



OPEN

Homocysteine level, body mass index and clinical correlates in Chinese Han patients with schizophrenia

Yuanyuan Huang^{1,10}, Kai Wu^{2,3,4,5,6,7,10}, Hehua Li^{1,10}, Jing Zhou^{2,3}, Dongsheng Xiong^{2,3}, Xia Huang^{2,3}, Jiahui Li^{2,3}, Ya Liu^{2,3}, Zhilin Pan^{2,3}, David T. Mitchell⁸, Fengchun Wu^{1,3}✉ & Xiang Yang Zhang^{1,9}✉

Obesity is common comorbidity in patients with schizophrenia. Previous studies have reported that homocysteine (Hcy) is increased in schizophrenia. However, no study has reported the association between BMI and Hcy levels in schizophrenia. This cross-sectional naturalistic study aimed to evaluate the relationship between BMI, Hcy and clinical symptoms in Chinese Han patients with chronic schizophrenia. Clinical and anthropometric data as well as plasma Hcy level and glycolipid parameters were collected. Psychopathology was measured with the Positive and Negative Syndrome Scale (PANSS). Our results showed that compared with the low BMI group, the high BMI group had a higher PANSS general psychopathology subscore, higher levels of blood glucose, total cholesterol and high-density lipoprotein (HDL) cholesterol (all $p < 0.05$). Hcy levels were negatively associated with BMI in patients ($p < 0.001$). Hcy level, the PANSS general psychopathology subscale, total cholesterol and education (all $p < 0.05$) were the influencing factors of high BMI. Our study suggest that Hcy level may be associated with BMI in patients with schizophrenia. Moreover, patients with high BMI show more severe clinical symptoms and higher glucose and lipid levels.

Schizophrenia is a severe psychiatric disorder characterized by chronic progressive impairments of physical, cognitive and psychosocial function. Weight gain is common in schizophrenia, which is a risk factor for some chronic diseases, such as diabetes, hypertension, and cardiovascular disease¹⁻⁴. In addition, obesity leads to a lower quality of life and 10 ~ 20 years of shorter life expectancy in schizophrenia⁵. Most studies have shown that weight gain in psychiatric patients is associated with lifestyle^{6,7}, metabolic abnormalities^{8,9}, and use of antipsychotic medications¹⁰.

Homocysteine (Hcy), a sulfur-containing amino acid, participates in the methionine cycle that influences brain development through multiple cellular pathways¹¹. There is growing evidence that Hcy levels are closely related to neuropsychiatric disorders such as Alzheimer disease¹², affective disorders, and schizophrenia¹³⁻¹⁶. Numerous studies reported that Hcy levels were increased in patients with acute and chronic schizophrenia^{17,18}. A previous study found that a 5- $\mu\text{mol/l}$ increase in Hcy levels increased the risk of schizophrenia by up to 70%¹⁹.

¹Department of Psychiatry, The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), 36 Mingxin Rd, Liwan District, Guangzhou 510370, China. ²Department of Biomedical Engineering, School of Materials Science and Engineering, South China University of Technology(SCUT), Guangzhou, China. ³Guangdong Engineering Technology Research Center for Translational Medicine of Mental Disorders, Guangzhou, China. ⁴Guangdong Engineering Technology Research Center for Diagnosis and Rehabilitation of Dementia, Guangzhou, China. ⁵National Engineering Research Center for Tissue Restoration and Reconstruction, South China University of Technology, Guangzhou, China. ⁶Key Laboratory of Biomedical Engineering of Guangdong Province, South China University of Technology, Guangzhou, China. ⁷Department of Nuclear Medicine and Radiology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan. ⁸Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center At Houston, Houston, TX, USA. ⁹CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, 16 Lincui Rd, Chaoyang District, Beijing 100101, China. ¹⁰These authors contributed equally: Yuanyuan Huang, Kai Wu and Hehua Li. ✉email: 13580380071@163.com; zhangxy@psych.ac.cn

Further research found that Hcy levels were positively correlated with the severity of negative symptoms¹⁸, duration of untreated psychosis²⁰, and cognitive deficits²¹ in patients with schizophrenia.

