RELATIONSHIP BETWEEN BODY MASS INDEX AND EXTRAPYRAMIDAL SYMPTOMS IN ASIAN PATIENTS WITH SCHIZOPHRENIA: THE RESEARCH ON ASIAN PSYCHOTROPIC PRESCRIPTION PATTERNS FOR ANTIPSYCHOTICS (REAP-AP)

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SUMMARY

Background: *Although an inverse relationship between body mass index (BMI) and Parkinson disease (PD) has been repeatedly reported, to our knowledge, the relationship between BMI and antipsychotic-induced extrapyramidal symptoms (EPS) has rarely been studied in patients with schizophrenia. Our study aimed to evaluate the relationship between BMI and EPS in patients with schizophrenia.*

Subjects and methods: *Using data from the Research on Asian Psychotropic Prescription Patterns for Antipsychotics (REAP-AP) study, we compared the prevalence of EPS in 1448 schizophrenia patients stratified as underweight, normal range, overweight pre-obese, overweight obese I, overweight obese II, and overweight obese III according to the World Health Organization (WHO) classification system for body weight status, and with underweight, normal range, overweight at risk, overweight obese I, and overweight obese II according to the Asia-Pacific obesity classification.*

Results: *In the first step of the WHO classification system for body weight status, adjusting for the potential effects of confounding factors, the multinomial logistic regression model revealed that underweight was significantly associated with greater rates of bradykinesia and muscle rigidity, and a lower rate of gait disturbance. In the second step of the Asia-Pacific obesity classification, adjusting for the potential effects of confounding factors, the multinomial logistic regression model revealed that underweight was significantly associated with a higher rate of muscle rigidity.*

Conclusion: *Findings of the present study consistently revealed that underweight was associated with a greater rate of muscle rigidity in a stepwise pattern among Asian patients with schizophrenia. Although the mechanism underlying the inverse relationship between BMI and muscle rigidity cannot be sufficiently explained, it is speculated that low BMI may contribute to the development of muscle rigidity regardless of antipsychotic "typicality" and dose in patients with schizophrenia.*

Key words: *antipsychotics - Asian, body mass index (BMI) - extrapyramidal symptoms (EPS) - muscle rigidity - schizophrenia*

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INTRODUCTION

An inverse relationship between body mass index (BMI) and Parkinson disease (PD) has been reported by previous studies, despite several controversies. Low BMI has been regarded as a risk factor for PD regardless of the confounding factors including smoking, caffeine and alcohol (Logroscino et al. 2007, Noyce et al. 2017). 5-hydroxytryptamine-1A (5-HT_{1A}) receptor agonist can reduce the motor deficits in PD as well as antipsychotic-

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induced extrapyramidal symptoms (EPS) in schizophrenia because serotonergic input from the dorsal raphe nucleus can modulate dopaminergic neurons of the substantia nigra. Hence, 5-HT$_{1A}$ receptor agonist has been regarded as a promising therapeutic agent for PD and schizophrenia (Haleem 2015, Ohno 2011). Also, from the viewpoint of neuro-inflammation, the microglial activation associated with both PD and EPS can be a cause for prostaglandin release (Arora et al. 2018). Furthermore, because the facilitatory role of dopamine D$_2$ receptor agonists on movement can be potentiated by blocking the cannabinoid CB$_1$ receptor, the endogenous cannabinoid system has been suggested as a novel therapeutic target for dopamine-related diseases including PD and psychosis (De Fonseca et al. 2001). It can, therefore, be speculated that common biological underpinnings may be shared by both core parkinsonian symptoms in PD and antipsychotic-induced EPS in schizophrenia. However, to our knowledge, the relationship between BMI and antipsychotic-induced EPS has been rarely studied. Therefore, using data from the Research on Asian Psychotropic Prescription Patterns for Antipsychotics (REAP-AP) study, the largest international collaborative psychiatric survey in Asia (Park et al. 2018), we aimed to clarify the relationship between BMI and EPS in Asian patients with schizophrenia. Among Asian patients with schizophrenia, BMI groups were categorized according to the World Health Organization (WHO) classification system for body weight status (World Health Organization 1998) and the Asia-Pacific obesity classification (International Obesity Task Force 2000). Additionally, we aimed to compare findings regarding the relationship between BMI and EPS according to the different obesity classification systems.

SUBJECTS AND METHODS

As described elsewhere (Park et al. 2018), in the fourth REAP-AP, a consecutive recruitment of 3,744 patients with schizophrenia was conducted from 71 survey centers in 15 Asian countries including Bangladesh, China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Myanmar, Pakistan, Singapore, Sri Lanka, Taiwan, Thailand and Vietnam from March to June 2016. The institutional review boards of Taipei City Hospital, Taipei, Taiwan (receipt number: TCHIRB-10412128-E) and other survey centers approved the study protocols and informed consent forms. All study subjects signed the informed consent form prior to their participation in the study. Using the predefined case report form, the baseline characteristics and pharmacotherapy-related details were collected by the study coordinators, under the supervision of clinical psychiatrists. In our study, the analysis of data from the REAP-AP study was performed, and the subjects who met the following inclusion criteria were selected: (i) a diagnosis of schizo-

phrenia according to the *International Classification of Diseases, 10th Revision* (ICD-10) (World Health Organization 1992), (ii) pharmacotherapy with antipsychotics, and (iii) availability of the complete Drug-induced Extrapyramidal Symptom Scale (DIEPSS) data (Inada 2009, Kim et al. 2002). Finally, we included 1448 schizophrenia patients recruited from India, Indonesia, Japan, Taiwan and Malaysia.

