Appetite Hormone Regulation Biotypes of Major Affective Disorders in Proinflammatory Cytokines and Executive Function

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Abstract

Backgrounds: Evidence indicates that appetite hormones, namely, insulin, leptin, and adiponectin, play crucial roles in the pathophysiology of major affective disorders. However, whether appetite hormone regulation biotypes differ among patients with major affective disorders remains unclear.

Methods: A total of 501 patients with major affective disorders (278 with bipolar disorder and 223 with major depressive disorder) were enrolled between 2018 and 2022 and clustered into biotype groups on the basis of fasting insulin, leptin, and adiponectin levels. Major affective disorder diagnoses were based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition. All participants underwent the Wisconsin Card Sorting Test and proinflammatory cytokine assessment.

Results: A k-means cluster analysis identified 3 biotype groups based on appetite hormone levels: a high insulin/leptin and low adiponectin group, a low insulin/leptin and high adiponectin group, and an intermediate group. The high insulin/leptin and low adiponectin group exhibited poorer performance on the Wisconsin Card Sorting Test and had higher C-reactive protein and tumor necrosis factor-α levels than did the other biotype groups after adjusting for diagnosis, body mass index, clinical symptoms, and psychotropic medication use.

Discussion: This study identified 3 appetite hormone regulation biotypes among patients with major affective disorders. These biotypes were associated with proinflammatory cytokine profiles and executive function.

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Studies have indicated that appetite hormones, such as insulin, leptin, and adiponectin, are involved in the pathomechanisms underlying bipolar disorder, major depressive disorder, and associated cognitive impairments.[1–4] Insulin is associated with neuroprotection, cognitive function, memory, synaptic plasticity, and selective attention and has anti-inflammatory effects. Leptin is believed to regulate neuronal excitability and synaptic plasticity in the hippocampus.[5] Resistance to leptin and insulin, characterized by increased synthesis and release of these hormones from adipocytes and pancreatic β-cells, respectively, can affect various physiological processes, including cognition and inflammation.[5–7] Adiponectin, exclusively secreted by adipocytes, plays a crucial role in energy homeostasis and glucose and lipid regulation and exhibits anti-inflammatory effects.[6,8] Adiponectin also regulates hippocampal cell proliferation.[9] In addition, previous studies have shown an association between the executive dysfunction and the appetite hormone regulation disturbance, as well as increased proinflammatory cytokines.[10–12] For example, Mac Giollabhui et al[12] indicated that more severe depressive symptoms and obesity may disrupt executive functioning via elevated levels of interleukin (IL)-6.

Increasing evidence indicates that the vegetative symptoms of a major depressive episode, including appetite and weight disturbances, fatigue, and loss of energy, are particularly associated with the dysregulation of appetite hormones.[13,14] Simmons et al[13] examined metabolic blood markers in patients with depression experiencing increased or decreased appetite and body weight. They found that patients with increased appetite and body weight exhibited more substantial metabolic dysregulation, including higher insulin and leptin levels and insulin resistance, compared with those

Clinical Points

- Our study was the first to classify the appetite hormone regulation biotypes of major affective disorders.
- The high insulin/leptin and low adiponectin group was related to poor executive function.
- The high insulin/leptin and low adiponectin group exhibited the highest levels of C-reactive protein and tumor necrosis factor-α.

with decreased appetite and body weight.[13] Everson-Rose et al[15] revealed that depressive symptoms, which were measured using the Epidemiologic Studies Depression scale, were associated with lower adiponectin levels among individuals with major depressive disorder. In addition, the study noted that increased appetite and body weight were associated with increased levels of C-reactive protein (CRP).[13] A UK biobank study involving 30,069 individuals who had experienced a major depressive episode revealed that polygenic risk scores for leptin and CRP were linked to depression with increased body weight. Of these individuals, 1,854 had increased body weight, and 28,215 did not have increased body weight.[16] Badini et al[16] found a similar genetic pattern of immune-metabolic traits in individuals with major depressive episodes, regardless of whether the diagnosis was bipolar disorder or major depressive disorder. These findings suggest that the vegetative symptom subtypes of major depressive episodes, such as increased or decreased appetite and body weight, may indicate the presence of distinct biotypes related to appetite hormone regulation.[13,14,16]