Evidence for the association between different BMI and Hcy levels in the general population have been presented, with a particular focus on the course of physical disease^{22,23}. However, results on the relationship between BMI and Hcy levels showed conflicting data²⁴. A recent meta-analysis reported that Hcy was positively correlated with obesity²⁵, while a recent study demonstrated opposite results in the general population²⁶. A recent cross-sectional study showed that Chinese bipolar disorder (BD) patients with hyperhomocysteinemia had elevated BMI¹⁶. Taken together, it appears that Hcy may play a role in high BMI or obesity in both healthy population and patients with psychiatric disorders.

Based on the higher prevalence of obesity and increased Hcy levels in patients with schizophrenia and the close relationship between Hcy and obesity, it is of great interest to explore their possible association in schizophrenia. To our best knowledge, no study has reported the association between BMI and Hcy levels in patients with schizophrenia. Therefore, the main purposes of this study were to bridge this gap by examining: (1) whether there were differences in plasma Hcy, clinical data, glucose and lipid metabolism parameters between high and low BMI groups in patients with schizophrenia; (2) whether there were a correlation between BMI, Hcy and clinical symptoms in Chinese Han patients with schizophrenia.

Methods

Subjects. Using a cross-sectional naturalistic design, 120 patients with schizophrenia were recruited from the Affiliated Brain Hospital of Guangzhou Medical University, a psychiatric teaching hospital with more than 120 years of history in Guangzhou city. The study was conducted from June, 2018 to May, 2019. Inclusion criteria included the following: (1) aged 18–60 years, Han Chinese; (2) confirmed DSM-V diagnostic criteria of schizophrenia by two experienced psychiatrists according to the Structured Clinical Interview for DSM-V (SCID); (3) a stable dose of antipsychotic drugs for ≥ 4 weeks before the start of the study.

Each subject underwent a complete medical history, physical examination, and laboratory tests. Any subjects with major medical abnormalities were excluded, including acute or unstable medical illnesses or any organic brain diseases. Also, subjects suffering from drug or alcohol abuse/dependence were excluded. The trained research staff collected general information and social-demographic characteristics through questionnaires. Other information, including a history of mental illness and medications were collected from medical records.

Clinical measurements. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the psychiatric symptoms of all patients, which was assessed by two psychiatrists who had received special training to ensure consistency. The inter-rater correlation coefficient (ICC) of PANSS total score remained above 0.8 through repeated evaluation.

BMI measurements. BMI [weight (kg) / height squared (m^2)] was calculated in a standardized fashion by assessing body weight and height. Height was measured when the subject was barefoot and upright. Weight was measured by a 0.1 kg electronic scale when the subjects wore light indoor clothing. Referring to the Chinese guidelines for adults²⁷, it was considered as overweight with $24 \leq \text{BMI} < 28 \text{ kg}/m^2$, and $\text{BMI} \geq 28 \text{ kg}/m^2$ was classified as obese. In this study, all patients were divided into high BMI group ($\text{BMI} \geq 24 \text{ kg}/m^2$) and low BMI group ($\text{BMI} < 24 \text{ kg}/m^2$).

Glycolipid metabolism and Hcy analysis. Venous blood was collected in the early morning from each patient after at least 8 h of fasting. The blood was collected with an EDTA tube and centrifuged (3000r/m) for 10 min within 30 min of collection. The plasma was isolated and stored at -80°C for testing.

The levels of plasma glucose, hemoglobin A1c (HbA1c), triglycerides (TGs), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were measured by commercially available kits from Beijing Leadman Biotechnology Co. Ltd. (Beijing, China) and by Beckman AU480 automatic biochemical analyzers (Olympus, Japan).

The Hcy levels were measured by Hcy assay kits (enzyme cycle assay), which were purchased from Beijing Leadman Biochemistry Co.Ltd. The assay method was in strict accordance with the instructions of the kit.

All biochemical analyses were performed by a technician in the clinical laboratory center of the hospital, who was blind to the status of subjects.

Statistical analysis. Demographic and clinical characteristics between groups were compared using analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables. Since TG and Hcy levels did not follow a normal distribution (Kolmogorov–Smirnov one-sample test, $p < 0.05$), we first log transformed the data to a normal distribution and then used the transformed values in subsequent statistical tests. Further analysis of covariance (ANCOVA) was performed to control for the confounding factors including education, sex, age, age of onset and antipsychotic treatment (type, dose and duration of treatment). Associations between variables were examined by using Pearson correlation coefficients. We adopted Bonferroni correction to control for multiple tests. Multivariate regression analysis (enter model) was used to assess significant factors associated with BMI after controlling for variables. SPSS version 18.0 was used for all statistical analyses. All p values were defined with a 2-tailed significance level at 0.05.