In the first step, BMI, defined as weight in kilograms (kg) divided by height in meters squared (m^2), was used to categorize schizophrenia patients into 6 groups according to the WHO classification system for body weight status (World Health Organization 1998) as follows: underweight (<18.50 kg/m^2), normal range (18.50–24.99 kg/m^2), overweight (pre-obese (25.00–29.99 kg/m^2)), overweight obese I (30.00–34.99 kg/m^2), overweight obese II (35.00–39.99 kg/m^2), and overweight obese III (>40.00 kg/m^2). However, compared with Europeans, Asians who exhibit risks associated with obesity are increased in those with lower BMIs, and Pacific Islanders exhibit lower body fat levels for the same BMI. Therefore, in the second step, schizophrenia patients were categorized into 5 groups according to the Asia-Pacific obesity classification (International Obesity Task Force 2000) as follows: underweight (<18.50 kg/m^2); normal range (18.50–22.99 kg/m^2); overweight at risk (23.00–24.99 kg/m^2); overweight obese I (25.00–29.9 kg/m^2); and overweight obese II (>30.00 kg/m^2).

The DIEPSS was used to evaluate the antipsychotic-induced EPS among the study subjects. All the DIEPSS items, which are gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, dyskinesia and overall severity, were rated on a 5-point Likert scale with scores 0 (normal) to 4 (severe). The inter-rater reliability, test-retest reliability and concurrent validity were assessed. According to the confirmed metric characteristics, the presence of gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, dyskinesia and overall severity was indicated by a score of 2 or higher in each of the items and the presence of parkinsonism was indicated by a total sum score of 5 or higher in 5 items including gait, bradykinesia, sialorrhea, muscle rigidity and tremor (Inada 2009, Kim et al. 2002).

The Brief Psychiatric Rating Scale (BPRS) (Leucht et al. 2005, Overall & Gorham 1962), the Charlson Comorbidity Index (CCI) (Charlson et al. 1987, Quan et al. 2005) and the Anatomical Therapeutic Chemical (ATC) classification (World Health Organization 2019) were used to evaluate the psychiatric symptoms, quantify the comorbid physical disease and classify the used psychotropic drugs among the study subjects, respectively. The BPRS items - somatic concern, anxiety, emotional withdrawal, conceptual disorganization, feelings of quilt, tension, mannerism and posturing, grandiosity, depressed mood, hostility, suspiciousness, hallucinatory behavior, motor retardation, uncooperativeness, unusual thought

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content, blunted affect, excitement and disorientation - were rated on a 7-point Likert scale from scores 1 (not present) to 7 (very severe) (Leucht et al. 2005, Overall & Gorham 1962). The CCI evaluated the comorbid physical diseases based on their weight and was regarded as a predictive factor for long-term outcome. Also, in our study, the CCI level was classified into 3 groups according to 1- and 2-year survival rates: 0-1, 2-3 and 4-5 (Charlson et al. 1987, Quan et al. 2005). Both the BPRS and the CCI were validated and confirmed by the study findings (Charlson et al. 1987, Leucht et al. 2005, Overall & Gorham 1962, Quan et al. 2005). In addition, based on the ATC classification system (World Health Organization 2019), psychotropic drugs were classified into antipsychotics (N05A), anticonvulsants (antiepileptics; N03A), antidepressants (N06A), anxiolytics (N05B and N05C) and antiparkinsonian drugs (N04). According to the definition of Tandon and coworkers (2010), antipsychotic medications were dichotomized into first- or second-generation antipsychotics in an association with "atypicality", which is defined as a favorable antipsychotic effect with a reduced risk of EPS.

In the first step for the WHO obesity classification, using analysis of covariance (ANCOVA) for continuous variables and the chi-squared (χ^2) test for discrete variables, baseline characteristics and antipsychotic-induced EPS in schizophrenia patients with underweight, normal range, pre-obese, obese I, obese II, and obese III were compared. Multinomial logistic regression analyses were used to adjust for the potential effect of confounding factors in terms of the differences in the proportions of antipsychotic-induced EPS according to the WHO obesity classification. In the second step for the Asia-Pacific obesity classification, using ANCOVA for continuous variables and the χ^2 test for discrete variables, baseline characteristics and antipsychotic-induced EPS in schizophrenia patients with underweight, normal range, at risk, obese I, and obese II were compared. Multinomial logistic regression analyses were used to adjust for the potential effect of confounding factors in terms of the differences in the proportions of antipsychotic-induced EPS according to the Asia-Pacific Obesity classification. Statistical significance was set at $P<0.05$ (two-tailed) for all the tests. All statistical analyses were conducted using IBM SPSS 24 (IBM Co., Armonk, NY, USA).