The metabolic overdrive hypothesis, which posits a shared dysfunction of insulin-signaling mechanisms in both bipolar mania and depression, may indicate the presence of distinct appetite hormone biotypes in bipolar disorder.[17] Calkin et al[18] reported that patients with bipolar disorder and insulin resistance had 3 times higher odds of experiencing a chronic or rapid cycling course of bipolar disorder than did patients without insulin resistance. In addition, patients with insulin resistance were found to have a higher body mass index (BMI) than were those without insulin resistance (31.6 vs 27.4).[18] An exploratory study involving 42 patients with bipolar mania found that those with hyperinsulinemia had higher levels of insulin and leptin during remission than did those without hyperinsulinemia, even after adequate mood stabilizer treatment.[19] On the basis of these findings, we hypothesize the existence of high insulin/leptin and low insulin/leptin subtypes of major affective disorders.

In the present study, we enrolled 501 patients with major affective disorders to examine the regulation of 3 appetite hormones, namely, insulin, leptin, and adiponectin. We performed k-means cluster analysis to identify potential biotypes based on appetite hormone regulation within this population. Studies have demonstrated that appetite hormones are associated with proinflammatory cytokines and play a key role in cognitive function. In the present study, we explored how different biotypes affect the levels of proinflammatory cytokines and cognitive function among patients with major affective disorders.

METHODS

Participants

The Taipei Veterans General Hospital Institutional Review Boards authorized this study in accordance with the Declaration of Helsinki. Written informed consents were provided by each participant as well as the parents of the adolescent participants. The current study involved the enrollment of 501 individuals, aged 12–64, who were diagnosed with major affective disorders, including major depressive disorder (n = 223) and bipolar disorder (n = 278). All participants were enrolled between 2018 and 2022. Major affective disorder diagnoses were based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition. The exclusion criteria included severe medical conditions including epilepsy, autoimmune illnesses, diabetes mellitus, and neurovascular diseases, as well as other severe mental health conditions like schizophrenia, eating disorders, neurodevelopmental disorders, organic mental disorders, and alcohol and substance use disorders. All patients were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMRS).[20,21] Additionally, the current investigation used the 3-depressive-symptom domain model of the MADRS, a well-validated method for studying Asian patients with major affective disorders in prior studies.[22] It includes dysphoria, retardation, and vegetative domains. The dysphoria domain is composed of MADRS items 2 (reported sadness), 9 (pessimistic thoughts), and 10 (suicidal thoughts). The retardation domain comprises MADRS items 1 (apparent sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel). Finally, the vegetative domain includes MADRS items 3 (inner tension), 4 (reduced sleep), 5 (reduced appetite).[22,23] Finally, we also included healthy individuals (n = 80) who were free of the mental and physical conditions listed above.

Measurement of Proinflammatory Cytokines and Appetite Hormones

Samples of fasting serum were collected between 9:00 AM and 12:00 PM in serum separator tubes, clotted

for 30 minutes, and then stored at −80°C until needed. Enzyme-linked immunosorbent assay (ELISA) kits (R&D systems, Minneapolis, MN, USA) were utilized to quantify the proinflammatory cytokines tumor necrosis factor (TNF)-α and CRP for each participant. Leptin, insulin, and adiponectin—3 appetite hormones—were also investigated. A radioimmunoassay kit (Coat-A Count Insulin; Diagnostic Product Corporation, Los Angeles, CA, USA) was used to measure the levels of insulin. A quantitative Human Adiponectin ELISA Kit (B-Bridge International, Inc, Mountain View, CA, USA) was used to assess the levels of adiponectin. A Human Leptin Quantikine ELISA Kit (R&D Systems, model: DLP00; USA) was used to measure the levels of leptin. The vendor's instructions were followed for each experiment. An ELISA plate reader equipped with a Bio-Tek Power Wave Xs and Bio-Tek's KC junior software was used to measure and evaluate the final absorbance of each combination sample at 450 nm (Winooski, VT, USA). The standard range was considered as specified in the vendor's instructions. A linear regression R-square value of at least 0.95 was considered a reliable standard curve.

