

# Relationship Between Serum Fibrinogen Level and Depressive Symptoms in an Adult Population with Spinal Cord Injury: A Cross-Sectional Study

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**Purpose:** Depression is associated with an inflammatory immune response. There are minimal data regarding the association of inflammatory markers with depression in patients with spinal cord injury (SCI). We aimed to investigate the association of inflammatory markers with depression in middle-aged and elderly SCI patients.

**Methods:** Data were obtained from the Midlife in the United States (MIDUS) study, a longitudinal study of a representative sample of the adult population. We analyzed the associations of serum levels of fibrinogen, interleukin-6, tumor necrosis factor- $\alpha$ , and C-reactive protein with depressive symptoms.

**Results:** The median participant age was 52.5 years; 44.9% of participants were men. Multivariate linear regression analyses showed that an increased serum fibrinogen level ( $\beta = 0.114$ ,  $p = 0.005$ ) was associated with higher Centre for Epidemiological Studies-Depression (CES-D) scores after adjustment for age, sex, body mass index (BMI), ethnicity, education, marital status, smoking, alcohol use, exercise, perceived stress score, and cardiovascular disease (CVD). Multivariate logistic regression analysis showed that an increased serum fibrinogen level was independently associated with a history of depression (odds ratio [OR] = 1.240, 95% confidence interval [CI] = 1.103–1.997,  $p = 0.012$ ) and depressive symptoms (OR = 1.884, 95% CI = 1.165–2.499,  $p < 0.001$ ; CES-D score  $\geq 16$ ) after adjustment for confounding factors. Stratified analysis revealed that the association between serum fibrinogen level and depressive symptoms was affected by antidepressant use.

**Conclusion:** Serum fibrinogen level had a significantly positive association with depressive symptoms in middle-aged and elderly patients with SCI. Future longitudinal cohort studies should evaluate the possible use of serum fibrinogen for diagnosis of depression in SCI patients.

**Keywords:** fibrinogen, depression, spinal cord injury, cross-sectional study

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## Introduction

Spinal cord injury (SCI) adversely affects all aspects of life in affected patients. SCI increases the risks of mental disorders such as depression. Depression represents an inflammatory immune response to the injury; it increases the risk of adverse consequences such as pain, substance abuse, and medical complications.<sup>1–4</sup> One-third of acute SCI patients are depressed.<sup>5–7</sup> A Canadian cohort study showed that 30% of patients were depressed at 6 years after SCI; more than 6.5% of the patients in that study had severe depression.<sup>8</sup> More than 10% of SCI patients in a cohort study from the United States had major depression.<sup>9</sup> Depression interferes with SCI rehabilitation

therapy because of negative expectations, reduced energy, and social withdrawal. Determining the risk factors for depression in SCI patients will allow early identification and treatment, thereby improving the outcomes of rehabilitation therapy.

The increased risk of depression in SCI patients has been linked to biological responses (eg, immune-mediated and inflammatory) and immune dysregulation with consequent neuroendocrine changes.<sup>10</sup> Depression and inflammation have a bidirectional relationship. Inflammation increases the risk of depression, and depression increases the inflammatory response, leading to a vicious circle.<sup>11,12</sup> Many studies have implicated chronic inflammation as the cause of adverse health outcomes in depressed patients.<sup>13–15</sup> Elevated levels of inflammatory markers, such as C-reactive protein (CRP) and cytokines, increase the risk of depression.<sup>16,17</sup> The inflammatory response involves secretion of pro-inflammatory cytokines and activation of immune cells, which cause changes in brain structure<sup>18,19</sup> and function.<sup>17</sup> In addition, exposure to pro-inflammatory cytokines produces depressive symptoms, which are attenuated by antidepressant use.<sup>20,21</sup>

Levels of inflammatory markers (eg, interleukin [IL]-1, tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], IL-6, and fibrinogen) are elevated in SCI patients, which may explain the link between SCI and depression. Similar to CRP, inflammatory markers (eg, fibrinogen, IL-6, and TNF- $\alpha$ ) also increase the risk of depression. Previous studies have measured the levels of inflammatory markers in severely depressed patients with SCI, but not in SCI patients with mild or moderate depression.