RESULTS

As shown in Table 1, among 1448 Asian patients with schizophrenia, the percentages of underweight, normal range, pre-obese, obese I, obese II, and obese III were 8.4% (n=122), 56.1% (n=812), 25.3% (n=366), 7.4% (n=107), 1.7% (n=25), and 1.1% (n=16), respectively. The percentage representation of the country (χ^2=60.692, $P<0.0001$), regional classification (χ^2=21.989, P=0.015), income group (χ^2=32.548, $P<0.0001$), enrollment as an outpatient (χ^2=41.957, $P<0.0001$), duration

of illness (χ^2=60.630, $P<0.0001$), duration of untreated psychosis (χ^2=20.028, P=0.029), antidepressants (χ^2=21.864, $P<0.0001$), age (F=1767.2, $P<0.0001$) and BPRS total score (F=1325.9, $P<0.0001$) were significantly different among schizophrenia patients with normal range, pre-obese, obese I, obese II, and obese III in terms of the WHO classification system for body weight status. Multinomial logistic regression analyses were used to adjust for the potential effects of age, regional classification, income group, enrollment as an outpatient, duration of illness, duration of untreated psychosis, antidepressants and BPRS total score. Additionally, underweight was defined as the reference category of the BMI classification in the multinomial logistic regression analyses. After adjusting for the effect of confounding factors, the presence of gait disturbance (normal range, adjusted odds ratio aOR=0.626, P=0.248; pre-obese, aOR=0.644, P=0.335; obese I, aOR=0.395, P=0.151; obese II, aOR=3.868, P=0.041; obese III, aOR=0.770, P=0.821), bradykinesia (normal range, aOR=0.518, P=0.035; pre-obese, aOR=0.246, P=0.671; obese I, aOR=0.387, P=0.054; obese II, aOR=1.451, P=0.544; obese III, aOR=1.704, P=0.474), and muscle rigidity (normal range, aOR=0.432, P=0.004; pre-obese, aOR=0.717, P=0.308; obese I, aOR=0.333, P=0.031; obese II, aOR=0.596, P=0.523; obese III, aOR=0.344, P=0.333) were significantly different among the divided patient groups based on the WHO classification system for body weight status.

As shown in Table 2, the percentages of underweight, normal range, at risk, obese I, and obese II were 8.4% (n=122), 37.1% (n=537), 19.0% (n=275), 25.3% (n=366), and 10.2% (n=148), respectively. The percentage representation of the country (χ^2=62.437, $P<0.0001$), regional classification (χ^2=23.577, P=0.003), income group (χ^2=32.841, $P<0.0001$), enrollment as an outpatient (χ^2=42.164, $P<0.0001$), duration of illness (χ^2=54.674, $P<0.0001$), antidepressants (χ^2=21.484, $P<0.0001$), and age (F=3557.8, $P<0.0001$) were significantly different among schizophrenia patients with underweight, normal range, at risk, obese I, and obese II in terms of the Asia-Pacific obesity classification. Multinomial logistic regression analyses were used to adjust for the potential effects of age, regional classification, income group, enrollment as an outpatient, duration of illness, and antidepressants. Additionally, underweight was defined as the reference category for the BMI classification in multinomial logistic regression analyses. After adjusting for the effect of confounding factors, the presence of muscle rigidity (normal range, aOR=0.569, P=0.035; at risk, aOR=0.387, P=0.003; obese I, aOR=0.241, P=0.715; obese II, aOR=0.430, P=0.034) and akathisia (normal range, aOR=0.641, P=0.176; at risk, aOR=0.440, P=0.034; obese I, aOR=0.643, P=0.214; obese II, aOR=0.436, P=0.094) were significantly different among the divided patient groups based on the Asia-Pacific obesity classification system.

Table 1. Antipsychotic-induced extrapyramidal symptoms divided into groups according to the World Health Organization (WHO) classification system for body weight status in Asian patients with schizophrenia (n=1448)