Assessment of Executive Function

The Wisconsin Card Sorting Test (WCST) was used in this study to assess executive function.[24] Strategic planning, well-organized searching, using environmental feedback to shift cognitive sets, guiding behavior toward a goal, and controlling impulsive responses were all necessary for WCST. WCST was frequently employed in our previous research.[25,26]

Statistical Analysis

For between-group comparisons, the F test was used for continuous variables and Pearson test was used for categorical variables. First, we used the generalized linear models (GLM) with an adjustment of demographic data (age, sex, and BMI) to compare the appetite hormone levels between the patient and healthy control groups. We also compared the executive function between the patient and control groups using the GLM with an additional adjustment of education. Second, we carried out a k-means cluster analysis based on the levels of appetite hormones, namely insulin, leptin, and adiponectin, among patients with major affective disorders.[27,28] An a priori search was conducted using the elbow method to determine the optimal number of clusters between 1 and 5, and 3 was found to be the most optimal number.[27,28] The Elbow Method is a visual approach to determining the optimal number of clusters by plotting the within-cluster sum of squares (WCSS) against the number of clusters (k). The ideal number of clusters is identified at the elbow point, where the rate of decrease in WCSS slows significantly. This indicates the point where adding more clusters provides minimal improvement in explaining the variance within the data, balancing model simplicity and accuracy.[27,28] The WCSSs for 2, 3, and 4 clusters were 1,056.84, 736.65, and 483.77, respectively, in the present study. So, 3 appetite hormone regulation biotypes included the high insulin/leptin and low adiponectin group, the low insulin/leptin and high adiponectin group, and the intermediate group. Finally, the serum levels of CRP and TNF-α did not meet the definition of normal distribution based on the Kolmogorov-Smirnov test, so they were transformed by log. We further estimated the log-transformed proinflammatory cytokine levels and executive function between 3 biotype subgroups using the GLM with an adjustment for age, sex, education, BMI, diagnosis, clinical symptoms (MADRS, YMRS), and medications (antidepressants, mood stabilizers, and second-generation antipsychotics). P values with 2 tails less than .05 were regarded as statistically significant. All data processing and statistical analyses were performed using the SPSS version 17 software (SPSS Inc).

RESULTS

In all, we enrolled 501 patients (male vs female = 348 vs 153) with major affective disorders at a mean age of 33.53 years and mean total MADRS and YMRS scores of 16.02 and 2.83 in the present study (Table 1). Age, sex, and BMI did not differ between the patient and healthy control groups (Table 1). Supplementary Figures 1 and 2 show that patients had higher levels of insulin ($P = .056$), leptin ($P = .002$), and TNF-α ($P = .030$) than did the controls after adjusting for age, sex, and BMI. In addition, patients with major affective disorder performed worse in the WCST (all $P < .05$) compared with the control group (Supplementary Figure 2). Furthermore, Table 1 also shows that 3 appetite hormone regulation biotypes did not differ in age, education, and diagnosis, age at onset, and total MADRS and YMRS scores. The depressive symptom domains, namely, dysphoria, retardation, and vegetative domains, did not differ between the 3 biotypes (Table 1). The high insulin/leptin and low adiponectin biotype was most obese compared with the other biotypes (Table 1).

Among the 3 appetite hormone regulation biotypes of major affective disorders, the high insulin/leptin and low adiponectin group exhibited higher % perseverative errors ($P = .022$ and .024) and lower numbers of categories completed ($P = .008$ and .015) in the WCST compared with the low insulin/leptin and high adiponectin and the intermediate groups (Figure 1). Furthermore, the highest log-transformed CRP levels were noted ($P = .003$) in the high insulin/leptin and low adiponectin group compared with the intermediate and the low insulin/leptin and high adiponectin groups (Figure 2). The high insulin/leptin and low adiponectin

