Increased Dipeptidyl Peptidase-4 Activity Is Associated With High Prevalence of Depression in Middle-Aged and Older Adults: A Cross-Sectional Study

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ABSTRACT

Objective: Obesity, inflammation, and decreased neuropeptide Y (NPY) are risk factors for depression. Dipeptidyl peptidase-4 (DPP4), a newly identified adipokine, has been proved to promote inflammation and NPY degradation. Hence, we aimed to investigate the association between plasma DPP4 activity and depression symptoms in middle-aged and older adults.

Methods: We cross-sectionally assessed 1,335 Chinese adults aged 45–76 years recruited from the Medical Examination Center, Guilin, China, between 2013 and 2014. The main outcome measures were plasma DPP4 activity, inflammatory markers, and NPY. Depression symptoms were determined by the score on the 9-item Patient Health Questionnaire (PHQ-9). Each of the 9 depression items of the PHQ-9 correspond to 1 of the *DSM-IV* diagnostic criteria for symptoms of major depressive disorder.

Results: Subjects in the highest quartile of DPP4 activity had higher body mass index (BMI), interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and PHQ-9 score compared with subjects in the lowest quartile ($P < .05$). Compared to patients without depression symptoms, patients with depression symptoms had higher BMI, waist-to-hip ratio, IL-6, hs-CRP, and DPP4 activity ($P < .05$). DPP4 activity was associated positively with IL-6, hs-CRP, and PHQ-9 score and negatively with NPY after adjustment for potential confounders ($P < .05$). The risk for depression symptoms increased with higher levels of DPP4 activity and inflammation and lower levels of NPY.

Conclusions: Increased DPP4 activity is independently associated with depression symptoms in middle-aged and older adults. The mechanisms might be partly explained by mutual influence among inflammation, NPY, and DPP4. These observations raise further interest in DPP4 activity for the potential effect on inflammation and NPY metabolism, as a risk biomarker, or even a possible therapeutic target for depression.

Trial Registration: Chinese Clinical Trial Registry (ChiCTR-EPC-14005273).

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Depression is a worldwide public health issue, and its prevalence is increasing dramatically.[1–4] Assessing depression risk and identifying potential targets for depression intervention have profound socioeconomic significance for public health. It is now clear that multiple traditional risk factors such as advanced age, gender differences, alcohol consumption, and obesity contribute to the development of depression.[5,6] In addition, accumulated clinical and basic scientific evidence reveals that inflammation also plays a critical role in the pathogenesis of depression.[7] Research has shown that immune activation and the production of proinflammatory cytokines (ie, interleukin-6 [IL-6], tumor necrosis factor alpha [TNF-α], interleukin 1 beta [IL-1β], and high-sensitivity C-reactive protein [hs-CRP]) affect brain function and mood regulation by regulating hypothalamic-pituitary-adrenal (HPA) axis activation, neurotransmitter systems, and neuroplasticity.[7] Moreover, a previous study[8] supported the contribution of neuropeptide Y (NPY), a neuropeptide expressed both in the central nervous system and in peripheral circulation, to antidepressive effect. NPY activity is exerted through the interaction with its receptors, designated Y1 through Y6. Full-length NPY preferentially binds to receptor Y1, mediating its antidepressive and anxiolytic effect, whereas the truncated form (NPY3-36) released by dipeptidyl peptidase-4 (DPP4) displays a higher affinity for the receptor Y2, mediating opposite effects through presynaptic inhibition of further NPY release.[9–11]

DPP4 is a widely expressed multifunctional serine peptidase that exists as a membrane-anchored cell-surface protein or in a soluble form in the plasma.[12] In addition to its role in the degradation of numerous substrates such as NPY, DPP4 has also been identified as a novel adipokine (adipokines are defined as adipose tissue–derived bioactive substances that are involved in the regulation of many vital processes such as energy metabolism, inflammation, cell proliferation, etc[13,14]), promoting inflammation and proinflammatory cytokine secretion through its interaction with mannose 6-phosphate receptors (M6P-R) and interleukin 12 (IL-12).[15–17] Furthermore, an animal study by Canneva and colleagues[8] showed a significantly higher concentration of NPY in the cerebrospinal fluid (CSF) of DPP4-deficient congenic rats, and this finding positively correlated with

Clinical Points

- The relationship between dipeptidyl peptidase-4 (DPP4; an adipose tissue-derived bioactive substance that is involved in promoting inflammation and neuropeptide Y [NPY] degradation) and depression remains unclear.
- DPP4 activity could serve as a risk biomarker or even a possible therapeutic target for depression.
- The mechanisms of depression might be partly explained by mutual influence between inflammation, NPY, and DPP4.

the blunted stress phenotype. These findings, along with the important role of inflammation and altered NPY levels in the pathogenesis of depression, motivated us to speculate that DPP4 activity may be positively correlated with symptoms of depression. To our knowledge, no study has evaluated the association between DPP4 activity and depression in humans. Consequently, in this study, we aimed to evaluate the mutual relationship between plasma DPP4 activity and depression symptoms in a cross-sectional population study of 1,335 middle-aged and older adults in China. The relationship between DPP4 activity and causative factors for depression mentioned above were also evaluated since we attempted to further explain the mechanism for such an association from a clinical perspective. Since hyperglycemia has a mutual effect on DPP4 and depression,[18,19] thus introducing an additional confounding factor, the current study was performed in a group of subjects with normal glucose tolerance.