We analyzed data from the Midlife in the United States (MIDUS) study, a longitudinal study of a representative sample of the United States adult population aged 34–84 years. We adjusted the data for covariates (demographic characteristics, lifestyle behaviors, and comorbidities) to determine the relationship between chronic inflammation and depression in SCI patients. We aimed to evaluate the relationships of serum levels of fibrinogen, IL-6, TNF- $\alpha$ , and CRP with depression in SCI patients.

## Methods

### Participants and Study Design

The MIDUS study investigated the relationships of psychological and behavioral factors with adverse health outcomes. The Biomarkers project, a sub-study of the MIDUS

study, involved comprehensive biological assessments of 1255 participants, and collected sufficient data to evaluate the relationships of behavioral and psychosocial factors with biological factors.<sup>22</sup> The Biomarkers project included 225 SCI patients (mean age, 52.4 years; range, 43.7–60.4 years). SCI patients with history of any trauma were included, and patients with active inflammatory diseases were excluded from the study. We selected the variables described below because they are most closely related to our factors of interest.

The MIDUS study Biomarkers project protocol has been published previously.<sup>22,23</sup> The data and specific codebooks from this study are available at <http://www.midus.wisc.edu/>. In brief, participants in the MIDUS study were selected from a national sample by using a random-digit dialing procedure. All participants in the first MIDUS survey who could safely travel to the clinic were included in the Biomarkers project. The participants were subsequently followed up by means of e-mails and phone calls. Survey data were collected between 2004 and 2009 at one of the three MIDUS study research centers (University of California-Los Angeles; Georgetown University; and University of Wisconsin-Madison). During the 2-day visit, participants were asked to complete self-administered questionnaires and participate in medical interviews. Participant blood specimens were also collected in accordance with a standardized protocol that was consistent across the three sites. The travel expenses of participants were reimbursed, and each participant was paid \$200 for their participation. This study complied with the Declaration of Helsinki. Approval was obtained from the ethics committees of the three research centers and written informed consent was obtained from all participants.

Fasting blood samples were collected from SCI patients during their 2-day visits in the study period (2004–2009). We measured the following serum inflammatory markers: fibrinogen, IL-6, TNF- $\alpha$ , and CRP. The measurement methods have been described in detail elsewhere.<sup>22–24</sup>

### Depression Score

The Centre for Epidemiological Studies-Depression (CES-D) scale was used to evaluate depression.<sup>25</sup> The CES-D scale is widely used in epidemiological studies, and a cutoff score of 16 indicates depression.<sup>26</sup> In addition, the participants were considered to have depression if they had a history of using antidepressant medications. The CES-D is a reliable scale for identifying depressive

symptoms and was easily administered by the well-trained research nurses in our study.

## Covariates

Self-administered questionnaires were used to collect data concerning sociodemographic characteristics (age, sex, body mass index [BMI], ethnicity, education, and marital status), lifestyle factors (tobacco use, alcohol use, and exercise), and history of cardiovascular diseases (CVD; heart disease, hypertension, transient ischemic attack, stroke, or diabetes). Marital status was recorded as “currently married” or “not currently married.” Education was recorded as “bachelor’s degree or higher” or “high school education or lower.” Smoking status was recorded as “current smoker” or “not a current smoker.” Drinking status was recorded as “current alcohol consumption” or “no current alcohol consumption.” Exercise was recorded as present in participants with a frequency of exercise “ $\geq 3$ /week.” History of depression or antidepressant use was dichotomized into “yes” or “no.” The Perceived Stress Scale is a 10-item tool for assessing the degree of stress in participants. Each item (eg, “In the past month, how often have you been upset because of something that happened unexpectedly?”) was rated on a 5-point scale ranging from 1 (never) to 5 (very often), and the responses were reverse-coded such that higher scores were indicative of greater perceived stress [ $\alpha = 0.84$ ].