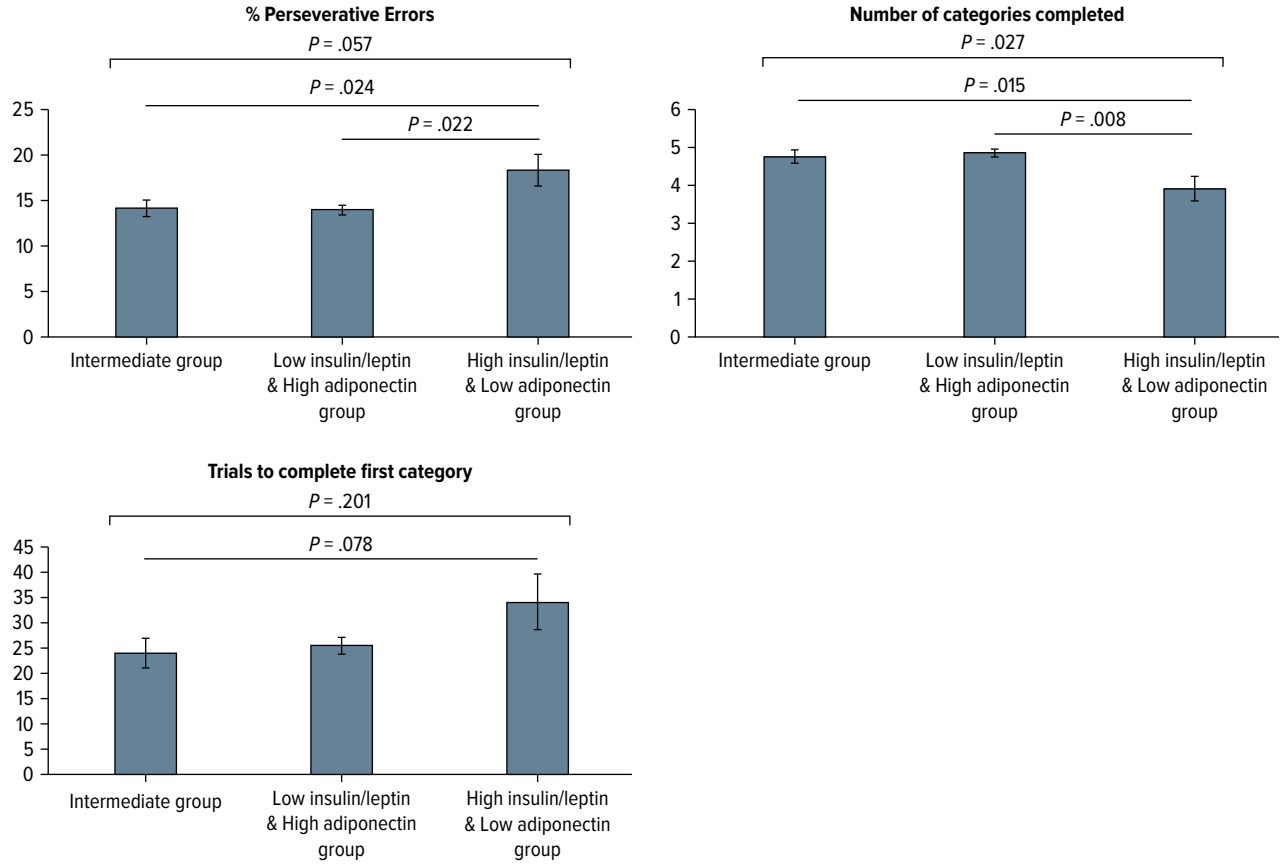
Table 1.