METHODS

Participants

A total of 1,335 Chinese adults, aged 45–76 years, who had undergone routine health examinations at the Medical Examination Center of Affiliated Hospital of Guilin Medical University, Guilin, China, between 2013 and 2014 were enrolled for analysis in this study. All subjects visited the Medical Examination Center spontaneously for routine health examinations consisting of extensive screening tests for the early detection of diabetes, hypertension, malignancy, and other age-related diseases. Exclusion criteria included (1) subjects who had taken drugs that could affect depression symptoms for more than 3 months or at any time within 12 months before the enrollment, such as statins, chlorpromazine, dilantin, isoniazid, levodopa, glucocorticoid, clonidine, reserpine, and antidepressant drugs; (2) subjects who had any disease that could affect depression symptoms or DPP4 activity, such as malignancy, hypothyroidism, diabetes, nonalcoholic fatty liver disease, acute inflammatory diseases, stroke, myocardial infarction, and heart, liver, and respiratory dysfunction; and (3) subjects with incomplete data (Supplementary eFigure1).

The study was approved by the Drugs/Medical Apparatus & Instruments Ethics Committee at Affiliated Hospital of Guilin Medical University, and all subjects gave informed consent. This study was registered with the Chinese Clinical Trial Registry (ChiCTR-EPC-14005273).

Clinical and Laboratory Measurements

A standard questionnaire was administered to the participants by trained staff to record demographic characteristics, lifestyle risk factors, marital status, education level, annual income, self-reported medical history, and medications. Measurements of body weight and height, body mass index (BMI), and waist-to-hip ratio have been described previously.[20] Subjects were instructed to maintain their usual physical activity and diet for at least 3 days before undergoing an oral glucose tolerance test. After an overnight fast of ≥ 10 hours, venous blood samples were collected to measure fasting plasma glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), blood lipids (including total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol), hs-CRP, IL-6, NPY, and DPP4 activity. Blood samples were also drawn at 30 and 120 minutes after a 75-gram glucose load to measure glucose and insulin concentrations.

Plasma glucose levels, insulin, HbA_{1c}, blood lipids, hs-CRP, IL-6, and DPP4 activity were measured as previously described.[17,18] Serum NPY levels were measured using the NPY Enzyme Immunoassay kit (Phoenix Pharmaceuticals, Inc, Burlingame, California).

Depression symptoms were assessed with the 9-item Patient Health Questionnaire (PHQ-9), which was widely used in epidemiologic study for the screening of depression.[5] Each of the 9 depression items of the PHQ-9 correspond to 1 of the *DSM-IV* diagnostic criteria for symptoms for major depressive disorder.[21] Responses to these 9 questions were on a 4-point Likert scale from 0 to 3, indicating that the participant experienced the symptom "not at all," "on several days," "on more than half the days," or "nearly every day," respectively, during the past 2 weeks for a total score ranging from 0 to 27. For our sample, the scores ranged from 0 to 23, with a median value of 2; a participant who scored ≥ 10 was defined as having depressive symptoms. This cutoff has been validated for the general population.[22] For those identified with clinically significant depressive symptoms (PHQ-9 score ≥ 10), a visit to a psychiatrist for further evaluation and treatment was suggested.

Statistical Analysis

All of the statistical analyses were performed using the SPSS 16.0 software (SPSS Inc, Chicago, Illinois) and SAS 9.3 software (SAS Institute, Cary, North Carolina). Normally distributed data were expressed as mean ± SD; whereas variables with a skewed distribution were reported as medians (interquartile range) and log transformed to approximate normality before analysis. Categorical variables were represented by frequency and percentage. Clinical and biochemical characteristics were compared by an analysis of covariance (χ^2 or *t* test). Associations between continuous variables were tested by Pearson correlation analysis and partial correlation analyses. Multivariate logistic regression models were used to estimate the odds ratios (ORs) for depression symptoms, elevated IL-6, elevated hs-CRP, PHQ-9 score, and decreased NPY. Kruskal-Wallis test

