Acta Neuropsychiatrica

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Association between fibroblast growth factor 19 and depressive symptoms: the moderating role of smoking

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Original Article

Cite this article: Li S, Chen L, Ma M, Hu Y, Wang F, Luo X, Chen Y-H, Gao H, Ren Y, Hu W, Kang Y, Wang W, Chen L, Li X, Liu Y, and Wu J. (2025) Association between fibroblast growth factor 19 and depressive symptoms: the moderating role of smoking. *Acta Neuropsychiatrica*. **37**(e74), 1–7. doi: 10.1017/neu.2025.10028

Received: 11 February 2025
Revised: 14 May 2025
Accepted: 26 June 2025

Keywords:
Fibroblast growth factor 19; smoking; Beck's Depression Inventory scores; cerebrospinal fluid; depressive symptoms

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Abstract

Objective: This study aimed to examine the relationship between fibroblast growth factor 19 (FGF19) and depressive symptoms, measured by Beck's Depression Inventory (BDI) scores and investigate the moderating role of smoking. *Methods:* This study involved 156 Chinese adult males (78 smokers and 78 non-smokers) from September 2014 to January 2016. The severity of depressive symptoms was evaluated using the BDI scores. Spearman rank correlation analyses were used to investigate the relationship between cerebrospinal fluid (CSF) FGF19 levels and BDI scores. Additionally, moderation and simple slope analyses were applied to assess the moderating effect of smoking on the relationship between the two. *Results:* FGF19 levels were significantly associated with BDI scores across all participants ($r = 0.26$, $p < 0.001$). Smokers had higher CSF FGF19 levels and BDI scores compared to non-smokers (445.9 ± 272.7 pg/ml vs 229.6 ± 162.7 pg/ml, $p < 0.001$; 2.7 ± 3.0 vs 1.3 ± 2.4, $p < 0.001$). CSF FGF19 levels were positively associated with BDI scores in non-smokers ($r = 0.27$, $p = 0.015$), but no similar association was found among smokers ($r = -0.11$, $p = 0.32$). Linear regression revealed a positive correlation between FGF19 and BDI scores ($\beta = 0.173$, $t = 2.161$, 95% CI: 0.015–0.331, $p < 0.05$), which was negatively impacted by smoking ($\beta = -0.873$, $t = -4.644$, 95% CI: −1.244 to −0.501, $p < 0.001$). *Conclusion:* These results highlight the potential role of FGF19 in individuals at risk for presence of or further development of depressive symptoms and underscore the importance of considering smoking status when examining this association.

Significant outcomes

- Smoking modulates the relationship between FGF19 and depressive symptoms as a moderator.
- Smokers have higher CSF FGF19 levels and BDI scores compared to non-smokers.
- Participants with higher BDI scores have higher CSF FGF19 levels.

Limitations

- This study has limitations in generalizability, as the sample consisted exclusively of Chinese adult males. Future studies should include more diverse populations (e.g., females, other ethnic groups) to enhance external validity.
- Although adjustments were made for several demographic and lifestyle factors (e.g., age, BMI, marital status), residual confounding due to unmeasured variables (e.g., genetic predispositions, comorbid metabolic or psychiatric conditions) cannot be ruled out.
- Additionally, potential recall bias related to self-reported smoking behaviour and depressive symptoms (BDI scores) may have affected the reliability of the data. Future studies should consider incorporating objective biomarkers (e.g., serum cotinine levels for smoking, clinician-rated depression scales) to strengthen measurement accuracy.

Introduction

Mental disorders are a major contributor to the global health-related burden, and depressive symptoms are a major contributor to this burden (Monroe & Harkness, 2022), which has a significant impact on quality of life (Tran *et al.*, 2020). The main manifestations of depressive symptoms include changes in somatic symptoms, negative affect and anhedonia, which can lead to significant personal and social burdens (Wojnowski & Zimmer, 1997). In addition, with an increase in many risk factors, such as economic stress and social isolation, it can temporarily lead to an increase in depressive symptoms (Laarne *et al.*, 2000). Given the high prevalence of depressive symptoms and its significant impact on quality of life, research regarding early detection and intervention of emerging depression symptoms is warranted.

