely to be current smokers ($P < 0.0001$). In women, those with depressive symptoms status were more likely to be unmarried, and have a lower level of education, physical activity, employ as Managers, household income, visiting to friends ($P < 0.0001$), total energy intake ($P < 0.001$) and vegetable intake ($P < 0.01$). A higher proportion of females with SDS scores ≥ 45 status were more likely to be current smokers and living alone ($P < 0.01$). Otherwise, no significant differences were observed between groups.

3.2. NLR and depressive symptoms

The gender-specific crude and adjusted associations between NLR and depressive symptoms are presented in Table 2. Among women, NLR levels (both as quartiles and as continuous variables) were positively associated with the presence of depressive symptoms in all models. After final multiple adjustments, the ORs of depressive symptoms were 1.00 (reference), 1.14 (95% CI 0.98, 1.33), 1.21 (95% CI 1.04, 1.42), 1.28 (95% CI 1.09, 1.49) and 1.28 (95% CI 1.10, 1.49), respectively, for participants with NLR in the 1 st, 2nd, 3rd, 4th, and 5th quintiles (P for trend < 0.01). The multivariate-adjusted OR for depressive symptoms per unit increase of NLR was 1.22 (95% CI 1.07, 1.39; $p < 0.01$). In men, after final adjustments, the ORs of depressive symptoms were 1.00 (reference), 1.05 (95% CI 0.91, 1.22), 1.02 (95% CI 0.88, 1.19), 1.11 (95% CI 0.96, 1.29) and 1.02 (95% CI 0.88, 1.19), respectively, for participants with NLR in the 1st, 2nd, 3rd, 4th, and 5th quintiles (P for trend $= 0.69$). The multivariate-adjusted OR for depressive symptoms per unit increase of NLR was 1.08 (95% CI 0.95, 1.23; $p = 0.24$). Moreover, we divided white blood cell count, neutrophil count, lymphocyte count into five categories according to quintiles of participants. After adjusting for several confounding factors, the ORs (95% CI) of depressive symptoms for increasing quintiles of white blood cell, neutrophil, and lymphocyte counts in women were 1.00, 0.97 (0.84, 1.13), 0.98 (0.84, 1.14), 1.04 (0.89, 1.21), and 1.02 (0.88, 1.2); 1.00, 1.11 (0.95, 1.29), 1.10 (0.94, 1.28), 1.20 (1.03, 1.40), and 1.18 (1.01, 1.37); 1.00, 0.95 (0.82, 1.11), 0.81 (0.69, 0.95), 0.88 (0.76, 1.02), and 0.85 (0.73, 0.98) respectively. In contrast, no significant relations were found between these hematological parameters and depressive symptoms in the final multivariate models in men. Similar results were found when these hematological parameters were analyzed as a continuous variable.

4. Discussion

The primary aim of the current study was to examine the association between NLR and depressive symptoms in Chinese adults. The most important finding of our study was that increased NLR values were significantly related to a higher prevalence of depressive symptoms in women, but not in men. To make this study more complete and comprehensive and to better investigate this research problem, we also assessed the association between the quintiles of WBC, neutrophil and lymphocyte counts, and severe depressive symptoms. To the best of our knowledge, this is the first large-scale general population study concerning the topic of NLR levels and depressive symptoms conducted in Asia.

NLR levels are useful in showing that inflammatory activation occurs in psychiatric diseases and can be used as reproducible biomarkers of systemic inflammation that can be measured routinely (Mazza et al., 2018). Demircan et al. found that patients with major depressive disorder had significantly higher levels of NLR compared with the control group. However, the difference in NLR levels between the treatment and control groups disappeared after the administration of SSRIs for three months (Demircan et al., 2016). Similarly, Demir and colleagues reported that NLR tended to be higher in the 41 depressive patients than in the healthy controls (Demir et al., 2015). Furthermore, Sunbul et al. conducted a study among 256 depressed patients and not only demonstrated that NLR levels were significantly higher in depressed patients, but also showed there was a positive correlation between NLR levels and HAM-D scores (Aydin Sunbul et al., 2016). A recent study also indicated that NLR as a subclinical inflammatory marker is associated with a later onset of depression (Ekinci and Ekinci, 2017). However, the use of a specific patient population rather than an general population and a relatively small sample size might limit the generalization of their findings.