	Underweight (n=122)	Normal range (n=812)	Overweight: Pre-obese (n=366)	Overweight: Obese I (n=107)	Overweight: Obese II (n=25)	Overweight: Obese III (n=16)	Statistical coefficient	Unadjusted P-value	Adjusted P-value*
Age, mean (SD) years	35.4 (13.7)	38.4 (12.9)	39.2 (11.5)	41.5 (12.1)	38.5 (11.3)	36.9 (7.1)	F=1767.2	<0.0001	-
Male, n (%)	69 (56.6)	504 (62.1)	234 (63.9)	53 (49.5)	13 (52.0)	10 (62.5)	χ²=9.506	0.091	-
Country									
India, n (%)	36 (29.5)	226 (27.8)	125 (34.2)	31 (29.0)	5 (20.0)	3 (18.8)	χ²=60.692	<0.0001	-
Indonesia, n (%)	52 (42.6)	293 (36.1)	85 (23.2)	18 (16.8)	9 (36.0)	6 (37.5)			
Japan, n (%)	7 (5.7)	83 (10.2)	41 (11.2)	10 (9.3)	4 (16.0)	0 (0.0)			
Malaysia, n (%)	21 (17.2)	105 (12.9)	67 (18.3)	29 (27.1)	5 (20.0)	3 (18.0)			
Taiwan, n (%)	6 (4.9)	105 (12.9)	48 (13.1)	19 (17.8)	2 (0.1)	4 (0.3)			
Regional classification**									
East Asian, n (%)	13 (10.7)	188 (23.2)	89 (24.3)	29 (27.1)	6 (24.0)	4 (25.0)	χ²=21.989	0.015	-
Southeast Asian, n (%)	73 (59.8)	398 (49.0)	152 (41.5)	47 (43.9)	14 (56.0)	9 (56.3)			
South Asian, n (%)	36 (29.5)	226 (27.8)	125 (34.2)	31 (29.0)	5 (20.0)	3 (18.8)			
Income group***									
High, n (%)	13 (10.7)	188 (23.2)	89 (24.3)	29 (27.1)	6 (24.0)	4 (25.0)	χ²=32.548	< 0.0001	-
Upper middle, n (%)	21 (17.2)	105 (12.9)	67 (18.3)	29 (27.1)	5 (20.0)	3 (18.8)			
Lower middle, n (%)	88 (72.1)	519 (63.9)	210 (57.4)	49 (45.8)	14 (56.0)	9 (56.3)			
Employment, n (%)	19 (15.6)	155 (19.1)	79 (21.6)	22 (20.6)	1 (4.0)	3 (18.8)	χ²=6.214	0.286	-
Outpatient, n (%)	58 (47.5)	340 (51.7)	238 (65.0)	78 (72.9)	21 (84.0)	10 (62.5)	χ²=41.957	<0.0001	-
Duration of illness							χ²=60.630	<0.0001	-
< 1 year, n (%)	26 (21.3)	158 (19.3)	33 (9.0)	8 (7.5)	2 (8.0)	0 (0.0)			
1-5 years, n (%)	33 (27.0)	177 (21.8)	79 (21.6)	20 (18.7)	6 (24.0)	2 (12.5)			
5-10 years, n (%)	28 (23.0)	136 (16.7)	65 (17.8)	12 (11.2)	7 (28.0)	2 (12.5)			
> 10 years, n (%)	35 (28.7)	341 (42.0)	189 (51.6)	67 (62.6)	10 (40.0)	12 (75.0)			
DUP									
< 3 months, n (%)	43 (35.2)	318 (39.2)	132 (36.1)	44 (41.1)	16 (64.0)	6 (37.5)	χ²=20.028	0.029	-
3-12 months, n (%)	51 (41.8)	232 (28.6)	124 (33.9)	37 (34.6)	4 (16.0)	5 (31.3)			
>1 year, n (%)	28 (23.0)	262 (32.3)	110 (30.1)	26 (24.3)	5 (20.0)	5 (31.3)			

According to the WHO classification system for body weight status, the body mass index was classified into the underweight (<18.50), normal weight (18.50-24.99), overweight: pre-obese (25.00-29.99), overweight: obese I (30.00-34.99), overweight: obese II (35.00-39.99), and overweight: obese III (>40.00)
* Adjusted for the effects of age, regional classification, income group, enrollment as an outpatient, duration of illness, DUP, total score on the BPRS, and antidepressants; Underweight was defined as the reference category of the BMI classification in the multinominal logistic regression analyses.
** Defined by United Nations classification: East Asia (Japan and Taiwan), South Asia (India) and Southeast Asia (Indonesia and Malaysia)
*** Defined by the World Bank list of economies : high income (Japan and Taiwan), upper middle income (Malaysia) and lower middle income (India and Indonesia)

BMI - body mass index; BPRS - Brief Psychiatric Rating Scale; CCI - Charlson comorbidity index; DUP - duration of untreated psychosis; FGA - first-generation antipsychotics; SGA - second-generation antipsychotics; WHO - World Health Organization; a - normal range; b - pre-obese; c - obese I; d - obese II; e - obese III