The neurotrophic hypothesis suggests that the neurobiological basis of mood disorders may be due to dysregulation of neurotrophic factors and their effects on brain circuits, which can cause a range of depressive symptoms (Xu *et al.*, 2021). The underlying mechanisms of the antidepressant effects of drugs may also be related to the modulation of multiple neurotrophic factors (Castrén & Monteggia, 2021; Wang *et al.*, 2022). Fibroblast growth factor (FGF) belongs to a large family of growth factors involved in brain development at an early age and in maintenance and repair throughout adulthood (Xu *et al.*, 2021). Recent studies have suggested new roles for FGF members in depression (Turner *et al.*, 2006; Lang & Borgwardt, 2013; Deng *et al.*, 2019).

Fibroblast growth factor 19 (FGF19) is a circulating hormone that regulates a wide range of biological functions, including energy homeostasis and brain development (Beenken & Mohammadi, 2009; Gadaleta & Moschetta, 2019). In a cross-sectional study, altered levels of FGF19 and FGF21 were found to be common causative mechanisms for metabolic and cognitive deficits in patients with major depressive disorder (Tang *et al.*, 2023). Moreover, FGF19 has been shown to be involved in cell proliferation and survival during embryonic brain development (Somm & Jornayvaz, 2018). Our previous study demonstrated a significant correlation between human cerebrospinal fluid (CSF) FGF19 levels and Beck Depression Inventory scores (Liu *et al.*, 2017).

Smoking is more common among people with mental health problems (Lawrence *et al.*, 2009; McClave *et al.*, 2010; Wootton *et al.*, 2020), especially those with depressive symptoms (Hall *et al.*, 1993). Multiple studies have found that smoking increases the risk of depressive symptoms (Coultas *et al.*, 2007; Hooshmand *et al.*, 2012). As we all known, people with depression are more likely to be smokers (Richards *et al.*, 2013; Fluharty *et al.*, 2017; Li *et al.*, 2022) and nicotine dependent (Dierker & Donny, 2008; Sweitzer *et al.*, 2008). However, depressive symptoms are often exacerbated in people who quit smoking (Gravely-Witte *et al.*, 2009). Tobacco contains substances such as nicotine, which primarily stimulates the brain. Nicotine acts mainly on nicotinic acetylcholine receptors (nAChRs), stimulating the release of norepinephrine, serotonin, dopamine, acetylcholine, gamma-aminobutyric acid, and glutamate in the brain (Haustein *et al.*, 2002; Picciotto *et al.*, 2002).

Until now, the association between FGF19 and smoking has been reported in some studies. For example, FGF19 has been implicated as a potential driver gene in laryngeal squamous cell cancer (LSCC) with clinical characteristics linked to smoking (Tan *et al.*, 2016). However, the direct relationship between smoking and FGF19 is not yet known. Moreover, whether smoking plays an important role in the relationship between FGF19 and depressive symptom remains unclear, although most studies suggest that smoking itself increases the risk of depression (Makarov, 1973; Orth, 2002). Therefore, based on previous studies, the aim of the present study is to explore the association between depressive symptom and FGF19 in the CSF of smokers and non-smokers by assessing Beck's Depression Inventory (BDI) scores.

Materials and methods

Participants

This cross-sectional analysis included 191 Chinese adults. After excluding participants with missing data, family history of psychiatric or neurological disorders, or systemic/CNS diseases (diagnosed via the Mini International Neuropsychiatric Interview), a total of 156 participants were included. Demographic and lifestyle data (age, BMI, marital and living status) were collected. Additionally, CSF samples and relevant clinical data were collected. Smoking status, including age of smoking initiation, daily cigarette consumption, smoking duration, and Fagerström Test for Nicotine Dependence (FTND) scores, was also recorded (Ríos-Bedoya *et al.*, 2008). Smokers were defined per WHO criteria ($\geq$ 1 year smoking history), and individuals with other substance use disorders were excluded. Non-smokers had no history of tobacco or other substance use. All participants provided written consent, and the procedures followed the ethical standards of the institutional anglasd/or national research committee, consistent with the 1964 Helsinki Declaration.

Biosample collection and laboratory tests

CSF samples were collected following established protocols, as described previously in detail (Li *et al.*, 2018). The levels of FGF19 in CSF were quantified using ELISA kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) as per the manufacturer's instructions (Xu *et al.*, 2019). Double-blind principles were applied throughout the process.