## Statistical Analysis

The Kolmogorov–Smirnov test and Q-Q plots were used to analyze the normality of data. A  $p$ -value  $\leq 0.05$  was considered statistically significant. Data with non-normal distribution were expressed as medians and interquartile ranges. Normally distributed data were expressed as means and standard deviations. First, Pearson correlation was performed to analyze the associations of serum levels of fibrinogen, IL-6, TNF- $\alpha$ , and CRP with CES-D scores. All continuous variables were standardized by calculation of  $z$ -scores. Multivariate linear regression analysis was conducted to assess the relationships of serum inflammatory markers with depression scores. Multivariate logistic regression was used to evaluate the associations of serum fibrinogen with depressive symptoms. The associations between serum fibrinogen level and depressive symptoms were also assessed using stratified analysis with antidepressant use as a covariate. All analyses were performed using SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA).

## Results

### Characteristics of Participants with SCI

The sociodemographic characteristics of 225 participants with SCI are presented in Table 1. The median participant age was 52.5 years. There were 101 (44.9%) male and 212 (94.2%) white participants. The participants were divided into two groups based on depressive symptoms (CES-D score  $\geq 16$ ). In comparison with participants who lacked depressive symptoms (CES-D score  $< 16$ ), participants with depressive symptoms were older, had a higher BMI, used alcohol more frequently, and exercised more frequently. Participants with depressive symptoms were also more likely to be married and educated, compared with participants who lacked depressive symptoms. Participants with history of depression or CVDs had a higher frequency of depressive symptoms than did participants without depression or CVDs. Participants with depressive symptoms had higher perceived stress scores and levels of fibrinogen, IL-6, TNF- $\alpha$ , and CRP than did participants without depressive symptoms. Pearson correlation showed significant associations of serum levels of fibrinogen ( $r = 0.170$ ;  $p = 0.001$ ; Figure 1), IL-6 ( $r = 0.184$ ;  $p = 0.006$ ; Figure 2), TNF- $\alpha$  ( $r = 0.169$ ,  $p = 0.012$ ; Figure 3), and CRP ( $r = 0.155$ ,  $p = 0.041$ , Figure 4) with depression. Multiple linear regression analysis showed that increased serum levels of fibrinogen ( $\beta = 0.011$ , 95% confidence interval [CI] = 0.006–0.015,  $p = 0.005$ ; model 2) and CRP ( $\beta = 0.010$ , 95% CI = 0.003–0.035,  $p = 0.009$ ; model 2) were associated with higher CES-D scores, after adjustment for age, sex, ethnicity, education, BMI, current smoking, current alcohol consumption, exercise, perceived stress score, and CVDs (Table 2).

### Multiple Logistic Regression Analysis of the Association Between Serum Fibrinogen Level and History of depression

As shown in Table 3, an increased serum fibrinogen level was positively associated with history of depression, both before adjustment (odds ratio [OR] = 1.374, 95% CI = 1.235–2.469,  $p < 0.001$ ) and after adjustment for age, sex, ethnicity, education, BMI, marital status, smoking, alcohol use, and exercise (OR = 1.311, 95% CI = 1.162–2.084,  $p = 0.005$ ; model 1). This association remained statistically significant after adjustment for other confounding factors, including the perceived stress score and current CVDs