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Table 1. Continues

	Underweight (n=122)	Normal range (n=812)	Overweight: Pre-obese (n=366)	Overweight: Obese I (n=107)	Overweight: Obese II (n=25)	Overweight: Obese III (n=16)	Statistical coefficient	Unadjusted P-value	Adjusted P-value*
Cigarette smoking									
Current, n (%)	29 (24.8)	260 (33.1)	95 (27.1)	28 (26.7)	6 (25.0)	4 (25.0)	χ^2=10.847	0.370	-
Previous, n (%)	12 (10.3)	59 (7.5)	33 (9.4)	8 (7.6)	3 (12.5)	3 (18.8)			
No, n (%)	76 (65.0)	466 (59.4)	222 (63.4)	69 (65.7)	15 (62.5)	9 (56.3)			
CCI level									
0-1, n (%)	101 (82.8)	627 (77.2)	275 (75.1)	73 (68.2)	16 (64.0)	15 (93.8)	χ^2=16.645	0.341	-
2-3, n (%)	19 (15.6)	162 (20.0)	85 (23.2)	29 (27.1)	8 (32.0)	1 (6.3)			
4-5, n (%)	2 (1.6)	23 (2.8)	6 (1.6)	5 (4.7)	1 (4.0)	0 (0.0)			
BPRS, mean (SD)	35.9 (13.9)	35.4 (13.3)	34.0 (12.6)	31.8 (11.8)	35.4 (13.3)	38.3 (14.1)	F=1325.9	<0.0001	-
Psychotropic drugs									
FGA, n (%)	41 (33.6)	283 (34.9)	133 (36.3)	35 (32.7)	13 (52.0)	8 (50.0)	χ^2=5.259	0.385	-
SGA, n (%)	104 (85.2)	677 (83.4)	307 (83.9)	94 (87.9)	19 (76.0)	11 (68.8)	χ^2=5.345	0.375	-
Antiparkinson, n (%)	49 (40.2)	308 (37.9)	124 (33.9)	48 (44.9)	11 (44.0)	2 (12.5)	χ^2=9.675	0.085	-
Anticonvulsants, n (%)	9 (7.4)	72 (8.9)	35 (9.6)	12 (11.2)	2 (8.0)	2 (12.5)	χ^2=1.422	0.922	-
Anxiolytics, n (%)	41 (33.6)	264 (32.5)	93 (25.4)	33 (30.8)	6 (24.0)	4 (25.0)	χ^2=7.317	0.198	-
Antidepressants, n (%)	9 (7.4)	53 (6.5)	53 (14.5)	14 (13.1)	2 (8.0)	2 (12.5)	χ^2=21.864	<0.0001	-
Gait, n (%)	9 (7.8)	66 (8.1)	28 (7.7)	5 (4.7)	6 (24.0)	2 (12.5)	χ^2=10.874	0.054	0.254 [a] 0.331 [b] 0.151 [c] 0.041 [d] 0.820 [e]
Bradykinesia, n (%)	18 (14.8)	89 (11.0)	46 (12.6)	8 (7.5)	5 (20.0)	3 (18.8)	χ^2=6.094	0.297	0.036 [a] 0.242 [b] 0.054 [c] 0.541 [d] 0.472 [e]
Sialorrhea, n (%)	9 (7.4)	67 (8.3)	27 (7.4)	8 (7.5)	3 (12.0)	2 (12.5)	χ^2=1.349	0.930	0.482 [a] 0.665 [b] 0.639 [c] 0.241 [d] 0.958 [e]

According to the WHO classification system for body weight status, the body mass index was classified into the underweight (<18.50), normal weight (18.50-24.99), overweight: pre-obese (25.00-29.99), overweight: obese I (30.00-34.99), overweight: obese II (35.00-39.99), and overweight: obese III (>40.00)

* Adjusted for the effects of age, regional classification, income group, enrollment as an outpatient, duration of illness, DUP, total score on the BPRS, and antidepressants; Underweight was defined as the reference category of the BMI classification in the multinominal logistic regression analyses.

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Table 1. Continues

	Underweight (n=122)	Normal range (n=812)	Overweight: Pre-obese (n=366)	Overweight: Obese I (n=107)	Overweight: Obese II (n=25)	Overweight: Obese III (n=16)	Statistical coefficient	Unadjusted P-value	Adjusted P-value*
Rigidity, n (%)	25 (20.5)	88 (10.8)	47 (27.5)	7 (6.4)	3 (12.0)	1 (6.3)	χ^2=13.628	0.021	0.005 [a] 0.251 [b] 0.032 [c] 0.537 [d] 0.347 [e]
Tremor, n (%)	20 (16.4)	136 (16.7)	72 (19.7)	16 (15.0)	4 (16.0)	3 (18.8)	χ^2=2.142	0.829	0.336 [a] 0.048 [b] 0.433 [c] 0.345 [d] 0.829 [e]
Akathisia, n (%)	15 (12.3)	59 (7.3)	28 (7.7)	5 (4.7)	2 (8.0)	0 (0.0)	χ^2=6.634	0.249	0.156 [a] 0.664 [b] 0.120 [c] 0.776 [d] 0.999 [e]
Dystonia, n (%)	9 (7.4)	37 (4.6)	20 (5.5)	1 (1.5)	1 (4.0)	0 (0.0)	χ^2=6.675	0.246	0.087 [a] 0.361 [b] 0.996 [c] 0.869 [d] 0.999 [e]
Dyskinesia, n (%)	4 (3.3)	43 (5.3)	14 (3.8)	3 (2.8)	2 (8.0)	0 (0.0)	χ^2=4.128	0.531	0.323 [a] 0.896 [b] 0.976 [c] 0.219 [d] 0.999 [e]
Overall, n (%)	23 (18.9)	134 (16.5)	63 (17.2)	15 (14.0)	5 (20.0)	2 (12.5)	χ^2=1.449	0.919	0.554 [a] 0.783 [b] 0.518 [c] 0.598 [d] 0.915 [e]
Parkinsonism, n (%)	25 (34.7)	131 (31.7)	68 (34.3)	16 (33.3)	5 (33.3)	3 (37.5)	χ^2=0.638	0.986	0.411 [a] 0.730 [b] 0.620 [c] 0.556 [d] 0.989 [e]

According to the WHO classification system for body weight status, the body mass index was classified into the underweight (<18.50), normal weight (18.50-24.99), overweight: pre-obese (25.00-29.99), overweight: obese I (30.00-34.99), overweight: obese II (35.00-39.99), and overweight: obese III (>40.00)
* Adjusted for the effects of age, regional classification, income group, enrollment as an outpatient, duration of illness, DUP, total score on the BPRS, and antidepressants;
Underweight was defined as the reference category of the BMI classification in the multinominal logistic regression analyses.
** Defined by United Nations classification: East Asia (Japan and Taiwan), South Asia (India) and Southeast Asia (Indonesia and Malaysia)
*** Defined by the World Bank list of economies : high income (Japan and Taiwan), upper middle income (Malaysia) and lower middle income (India and Indonesia)
BMI - body mass index; BPRS - Brief Psychiatric Rating Scale; CCI - Charlson comorbidity index; DUP - duration of untreated psychosis; FGA - first-generation antipsychotics;
SGA - second-generation antipsychotics; WHO - World Health Organization; a - normal range; b - pre-obese; c - obese I; d - obese II; e - obese III