	All subjects	Subjects with high BMI	Subjects without low BMI	F/χ^2	p value
	N = 120	N = 51	N = 69		
Age, mean (SD), years	46.92 (4.41)	47.88 (12.55)	46.20 (13.15)	0.50	0.482
Education, mean (SD), years	11.05 (3.59)	12.49 (3.45)	9.99 (3.32)	16.13	<0.001**
Gender, male/female, n / n	76 / 44	32 / 19	44 / 25	0.01	0.908
Family history, n (%)	29 (24.37%)	14 (27.45%)	15 (21.74%)	0.52	0.521
Married, n (%)	76 (63.86%)	20 (39.22%)	24 (34.78%)	0.25	0.702
Smoking, n (%)	22 (18.49%)	10 (19.61%)	12 (17.39%)	0.10	0.814
BMI, mean (SD), kg/m ²	24.27 (4.41)	28.24 (2.82)	21.33 (2.76)	179.87	<0.001**
Age of onset, mean (SD), years	25.94 (9.16)	26.58 (10.02)	25.46 (7.79)	0.42	0.519
Duration of illness, mean (SD), days	256.85 (155.42)	274.45 (151.17)	243.58 (158.41)	1.10	0.296
Clozapine / Olanzapine, n (%)	41 / 27 (56.67%)	17 / 9 (50.98%)	24 / 18 (60.87%)	1.20	0.377
PANSS scores					
PANSS Total, mean (SD)	58.59 (16.71)	59.94 (18.95)	57.59 (14.90)	0.58	0.449
P subscore, mean (SD)	11.72 (5.45)	11.35 (5.67)	12.00 (5.33)	0.41	0.523
N subscore, mean (SD)	17.72 (8.13)	17.73 (8.32)	17.71 (8.05)	0.00	0.992
G subscore, mean (SD)	29.19 (7.78)	30.86 (8.84)	27.96 (6.71)	4.19	0.043*

Table 1. Socio-demographic data and clinical profiles of schizophrenia patients with high or low BMI. *BMI* body mass index, *PANSS* positive and negative symptoms scale, *P* positive symptom, *N* negative symptom, *G* general psychopathology syndrome.

	Subjects with high BMI	Subjects without low BMI	F	df	p value
	N = 51, mean (SD)	N = 69, mean (SD)			
Cardo-metabolic					
Glucose, mmol/L	5.23 (1.17)	4.70 (1.21)	5.812	1,118	0.017*
HbA1c, %	5.45 (0.52)	5.55 (0.86)	0.278	1,118	0.599
TG, mmol/L	1.65 (1.09)	1.64 (0.80)	0.002	1,118	0.960
TC, mmol/L	4.76 (1.09)	4.36 (0.86)	4.921	1,118	0.028*
HDL, mmol/L	1.42 (0.20)	1.23 (0.52)	4.647	1,118	0.033*
LDL, mmol/L	2.91 (0.93)	2.65 (0.73)	2.981	1,118	0.087
Homocysteine, mmol/L	14.04 (8.17)	22.19 (14.43)	26.011	1,117	<0.001**

Table 2. Homocysteine level and cardo-metabolic profiles of schizophrenia patients with high or low BMI. *TG* Triglyceride, *TC* Total cholesterol, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *HbA1c* Hemoglobin A1c. Triglyceride and homocysteine: data were compared after logarithmic transformation, and descriptive data were original data.

Results

Demographics characteristics. A total of 120 patients including 76 males and 44 females were recruited. Their average age was 46.92 ± 4.41 years and the mean education level was 11.05 ± 3.59 years. The average illness duration was 256.85 ± 155.42 months and the age of onset was 25.94 ± 9.16 years.

Socio-demographic data and clinical profiles of patients with high BMI ($n = 51$) and low BMI ($n = 69$) groups are displayed in Table 1. There was no significant difference in demographic and clinical characteristics between the two groups (all $p > 0.05$), except for the education level and BMI (both $p < 0.001$; Bonferroni corrected both $p < 0.01$).