Demographic and Clinical Characteristics Between Groups

				Patients (n = 501)				
	Healthy controls (n = 80)	Patients (n = 501)	*P* value	Intermediate group (A) (n = 109)	Low insulin/leptin and high adiponectin group (B) (n = 357)	High insulin/leptin and low adiponectin group (C) (n = 35)	*P* value	Post hoc
Age, y, mean (SD, range)	32.10 (9.85, 15–61)	33.53 (14.52, 12–64)	.395	32.47 (15.07, 13–64)	34.09 (14.15, 12–64)	31.17 (16.38, 12–62)	.362	
Sex, n (%)			.155				<.001	
Female	49 (61.3)	348 (69.5)		99 (90.8)	217 (60.8)	32 (91.4)		
Male	31 (38.8)	153 (30.5)		10 (9.2)	140 (39.2)	3 (8.6)		
BMI, mean (SD, range)	23.12 (3.66, 17.36–35.72)	23.95 (4.84, 14.39–42.94)	.144	25.96 (4.69, 14.39–41.57)	22.73 (4.12, 14.88–38.91)	30.13 (5.46, 17.97–42.94)	<.001	C>A>B
Education, y, mean (SD, range)	15.96 (1.99, 12–23)	13.06 (3.11, 6–23)	<.001	12.76 (3.39, 6–18)	13.21 (3.00, 6–23)	12.57 (3.27, 6–18)	.267	
Diagnosis, n (%)							.649	
BD		278 (55.5)		59 (54.1)	197 (55.2)	22 (62.9)		
MDD		223 (44.5)		50 (45.9)	160 (44.8)	13 (37.1)		
Age at onset, years, mean (SD, range)		27.57 (12.43, 12–64)		26.62 (12.62, 12–62)	28.15 (12.43, 12–63)	24.23 (12.06, 12–59)	.142	
MADRS scores, mean (SD, range)		16.02 (10.44, 0–45)		15.24 (10.24, 0–40)	16.35 (10.35, 0–45)	15.14 (12.03, 0–36)	.546	
Dysphoria		4.54 (3.57, 0–13)		4.46 (3.59, 0–12)	4.60 (3.53, 0–13)	4.29 (3.9, 0–12)	.852	
Retardation		7.26 (4.60, 0–20)		7.00 (4.47, 0–16)	7.38 (4.59, 0–20)	6.80 (5.24, 0–16)	.629	
Vegetative		4.22 (3.27, 0–15)		3.78 (3.06, 0–12)	4.38 (3.30, 0–15)	4.06 (3.54, 0–12)	.239	
YMRS scores, mean (SD, range)		2.83 (4.18)		2.46 (4.16)	3.01 (4.33)	2.11 (2.18)	.279	
Medications, n (%)								
Antidepressants		271 (54.1)		55 (50.5)	201 (56.3)	15 (42.9)	.216	
Mood stabilizers		177 (35.3)		31 (28.4)	128 (35.9)	18 (51.4)	.043	
SGA		264 (52.7)		58 (53.2)	182 (51.0)	24 (68.6)	.137	
Appetite hormones, mean (SD, range)								
Insulin (μU/mL)	7.45 (14.09, 0.09–105.07)	13.92 (28.94, 0.05–298.67)	.050	18.39 (30.73, 0.22–149.82)	9.30 (18.25, 0.05–176.19)	47.05 (66.42, 2.07–298.67)	<.001	C>A>B
Leptin (pg/mL)	12,810.95 (12,434.65, 1,048.20–69,451.51)	11,636.81 (10,910.08, 141.10–76,570.07)	.381	19,895.52 (4,901.86, 13,041.83–30,550.20)	6,202.51 (3,374.04, 141.10–13,358.00)	41,346.64 (10,841.49, 31,075.94–76,570.07)	<.001	C>A>B
Adiponectin (ng/mL)	7,588.73 (21,439.14, 94.43–19,097.10)	5,774.58 (4,748.53, 75.10–25,420.88)	.097	5,614.62 (4,874.57, 510.70–25,420.88)	6,038.83 (4,804.33, 75.10–25,291.00)	3,577.36 (2,942.23, 671.12–14,951.80)	.012	C<A~B

Abbreviations: BD = bipolar disorder, BMI = body mass index, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, SGA = second-generation antipsychotics, YMRS = Young Mania Rating Scale.

Figure 1.
Generalized Linear Models for Estimated Executive Function Between 3 Patient Subgroups[a]



[a]Adjusting for age, sex, education, BMI, diagnosis, clinical symptoms (MADRS, YMRS), and medications (antidepressants, mood stabilizers, SGA).
Abbreviations: BMI = body mass index, MADRS = Montgomery-Asberg Depression Rating Scale, SGA = second generation antipsychotics, YMRS = Young Mania Rating Scale.

group exhibited the highest log-transformed levels of TNF-α (P = .010) compared with the other 2 biotypes (Figure 2).