Assessment of depressive symptoms

The Beck's Depression Inventory-II (BDI-II) was used, consisting of 13 items scored from 0–3. A total score > 4 indicated depressive symptoms, with scores categorised into mild (5–7), moderate (8–15), and severe ($\geq$ 16). Assessments were conducted one day prior to CSF Collection.

Statistical analysis

Continuous variables were compared using independent t-tests or Wilcoxon rank-sum tests; categorical variables were assessed with χ^2 tests. Spearman correlations were used to examine associations between FGF19 and BDI scores across the full sample and subgroups (smokers vs. non-smokers). Multiple linear regression and moderation analyses (including interaction terms) were conducted with adjustments for age, BMI, marital and living status. All analyses were performed in R (v4.3.0), with statistical significance set at $p < 0.05$ (two-tailed).

Results

Population characteristics

In our sample, 63 individuals had BDI scores less than 1, while 93 individuals scored 1 or higher. Notably, 19 participants scored $\geq$ 5; among them, 5 had scores below 8, and 14 had scores between 8

https://doi.org/10.1017/neu.2025.10028

Table 1. Comparisons between non-smokers and smokers

Characteristic	Non-smokers	Smokers	*p*-value[2]
	N = 78[1]	*N* = 78[1]	
Demographics			
Age*	29.8 (9.9)	33.7 (10.0)	0.014
BMI*	25.0 (4.2)	25.8 (3.6)	0.036
SBP	130.2 (12.7)	126.9 (13.1)	0.108
DBP	75.0 (8.9)	76.2 (11.4)	0.455
Marriage			0.009
Married	39 (50%)	23 (29%)	
Unmarried	39 (50%)	55 (71%)	
Living status			< 0.001
Living in family	56 (72%)	73 (94%)	
Living with others	22 (28%)	5 (6.4%)	
Smoking			
FTND score*		3.3 (2.2)	
Smoking onset*		20.0 (3.8)	
Smoking period*		13.4 (8.9)	
Biochemical indicators			
FGF19 (pg/ml)*	229.6 (162.7)	445.9 (272.7)	< 0.001
Depression			
BDI scores*	1.3 (2.4)	2.7 (3.0)	< 0.001

*Data with non-normal distribution.
Note: *p*-values for comparisons between smokers and non-smokers were calculated using the Chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables.
Abbreviation: FGF19, fibroblast growth factor 19; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BDI, Beck's Depression Inventory-II; FTND, Fagerström Test for Nicotine Dependence; Smoking onset, age at smoking initiation (years).

and 16 (please refer to Supplementary Table 1).The study included 156 participants, equally divided into smokers and non-smokers. Significant differences in age, BMI, marital status, and living status were observed ($p < 0.05$). Smokers exhibited higher CSF FGF19 and BDI scores than non-smokers (445.9 ± 272.7 pg/ml vs. 229.6 ± 162.7 pg/ml, $p < 0.001$; 2.7 ± 3.0 vs. 1.3 ± 2.4, $p < 0.001$). No significant differences were observed in blood pressure ($p > 0.05$). For detailed demographics and biochemical indicators, please see Table 1. Additionally, we have included a new Supplementary Table 2, which presents the median and IQR for non-normally distributed variables to improve transparency and data interpretation.

FGF19 and BDI correlations

The level of FGF19 was significantly associated with BDI scores across all participants ($r = 0.26$, $p < 0.001$) (Figure 1A). FGF19 levels in CSF were positively associated with BDI scores in non-smokers, but no similar result was found among smokers ($r = 0.27$, $p = 0.015$; $r = -0.11$, $p = 0.32$) (Figure 1B). FTND scores positively correlated with years of smoking ($r = 0.44$, $p < 0.001$), and negatively with age at smoking initiation ($r = -0.43$, $p < 0.001$), adjusted for age (see Figure 1C).

Moderation analysis

Based on the correlations in Figure 1, we further explored the inhibitory effect of smoking on the relationship between FGF19 and depressive symptoms severity using moderation analysis, adjusted for age, living status, BMI, and marital status (Table 2).

