The monocyte-to-lymphocyte ratio and depression in diabetes patients

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Abstract

Background: The purpose of this study was to determine the association between The monocyte-to-lymphocyte ratio (MLR) and depression with diabetes mellitus.

Method: We examined data from the US National Health and Nutrition Examination Survey from 2009 to 2016. Cox proportional hazard models were used to calculate the associations between MLR and depression. For precise investigation of the relationship, we also plotted the smooth curve fit and generated a two-piecewise linear regression model using the penalized spline method.

Result: We enrolled 2820 diabetes patients in the database. Diabetes patients who had high MLR tended to be young, female, obese, unmarried, and had low levels of education. For tertile analysis, the ORs and 95% CIs of clinically relevant depression in tertile analysis were 1.03 (0.91, 1.17) for the second group and 1.62 (1.44, 1.82) for the third group in the unadjusted model compared to the control group. A similar trend was observed for the adjusted model and the quartiles analysis. We found the inflection point of MLR was 2.7. There is a positive association between MLR and depression above the threshold, and no relationship was found when MLR was below the threshold in diabetes patients.

Conclusion: There is a nonlinear relationship between MLR and depression in diabetes patients. High level of MLR more than the inflection point may add prognostic information for depression in diabetes patients.

1. Background

Depression is associated with diabetes mellitus (DM)[1]. Depression in diabetes patients is a condition that negatively impacts patient engagement and adherence to medication, leading to reduced quality of life, inadequate glucose control, increased functional disability, elevated risk of mortality, and increased health expenditures[2–4]. Greater risk of developing depressive symptoms is found in DM patients, and depression patients are also susceptible to DM[5]. A study found that almost 30% of diabetes patients suffered from depression[6], however, the morbidity of depression in diabetes is usually underestimated. There are various tests for diagnosing and monitoring depression disorders. The Back Depression Inventory (BDI-II) and the 9-item Patient Health Questionnaire (PHQ-9) are usually used to diagnose major depression disorder (MDD)[7, 8]. However, these tools are not easy to use by non-psychiatrists, and they may be inaccurate in patients with both with depression and DM because there are few symptom overlaps between the conditions[9]. Therefore, it is important to identify early biomarkers to diagnose depression in diabetes patients.

Several lines of evidence support the notion that the immune dysfunction and inflammation activation play significant roles in the pathogenesis of MDD and DM[10, 11]. Increased serum levels of pro-inflammation cytokines and chemokines are found in MDD patients[12]. Depression can be attenuated in a diabetes mouse model with decreased levels of inflammatory biomarkers Interleukin-1 (IL-1) and Interleukin-6 (IL-6)[13]. These data suggest that changes in levels of inflammation may be used to predict

depression in patients with DM. The monocyte-to-lymphocyte ratio (MLR) may be a biomarker of systemic inflammation to predict the severity and prognosis in malignant tumors and cardiovascular diseases. MLR is a low-cost biomarker that can be calculated simply from complete blood counts[14, 15]. Higher neutrophil-to-lymphocyte ratio (NLR) and MLR are strongly association with increased multiple sclerosis -related neurological disability and brain atrophy[16]. In patients with DM, higher MLR is an independent risk factor for diabetic retinopathy[17]. However, there are no data about the association between MLR and depression in DM patients. Therefore, investigating the usage of LMR in DM patients with depression is worthwhile.

2. Methods

2.1 Data source

The National Health and Nutrition Examination Survey (NHANES) is directed by the Centers for Disease Control and Prevention (CDC)[18]. It was initiated from 1999 and is updated in 2-year cycles. NHANES is a strict, long-term, and large-scale survey representative of the civilians of the United States. Through interviews, examinations, questionnaires and anthropometry, NHANES monitors the health and nutrition status of the general American population. Other detail information regarding sampling, design, and components can be found at http://www.cdc.gov/nchs/nhanes. For our analyses, we combined data from four cycles of the NHANES survey (2009–2010, 2011–2012, 2013–2014, and 2015–2016).

2.2 Assessment of depression and diabetes mellitus

Patients with diagnosed diabetes were identified by following: self-reported diagnosis of diabetes or “sugar diabetes” at age ≥ 30 years, and not pregnant at the time of interview/examination. The Patient Health Questionnaire (PHQ-9) was used to identify the depression in diabetes patients. It ranges from 0 to 27; and (0–4) is regarded as “none or minimum”, (5–9) is “mild,” (10–14) as “moderate,” (15–19) is “moderately severe,” and (20–27) is “severe.” According to previous research, patients with PHQ-9 scores ≥ 10 are defined as having clinically relevant depression (CRD). PHQ-9 score ≥ 10 has shown a sensitivity of 88% and a specificity of 88% for diagnosing depression for patients[8].