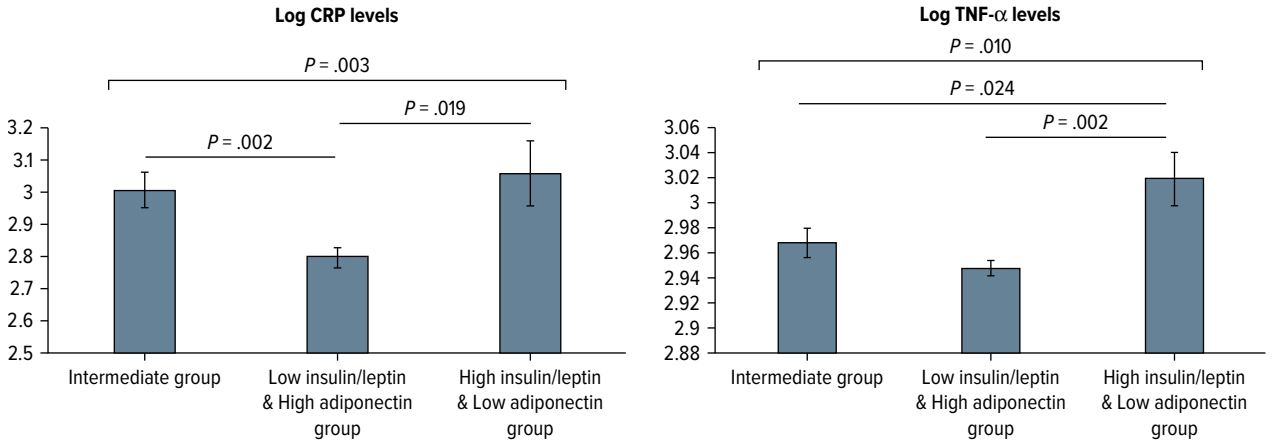
DISCUSSION

We used k-means cluster analysis and categorized patients into 3 appetite hormone regulation biotype groups: a high insulin/leptin and low adiponectin group, a low insulin/leptin and high adiponectin group, and an intermediate group. The biotypes corresponded to BMI phenotypes of obese (approximately 30), normal (approximately 22), and overweight (approximately 25), respectively. No differences in clinical symptoms were observed between the biotypes. The high insulin/leptin and low adiponectin group exhibited poorer performance in the executive function test and had higher levels of proinflammatory cytokines (CRP and TNF-α) than did the other 2 groups, even after adjusting for BMI, diagnoses, mood symptoms, and medications.

Cognitive flexibility, as indicated by the percentage of perseverative errors and the number of categories completed in the WCST, is a key aspect of executive function.[29,30] Increasing evidence suggested that cognitive inflexibility was associated with various mental health adversities, including decreased problem-solving function and impaired strategy updating function.[31] A meta-analysis involving 1,145 individuals with obesity and 382 individuals with overweight demonstrated that participants with obesity exhibited poorer performance than did those with normal weight in tasks assessing cognitive flexibility.[32] Cserjési et al[33] reported that decreased cognitive flexibility was particularly observed in individuals with obesity experiencing depressive mood. Shapiro et al[34] found an association between higher fasting glucose levels and decreased cognitive flexibility among healthy individuals. Wroolie et al[35] observed a relationship between insulin resistance and decreased cognitive flexibility, especially in individuals with depression aged <45 years. A Scottish cohort study[36] involving 1,057 individuals with type 2 diabetes revealed that higher leptin levels were associated with poorer

Figure 2.

Generalized Linear Models for Estimated Log-Transformed Proinflammatory Cytokine Levels Between 3 Patient Subgroups[a]



[a]Adjusting for age, sex, education, BMI, diagnosis, clinical symptoms (MADRS, YMRS), and medications (antidepressants, mood stabilizers, SGA).
Abbreviations: BMI = body mass index, CRP = C-reactive protein, MADRS = Montgomery-Asberg Depression Rating Scale, SGA = second generation antipsychotics, TNF-α = tumor necrosis factor-α, YMRS = Young Mania Rating Scale.

overall cognitive function, particularly in mental flexibility and executive function. Schuur et al[37] examined the metabolic profiles and cognitive function of 1,898 mid-life adults (mean age 48 years) and found that individuals with obesity had insulin resistance, lower adiponectin levels, and higher CRP levels. They also identified a correlation between insulin resistance and poor executive function.[37] Our findings suggest that a small subset of patients with major affective disorders who experienced prominent appetite hormone dysregulation (high insulin, high leptin, and low adiponectin) exhibited significant impairment in executive function, specifically cognitive flexibility, independent of mood symptoms.

Increasing evidence has suggested a strong association between appetite hormone dysregulation and proinflammatory cytokines.[13,14,16,38] de Melo et al[39] proposed a shared metabolic (insulin resistance) and immune-inflammatory (low-grade systemic inflammation) pathway underlying mood disorders (bipolar disorder and major depressive disorder) and metabolic syndrome (obesity). A neuroimaging study found that decreased reward-related corticostriatal functional connectivity was associated with anhedonia, psychomotor slowing, and elevated CRP levels in patients with major depressive disorder.[40] Goldsmith et al[41] demonstrated that a composite score of 5 glucose-related markers (nonfasting glucose, insulin, leptin, adiponectin, and resistin) was negatively correlated with reward-related corticostriatal functional connectivity among patients with major depressive disorder. They suggested that inflammation and metabolic dysfunction contribute to deficits in reward-related brain circuits and the clinical symptoms of major affective disorders.[41] Badin et al[16] highlighted that a genetic predisposition to immunometabolic risk, characterized by high leptin and CRP levels, plays a crucial role in the neurovegetative symptoms of major depressive episodes in both bipolar disorder and major depressive disorder. Our findings are in line with those of Goldsmith et al[41] and Badin et al[16] and support the shared metabolic and immune-inflammatory model proposed by de Melo et al.[39] Specifically, in the present study, we found that patients with major affective disorders in the high insulin/leptin and low adiponectin group had a higher BMI and CRP and TNF-α levels than did those in the other 2 biotype groups.