Multiple linear regression analyses indicated that both FGF19 and smoking were independently associated with BDI scores. Specifically, FGF19 was positively associated with BDI scores ($\beta = 0.173$, 95% CI: 0.015–0.331, $t = 2.161$, $p < 0.05$, adj. $R^2 = 0.033$), and smoking also showed a significant positive association ($\beta = 0.444$, 95% CI: 0.120–0.769, $t = 2.708$, $p < 0.01$, adj. $R^2 = 0.049$) in Model 1 and Model 2, respectively (Table 2). In Model 3, we included the interaction term between FGF19 and smoking. Results showed a significant interaction effect ($\beta = -0.873$, 95% CI: −1.244 to −0.501, $t = -4.644$, $p < 0.001$, adj. $R^2 = 0.167$), indicating that smoking moderated the relationship between FGF19 and BDI scores (Table 2; Figure 2A).

The moderating effect of smoking was further supported by an increase in the F-value from 2.062 in Model 1 to 5.426 in Model 3 ($\Delta F = 3.364$, $p < 0.001$). To clarify this moderation effect, we performed a simple slopes analysis to explore the association between FGF19 and BDI scores within non-smokers and smokers (Table 3; Figure 2B). Among non-smokers, FGF19 showed a significant positive association with BDI scores ($\beta = 0.741$, 95% CI: 0.424–1.058, $t = 4.618$, $p < 0.001$), whereas in smokers, this association was not statistically significant ($\beta = -0.132$, 95% CI: −0.322–0.058, $t = -1.372$, $p = 0.172$).

Discussion

Our study indicates that cigarette smoking is positively associated with CSF FGF19 levels and depressive symptoms as assessed by BDI scores (see Table 1). Moreover, we found a positive association between CSF FGF19 levels and BDI scores in non-smokers, while this effect was absent in smokers, consistent with our previous research (Liu *et al.*, 2017). Further analysis using moderation models indicated that smoking inhibits the association between FGF19 and depressive symptoms, exerting a negative moderation effect.

We found that CSF FGF19 levels increased in individuals with higher BDI scores, suggesting that FGF19 may play a significant role in depressive symptoms. FGF19, a member of the fibroblast growth factor (FGF) family, is known to influence brain development (Nishimura *et al.*, 1999; Somm & Jornayvaz, 2018). For instance, the mouse ortholog FGF15 has been shown to exert neuroprotective effects against oxidative stress (Zhang *et al.*, 2019). FGF15 has also been implicated in depression via the Farnesoid X Receptor (FXR) signalling axis (Cai *et al.*, 2023; Wang *et al.*, 2025). Consistent with our findings, Tang and colleagues (2023) reported a positive association between plasma FGF19 levels and BDI in patients with MDD and proposed that fluctuations in FGF19 might contribute to the metabolic and cognitive disturbances observed in MDD patients (Tang *et al.*, 2023). FGF19 is known to regulate bile acid metabolism, and BAs have neuroprotective effects, enhancing BDNF release and stimulating the BDNF–TrkB pathway (Li *et al.*, 2020; Zhai *et al.*, 2023). Numerous studies have indicated that BDNF has potential antidepressant effects (Zhang *et al.*, 2016; Phillips, 2017; Zhang & Liao, 2020). A clinical study demonstrated that individuals with the BDNF val66met genotype exhibited