2.3 MLR and depression in diabetes patients

Monocytes and lymphocytes counts were analyzed on an automated hematology analyzing device and were expressed as 1000 cells/μL. The MLR was calculated as monocyte count/lymphocytes count. We also evaluated the morbidity rate of depression in diabetes patients based on each value of MLR. To identify associations between MLR and depression in diabetes patients, we treated them as continuous variables and tertiles in order to apply the available data more efficiently and flexibly.

2.4 Study variables

We used structure query language (SQL) to extract data from the database. The variables included age, sex, race, education, and marital status. Vital signs variables included systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and waist circumference. Laboratory variables included total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol

(HDL), triglycerides, red cell distribution width (RDW), cholesterol, glucose, and HbA1c. Diabetes-related variables included diabetes mellitus, family history of diabetes and the use of insulin. Comorbidities included coronary artery disease (CAD), chronic heart failure (CHF), diabetic retinopathy (DR) and stroke. The total PHQ-9 score was also presented.

2.5 Statistical analyses

We enrolled 2820 diabetes patients in NHANES database from 2009 to 2016. According to value of MLR, we divided all patients into three subgroups. Patients with MLR value < 2.7 were regarded as the low group, 2.7–3.45 were the medium group, and > 3.45 were the high group. Continuous variables were expressed as mean ± standard deviation or interquartile range (IQR), and frequencies for categorical data. Differences betwen groups were compared using the Kruskal–Wallis test for continuous variables and the χ2 test or Fisher's exact test (expected frequency < 10) for categorical variables. A value of $p < 0.05$ was considered statistically significant.

We used the multivariate Cox proportional hazards model to analyze the association between MLR and depression in DM patients. To analyze the data in detail, we divided the MLR into tertials or quartiles. or(ORs) with 95% confidence intervals (CIs) was used to express the results of statistical analyses. Model 1 was adjusted for the confounders age, sex, and race. Model 2 was adjusted for age, sex, race, marital status, education, CHF, CHD, and stroke.

To identify the nonlinear relationship between MLR and depression in diabetes patients, we established a weighted generalized additive model and plotted a smooth curve fit (using the penalized spline method). We calculated the point of inflection by applying a recursive algorithm. Later, we established a weighted two-piecewise linear regression model.

R software (http://www.R-project.org) was used to perform the statistical analyses. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1 Characteristics of enrolled participants

We enrolled 2820 participants in the analysis and divided them into three groups according to the value of MLR: < 2.7 were regarded as the low group, 2.7–3.45 were the medium group, and > 3.45 were the high group. The general characteristics of each group are summarized in Table 1, including demographics, vital signs, laboratory parameters, diabetes-related variables, and comorbidities. In summary, diabetes patients who had high MLR tended to be young, female, obese, unmarried, and had low levels of education. They were more likely to have high levels of triglycerides and RDW, low levels of HDL, and higher risk of co-morbid DR and depression.

Table 1

Characteristics of the study patients according to MLR[a]

Characteristics	2.7<	2.7–3.45	> 3.45	P-value
N, participants(%)	712	967	1141	
Demographics				
Age, years	63.2 ± 14.8	62.6 ± 14.2	59.1 ± 15.1	< 0.001
Sex, n(%)				< 0.001
Male	409 (57.4%)	512 (52.9%)	527 (46.2%)	
Female	303 (42.6%)	455 (47.1%)	614 (53.8%)	
Race, n(%)				0.231
Non-Hispanic White	122 (17.4%)	194 (20.2%)	198 (17.5%)	
Non-Hispanic Black	98 (14.0%)	149 (15.5%)	163 (14.4%)	
Mexican American	181 (25.8%)	249 (26.0%)	304 (26.9%)	
Other	300 (42.8%)	367 (38.2%)	467 (41.2%)	
Education, n(%)				< 0.001
Less than College	350 (50.5%)	588 (62.2%)	756 (68.3%)	
College and above	290 (41.9%)	274 (28.9%)	276 (24.9%)	
Refused	53 (7.6%)	84 (8.9%)	75 (6.8%)	
Marital status, n(%)				< 0.001
Married/Living with partner	386 (55.3%)	546 (57.1%)	600 (53.3%)	
Widowed/Divorced/Separated	239 (34.2%)	303(31.7%)	351 (31.3%)	
Never married	73 (10.5%)	86 (9.0%)	108 (9.6%)	
Vital signs				
Blood pressure, mmHg				
Systolic blood pressure	131.9 ± 19.8	132.8 ± 20.0	130.4 ± 19.7	0.026

[a] All estimates are weighted to be nationally representative.