Table 2. Antipsychotic-induced extrapyramidal symptoms divided into groups according to the Asia-Pacific obesity classification in Asian patients with schizophrenia (n=1448)

	Underweight (n=122)	Normal range (n=537)	Overweight: At risk (n=275)	Overweight: Obese I (n=366)	Overweight: Obese II (n=148)	Statistical coefficient	Unadjusted P-value	Adjusted P-value*
Age, mean (SD) years	35.4 (13.7)	38.1 (13.2)	39.0 (12.4)	39.2 (11.5)	40.5 (11.6)	$F=3557.8$	<0.0001	-
Male, n (%)	69 (56.6)	333 (62.0)	171 (62.2)	234 (63.9)	76 (51.4)	$\chi^2=8.519$	0.074	-
Country						$\chi^2=62.437$	<0.0001	-
India, n (%)	36 (29.5)	138 (25.7)	88 (32.0)	125 (34.2)	39 (26.4)			
Indonesia, n (%)	52 (42.6)	207 (38.5)	86 (31.3)	85 (23.2)	33 (22.3)			
Japan, n (%)	7 (5.7)	64 (11.9)	19 (6.9)	41 (11.2)	14 (9.5)			
Malaysia, n (%)	21 (17.2)	63 (11.7)	42 (15.3)	67 (18.3)	37 (25.0)			
Taiwan, n (%)	6 (4.9)	65 (12.1)	40 (14.5)	48 (13.1)	25 (16.9)			
Regional classification**						$\chi^2=23.577$	0.003	-
East Asian, n (%)	13 (10.7)	129 (24.0)	59 (21.5)	89 (24.3)	39 (26.4)			
Southeast Asian, n (%)	73 (59.8)	270 (50.3)	128 (46.5)	152 (41.5)	70 (47.3)			
South Asian, n (%)	36 (29.5)	138 (25.7)	88 (32.0)	125 (34.2)	39 (26.4)			
Income group***						$\chi^2=32.841$	<0.0001	-
High, n (%)	13 (10.7)	129 (24.0)	59 (21.5)	89 (24.3)	39 (26.4)			
Upper middle, n (%)	21 (17.2)	63 (11.7)	42 (15.3)	67 (18.3)	37 (25.0)			
Lower middle, n (%)	88 (72.1)	345 (64.2)	174 (63.3)	210 (48.6)	72 (48.6)			
Employment, n (%)	19 (15.6)	100 (18.6)	55 (20.0)	79 (21.6)	26 (17.6)	$\chi^2=2.847$	0.584	-
Outpatient, n (%)	58 (47.5)	268 (49.9)	152 (55.3)	238 (65.0)	109 (73.6)	$\chi^2=42.164$	<0.0001	-
Duration of illness						$\chi^2=54.674$	<0.0001	-
< 1 year, n (%)	26 (21.3)	108 (20.1)	50 (18.2)	33 (9.0)	10 (6.8)			
1-5 years, n (%)	33 (27.0)	121 (22.5)	56 (20.4)	79 (21.6)	28 (18.9)			
5-10 years, n (%)	28 (23.0)	85 (15.8)	51 (18.5)	65 (17.8)	21 (14.2)			
> 10 years, n (%)	35 (28.7)	223 (41.5)	118 (42.9)	189 (51.6)	89 (60.1)			
DUP						$\chi^2=14.492$	0.070	-
< 3 months, n (%)	43 (35.2)	210 (39.0)	108 (39.3)	132 (36.1)	66 (44.6)			
3-12 months, n (%)	51 (41.8)	152 (28.3)	80 (29.1)	124 (33.9)	46 (31.1)			
> 1 year, n (%)	28 (23.0)	175 (32.6)	87 (31.6)	110 (30.1)	36 (24.3)			

According to the WHO classification system for body weight status, the body mass index was classified into the underweight (<18.50), normal weight (18.50-24.99), overweight: pre-obese (25.00-29.99), overweight: obese I (30.00-34.99), overweight: obese II (35.00-39.99), and overweight: obese III (>40.00)
* Adjusted for the effects of age, regional classification, income group, enrollment as an outpatient, duration of illness, DUP, total score on the BPRS, and antidepressants; Underweight was defined as the reference category of the BMI classification in the multinominal logistic regression analyses.
** Defined by United Nations classification: East Asia (Japan and Taiwan), South Asia (India) and Southeast Asia (Indonesia and Malaysia)
*** Defined by the World Bank list of economies : high income (Japan and Taiwan), upper middle income (Malaysia) and lower middle income (India and Indonesia)

BMI - body mass index; BPRS - Brief Psychiatric Rating Scale; CCI - Charlson comorbidity index; DUP - duration of untreated psychosis; FGA - first-generation antipsychotics; SGA - second-generation antipsychotics; WHO - World Health Organization; a - normal range; b - at risk; c - obese I; d - obese II