https://doi.org/10.1017/neu.2025.10028

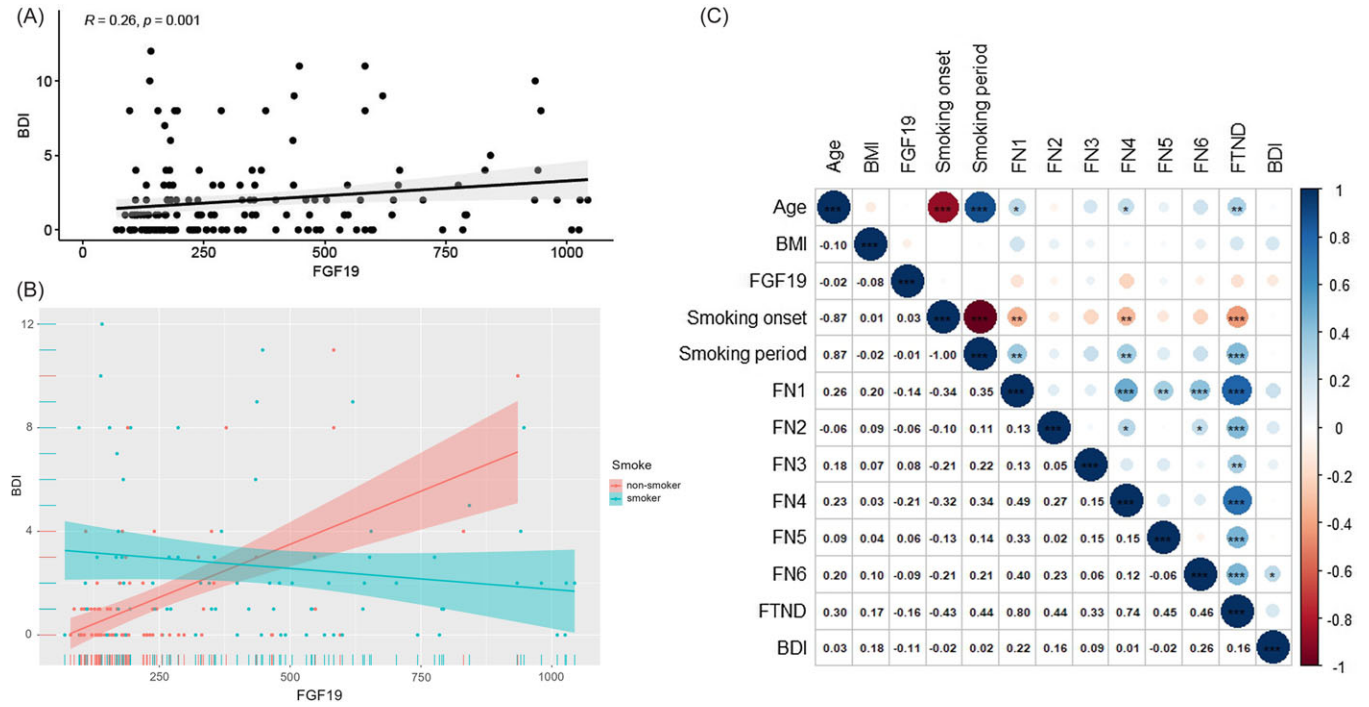

Figure 1. Correlation analysis between FGF19 and BDI scores.

Note: (A) Spearman correlation analysis between FGF19 levels and BDI scores in all participants. (B) Bivariate correlation matrix using Spearman's rank correlation for study variables in non-smokers and smokers. (C) Spearman correlations between internal smoking-related indicators and depressive symptoms in smokers.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

In Panel C: left-side numbers indicate Spearman correlation coefficients. Blue circles represent positive correlations; red circles indicate negative correlations. Darker shades indicate stronger absolute correlation values.

Abbreviations: FGF19, fibroblast growth factor 19; BMI, body mass index; BDI, Beck's Depression Inventory; FTND, Fagerström Test for Nicotine Dependence; FN, FTND item scores; Smoking onset, age of smoking initiation (adjusted for age).

Table 2. Linear regression table for the moderation analysis

	Model 1			Model 2			Model 3		
	β	**95%CI**	***t***	***β***	**95%CI**	***t***	***β***	**95%CI**	***t***
Age	0.015	[−0.206, 0.236]	0.135	0.012	[−0.206, 0.232]	0.11	0.054	[−0.152, 0.260]	0.52
BMI	0.119	[−0.043, 0.280]	1.454	0.092	[−0.067, 0.252]	1.141	0.096	[−0.054, 0.247]	1.265
Marriage	0.271	[−0.179, 0.722]	1.19	0.222	[−0.225, 0.669]	0.981	0.072	[−0.353, 0.497]	0.335
Living	0.026	[−0.479, 0.531]	0.102	0.075	[−0.430, 0.580]	0.294	0.083	[−0.391, 0.556]	0.345
FGF19	0.173*	[0.015, 0.331]	2.161	–	–	–	0.741***	[0.424,1.058]	4.618
Smoke	–	–	–	0.444**	[0.120, 0.769]	2.708	0.195	[−0.146, 0.537]	1.129
FGF19* Smoke	–	–	–	–	–	–	−0.873***	[−1.244, −0.501]	−4.644
Adj. R^2	0.033			0.049			0.167		
F	2.062 (5,150)			2.615 (5,150)			5.426 (7,148)		

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Note: Model 1 includes FGF19 as the independent variable and BDI scores as the dependent variable. Model 2 includes smoking status as the independent variable and BDI scores as the dependent variable. Model 3 includes FGF19, smoking, and their interaction term (FGF19 × smoking) as independent variables. All models were adjusted for age, BMI, marital status, and living status. All analyses were conducted as moderation analyses.