[b] Clinically relevant depression measured by Patient Health Questionnaire (PHQ-9): No for minimum to mild (0–9), Yes for moderate to severe (10–27).

Abbreviations: HDL cholesterol high density lipoprotein cholesterol; LDL cholesterol low density lipoprotein cholesterol

Characteristics	2.7<	2.7–3.45	>3.45	P-value
Diastolic blood pressure	68.0 ± 14.4	67.7 ± 14.7	68.5 ± 13.7	0.494
Body mass index, kg/m2	30.7 ± 7.0	31.7 ± 7.1	34.0 ± 8.2	< 0.001
Waist circumference, cm	105.1 ± 14.9	107.9 ± 15.9	112.8 ± 17.0	< 0.001
Laboratory parameters				
Total cholesterol, mg/dL	176.9 ± 43.8	180.2 ± 44.9	181.3 ± 45.8	0.117
HDL cholesterol, mg/dL	51.9 ± 17.1	48.5 ± 13.5	45.9 ± 13.4	< 0.001
LDL cholesterol, mg/dL	100.4 ± 37.0	101.8 ± 35.5	99.0 ± 34.7	0.508
Triglyceride, mg/dL	126.9 ± 87.6	146.4 ± 97.0	171.6 ± 140.8	< 0.001
The fasting glucose (mg/dL)	93.7 ± 78.0	87.2 ± 86.0	86.8 ± 92.0	0.353
HbA1c, %	32.6 ± 65.6	37.3 ± 70.9	29.3 ± 60.1	0.039
Red cell distribution width (%)	13.5 ± 1.1	13.6 ± 1.1	13.7 ± 1.1	< 0.001
Diabetes-related variables, n(%)				
Diabetes mellitus				< 0.001
Yes	712 (100.0%)	967 (100.0%)	1141 (100.0%)	
Family history of diabetes				0.415
Yes	251 (72.3%)	337 (68.6%)	398 (68.5%)	
No	96 (27.7%)	154 (31.4%)	183 (31.5%)	
Taking insulin, n(%)				0.784
Yes	157 (22.3%)	219 (22.8%)	266 (23.6%)	
No	547 (77.7%)	743 (77.2%)	859 (76.4%)	
Comorbidities, n(%)				
Diabetic retinopathy				0.003
Yes	176 (24.9%)	232 (24.0%)	342 (30.1%)	
No	532 (75.1%)	733 (76.0%)	793 (69.9%)	

[a] All estimates are weighted to be nationally representative.

[b] Clinically relevant depression measured by Patient Health Questionnaire (PHQ-9): No for minimum to mild (0–9), Yes for moderate to severe (10–27).

Abbreviations: HDL cholesterol high density lipoprotein cholesterol; LDL cholesterol low density lipoprotein cholesterol

Characteristics	2.7<	2.7–3.45	>3.45	P-value
Chronic heart failure				0.948
Yes	66 (9.5%)	95 (10.0%)	111 (9.9%)	
No	628 (90.5%)	858 (90.0%)	1010 (90.1%)	
Coronary heart disease				0.970
Yes	78 (11.2%)	104 (11.0%)	121 (10.8%)	
No	618 (88.8%)	842 (89.0%)	996 (89.2%)	
Stroke				0.750
Yes	59 (8.5%)	90 (9.4%)	106 (9.4%)	
No	639 (91.5%)	869 (90.6%)	1018 (90.6%)	
Clinically relevant depression[b]				< 0.001
Yes	75 (11.7%)	107 (12.1%)	188 (18.2%)	
No	568 (88.3%)	780 (87.9%)	846 (81.8%)	
[a] All estimates are weighted to be nationally representative.				
[b] Clinically relevant depression measured by Patient Health Questionnaire (PHQ-9): No for minimum to mild (0–9), Yes for moderate to severe (10–27).				
Abbreviations: HDL cholesterol high density lipoprotein cholesterol; LDL cholesterol low density lipoprotein cholesterol				