Table 2. Continues

	Underweight (n=122)	Normal range (n=537)	Overweight: At risk (n=275)	Overweight: Obese I (n=366)	Overweight: Obese II (n=148)	Statistical coefficient	Unadjusted P-value	Adjusted P-value*
Cigarette smoking								
Current, n (%)	29 (24.8)	186 (35.9)	74 (27.7)	95 (27.1)	38 (26.2)	χ^2=15.014	0.059	-
Previous, n (%)	12 (10.3)	41 (7.9)	18 (6.7)	33 (9.4)	14 (9.7)			
No, n (%)	76 (65.0)	291 (56.2)	175 (65.5)	222 (63.4)	93 (64.1)			
CCI level								
0-1, n (%)	101 (82.8)	422 (78.6)	205 (74.5)	275 (75.1)	104 (70.3)	χ^2=18.255	0.108	-
2-3, n (%)	19 (15.6)	96 (17.9)	66 (24.0)	85 (23.2)	38 (25.7)			
4-5, n (%)	2 (1.6)	19 (3.6)	4 (1.5)	6 (1.6)	6 (4.1)			
BPRS, mean (SD)	35.9 (1.4)	35.9 (0.7)	34.5 (1.0)	34.0 (0.8)	33.0 (1.2)	F=1.635	0.163	-
Psychotropic drugs								
FGA, n (%)	41 (33.6)	186 (34.5)	98 (35.6)	133 (36.3)	56 (37.8)	χ^2=0.915	0.922	-
SGA, n (%)	104 (85.2)	446 (83.1)	231 (84.0)	307 (83.9)	124 (83.8)	χ^2=0.406	0.982	-
Antiparkinson, n (%)	49 (40.2)	203 (37.8)	105 (38.2)	124 (33.9)	61 (41.2)	χ^2=3.363	0.499	-
Anticonvulsants, n (%)	9 (7.4)	47 (8.8)	25 (9.1)	35 (9.6)	16 (10.8)	χ^2=1.133	0.889	-
Anxiolytics, n (%)	41 (33.6)	171 (31.8)	93 (33.8)	93 (25.4)	43 (29.1)	χ^2=7.065	0.132	-
Antidepressants, n (%)	9 (7.4)	37 (6.9)	16 (5.8)	53 (14.5)	18 (12.2)	χ^2=21.484	<0.0001	-
Gait, n (%)	41 (33.6)	171 (31.8)	93 (33.8)	93 (25.4)	43 (29.1)	χ^2=0.403	0.982	0.942 [a] / 0.923 [b] / 0.657 [c] / 0.449 [d]
Bradykinesia, n (%)	18 (14.8)	64 (11.9)	25 (9.1)	46 (12.6)	16 (10.8)	χ^2=3.325	0.505	0.335 [a] / 0.118 [b] / 0.801 [c] / 0.551 [d]
Sialorrhea, n (%)	9 (7.4)	48 (8.9)	19 (6.9)	27 (7.4)	13 (8.8)	χ^2=1.466	0.833	0.507 [a] / 0.914 [b] / 0.969 [c] / 0.735 [d]

According to the WHO classification system for body weight status, the body mass index was classified into the underweight (<18.50), normal weight (18.50-24.99), overweight: pre-obese (25.00-29.99), overweight: obese I (30.00-34.99), overweight: obese II (35.00-39.99), and overweight: obese III (>40.00).
* Adjusted for the effects of age, regional classification, income group, enrollment as an outpatient, duration of illness, DUP, total score on the BPRS, and antidepressants;
Underweight was defined as the reference category of the BMI classification in the multinominal logistic regression analyses.
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Table 2. Continues

	Underweight (n=122)	Normal range (n=537)	Overweight: At risk (n=275)	Overweight: Obese I (n=366)	Overweight: Obese II (n=148)	Statistical coefficient	Unadjusted P-value	Adjusted P-value*
Rigidity, n (%)	25 (20.5)	65 (12.1)	23 (8.4)	47 (12.8)	11 (7.4)	χ^2=15.017	0.004	0.035 [a] 0.003 [b] 0.241 [c] 0.034 [d]
Tremor, n (%)	20 (16.4)	95 (17.7)	41 (14.9)	72 (19.7)	23 (15.5)	χ^2=2.980	0.561	0.635 [a] 0.835 [b] 0.217 [c] 0.811 [d]
Akathisia, n (%)	15 (12.3)	43 (8.0)	16 (5.8)	28 (7.7)	7 (4.7)	χ^2=6.988	0.137	0.176 [a] 0.034 [b] 0.214 [c] 0.094 [d]
Dystonia, n (%)	9 (7.4)	28 (5.2)	9 (3.3)	20 (5.5)	2 (1.4)	χ^2=7.708	0.103	0.511 [a] 0.134 [b] 0.721 [c] 0.069 [d]
Dyskinesia, n (%)	4 (3.3)	27 (5.0)	16 (5.8)	14 (3.8)	5 (3.4)	χ^2=2.661	0.616	0.442 [a] 0.283 [b] 0.607 [c] 0.727 [d]
Overall, n (%)	23 (18.9)	84 (15.6)	50 (18.2)	63 (17.2)	22 (14.9)	χ^2=1.698	0.791	0.624 [a] 0.926 [b] 0.951 [c] 0.997 [d]
Parkinsonism, n (%)	25 (34.7)	91 (34.1)	40 (27.4)	68 (34.3)	24 (33.8)	χ^2=2.499	0.646	0.612 [a] 0.246 [b] 0.809 [c] 0.965 [d]

According to the WHO classification system for body weight status, the body mass index was classified into the underweight (<18.50), normal weight (18.50-24.99), overweight: pre-obese (25.00-29.99), overweight: obese I (30.00-34.99), overweight: obese II (35.00-39.99), and overweight: obese III (>40.00).