Abbreviations: FGF19, fibroblast growth factor 19; BMI, body mass index; BDI, Beck's Depression Inventory-II.

reduced BDNF secretion, deficits in situational memory function, and an increased risk of anxiety and depression (Egan *et al.*, 2003; Hariri *et al.*, 2003). Intracerebroventricular injection of FGF19 in mice has been shown to suppress HPA axis activity (Perry *et al.*, 2015), suggesting that reduced FGF19 may impair stress regulation and contribute to depressive symptoms.

Smoking is known to impair glucose metabolism and insulin sensitivity (Chiolero *et al.*, 2008), which may in turn, influence FGF19 signalling. FGF19 plays a critical role in bile acid synthesis and glucose homeostasis (Potthoff *et al.*, 2011, Degirolamo *et al.*, 2016). Disruption of the FXR–FGF19 axis has been implicated in metabolic disorders such as inflammatory bowel disease (IBD),

https://doi.org/10.1017/neu.2025.10028

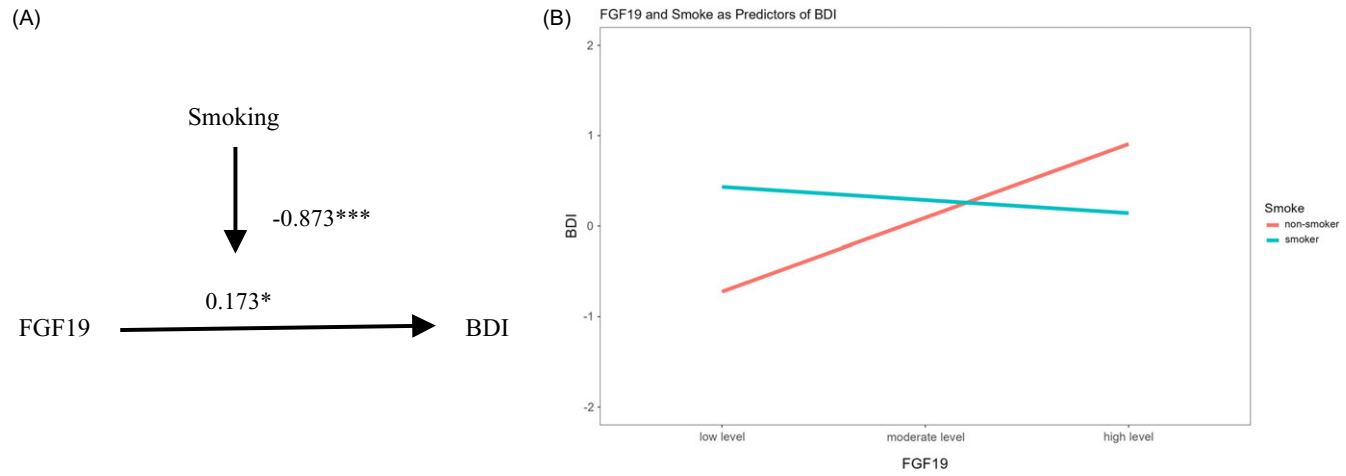

Figure 2. Moderation effect of smoking on FGF19 and BDI scores.
Note: The two regression lines represent the association between FGF19 and BDI scores in non-smokers and smokers.
Abbreviations: FGF19, fibroblast growth factor 19; BDI, Beck's Depression Inventory-II.

Table 3. Simple slopes analysis

Smoke	β	t	p	95%CI
Non-smoker	0.741	4.618	< 0.001	[0.424, 1.058]
Smoker	−0.132	−1.372	0.172	[−0.322, 0.058]

obesity, and type 2 diabetes (Gadaleta *et al.*, 2020; Bag Soytas *et al.*, 2021; Lyutakov *et al.*, 2021). Reduced circulating FGF19 levels in patients with active IBD and obesity further support its involvement in maintaining metabolic balance (Schreuder *et al.*, 2010; Mráz *et al.*, 2011). Thus, smoking-induced metabolic dysregulation may impair FGF19 function and thereby modulate its association with depressive symptoms (Wang *et al.*, 2024).