Table 1. Characteristics of Study Participants According to DPP4 Quartiles

Characteristic[a]	Quartile 1 (n = 334) < 11.10	Quartile 2 (n = 333) 11.11–15.72	Quartile 3 (n = 335) 15.73–20.99	Quartile 4 (n = 333) ≥ 21.00	*P* Value
DPP4 activity, nmol/min/mL	7.92 ± 2.20	13.54 ± 1.35	18.12 ± 1.51	25.76 ± 3.59	< .001
Age, y	58.5 ± 7.7	58.0 ± 7.3	58.9 ± 7.5	59.6 ± 8.1	.029
Percent women, %	66.5	70.9	70.4	65.2	.289
Body mass index, kg/m^2	22.8 ± 3.7	22.9 ± 3.6	23.5 ± 3.8	24.0 ± 3.9	< .001
Waist-to-hip ratio	0.86 ± 0.07	0.86 ± 0.08	0.87 ± 0.08	0.90 ± 0.09	< .001
Current smoking, %	20.1	15.9	20.9	19.5	.373
Alcohol consumption, %	13.8	15.0	23.9	23.4	< .001
Leisure-time physical activity, %	61.1	66.1	57.9	58.9	.134
Marital status					.412
Married, %	90.4	93.4	91.9	88.9	
Single, %	1.5	1.5	1.2	1.2	
Widowed, %	8.1	5.1	6.9	9.9	
Education level					.291
≤ Primary school	43.4	42.0	43.0	47.1	
Middle school	44.6	49.5	43.9	41.4	
≥ High school	12.0	8.4	13.1	11.4	
Annual income					< .001
≤ rmb5,000 (US $745.90)	6.0	4.5	3.9	5.7	
rmb5,000–rmb30,000 (US $745.90–$4,475.41)	39.8	38.7	57.6	50.5	
> rmb30,000 (US $4,475.41)	54.2	56.8	38.5	43.8	
Triglycerides, mmol/L[b]	1.16 (0.89–1.69)	1.30 (0.99–1.91)	1.35 (1.02–1.87)	1.44 (1.07–1.93)	.001
Total cholesterol, mmol/L[b]	5.11 ± 0.92	5.10 ± 1.05	5.22 ± 0.94	5.23 ± 1.02	.378
Low-density lipoprotein cholesterol, mmol/L[b]	3.11 ± 0.81	3.09 ± 0.89	3.20 ± 0.79	3.27 ± 0.84	.113
High-density lipoprotein cholesterol, mmol/L[b]	1.45 ± 0.33	1.44 ± 0.36	1.48 ± 0.33	1.45 ± 0.34	.349
IL-6, pg/mL[b]	1.25 ± 0.27	1.31 ± 0.30	1.33 ± 0.31	1.50 ± 0.60	< .001
hs-CRP, mg/L[b]	1.14 ± 0.24	1.16 ± 0.22	1.22 ± 0.21	1.31 ± 0.36	< .001
NPY, ng/mL[b]	0.150 ± 0.045	0.145 ± 0.040	0.154 ± 0.051	0.151 ± 0.044	.001
PHQ-9 score[b]	2.33 ± 3.20	2.46 ± 3.38	3.83 ± 4.44	5.60 ± 5.28	< .001

[a]Data are expressed as mean ± SD, median (interquartile range), or percentage for normally distributed continuous various, abnormally distributed continuous variables, and categorical variables, respectively. Cigarette smoking was defined as having smoked at least 100 cigarettes in one's lifetime. Alcohol consumption was defined as consumption of ≥ 30 g of alcohol per week for 1 year or more. Regular leisure-time physical activity was defined as participation in ≥ 30 min of moderate or vigorous activity per day for at least 3 days per week.
[b]Adjusted for age, gender, and body mass index.
Abbreviations: DPP4 = dipeptidyl peptidase-4, hs-CRP = high-sensitivity C-reactive protein, IL-6 = interleukin-6, NPY = neuropeptide Y, PHQ-9 = 9-item Patient Health Questionnaire, rbm = renminbi (Chinese currency).

and Cochran-Armitage test were used to examine trend associations between DPP4 quartiles and IL-6, hs-CRP, NPY, PHQ-9 score, and categorically defined depression. Owing to a lack of current global guidelines regarding the normal range of IL-6, hs-CRP, and NPY, the upper quartiles of IL-6 and hs-CRP were defined as elevated, whereas the lower quartiles of NPY were defined as decreased.

RESULTS

Clinical and Laboratory Characteristics

Among the 1,335 subjects included in this study, 148 patients (11.1%) had depression symptoms. The prevalences of depression symptoms according to DPP4 quartiles were 6.9%, 5.7%, 12.2%, and 19.5%, respectively. The subjects with higher DPP4 activity had higher age, more alcohol consumption, and lower annual income (all $P < .05$). With respect to metabolic parameters and PHQ-9 score, the subjects in the higher DPP4 quartiles exhibited higher BMI, waist-to-hip ratio, triglycerides, IL-6, hs-CRP, and PHQ-9 score (all $P < .05$). Gender, current smoking, leisure-time physical activity, marital status, education level, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol did not differ significantly across DPP4 activity categories (Table 1). Compared with patients without depression symptoms, the subjects with depression symptoms had higher BMI, waist-to-hip ratio, IL-6, hs-CRP, and DPP4 activity; were more likely to be female; and exhibited higher prevalence of smoking and lower prevalence of leisure-time physical activity and annual income. Age, alcohol consumption, marital status, education level, and NPY did not differ significantly between those with and without depression symptoms (Supplementary eTable1).