**Table 1** Characteristics of Participants with Spinal Cord Injury

Variables	Total (N=225)	CES-D Score <16 (N=174)	CES-D Score ≥ 16 (N=51)	P value
Age (Y)	52.4 (43.7–60.4)	50.5 (41.4–57.9)	57.4 (45.6–62.5)	<0.001
Gender (male/female)	101 (44.9)	79 (45.4)	22 (43.1)	0.438
BMI	27.4±6.6	26.1±6.2	28.3±7.2	0.006
Race (white), n (%)	212 (94.2)	165 (94.8)	47 (92.2)	0.106
Education (with bachelor's degree or higher), n (%)	129 (57.3)	88 (50.6)	41 (80.4)	<0.001
Currently married, n (%)	45 (20.8)	27 (15.5)	18 (35.3)	<0.001
Current smoker, n (%)	32 (14.2)	24 (13.8)	8 (15.7)	0.096
Current drinker, n (%)	46 (20.4)	26 (14.9)	20 (39.2)	0.002
Frequency of exercises ≥3/ week, n (%)	149 (66.2)	127 (73.0)	22 (43.1)	<0.001
Depression score	13 (8–19)	8 (2–14)	26 (16–35)	<0.001
Perceived stress score	20 (16–24)	13 (6–17)	23 (18–29)	<0.001
Ever diagnosed depression	22 (9.8)	14 (8.0)	8 (15.7)	0.012
Antidepressants, n (%)	26 (11.5)	5 (2.9)	21 (41.2)	<0.001
<b>Currently diagnosed CVDs</b>				
Heart disease, n (%)	30 (13.3)	23 (13.2)	7 (13.7)	0.302
Hypertension, n (%)	81 (36.0)	55 (31.6)	26 (51.0)	0.007
TIA or stroke, n (%)	14 (6.2)	9 (5.2)	5 (9.8)	0.028
Diabetes, n (%)	23 (10.2)	16 (9.1)	7 (13.7)	0.049
<b>Serum inflammatory markers</b>				
Serum fibrinogen (mg/dL)	359.28±79.33	304.21±75.81	425.26±83.47	<0.001
Serum IL-6 (pg/mL)	2.18 (1.46–3.49)	2.01 (1.29–3.15)	2.67 (1.48–3.72)	<0.001
Serum TNF-α (pg/mL)	2.26 (1.76–2.52)	2.09 (1.47–2.33)	2.50 (1.91–2.84)	<0.001
Serum C-reactive protein (ug/mL)	1.63 (0.75–3.89)	1.34 (0.59–3.62)	1.90 (0.84–4.56)	<0.001

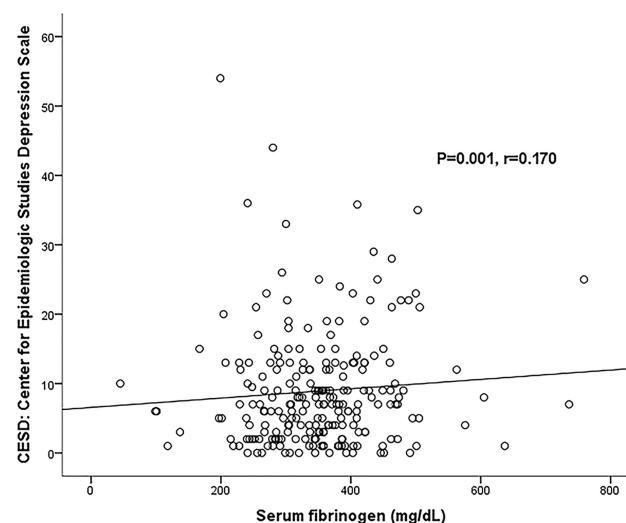
**Abbreviations:** BMI, body mass index; CVDs, cardiovascular diseases; TIA, transient ischemic attack; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; CES-D, epidemiological studies-depression.

(OR = 1.240, 95% CI = 1.103–1.997,  $p = 0.012$ , model 2). However, there was no significant association between CRP and history of depression (data not shown).

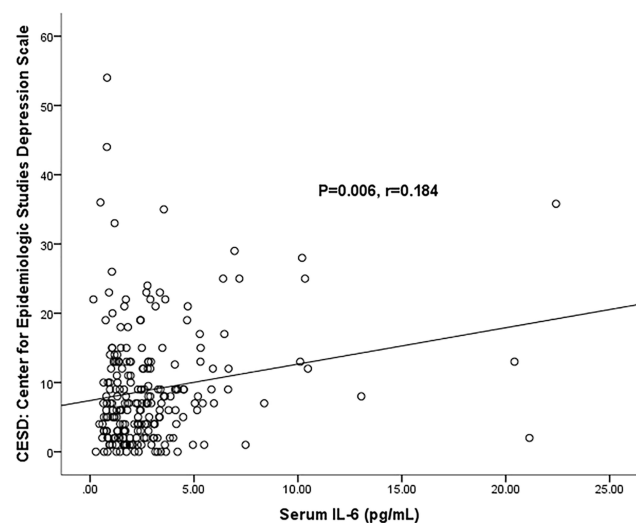
## Multiple Logistic Regression Analysis of the Association Between Serum Fibrinogen Level and Depressive Symptoms (CES-D Score ≥ 16)