3.2 Association between MLR and clinically relevant depression in diabetics

We established two models to measure the independent effects of MLR and CRD in diabetes patients. ORs and 95% CIs are displayed in Table 2. Compared to the first group, the HRs and 95% CIs of clinically relevant depression in tertile analysis were 1.03 (0.91, 1.17) for the second group and 1.62 (1.44, 1.82) for the third group in the unadjusted model. After adjusting for age, sex and race, the HR (95% CI) of depression in diabetes patients for the second and third group were 0.99 (0.87, 1.13) and 1.47 (1.30, 1.66), compared to the first group respectively. In model II, the HRs (95% CI) for the second and third group were 0.94 (0.81, 1.08) and 1.29 (1.13, 1.47) compared to the reference, respectively. The same trend was found in the unadjusted model, model I, and model II for quartiles analyses.

Table 2
Associations of MLR with clinically relevant depression among adults.

Exposure	Unadjusted[a]			Model I[b]			Model II[c]		
	HR (95% CIs)	p value	p trend	HR (95% CIs)	p value	p trend	HR (95% CIs)	p value	p trend
Tertiles			< 0.0001			< 0.0001			< 0.0001
0.5–2.7	1.0			1.0			1.0		
2.7–3.45	1.03 (0.91, 1.17)	0.6354		0.99 (0.87, 1.13)	0.8979		0.94 (0.81, 1.08)	0.3563	
3.45–57.5	1.62 (1.44, 1.82)	< 0.0001		1.47 (1.30, 1.66)	< 0.0001		1.29 (1.13, 1.47)	0.0002	
Quartiles			< 0.0001			< 0.0001			< 0.0001
0.5–2.5	1.0			1.0			1.0		
2.5–3	0.98 (0.85, 1.14)	0.8124		0.98 (0.84, 1.14)	0.7759		0.94 (0.81, 1.08)	0.3563	
3. – 3.7	1.15 (1.00, 1.33)	0.0493		1.10 (0.95, 1.28)	0.1953		1.29 (1.13, 1.47)	0.0002	
3.7–57.5	1.73 (1.51, 1.99)	< 0.0001		1.59 (1.38, 1.83)	< 0.0001		1.18 (1.09, 1.27)	< 0.0001	

Abbreviation: MLR, Monocyte to Lymphocyte Ratio; HR: hazard ratios; CI: confidence interval

[a]Non-adjusted model adjust for: None

[b]Adjust I model adjust for: age, sex, race

[c]Adjust II model adjust for: age, sex, race, marital status, education, chronic heart failure, coronary heart disease, stroke

3.3 Nonlinear correlation between MLR and clinically relevant depression in diabetics

The relationship between MLR and clinically relevant depression in diabetes patients appeared to be nonlinear. For precise investigation of the relationship, we plotted the smooth curve fit (Fig. 1). We generated a two-piecewise linear regression model using the penalized spline method (Table 3). The

inflection point of MLR was 2.7. When value of MLR was higher than the inflection point, the HR (95% CI) was 1.4 (1.3, 1.5) (P = 0.006). To the left of the inflection point, the relationship was not significant [HR 1.0 (0.8, 1.2)].

Table 3
Threshold and saturation effect analysis of MLR on the prevalence of depression

MLR	HRs (95% CIs)[a]
Standard logistic regression model	1.3 (1.2, 1.4)
Fitting model by two-piecewise linear regression	
Inflection point of MLR	
< 2.7	1.0 (0.8, 1.2)
> 2.7	1.4 (1.3, 1.5)
P for log likelihood ratio test	0.006
Abbreviation: MLR, Monocyte to Lymphocyte Ratio; HR: hazard ratio; CI: confidence interval.	
[a]Adjusted for age, sex, race, education, BMI, HBA1C in quartiles, chronic conditions including hypertension(yes/no), stroke(yes/no), DR (yes/no) and CHD (yes/no), and medication use including glucose-lowering drugs(yes/no) and Insulin use (yes/no) .	

4. Discussion

Clinically relevant depression in diabetes patients correlated with MLR in a nonlinear manner. Higher MLRs were found in diabetes patients with depression than those without in a cohort of the US population when the level of MLR was more than 2.7. Increased MLR might predict high risk of depression in diabetes patients.