Correlation Analysis Between DPP4 Activity and Other Variables

Pearson correlation analysis demonstrated that DPP4 activity was positively associated with age ($r = 0.076$, $P = .005$), BMI ($r = 0.133$, $P = .005$), waist-to-hip ratio ($r = 0.179$, $P < .001$), IL-6 ($r = 0.260$, $P < .001$), hs-CRP ($r = 0.258$, $P < .001$), and PHQ-9 score ($r = 0.319$, $P < .001$). No significant association was found between DPP4 activity and NPY. After adjustments for age, BMI, gender, current smoking, alcohol consumption, leisure-time physical activity, marital status, education level, and annual income, the association between IL-6, hs-CRP, PHQ-9 score, and DPP4 activity remained significant. Interestingly, DPP4 activity was found to be

Table 2. Correlations Between DPP4 Activities Versus Metabolic Parameters and PHQ-9 Score

	DPP4 Activity[a]		DPP4 Activity[b]	
	r	*P*	*r*	*P*
Age	0.076	.005	…	…
BMI	0.133	.005	…	…
WHR	0.179	<.001	…	…
NPY	0.040	.145	−0.073	.008
IL-6	0.260	<.001	0.249	<.001
hs-CRP	0.258	<.001	0.233	<.001
PHQ-9 score	0.319	<.001	0.303	<.001

[a]*P* value determined by Pearson correlation analysis with respect to the DPP4 activity.
[b]*P* value determined by partial correlation analysis with respect to the DPP4 activity adjusted for age, BMI, gender, current smoking, alcohol consumption, leisure-time physical activity, marital status, education level, and annual income.
Symbol: … = not applicable.
Abbreviations: BMI = body mass index, DPP4 = dipeptidyl peptidase-4, hs-CRP = high-sensitivity C-reactive protein, IL-6 = interleukin-6, NPY = neuropeptide Y, PHQ-9 = 9-item Patient Health Questionnaire, WHR = waist-to-hip ratio.

negatively associated with NPY after adjustments for these variables (Table 2). A strong positive association was found between NPY and BMI in all subjects ($r = 0.418$, $P < .001$). The prevalence of depression symptoms, PHQ-9 score, and IL-6 and hs-CRP levels were increased with rising DPP4 quartiles (all $P < .001$) (Supplementary eTable2).

As presented in Table 3, the ORs for increased IL-6, hs-CRP, and PHQ-9 score and decreased NPY were higher with increasing DPP4 quartiles after adjustment for confounders. In the highest DPP4 quartiles, the ORs were 2.24 (95% confidence interval [CI], 1.54–3.24) for elevated IL-6, 2.21 (95% CI, 1.52–3.21) for elevated hs-CRP, 2.93 (95% CI, 1.74–4.93) for elevated PHQ-9 score, and 1.57 (95% CI, 1.04–2.38) for decreased NPY after adjustments for age, BMI, gender, current smoking, alcohol consumption, leisure-time physical activity, marital status, education level, and annual income. NPY was not found to be decreased with increasing DPP4 quartiles in the crude model (Table 3).

Associations Between DPP4 Activity and Depression Symptoms

Multivariate logistic regression analysis demonstrated that the ORs for depression symptoms were significantly higher with increasing DPP4 quartiles. The OR was 2.93 (95% CI, 1.74–4.93) for depression symptoms after adjustments for age, BMI, gender, current smoking, alcohol consumption, leisure-time physical activity, marital status, education level, and annual income. Interestingly, further adjustment for NPY and IL-6 only reduced the magnitude of the OR for depression symptoms (1.89 [95% CI, 1.09–3.29], $P = .011$) (Table 4).

The risk of depression symptoms was more pronounced among participants with rising DPP4 activity and higher levels of IL-6 (Figure 1A) and hs-CRP (Figure 1B) and lower levels of NPY (Figure 1C). Even in the lowest quartile of IL-6 and hs-CRP and highest quartile of NPY, the risks for depression symptoms were 1.93- to 3.45-fold higher in the highest DPP4 quartile than in the lowest quartile (Figure 1).

DISCUSSION

In this study, we found a significant and independent association between DPP4 activity and the risk of depression symptoms and the pathogenic factors of depression such as inflammation and decreased levels of NPY in peripheral circulation in middle-aged and older adults. Moreover, the underlying mechanisms may be partly explained by the mutual influence between inflammation, NPY, and DPP4.