As shown in Table 4, an increased serum fibrinogen level was positively associated with any depressive symptoms, both before adjustment (OR = 1.970, 95% CI = 1.248–2.733,  $p < 0.001$ ) and after adjustment for age, sex, ethnicity, education, BMI, current marital status, smoking, alcohol use, and exercise (OR = 1.923, 95% CI = 1.224–2.681,  $p < 0.001$ ; model 1). This association remained statistically significant after adjustment for other confounding factors, including the perceived stress score and current CVDs (OR = 1.884, 95% CI = 1.165–2.499,  $p < 0.001$ ; model 2).

We repeated the analysis with antidepressant use as a covariate and found a strongly positive association between serum fibrinogen level and risk of depressive



**Figure 1** The relationship between serum fibrinogen and depression score (CES-D scale) in all subjects.

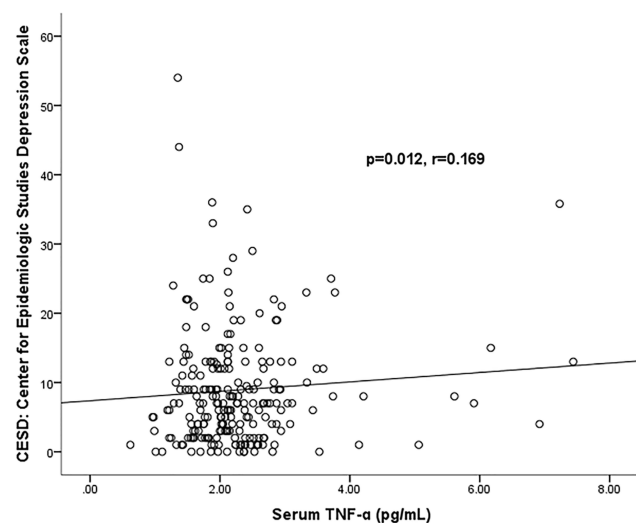


**Figure 2** The relationship between serum IL-6 and depression score (CES-D scale) in all subjects.

symptoms in SCI participants without antidepressant use (OR = 1.892, 95% CI = 1.461–2.420,  $p < 0.001$ ; model 2; Table 5). However, there was no significant association in participants with antidepressant use (OR = 1.134, 95% CI = –0.577 to –1.448,  $p = 0.079$ ; model 2).

## Discussion

We investigated the associations between depressive symptoms and inflammatory markers (fibrinogen, IL-6, TNF- $\alpha$ , and CRP) in middle-aged and elderly patients with SCI. Serum fibrinogen, IL-6, and TNF- $\alpha$  levels had strong and independent associations with depression scores, according to multivariate linear regression analysis.



**Figure 3** The relationship between serum TNF- $\alpha$  and depression score (CES-D scale) in all subjects.

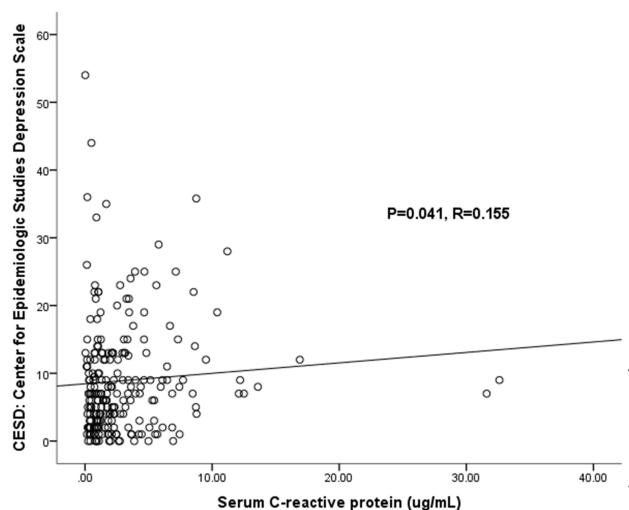
**Table 2** Multiple Linear Regression Analysis for Relationship Between Inflammatory Markers and Depression Score