Clinical symptoms in high versus low BMI groups. The high BMI patients had higher PANSS general psychopathology subscore than the low BMI patients ($p < 0.05$; Bonferroni corrected $p > 0.05$). When education, sex, and age were added as covariates, there was still a significant difference in PANSS general psychopathology subscore ($F_{1,118} = 4.013$, $p = 0.049$, $r^2 = 0.008$). There was no significant difference in PANSS total, positive symptom or negative symptom scores between the two groups (all $p > 0.05$).

In addition, since the number of patients treated with clozapine/olanzapine was imbalanced between the two groups (50.98% vs. 60.87%), we performed ANCOVA with antipsychotic type as a covariate. The result still showed significant difference in PANSS general psychopathology subscore ($F_{1,118} = 4.331$, $p = 0.040$, $r^2 = 0.012$) (Table 1).

Homocysteine and glycolipid metabolism in high versus low BMI groups. As shown in Table 2, compared to the low BMI group, the high BMI group had significantly higher levels of glucose ($F_{1,118} = 5.812$,

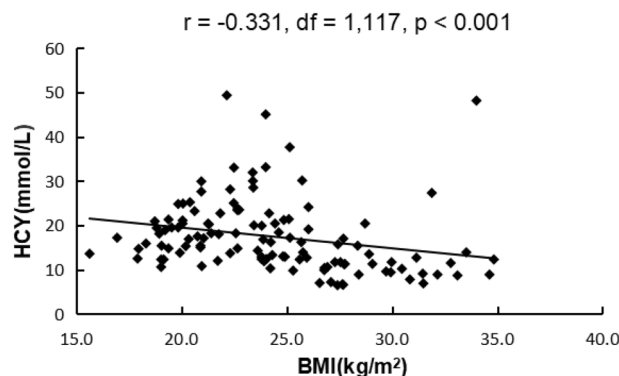


Figure 1. Correlation analysis showed that HCY levels were negatively associated with BMI.

	Coefficients		t	p value	95.0% confidence interval for B	
	B	S.E			Lower bound	Upper bound
Homocysteine	-3.789	1.491	-2.542	0.012	-6.743	-0.836
G subscore	0.103	0.049	2.092	0.039	0.005	0.201
Total cholesterol	0.979	0.389	2.518	0.013	0.209	1.749
Education	0.293	0.104	2.817	0.006	0.087	0.5

Table 3. Predictors generated by multiple linear regression with BMI as response variable.

$p = 0.017$), total cholesterol ($F_{1,118} = 4.921$, $p = 0.028$), and HDL cholesterol ($F_{1,118} = 4.647$, $p = 0.033$), but lower Hcy level ($F_{1,117} = 26.011$, $p < 0.001$). After controlling for covariates including antipsychotic drugs, there were significant differences in HDL cholesterol ($F_{1,118} = 4.174$, $p = 0.044$, $r^2 = 0.073$) and Hcy levels ($F_{1,118} = 23.721$, $p < 0.001$, $r^2 = 0.183$) between the high and low BMI groups. However, no significant differences in glucose, HbA1c, TGs, and LDL cholesterol were found between two groups (all $p > 0.05$).

Relationship between BMI, Hcy, clinical symptoms and glycolipid metabolism. Pearson correlation analyses showed that BMI was negatively associated with Hcy ($r = -0.331$, $df = 1,117$, $p < 0.001$), but positively with glucose ($r = 0.263$, $df = 1,118$, $p = 0.004$), total cholesterol ($r = 0.228$, $df = 1,118$, $p = 0.001$) or HDL cholesterol ($r = -0.180$, $df = 1,118$, $p = 0.05$). However, only the significant association between BMI and Hcy passed the Bonferroni correction ($p < 0.01$) (Fig. 1). In addition, glucose level was positively correlated with positive subscore ($r = 0.223$, $p = 0.015$; Bonferroni corrected $p > 0.05$) and HDL ($r = 0.194$, $p = 0.034$; Bonferroni corrected $p > 0.05$).

Multiple regression analysis showed that Hcy levels ($\beta = -3.789$, $t = -2.542$, $p = 0.012$), the PANSS general psychopathology subscale ($\beta = 0.103$, $t = 2.092$, $p = 0.039$), total cholesterol ($\beta = 0.979$, $t = 2.518$, $p = 0.013$) and education ($\beta = 0.293$, $t = 2.817$, $p = 0.006$) were independent contributors to the BMI after controlling for age, gender, glucose, and HDL cholesterol and antipsychotic drugs (Table 3).