Our study has several strengths. First, potential confounders such as chronic disease and drug use were carefully controlled by strict exclusion criteria. Second, to our knowledge, this was the first study evaluating the relationship between DPP4 activity and depression symptoms in humans; furthermore, we had various covariables available for further explaining the mechanism for such a relationship from a clinical perspective, including IL-6, hs-CRP, NPY, and various other determinants of depression. Third, previous studies have already demonstrated some other biomarkers in the circulation used to assess the depression risk[23,24]; however, rational treatment by targeting these biomarkers is still not available in clinical practice. In the current study, our data indicated that increased DPP4 activity might be not only a novel biomarker assessing the depression risk in adults, but also a possible therapeutic target for the prevention and treatment of depression in humans since DPP4 inhibitors have been widely used as a novel antidiabetic therapy in clinical practice.

Our data indicated that the prevalence of depression symptoms was 11.1%. This prevalence was higher than that reported by other studies conducted in China[3,5]; reasons for this difference could be summarized as follows: (1) our research was not a population-based study—all enrolled subjects visited the Medical Examination Center spontaneously for routine health examinations; (2) the number of women was much higher than the number of men; and (3) we used different diagnostic and screening tools and criteria.

Current collective evidence has suggested that depression is associated with higher levels of inflammation, with perhaps a reduction in NPY in peripheral circulation or CSF.[25–27] In this study, we found that plasma DPP4 activity was significantly and positively associated with PHQ-9 score and depression symptoms in subjects with normal glucose tolerance, consistent with previous studies; such association was paralleled by a significant enhancement in inflammation and a reduction in NPY in peripheral circulation after adjustment for possible confounders, confirming the important role of inflammation and impaired NPY metabolism in the pathogenesis of depression. Although the pathogenesis of increased DPP4 activity with higher risk of depression symptoms in humans remains to be elucidated, we still try to explain this association by asking whether the elevation in DPP4 activity leads to an increased risk of depression or vice versa.

It is generally accepted that depression increases the risk of obesity; there are several plausible explanations for such

Table 3. Adjusted Odds Ratios and 95% Confidence Intervals for Increased Inflammation Markers, PHQ-9 Score, and Decreased NPY According to DPP4 (Categorical and Continuous Variables)

	Categorical Variable				*P* for Trend	Continuous Variable	*P*
	Quartile 1	Quartile 2	Quartile 3	Quartile 4			
Elevated IL-6							
Model 1[a]	1.0	1.44 (0.99–2.10)	1.43 (0.98–2.09)	2.31 (1.61–3.32)	<.001	1.050 (1.031–1.069)	<.001
Model 2[b]	1.0	1.48 (1.01–2.16)	1.46 (0.99–2.14)	2.24 (1.54–3.24)	<.001	1.047 (1.028–1.066)	<.001
Elevated hs-CRP							
Model 1[a]	1.0	1.19 (0.81–1.75)	1.65 (1.14–2.39)	2.41 (1.68–3.45)	<.001	1.051 (1.032–1.070)	<.001
Model 2[b]	1.0	1.23 (0.82–1.82)	1.62 (1.10–2.38)	2.21 (1.52–3.21)	<.001	1.044 (1.024–1.063)	<.001
Decreased NPY							
Model 1[a]	1.0	1.11 (0.78–1.57)	1.05 (0.74–1.49)	1.02 (0.72–1.45)	.950	0.998 (0.980 to 1.016)	.831
Model 2[b]	1.0	1.14 (0.76–1.71)	1.34 (0.88–2.02)	1.57 (1.04–2.38)	.173	1.025 (1.003–1.047)	.025
Elevated PHQ-9 score							
Model 1[a]	1.0	0.82 (0.44–1.53)	1.89 (1.10–3.22)	3.28 (1.98–5.42)	<.001	1.091 (1.064–1.118)	<.001
Model 2[b]	1.0	0.81 (0.43–1.54)	1.56 (0.90–2.71)	2.93 (1.74–4.93)	<.001	1.088(1.060–1.118)	<.001

[a]Model 1 = crude model.
[b]Model 2 = Model 1 + age + gender + BMI + current smoking + alcohol consumption + leisure-time physical activity + marital status + education level + annual income.
Abbreviations: BMI = body mass index, DPP4 = dipeptidyl peptidase-4, hs-CRP = high-sensitivity C-reactive protein, IL-6 = interleukin-6, NPY = neuropeptide Y, PHQ-9 = 9-item Patient Health Questionnaire.

Table 4. Logistic Regression Analysis of the Association of DPP4 Activity and Depression Symptoms[a]