Inflammatory cytokines are critically important serum biomarkers to the diagnosis, prognosis, and treatment evaluation of disease (Dinan, 2009; Hashmi et al., 2013). However, increased costs and limited availability are two important barriers to the regular monitoring of inflammatory cytokines levels in patients suffering from depression. White blood cell count, which is widely used as a marker of systemic inflammation, is cheap and readily available (Aydin Sunbul et al., 2016). WBC subtypes such as neutrophil, lymphocyte, and monocyte

Table 1
Participant characteristics by SDS scores.

Characteristics	SDS		*P* value [a]
	< 45	≥45	
Men			
No. of subjects	11485	2194	–
Age (years)	40.5 (40.5, 40.6) [b]	40.5 (40.5, 40.6)	0.64
BMI (kg/m^2)	25.6 (25.5, 25.7)	25.4 (25.2, 25.5)	< 0.01
Waist (cm)	88.1 (88.0, 88.3)	87.9 (87.5, 88.3)	0.35
TC (mmol/L)	4.79 (4.78, 4.81)	4.79 (4.75, 4.82)	0.84
TG (mmol/L)	1.40 (1.38, 1.41)	1.41 (1.38, 1.45)	0.38
LDL (mmol/L)	2.83 (2.81, 2.84)	2.81 (2.78, 2.84)	0.31
HDL (mmol/L)	1.20 (1.19, 1.20)	1.19 (1.18, 1.20)	0.70
SBP (mmHg)	123.3 (123.0, 123.6)	123.1 (122.5, 123.7)	0.50
DBP (mmHg)	78.8 (78.6, 78.9)	78.6 (78.2, 79.0)	0.55
FBG (mmol/L)	5.10 (5.08, 5.11)	5.11 (5.08, 5.15)	0.34
Physical activity (MET × h/week)	12.1 (11.8, 12.4)	8.72 (8.25, 9.21)	< 0.0001
Total energy intake (kcal/d)	2078.6 (2068.6, 2088.6)	2080.6 (2057.9, 2103.6)	0.87
Vegetable intake (g/day)	258.9 (256.1, 261.7)	260.5 (254.1, 267.0)	0.67
Fruit intake (g/day)	246.1 (241, 251.3)	246.5 (235.0, 258.6)	0.98
EPA and DHA intake (g/day)	4.34 (4.29, 4.39)	4.53 (4.41, 4.66)	< 0.01
Metabolic syndromes (yes, %)	34.0	34.6	0.65
Smoking status (%)			
Smoker	36.7	42.9	< 0.0001
Ex-smoker	9.66	9.50	0.77
Non-smoker	53.7	47.6	< 0.0001
Drinker (%)			
Everyday	8.66	8.97	0.57
Sometime	72.1	70.9	0.23
Ex-drinker	9.38	10.0	0.34
Non-drinker	9.89	10.1	0.74
Marital status (married, %)	87.6	87.5	0.72
Living alone (yes, %)	9.55	10.6	0.17
Education (≥ College graduate, %)	70.0	62.2	< 0.0001
Employment status (%)			
Managers	45.7	41.0	< 0.0001
Professionals	20.3	21.0	0.48
Other	34.1	38.0	< 0.001
Household income (≥ 10,000 Yuan, %)	39.0	27.0	< 0.0001
Visiting friend (yes, %)	57.0	51.4	< 0.0001
Women			
No. of subjects	9552	2126	–
Age (years)	39.0 (39.0, 39.0)	39.0 (38.9, 39.0)	0.39
BMI (kg/m^2)	22.8 (22.7, 22.9)	22.8 (22.6, 22.9)	0.48
Waist (cm)	75.4 (75.2, 75.5)	75.5 (75.1, 75.8)	0.64
TC (mmol/L)	4.65 (4.63, 4.67)	4.67 (4.64, 4.71)	0.24
TG (mmol/L)	0.91 (0.90, 0.92)	0.90 (0.89, 0.92)	0.47
LDL (mmol/L)	2.62 (2.60, 2.63)	2.64 (2.60, 2.67)	0.27
HDL (mmol/L)	1.50 (1.49, 1.51)	1.51 (1.49, 1.52)	0.67
SBP (mmHg)	114.8 (114.5, 115)	114.6 (114, 115.2)	0.62
DBP (mmHg)	71.7 (71.5, 71.8)	71.8 (71.5, 72.2)	0.43
FBG (mmol/L)	4.85 (4.84, 4.86)	4.83 (4.80, 4.85)	0.08
Physical activity (MET × h/week)	9.38 (9.14, 9.62)	6.89 (6.52, 7.29)	< 0.0001
Total energy intake (kcal/d)	1933.2 (1921.5, 1945.0)	1884.8 (1860.7, 1909.2)	< 0.001
Vegetable intake (g/day)	240.2 (237.3, 243.0)	230.4 (224.7, 236.2)	< 0.01
Fruit intake (g/day)	291.6 (286.3, 297.1)	280.4 (269.6, 291.5)	0.08
EPA and DHA intake (g/day)	3.64 (3.59, 3.69)	3.69 (3.59, 3.79)	0.36
Metabolic syndromes (yes, %)	14.4	14.7	0.88
Smoking status (%)			
Smoker	1.29	2.17	< 0.01
Ex-smoker	0.72	0.91	0.37
Non-smoker	98.0	96.9	< 0.01
Drinker (%)			
Everyday	0.68	0.90	0.29
Sometime	40.1	40.1	0.97
Ex-drinker	9.38	10.5	0.12
Non-drinker	49.8	48.4	0.26
Marital status (married, %)	85.5	82.0	< 0.0001
Living alone (yes, %)	6.97	8.81	< 0.01
Education (≥ College graduate, %)	66.7	59.2	< 0.0001
Employment status (%)			
Managers	42.8	37.8	< 0.0001
Professionals	12.9	12.7	0.73
Other	44.3	49.6	< 0.0001
Household income (≥ 10,000 Yuan, %)	36.5	26.3	< 0.0001