Variables	S $\beta$	$\beta$ (95% CI)	P value
Serum fibrinogen			
Crude	0.126	0.014 (0.010–0.020)	0.001
Model 1	0.119	0.012 (0.008–0.017)	0.004
Model 2	0.114	0.011 (0.006–0.015)	0.005
Serum IL-6			
Crude	0.057	0.010 (–0.019–0.022)	0.162
Model 1	0.053	0.008 (–0.017–0.020)	0.198
Model 2	0.051	0.006 (–0.013–0.015)	0.224
Serum TNF- $\alpha$			
Crude	0.079	0.013 (–0.014–0.029)	0.132
Model 1	0.071	0.011 (–0.012–0.026)	0.174
Model 2	0.068	0.009 (–0.010–0.024)	0.208
Serum C-reactive protein			
Crude	0.137	0.016 (0.009–0.051)	<0.001
Model 1	0.128	0.014 (0.006–0.042)	0.003
Model 2	0.121	0.010 (0.003–0.035)	0.009

**Notes:** Crude: No adjustment. Model 1: Adjusted for age, gender, race, education, BMI, currently married, current smoker, current drinker and exercise. Model 2: Adjusted for age, gender, race, education, BMI, currently married, current smoker, current drinker, exercise, perceived stress score and currently diagnosed CVDs.

**Abbreviations:** BMI, body mass index; CVDs, cardiovascular diseases; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; IL-6, interleukin-6.

An increased serum fibrinogen level was associated with an increased risk of depressive symptoms after adjustment for confounding factors in the multivariate logistic regression analysis. However, this association between serum



**Figure 4** The relationship between serum C-reactive protein and depression score (CES-D scale) in all subjects.



**Table 3** Multiple Logistic Regression Analysis for Relationship Between Serum Fibrinogen and History of Depressive Symptoms

Variables	OR	95% CI	P value
<b>Crude</b>	1.374	1.235–2.469	<0.001
<b>Model 1</b>	1.311	1.162–2.084	0.005
<b>Model 2</b>	1.240	1.103–1.997	0.012

**Notes:** Crude: No adjustment. Model 1: Adjusted for age, gender, race, education, BMI, currently married, current smoker, current drinker and exercise. Model 2: Adjusted for age, gender, race, education, BMI, currently married, current smoker, current drinker, exercise, perceived stress score and currently diagnosed CVDs.

**Abbreviations:** BMI, body mass index; CVDs, cardiovascular diseases.

**Table 4** Multiple Logistic Regression Analysis for Relationship Between Serum Fibrinogen and Depressive Symptoms (CES-D Score  $\geq$  16)

Variables	OR	95% CI	P value
<b>Crude</b>	1.970	1.248–2.733	<0.001
<b>Model 1</b>	1.923	1.224–2.681	<0.001
<b>Model 2</b>	1.884	1.165–2.499	<0.001

**Notes:** Crude: No adjustment. Model 1: Adjusted for age, gender, race, education, BMI, currently married, current smoker, current drinker and exercise. Model 2: Adjusted for age, gender, race, education, BMI, currently married, current smoker, current drinker, exercise, perceived stress score and currently diagnosed CVDs.