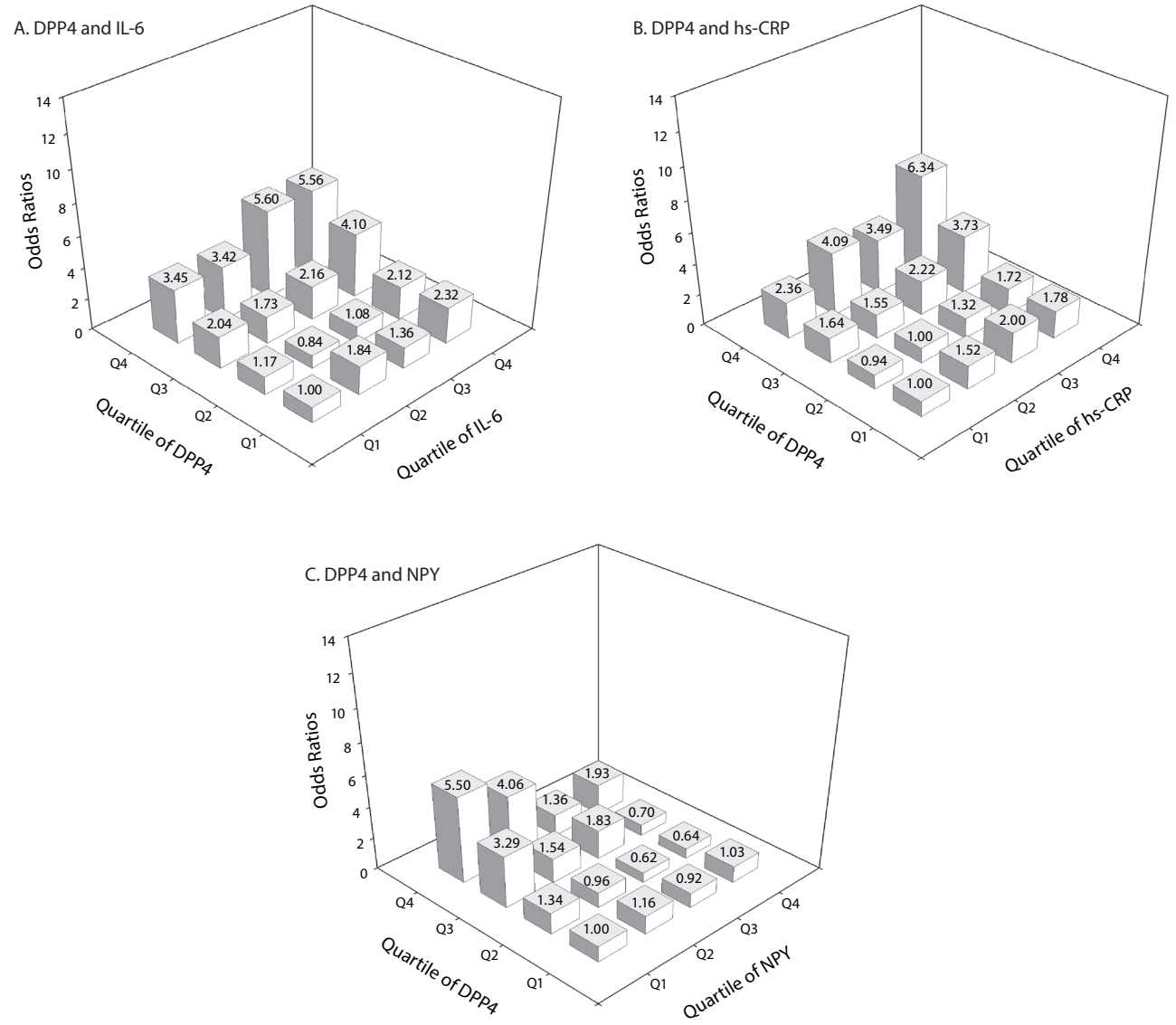
	Categorical Variable				*P* for Trend	Continuous Variable	*P*
	Quartile 1	Quartile 2	Quartile 3	Quartile 4			
DPP4 activity, nmol/min/mL	<11.10	11.11–15.72	15.73–20.99	≥21.00	…	…	…
Depression symptoms, n (%)	23 (6.9%)	19 (5.7%)	41 (12.2%)	65 (19.5%)	…	148 (11.1%)	…
Model 1[b]	1.0	0.82 (0.44–1.53)	1.89 (1.10–3.22)	3.28 (1.98–5.42)	<.001	1.091 (1.064–1.118)	<.001
Model 2[c]	1.0	0.81 (0.43–1.54)	1.56 (0.90–2.71)	2.93 (1.74–4.93)	<.001	1.088 (1.060–1.118)	<.001
Model 3[d]	1.0	0.79 (0.42–1.51)	1.56 (0.90–2.71)	2.83 (1.68–4.77)	<.001	1.087 (1.059–1.116)	<.001
Model 4[e]	1.0	0.77 (0.40–1.46)	1.42 (0.81–2.48)	1.89 (1.09–3.29)	.011	1.058 (1.028–1.088)	<.001

[a]Values shown are odds ratios (with 95% CIs) unless otherwise noted.
[b]Model 1 = crude model.
[c]Model 2 = Model 1 + age + gender + BMI + current smoking + alcohol consumption + leisure-time physical activity + marital status + education level + annual income.
[d]Model 3 = Model 2 + NPY.
[e]Model 4 = Model 3 + IL-6.
Symbol: … = not applicable.
Abbreviations: BMI = body mass index, DPP4 = dipeptidyl peptidase-4, IL-6 = interleukin-6, NPY = neuropeptide Y.