We addressed several limitations in this study. First, other studies have reported the detrimental effects of psychotropic medications, particularly mood stabilizers and atypical antipsychotics, on appetite hormone profiles.[42–44] In the present study, we continued psychotropic medications for ethical reasons because discontinuing them could be harmful to patients with major affective disorders. This approach also provided more realistic data. To account for these factors, we adjusted for the use of psychotropic medications when comparing executive function and proinflammatory cytokines between biotypes. Future studies involving drug-free patients may be necessary to validate our findings. Second, the classification of appetite hormone regulation biotypes in this study was based on the levels of insulin, leptin, and adiponectin. Future studies should explore whether the inclusion of additional appetite regulation hormones, such as ghrelin, resistin, cholecystokinin, and glucagon-like peptide-1, can enhance the accuracy of biotype classification.[45] Third, we

only assessed executive function using the WCST in the present study. Future studies should use other neuropsychological measures to elucidate the association between appetite hormone regulation biotypes and other neurocognitive functions, such as inhibitory control function. Fourth, our finding revealed that the patients in the high insulin/leptin and low adiponectin group exhibited the highest BMI levels compared with patients in the other 2 biotype groups. Previous studies have shown the benefit of lifestyle and behavioral modification, as well as several medications (ie, metformin and glucagon-like peptide-1 receptor agonists) for obese patients with major affective disorders.[44,46] Our study may inspire the clinicians and researchers to further investigate whether those strategies may be beneficial for the patients with high insulin/leptin levels and low adiponectin levels. For example, Calkin et al[47] discovered that metformin may improve clinical outcomes, such as decreased depressive symptoms and increased overall function, among patients with bipolar disorder who had insulin resistance. Fifth, the appetite hormone regulation biotypes were classified by the data-driven k-means cluster analysis but not by the clear cut-off points of appetite hormone levels in the present study. Our exploratory study may inspire clinicians to further investigate the optimal cut-off levels of appetite hormones for the definition of appetite hormone regulation biotypes. Sixth, the face validity of the vegetative symptoms was not high based on Suzuki et al.'s[22] 3-depressive-symptom domain model of the MADRS. Further studies using the vegetative symptom-specific measures would be necessary to elucidate an association between the appetite hormone regulation biotypes and vegetative symptoms of depression. Seventh, our study only analyzed the CRP and TNF-α levels between 3 appetite hormone regulation biotypes. Further studies would be required to elucidate the role of appetite hormone regulation biotypes on other cytokines, such as IL-2 and IL-6. In addition, the fasting serum levels of selected biomarkers were only measured once using the corresponding ELISA kits. Further studies would be required to validate our findings. Eighth, only 65 (13%) adolescents with major affective disorder were included in our total sample of 501 patients. Due to the limited statistical power related to the small sample size, we did not perform additional subanalyses based on the adolescent and adult groups. Further studies with a large sample of adolescent subjects would be required to validate our findings. Ninth, the present study focused on the appetite hormone regulation biotypes of major affective disorders after adjusting for the affective disorder diagnoses. Further studies would be necessary to determine whether the appetite hormone regulation biotypes may differ among major depressive disorder, bipolar I disorder, and bipolar II disorder. Tenth, we found no significant differences in clinical symptoms between the 3 appetite hormone regulation biotypes, although the high insulin/leptin and low adiponectin biotype was associated with poor executive function and increased levels of proinflammatory cytokines. Our findings may imply evidence that major affective disorders are heterogeneous conditions with complicated etiologies. A single pathomechanism, such as the appetite hormone dysregulation in the present study, may not comprehensively explain the clinical symptoms of major affective disorders. Finally, the patient sample of our study was Taiwanese, which may limit generalization of the findings to other ethnic/national groups. Further research on other ethnic groups would be necessary to validate our findings.

In conclusion, major affective disorders can be classified into 3 appetite hormone regulation biotype groups: a high insulin/leptin and low adiponectin group, a low insulin/leptin and high adiponectin group, and an intermediate group. Among these groups, the high insulin/leptin and low adiponectin group exhibited the worst executive function (cognitive flexibility) and the highest proinflammatory cytokine levels. Appetite hormone regulation biotypes may assist clinicians to choose optimal medications for patients with major affective disorders. For example, atypical antipsychotics of "-pine" may be the least choice for patients with high insulin/leptin levels and low adiponectin levels. Further research is needed to determine whether novel treatments targeting appetite hormone dysregulation could be beneficial for patients with this biotype.