(*continued on next page*)

Table 1 (*continued*)

Characteristics	SDS		*P* value [a]
	< 45	≥45	
Visiting friend (yes, %)	66.0	56.4	< 0.0001

SDS, self-rating depression scale; BMI, body mass index; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
[a] Analysis of variance or logistic regression analysis.
[b] Least square mean (95% confidence interval) (all such values).

may reflect different aspects of inflammatory processes in many chronic conditions. Neutrophils, the most abundant type of leukocytes, are essential for initiating and regulating innate and adaptive immunity. Neutrophils are the earliest immune cells that react to inflammation and play a key role in regulating the trafficking of immune cells to the sites of inflammation (Aydin Sunbul et al., 2016). Importantly, the activation of neutrophils can cause oxidative stress by releasing reactive oxygen species (ROS), which may contribute to the pathogenesis of depression (Salim, 2014). Lymphocytes are another important component of circulating leukocytes, mainly mediating the adaptive immune response, which works in close collaboration with innate immunity. For the current analysis, we measured NLR as a marker of systemic inflammation and this ratio represents the relationship between two different immune pathways. Neutrophil counts reflect a nonspecific inflammatory process, whereas lymphocyte counts relate to physiological stress and represent an important regulatory component of the immune system (Avanzas et al., 2004). Since NLR mirrors both immune pathways and may be less affected by confounding conditions, it has much better stability and can offer more valuable information than other leukocyte parameters or other commonly used inflammation markers (Gibson et al., 2007; Matthews et al., 1985).

Gender is a definite risk factor for mood disorders (Zhang et al., 2005), residual confounding or moderating effects from gender remained a problem if gender was used as a simple covariate instead of a stratifying variable (Rothman, 2012). There are significant differences in the clinical manifestations between men and women with depression (Marcus et al., 2005), likely due to a combination of social, psychological, and biological factors (Edwards et al., 2006; Kudielka and Kirschbaum, 2005). Taking these factors into consideration, we analyzed men and women separately. In this large population-based study, the association between elevated NLR levels and a higher prevalence of depressive symptoms was significant among women but not among men. This finding indicates that women may be more prone than men to develop mood-related symptoms in response to elevated inflammation. Compared with men, women exhibited heightened proinflammatory activity and were more likely to develop autoimmune diseases (Quintero et al., 2012; Yang and Kozloski, 2011), both of which increased the risk of subsequent depression (Benros et al., 2013; Duivis et al., 2011). Transient increases in inflammation also prompted greater feelings of social isolation and loneliness for women than for men, which correlated with the onset of depression (Kessler et al., 1993). Furthermore, relationship distress, physical inactivity, and childhood adversity, all of which increase the risk for depression, are more strongly tied to inflammation for women than for men (Cyranowski et al., 2000; Keyes et al., 2012; Troiano et al., 2008). The sex hormone estrogen is generally anti-inflammatory, and low levels of estrogen may make postmenopausal women more susceptible to depression due to increased inflammation (Straub, 2007). Therefore, hormonal difference and menopausal status might be another explanation for gender differences in inflammatory-related depressive symptoms (Clendenen et al., 2011; Sites et al., 2002).