causal association. Depression is associated with disruption to the hypothalamic-pituitary-adrenal axis, which may be involved in the causal link between depression and obesity.[28] Moreover, depression is associated with poor health behaviors (ie, physical inactivity, poor diet, or sleep disturbance), which might increase the risk of obesity. Finally, depressed subjects had a higher prevalence of various comorbidities, and these physical limitations might also be associated with weight gain and obesity. Although we controlled for a large number of diseases and other medical conditions, unmeasured and residual confounding is still possible.[6] A previous study[15] has indicated that DPP4 is a novel adipokine secreted from adipose tissue; similarly, our data also supported an independent and positive relationship between BMI, waist-to-hip ratio, and DPP4 activity. Taken together, it is plausible to speculate that depression-induced obesity leads to an increase in adipose tissue in the body, which further promotes DPP4 secretion from adipose tissue into the circulation. If this speculation is proved by future studies, DPP4 activity might serve as a suitable biomarker to assess the risk of depression in adults.

Since our study is cross-sectional, we cannot draw a causal conclusion that depression promotes the development of obesity and enhances DPP4 secretion from adipose tissue. The parallel increase in DPP4 activity and depression risk could also be interpreted in the opposite way. The proinflammatory role of DPP4 has been well addressed by previous basic research[16]; furthermore, DPP4-induced inflammation has been suggested to play an important role in the development of various low-grade inflammation diseases, such as diabetes, atherosclerosis, etc.[17,18,29] Interestingly, with the deeper and broader research on depression, this psychiatric condition has also been suggested to be associated with inflammation.[7] Immune activation and proinflammatory cytokine (ie, IL-6, hs-CRP, TNF-α, etc) production may be involved in the pathogenesis of depression.[30–36] Consequently, we speculate that DPP4-induced inflammation might also have an impact on the development of depression. In this study, this speculation was further confirmed by our findings that inflammation markers increased significantly with rising DPP4 quartiles;

Figure 1. Adjusted Odds Ratios for Depression Symptoms According to Quartiles[a]



[a]Adjusted for age, gender, body mass index, current smoking, alcohol consumption, leisure-time physical activity, marital status, education level, and annual income.
Abbreviations: DPP4 = dipeptidyl peptidase-4, hs-CRP = high-sensitivity C-reactive protein, IL-6 = interleukin-6, NPY = neuropeptide Y.

more importantly, the risk of depression symptoms was more pronounced among patients with rising DPP4 activity and higher levels of IL-6 and hs-CRP. Since DPP4 may be a pathogenic factor for inflammation, it could also promote depression development by activating the immune system and promoting proinflammatory cytokine secretion. However, this speculation remains to be clarified by further research because of the cross-sectional nature of our study. In addition, we found that the ORs for depression symptoms according to DPP4 quartiles were not substantially attenuated by additional adjustment for inflammatory markers; even within the lowest IL-6 and hs-CRP quartile, the risks for depression symptoms were 2.36- to 3.45-fold higher in the highest DPP4 quartile than in the lowest quartile, suggesting that elevated DPP4 activity could promote depression development through a pathway not fully overlapping with inflammation.

Altered NPY levels in CSF or peripheral circulation have also been proved to be associated with depression. Hashimoto et al[27] found that impaired NPY and reduced plasma NPY in patients with major depressive disorder could be involved in the pathogenesis of major depressive disorder. Furthermore, significantly lower CSF NPY was found in depressed patients in the study by Hou and colleagues.[26] However, another study[37] failed to observe any significant differences in NPY levels. In our study, our data also indicated a nonsignificant difference in peripheral NPY levels between subjects with depression and those without depression. These apparent discrepancies could be due to methodological differences or more likely to the heterogeneous nature of the disease.

Moreover, peripheral NPY has not been proven to reflect NPY in the CNS.[25] A recent study by Baker et al[38] reported that levels of NPY from CSF and plasma collected concurrently showed no cross-correlation. In conclusion, although NPY from plasma or serum has been used previously in several psychiatric conditions, its validity as an accurate biomarker is still questionable.

In addition to the nonsignificant differences in NPY levels in the 2 categories in our study, we found no negative association between DPP4 activity and NPY levels as estimated by Pearson correlation analysis. However, when partial correlation analysis was used to reassess this relationship between DPP4 activity and NPY, a negative and independent association was found between these 2 variables after adjustment for BMI. Moreover, a similar trend was also found when using multivariate logistic regression analysis to evaluate the ORs for decreased NPY according to DPP4 quartiles. The possible explanation for such an interesting relationship between DPP4 activity and NPY might be due to 1 of the confounders in our study—obesity. Previous studies[39] have demonstrated a positive relationship between NPY levels and risk of obesity; our data also supported a strong association between DPP4 activity and BMI. Consequently, we speculate that obesity accompanied with increased levels of NPY might mask the truly inverse relationship between DPP4 and NPY in our study. Although the ORs for depression symptoms got more pronounced with higher DPP4 activity and lower NPY after adjustment for possible confounders including BMI, indicating an important role of impaired NPY metabolism in the pathogenesis of depression, NPY levels in the peripheral circulation might not be suitable to serve as a biomarker to assess the depression risk.