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Supplementary Material

Article Title: Appetite Hormone Regulation Biotypes of Major Affective Disorders in Proinflammatory Cytokines and Executive Function

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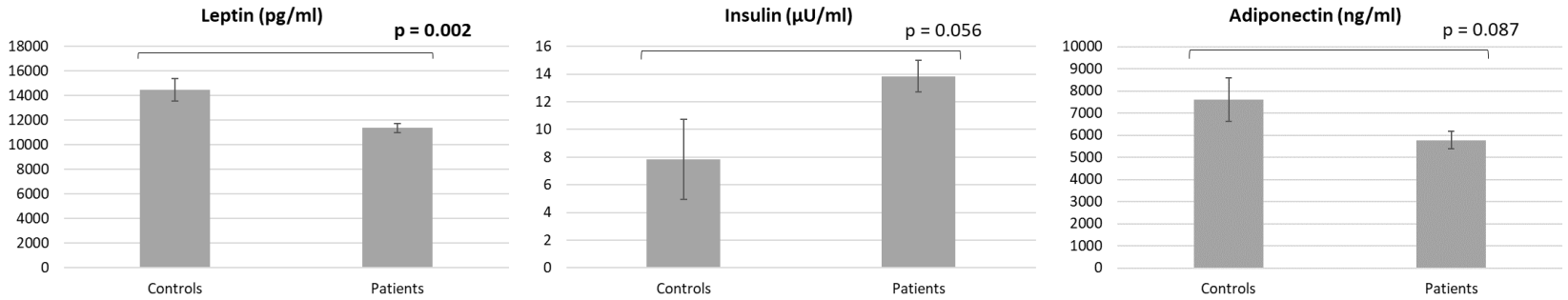
LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Figure 1** GLMs for Estimated Appetite Hormone Levels Between the Control and Patient Groups
2. **Figure 2** GLMs for Estimated Proinflammatory Cytokine Levels and Executive Function Between the Control and Patient Groups

DISCLAIMER

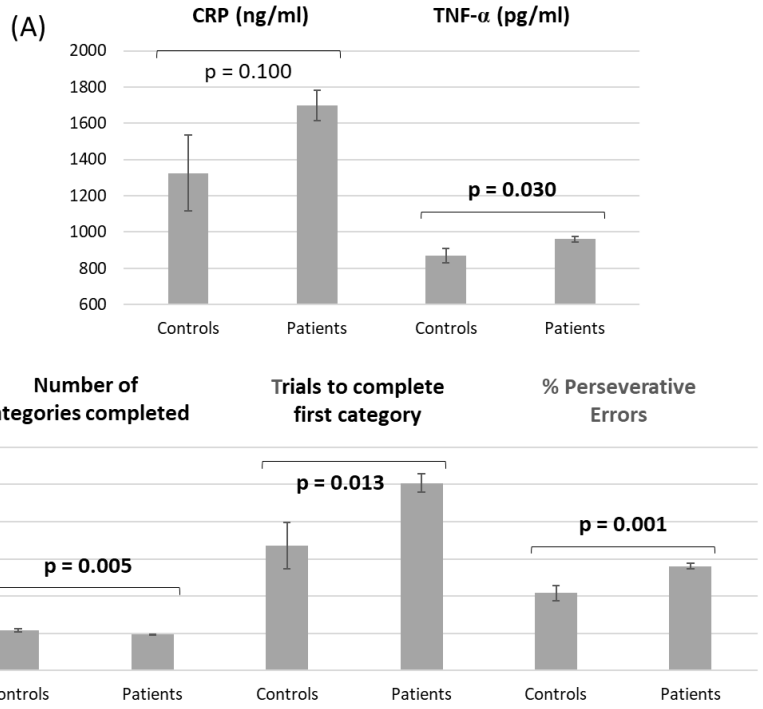
This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary figure 1. GLMs for estimated appetite hormone levels between the control and patient groups



Note: adjusting for age, sex, and BMI.

Supplementary figure 2. GLMs for estimated proinflammatory cytokine levels and executive function between the control and patient groups



Note: A: adjusting for age, sex, and BMI: B: adjusting for age, sex, BMI, and education.