Inflammation plays a critical role in the initiation and progression of depression in diabetes patients. High levels of cytokines and chemokines induced insulin resistance, and interfered with the function of pancreatic cells[19]. Proinflammatory cytokines play important roles in the pathophysiology of depression, including downregulated neurotransmitter levels, impaired synaptic plasticity, and disturbed neuroendocrine function[20]. We found that increased MLR in DM patients was association with high risk of depression, possibly representing a proinflammatory response. Elevated MLR is a biomarker for endothelial dysfunction and system inflammation in malignancies[21], while MLR was used to predict poor prognosis in psychiatric diseases. Ikbal et al. found that MLR was higher in patients in the manic state of bipolar disorder than the control group[22]. Mario et al. found higher MLR in both major depression disorder and the depressive phase bipolar disorder than in the bipolar disorder manic phase[23]. These results were similar to those of our study, in that the high value of MLR was associated

with elevated risk of depression. We might explain the role of MLR in depression in DM patients from two aspects: monocytes and lymphocytes.

Monocytes are derived from the bone marrow (BM). BM-derived monocytes were shown to be trafficked and recruited into the central nervous system (CNS) under conditions of psychological stress[24, 25]. Accumulation of BM-derived monocytes in the brain amplified pro-inflammation signaling[26]. Finally, increased levels of inflammation cytokines and chemokines (IL-1β, TNF-α, IL-6, CXCL) are implicated in depressive behavior[27]. In support of this idea, Torres et al. found that depressed patients who committed suicide had higher levels of monocyte marker Iba-1 than did the control group without depression[28]. Researchers also found increased numbers of $CD11b^{+}$ $CD45^{hi}$ cells, marker of monocytes, in the brains of a depression mouse model caused by repeated social defeat[29]. These data suggest that elevated levels of monocytes might mediate stress-induced inflammation responses in DM patients. On the other hand, BM-derived monocytes mediated depression-related functions activated by microglia[30]. Microglia activation is implicated in inflammatory responses and depression-like behavior caused by stress[31]. For instance, Elaine al et. performed a PET imaging study and found that duration of untreated major depressive disorder was significantly associated with levels of a biomarker of microglial activation, translocator protein (TSPO). They found that TSPO total distribution volume in brain predicted the duration of untreated major depressive disorder; it was greater in depressed patients with long duration disease than in those with short duration[32]. Taken together, the data suggest that microglia activation and neuroinflammatory might be the reason why diabetes patients with depression have high levels of monocytes.

Lymphocytes are a subgroup of leukocytes and mediate immune regulatory roles in inflammatory diseases. Activation and disturbance of stress systems in DM patients mediated the activation of the Hypothalamic-pituitary-adrenal axis (HPA-axis) and sympathetic nervous system (SNS)[33]. Chronic stress increased the number of leukocytes, while it was a selective increase for myeloid cells, not for lymphocytes in the BM. With proliferating and expanding of myeloid progenitor cells in the BM, chronic stress induced increased monocyte release from BM and reductions in lymphocytes and erythrocytes[34]. For example, Heidt and colleagues found that chronic variable stress elevated proliferation of hematopoietic stem cell and selective increased output of inflammatory monocytes in the periphery[35]. Furthermore, sustained activation of the HPA-axis caused by chronic stress was associated with promoted apoptosis of lymphocytes[36]. The reduction caused by abnormal monocyte proliferation and increased apoptosis of lymphocytes might explain the greater degree of lymphocytopenia in DM patients with depression than in those without. In general, high MLR in patients with combined depression and DM might represent monocyte activation and neuroinflammation induced by chronic stress.

There are some limitations in our study. First, as a cross-sectional survey, NHANES cannot provide longitudinal follow-up, and temporal alterations in MLR cannot be evaluated in diabetes patients. Second, it is less rigorous to diagnose depression only using PHQ-9, because this depends on clinical and methodological settings. Therefore, designs of experimental research have been more suitable to solve

this problem. Third, it is difficult to distinguish whether patients are depressed after diabetes, or whether they have depression before diabetes. In other words, the train of causation cannot be determined.

5. Conclusion

We found a nonlinear relationship between MLR and depression in patients with diabetes patients. When the level of MLR was above the inflection point (2.7), high MLR is associated with increased risk of clinically relevant depression in diabetes patients. Further research with longitudinal follow-up of MLR in patients of diabetes combined with depression is needed.