* Adjusted for the effects of age, regional classification, income group, enrollment as an outpatient, duration of illness, DUP, total score on the BPRS, and antidepressants; Underweight was defined as the reference category of the BMI classification in the multinominal logistic regression analyses.
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Shu-Yu Yang, Sih-Ku Lin, Kang Sim, Yu-Tao Xiang, Afzal Javed, Norman Sartorius, Naotaka Shinfuku & Yong Chon Park:
RELATIONSHIP BETWEEN BODY MASS INDEX AND EXTRAPYRAMIDAL SYMPTOMS IN ASIAN PATIENTS WITH SCHIZOPHRENIA:
THE RESEARCH ON ASIAN PSYCHOTROPIC PRESCRIPTION PATTERNS FOR ANTIPSYCHOTICS (REAP-AP)
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DISCUSSION

In summary, in terms of the WHO classification system for body weight status, underweight (rather than normal range, pre-obese, obese I, obese II, or obese III) was associated with greater rates of bradykinesia and muscle rigidity and lower rates of gait disturbance among Asian patients with schizophrenia. Furthermore, in terms of the Asia-Pacific obesity classification, underweight (rather than normal range, at risk, obese I, or obese II) was associated with greater rates of muscle rigidity and akathisia. Although different obesity classification systems were used, our findings consistently revealed that underweight was associated with a greater rate of muscle rigidity, in a stepwise pattern, among the 1448 Asian patients with schizophrenia.

Previous investigations on the relationship between BMI and muscle rigidity have been rare and insufficient. Since muscle rigidity is regarded as a typical of PD, based on the speculations about the relationship between BMI and PD (Logroscino et al. 2007, Noyce et al. 2017), an inverse relationship between BMI and muscle rigidity can be elucidated. First, the alterations in the autonomic nervous system, which are associated with appetite or metabolism regulation, may increase the vulnerability to muscle rigidity. The appetite and weight regulation is closely implicated in hypothalamus. Also, schizophrenia patients usually have structural and functional disturbances in the hypothalamus (Klomp et al. 2012). Thus, there is a possibility that the hypothalamic disturbances may precede the decrease in BMI and vulnerability to muscle rigidity in patients with schizophrenia. Second, increased body fat may have a protective effect on the vulnerability to EPS in patients with schizophrenia (Cheshire & Wszolek 2005). Namely, the levels of circulating and central insulin, which can be affected by the high level of BMI, may reduce neurodegeneration (Craft and Watson 2004). Third, brain-derived neurotrophic factor (*BDNF*) and regulatory-associated protein of mTOR (*RAPTOR*) have been proposed as the candidate genes for the link between BMI and PD (Logroscino et al. 2007, Noyce et al. 2017). Since *BDNF* is a potential therapeutic agent for neurodegenerative diseases (Nagahara & Tuszynski 2011) and *RAPTOR* contributes to the links between the mTOR pathway, macroautophagy, and PD (Bove et al. 2011), these genes may also be associated with the inverse relationship between BMI and muscle rigidity. Fourth, poor nutrition-related weight loss, anemia, and other physical complications might be a contributory factor to the occurrence of muscle rigidity.

Our study has several limitations. First, the REAP-AP was designed as a cross-sectional study. The inferences about temporal causality were limited. Second, physical activity may be inversely associated with both BMI and EPS (Xu et al. 2010). Third, the possibility that statistical significance may be different from clinical significance cannot be excluded. The potential effects of physical activity on the relationship between BMI and EPS were not adjusted in our study. Despite these limitations, our study sufficiently demonstrates that the BMI is inversely related with muscle rigidity in Asians with schizophrenia. Our findings suggest that low BMI may be a risk factor for motor rigidity irrespective of antipsychotic "typicality" and dose in patients with schizophrenia.

CONCLUSION

Findings of the present study consistently revealed that underweight was associated with a greater rate of muscle rigidity in a stepwise pattern among Asian patients with schizophrenia. Although the mechanism underlying the inverse relationship between BMI and muscle rigidity cannot be sufficiently explained, it is speculated that low BMI may contribute to the development of muscle rigidity regardless of antipsychotic "typicality" and dose in patients with schizophrenia.

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Contribution of individual authors:

Seon-Cheol Park: analyzed the data, wrote the first draft of the manuscript, revision of manuscript, agree with results and conclusions and accept final manuscript.

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Norman Sartorius, Naotaka Shinfuku & Yong Chon Park: conceived and designed the study, revision of manuscript, agree with results and conclusions and accept final manuscript.

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