Compared with previous studies, the current study has several strengths that deserve noting. The participants in this analysis were selected from a large population-based sample and therefore more generalizable than studies conducted in specific clinical populations. In addition, we adjusted for considerable potential confounding factors, which can influence the association between inflammatory markers and depression. However, the associations remained statistically significant after adjusting for these potential confounders, suggesting that elevated NLR levels are independently associated with the presence of depressive symptoms. Of course, there are also several limitations of this study. First, the cross-sectional design of the study precludes establishing causality of the association. Second, the assessment of depressive symptoms was performed using a self-administrated rating scale rather than a structured clinical diagnostic interview or clinician diagnosis. Third, although a wide range of potential confounders have been taken into consideration, we still could not exclude the possibility that the observed association is attributable to residual or unmeasured confounding.

4.1. Conclusion

In summary, this study showed a positive association between depressive symptoms and NLR levels in women but not in men, which persisted even after adjusting for potential confounders. These findings support the view that inflammation is related to depression, but this association may be gender-specific. Additional experimental and longitudinal studies are needed to better understand the biological mechanisms of sex diff ;erences, as well as determine whether or not an increased level of NLR is a result of depression.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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Table 2
Adjusted relationships of NLR to depressive symptom.

	Quintiles of neutrophil/lymphocyte ratio (range)					*P* for trend [a]	Continuous	*P* values
	Level 1	Level 2	Level 3	Level 4	Level 5			
Men								
neutrophil/lymphocyte ratio (range)	0.11-1.23	1.23-1.49	1.49-1.75	1.75-2.14	2.14-20.7	–		–
No. of subjects	2736	2739	2732	2717	2755	–		–
No. of depressive symptom (SDS ≥ 45)	422	440	427	453	449	–		–
Crude	1.00 (reference)	1.05 (0.91, 1.22) [b]	1.02 (0.88, 1.18)	1.11 (0.96, 1.28)	1.08 (0.93, 1.24)	0.27	1.12 (0.98, 1.27)	0.09
Adjusted for age and BMI	1.00 (reference)	1.06 (0.91, 1.23)	1.03 (0.89, 1.19)	1.12 (0.97, 1.29)	1.09 (0.94, 1.26)	0.22	1.13 (0.99, 1.28)	0.07
Multiple adjusted [c]	1.00 (reference)	1.05 (0.91, 1.22)	1.03 (0.88, 1.19)	1.12 (0.97, 1.30)	1.03 (0.89, 1.20)	0.60	1.08 (0.95, 1.23)	0.24
Women								
neutrophil/lymphocyte ratio (range)	0.25-1.24	1.24-1.52	1.52-1.80	1.80-2.22	2.22-10. 6	–		–
No. of subjects	2342	2333	2326	2341	2336	–		–
No. of depressive symptom (SDS ≥ 45)	377	406	431	453	457	–		–
Crude	1.00 (reference)	1.10 (0.95, 1.28)	1.19 (1.02, 1.38)	1.25 (1.07, 1.45)	1.27 (1.09, 1.48)	< 0.001	1.22 (1.07, 1.39)	0.02
Adjusted for age and BMI	1.00 (reference)	1.10 (0.95, 1.29)	1.19 (1.03, 1.39)	1.25 (1.08, 1.46)	1.28 (1.10, 1.49)	< 0.001	1.23 (1.08, 1.40)	< 0.01
Multiple adjusted	1.00 (reference)	1.15 (0.98, 1.34)	1.22 (1.04, 1.42)	1.28 (1.09, 1.49)	1.28 (1.10, 1.49)	< 0.01	1.22 (1.07, 1.39)	< 0.01

SDS, self-rating depression scale; BMI, body mass index.
[a] Obtained by using multiple logistic regression analysis.
[b] Adjusted odds ratio (95% confidence interval) (all such values).
[c] Adjusted for age, BMI, smoking status, drinking status, physical activity, marital status, total energy intake, household incomes, occupations, educational levels, visiting friends, living alone, metabolic syndrome, EPA and DHA intake, vegetable intake and fruit intake.

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