Declarations

Ethics approval and consent to participate

Not applicable

Authors' contributions

Depu Zhou: Date analyze and writing. **Jie Wang**: Data collection. **Xiaokun Li**: Writing-Reviewing and Editing.

Availability of data and materials

All the data used to support this study are available from the corresponding author upon request.

Conflicting Interest

The authors declare that there is no conflict of interest.

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Figures

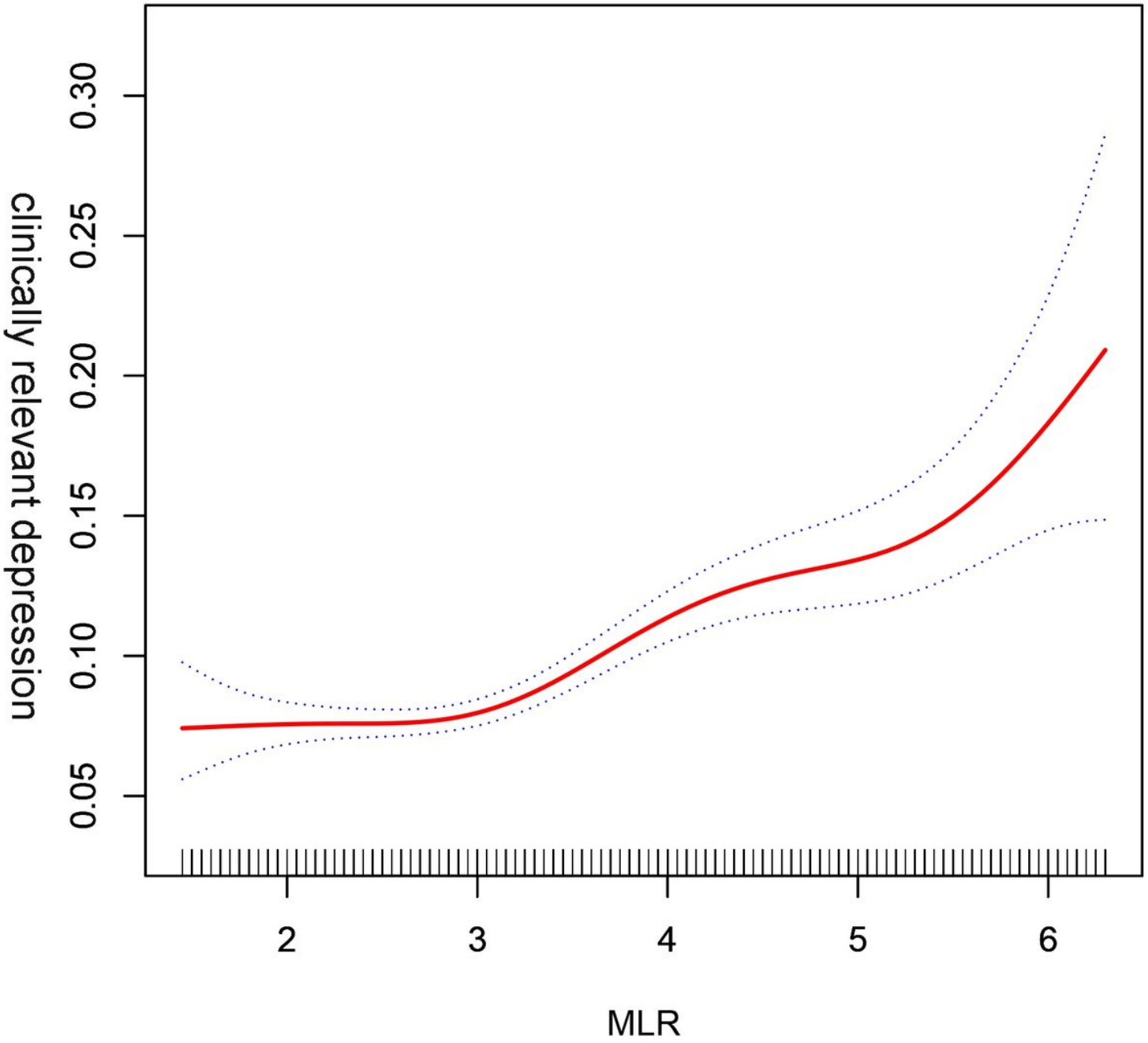

Figure 1

Association of MLR levels with prevalence of depression in diabetes. Dashed lines are 95% confidence intervals.