**Abbreviations:** BMI, body mass index; CVDs, cardiovascular diseases; CES-D, epidemiological studies-depression.

fibrinogen and depressive symptoms was affected by antidepressant use in the stratified analysis. Our results are consistent with previous findings that antidepressants may influence inflammation.<sup>27,28</sup> SCI often leads to long-term disability because of reduced mobility and loss of physical function.<sup>29–31</sup> Notably, inflammation after SCI may have a major impact on physical activity.<sup>31,32</sup> However, there are minimal data concerning the effects of inflammation on neuropsychiatric disorders, especially depression, in SCI patients.<sup>33–35</sup> Depression interferes with SCI rehabilitation because of negative expectations, reduced energy, and social withdrawal. More than 20% of SCI patients are

depressed,<sup>36–38</sup> which is 4–5-fold greater than the world-wide prevalence of depression.<sup>39</sup>

Our results add to the emerging evidence concerning associations between serum levels of inflammatory markers and depressive symptoms.<sup>5,8,9,18,36–39</sup> Few studies have analyzed the associations of fibrinogen, IL-6, and TNF- $\alpha$  with depression in SCI patients. Recent sex-specific analyses support a role for inflammation in the onset of depression in SCI patients. A previous study concerning the roles of inflammatory markers in depression in female patients with suspected coronary ischemia found a robust association between CRP and depression, but inflammatory markers minimally contributed to the association between depression and CVD.<sup>40,41</sup> Similarly, a prospective study found evidence of a positive association between depressive symptoms and risk of incident stroke; however, inflammation (represented by baseline CRP) did not mediate this association.<sup>42</sup> Chronic inflammation in depressed patients may be a result of oxidative reactions. In our study, serum fibrinogen and CRP levels were positively associated with the depression score, consistent with findings in previous studies. In contrast to our results, a previous study found reduced serum fibrinogen levels in depressed patients. This discrepancy may have resulted from differences in study populations and analysis methods. We also found elevated serum IL-6, TNF- $\alpha$ , and CRP levels in the present investigation, similar to the results in previous studies,<sup>43,44</sup> however, some previous studies have reported normal or reduced inflammatory marker levels in depressed patients.<sup>45</sup> The normal serum IL-6, TNF- $\alpha$ , and CRP levels observed in this study may have resulted from the inclusion of patients with a history of SCI and mild to moderate depression, rather than patients with severe depression alone.

**Table 5** Multiple Logistic Regression Analysis for Relationship Between Serum Fibrinogen and Depressive Symptoms (CES-D Score  $\geq$  16) Stratified by Antidepressants Use

Variables	Crude	Model 1	Model 2
Antidepressants use	1.267 (1.016–1.920)	1.205 (1.002–1.739)	1.134 (–0.577–1.448)
P value	0.014	0.040	0.079
No antidepressants use	2.255 (1.512–3.162)	2.003 (1.484–2.986)	1.892 (1.461–2.420)
P value	<0.001	<0.001	<0.001

**Notes:** Crude: No adjustment. Model 1: Adjusted for age, gender, race, education, BMI, currently married, current smoker, current drinker and exercise. Model 2: Adjusted for age, gender, race, education, BMI, currently married, current smoker, current drinker, exercise, perceived stress score and currently diagnosed CVDs.

**Abbreviations:** BMI, body mass index; CVDs, cardiovascular diseases; CES-D, epidemiological studies-depression.

## Limitations

First, this was a cross-sectional study with a small sample size. Second, depressive symptoms were assessed using a self-administered questionnaire, instead of a clinical interview. However, the scales used have good predictive value and discriminatory validity in both normative and clinical populations, as well as disabled people. Third, we included all SCI patients and did not categorize them based on their severity, classification, and treatment, which may have led to bias in the study results. Fourth, the results of the self-administered questionnaire may have been biased because many patients overstate or understate their lifestyle habits (eg, smoking and drinking alcohol).

## Conclusions

An elevated serum fibrinogen level was significantly positively associated with an increased risk of depressive symptoms among middle-aged and elderly SCI patients. Future longitudinal cohort studies should assess the predictive value of serum fibrinogen for diagnosis of depression in SCI patients.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (NSFC; grant. no. 81860225).

## Disclosure

The authors report no conflicts of interest in this work.

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