One possible explanation is that chronic exposure to inflammation, as seen in smokers, may create an immunologically 'tolerant' state (Esquivel *et al.*, 2014). Smoking is a known pro-inflammatory factor that elevates cytokines such as TNF-α and IL-6 (Sanada *et al.*, 2018; Womack & Justice, 2020), and inflammation has been shown to downregulate FGF15 expression in animal models (Gadaleta *et al.*, 2020). However, the specific mechanisms through which nicotine influences central nervous system metabolism and inflammation to impact depression remain unclear and warrant further investigation. Our findings contribute to this area by suggesting that smoking may interfere with the regulatory role of CSF FGF19 in depressive symptomatology.

Based on our findings, we hypothesise that elevated BDI scores may be linked to increased FGF19 levels, as a compensatory mechanism to counteract depressive symptoms, potentially via modulation of the BDNF–TrkB axis or HPA axis. However, this relationship was not observed in smokers, suggesting that smoking status could modulate the interaction between FGF19 and depressive symptoms. Further research is needed to elucidate the precise role of smoking in this context. This finding is consistent with our previous research, which also found that CSF FGF19 was positively correlated with BDI scores (Liu *et al.*, 2017). Smoking is widely recognised as a detrimental lifestyle habit (Tsai *et al.*, 2019; Wiegman *et al.*, 2020; Ma *et al.*, 2021). Therefore, we hypothesise that this may be one reason for the negative impact of smoking on the association between FGF19 and BDI scores.

To our knowledge, this is the first study to assess the role of smoking on FGF19-induced depressive symptoms (expressed as BDI) in Chinese men. Our findings indicate that the positive effects of CSF FGF19 on BDI are negatively impacted by smoking.

However, this study has several limitations. First, causal inferences cannot be drawn from a case-control design, and the small sample size may limit the statistical power to examine associations and moderation. Therefore, evidence from prospective studies with larger sample sizes is warranted. Second, retrospective recall bias may occur with the use of subjective depression measures and smoking assessments. Additionally, other potential confounders may affect our understanding of the relationship between smoking and depressive disorders. Finally, the lower prevalence of smoking in women and the recruitment of only men result in limited applicability and generalizability.

Conclusion

These findings support a potential role of FGF19 in depression and highlight the importance of considering smoking status when evaluating this association. The findings of this study have important clinical implications. First, they emphasise the need to consider smoking when assessing the relationship between FGF19 and depressive symptoms. Clinicians may need to integrate smoking cessation strategies into treatment plans for patients with depressive symptoms who also use tobacco. Future research should explore potential mechanisms and develop effective interventions. Overall, these results highlight the potential role of FGF19 in individuals at risk for presence of depressive symptoms and underscore the importance of considering smoking status when examining this association.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/neu.2025.10028.

Data availability statement. The raw data supporting the conclusions of this article will be made available by the authors on request.

Acknowledgements. We thank all the teachers, students and related participants for their involvement in this study.

Author contribution. Writing-Review & Editing, Y.L., F.W., X.L., Y.C., W.W., L.C., X.L. and J.W.; Supervision, Y.L., X.L. and J.W.; Writing-Original Draft Preparation, S.L., L.C., M.M., Y.H.; Methodology, Y.C., L.C. and W.W.; Formal Analysis, M.M.; Visualisation, F.W., X.L., W.H. and Y.K. ; Investigation, Y.H., H.G. and Y.R.; Project administration, F.W., W.H. and Y.K.. All authors read and approved the final manuscript.

Funding statement. This work was supported by the Natural Science Foundation of Xinjiang Uygur Autonomous Region (2018D01C239); the Natural Science Foundation of Beijing Municipality (7152074); and the Tianshan Youth Project - Outstanding Youth Science and Technology Talents of Xinjiang (2017Q007).

Competing interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical standards. This study was reviewed and approved by Institutional Review Board of Inner Mongolian Medical University with the approval number: YKD2014031, dated March 11th, 2014. The studies were conducted in accordance with the local legislation and institutional requirements. All participants (or their legal guardians) provided written informed consent to participate in the study and for their data to be published.

Consent for publication. All authors have given their consent to the publication of the article.

Inclusion of identifiable human data. No potentially identifiable human images or data is presented in this study.

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https://doi.org/10.1017/neu.2025.10028