Discussion

To our best knowledge, this is the first study to examine the association between Hcy levels and BMI in patients with schizophrenia. The main findings of this study included: (1) The level of Hcy was significantly lower in the high BMI group than that in the low BMI group in patients with schizophrenia. (2) The high BMI patients had higher glucose and lipid levels than low BMI patients. (3) There were significant associations between BMI, Hcy, clinical symptoms and glycolipid metabolism in patients with chronic schizophrenia.

Our study showed that Hcy levels were significantly lower in the schizophrenia patients with high BMI, and that Hcy levels were negatively associated with BMI, which were consistent with some previous studies reporting a negative correlation between Hcy and BMI in the general population^{28,29}. Also, a recent large sample of study including 5300 overweight/obese individuals and 5807 normal weight individuals showed that Hcy levels were significantly lower in overweight/obese persons than normal weight controls²⁶. However, some previous studies have reported inconsistent results about the relationship between Hcy levels and obesity. For example, some studies showed that compared to non-obese subjects, the Hcy levels were significantly greater in obese subjects suffering from physical disease, such as coronary artery disease and polycystic ovaries³⁰⁻³². The inconsistent results may be due to the differences in subjects that were from different diseases, regions, races, or genetic backgrounds. Other demographic and clinical factors such as diet habits, physical activity, drug treatment, chronic inflammation or the methods of measuring Hcy may also be implicated in the these inconsistent results. Interestingly, we found that Hcy was negatively associated with BMI in schizophrenia, which was inconsistent with most of previous studies showing that high Hcy may be related to obesity and increase the risk of coronary heart

disease^{33,34}. This may be attributed to the effects of different diseases, different stages of disease development¹⁸, or medication treatment regimens³⁵. Petronijević et al.¹⁸ proposed that schizophrenia patients had increased plasma Hcy levels in the acute phase, but Hcy levels were significantly decreased after one month of antipsychotic treatment in the remission phase. Several drugs such as antiepileptic drugs³⁶, fibrates³⁷ and antipsychotic drugs³⁵ may interfere with the one-carbon metabolic pathway, leading to changes in Hcy levels³⁶. We speculated that the changes in Hcy levels observed in this study may be due to antipsychotic treatment and altered symptoms in patients with schizophrenia. Moreover, some researchers found that an increase in Hcy concentration was associated with an increase in the percentage of adipose tissue³⁸, which regulated body fat through epigenetic inheritance of gene expression, leading to the occurrence and development of obesity^{31,39}. Conversely, a previous study reported that Hcy had a negative association with both fat mass and lean mass during weight loss⁴⁰. BMI, as a proxy for general obesity, cannot distinguish lean mass and adipose tissue, which may also confuse the relationship between obesity and HCY. Although the mechanism was still unclear, these results suggest that the Hcy metabolic pathway may play an important role in obesity²⁵. In addition, we found that Hcy level was negatively correlated with blood glucose and HDL, which is consistent with previous reports⁴¹ that hyperhomocysteinemia (HHcy) was associated with low levels of HDL. Also, Hcy was associated with glucose metabolism, lipid metabolism, hyperglycemia⁴², and hyperlipidemia⁴³.

Another important finding of our study was that obese patients had more severe clinical symptoms, showing that the patients with high BMI had higher PANSS general psychopathology subscore than those with low BMI, and BMI was positively associated with PANSS general psychopathology subscore, which is in line with the finding of previous studies^{2,44}. Patients with schizophrenia who had greater severity of psychopathological symptoms may directly affect their enthusiasm for activity, leading to more significant obesity⁴⁵. However, some previous studies have reported opposite results, showing that weight gain was associated with less psychopathological symptoms^{46,47}, or that there was no correlation between PANSS and BMI in patients with schizophrenia treated with multiple antipsychotic drugs for one year⁴⁴. Kemp et al. also found that some complex factors, such as medical adherence and treatment time may confuse the results⁴⁸. In addition, several studies also showed that weight gain may be due to treatment of antipsychotic medications, including clozapine, olanzapine, and haloperidol^{48–50}. In order to rule out the effects of certain drugs, we included the antipsychotic treatment as covariates and found that there was still a significant correlation, suggesting that the relationship between high BMI and clinical psychopathological symptoms may be more than just a matter of antipsychotic treatment. Although the results were inconsistent in these studies, they all indicated that high BMI showed a certain correlation with clinical symptoms; however, more in-depth studies are needed to explore their causal relationship.