Some limitations of our study should also be considered. First, this study is an epidemiologic cross-sectional study that somehow fails to address the causal role of DPP4 in the pathogenesis of depression, which needs to be elucidated by further investigation. Second, we did not confirm a definitive diagnosis of depression. However, the psychometric properties of the PHQ-9 are well documented, and it is increasingly being used as a brief diagnostic and severity measure of depression in research and clinical practice.[40,41] For those identified with clinically significant depressive symptoms (PHQ-9 score ≥ 10), a visit to a psychiatrist for further evaluation and treatment was suggested. Third, NPY levels in CSF were not determined in our study, only plasma levels of NPY were available; the link between DPP4 and NPY should be exercised with caution since correlation between those 2 markers appeared to be weak. Finally, only plasma levels of inflammatory markers were measured in this study; peripheral markers of inflammation may not reflect actual brain inflammation.

This study provides the first evidence that increased DPP4 activity accompanied with enhanced inflammation and decreased NPY levels are independently and positively associated with PHQ-9 score and depression symptoms in middle-aged and older adults. From a clinical perspective, we speculate that the underlying mechanisms may be partly explained by mutual influence between inflammation, NPY, and DPP4. Moreover, independent of the mechanism, elevated DPP4 activity in adults could be a novel biomarker to assess the risk of depression. In addition, if increased DPP4 activity could increase the risk of depression, DPP4 activity might serve as a suitable therapeutic target for the prevention and treatment of depression in clinical practice. However, further research is still needed in this regard.

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Drug names: clonidine (Catapres and others), isoniazid (Isoniazid and others), levodopa (Sinemet and others), phenytoin (Dilantin, Phenytek, and others), reserpine (Serpasil and others).

Author contributions: Study design, conduct, data collection, data analysis, and interpretation: Drs Zheng, Y. Liu , Qin, Zhang, G. Li, and Q. Li. Data analysis: Drs Zheng, Qin, and G. Li. Drafting manuscript: Drs Zheng and Yang. Approving final manuscript: Drs Zheng, Zhang, and H. Liu. Drs Zheng and Q. Li take responsibility for the integrity of data analysis.

Potential conflicts of interest: None reported.

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Ethical standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Increased Dipeptidyl Peptidase-4 Activity Is Associated With High Prevalence of Depression in Middle-Aged and Older Adults: A Cross-Sectional Study

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List of Supplementary Material for the article

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Supplementary eTable1. Characteristics of the 1335 participants by depression symptoms.

	Depression symptoms		
	No	Yes	P Value
n	1187	148	-
Age (years)	58.6±7.6	59.5±8.1	0.155
Percent women (%)	67.0	78.4	0.005
BMI (kg/m^2)	23.2±3.7	24.3±4.1	0.001
WHR	0.87±0.08	0.90±0.09	<0.001
Current smoking (%)	18.2	26.4	0.017
Alcohol consumption (%)	18.4	23.6	0.129
Leisure-time physical activity (%)	62.3	50.7	0.006
Marital status			0.147
Married (%)	91.7	87.2	
Single (%)	1.3	1.4	
Widowed (%)	7.0	11.5	
Education level			0.331
≦Primary school	44.1	42.6	
Middle school	45.2	42.6	
≥High school	10.8	14.9	
Annual income, RMB			0.003
≦5000	4.5	9.5	
5000-30000	45.9	52.7	
>30000	49.6	37.8	
IL-6(pg/ml)	1.31±0.31	1.66±0.78	<0.001
hs-CRP(mg/L)	1.18±0.23	1.40±0.45	<0.001
NPY(ng/ml)	0.149±0.045	0.154±0.052	0.260
DPP4 activity(nmol/min/ml)	15.85±6.71	20.16±7.51	<0.001

Supplementary eTable2. Trend associations between DPP4 quartiles and IL-6, hs-CRP, NPY and categorically defined depression.

	DPP4 quartiles					
	Q1	Q2	Q3	Q4	χ^2	P
IL-6 (pg/ml) [a]	1.25±0.27	1.31±0.30	1.33±0.31	1.50±0.60	31.76	<0.001
hs-CRP (mg/L) [a]	1.14±0.24	1.16±0.22	1.22±0.21	1.31±0.36	59.24	<0.001
NPY (ng/ml) [a]	0.150±0.045	0.145±0.040	0.154±0.051	0.151±0.044	3.49	0.323
PHQ-9 score [a]	2.33±3.20	2.46±3.38	3.83±4.44	5.60±5.28	145.70	<0.001
Depression (%)[b]	6.9	5.7	12.2	19.5	34.91	<0.001

[a] Kruskal-Wallis test
[b] Cochran Armitage test

Supplementary eFigure1: Trial profile