Several related factors for obesity were also identified in patients with schizophrenia in our study. We found that BMI was associated with glycolipid metabolism, showing that compared with low BMI patients, high BMI patients had higher blood glucose and lipid levels, especially total cholesterol, which is consistent with most of previous studies^{51–53}. Moreover, a recent study also reported that BMI was positively associated with TGs in Chinese patients with schizophrenia⁵⁴. Also, we found that high BMI was inversely correlated to education levels, which is consistent with previous studies^{2,55,56}. In addition, most of the previous studies demonstrated that atypical antipsychotic treatment may lead to increased obesity in schizophrenia^{57,58}. In this study, however, we did not find that BMI was significantly associated with clozapine/olanzapine treatment. Clinically, psychiatrists were cautious in the use of clozapine or olanzapine to high BMI patients, often switching to other antipsychotic drugs when a patient was becoming obese. Perhaps this is the main reason that we did not find significant association between obesity and clozapine/olanzapine treatment.

There are several methodological limitations of this study. First, a cross-sectional study design cannot directly show the causal relationship between obesity and Hcy in schizophrenia patients. Second, most of the subjects in this study were inpatients and some of them had been in the hospital for a long time. In general, they had more severe negative symptoms, a longer course of disease, and a long history of antipsychotic treatment, which may have influenced their Hcy levels³⁵. Therefore, our findings in this study should be confirmed in a large sample of patients with first-episode and drug-naïve schizophrenia. Third, there are some other confounding factors that may affect Hcy levels and obesity, such as physical exercise, diet, nutrition and psychotropic drugs. However, we did not collect these data in this study, which should be remedied in future studies. Fourth, previous studies found that there was sex difference in obesity in patients with schizophrenia⁵⁹. However, in this study, we included much fewer female patients than male patients, which may have affected the results due to an imbalance in the sex ratio. Finally, our study did not have a healthy control group. Therefore, the results in this study should be considered preliminary.

Conclusions

In summary, we demonstrated that high BMI was associated with lower Hcy levels, higher total cholesterol levels, and more severe psychopathological symptoms in patients with chronic schizophrenia. Moreover, Hcy was negatively associated with high BMI in these schizophrenia patients. Also, our results showed that high BMI patients had higher education levels but was not correlated with clozapine/olanzapine use. Future study in a large sample size with balanced male and female patients using a prospective and longitudinal design will be needed to explore the relationship between Hcy and obesity in first-episode and drug-naïve patients with schizophrenia.

Compliance with ethical standards. All procedures were based on the Declaration of Helsinki issued by the National Institutes of Health. The research scheme has been approved by the Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University before the study began. Written informed consents were obtained from each subject before participating in this study.

Received: 14 April 2020; Accepted: 19 August 2020

Published online: 30 September 2020

References

- Laursen, T. M., Nordentoft, M. & Mortensen, P. B. Excess early mortality in schizophrenia. *Annu. Rev. Clin. Psychol.* **10**, 425–448 (2014).
- Li, Q. *et al.* The prevalence, risk factors and clinical correlates of obesity in Chinese patients with schizophrenia. *Psychiatry Res.* **251**, 131–136 (2017).
- Pillinger, T. *et al.* Cardiac structure and function in patients with schizophrenia taking antipsychotic drugs: an MRI study. *Transl. Psychiatry* **9**, 163 (2019).
- Tian, Y. *et al.* Obesity in Chinese patients with chronic schizophrenia: Prevalence, clinical correlates and relationship with cognitive deficits. *Schizophr. Res.* **215**, 270 (2019).
- Walker, E. R., McGee, R. E. & Druss, B. G. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry* **72**, 334–341 (2015).
- Barker, M. K. *et al.* Diet and cardiometabolic side effects in children treated with second-generation antipsychotics. *Clin. Nutr. ESPEN* **23**, 205–211 (2018).
- Correll, C. U., Lencz, T. & Malhotra, A. K. Antipsychotic drugs and obesity. *Trends Mol. Med.* **17**, 97–107 (2011).
- Vancampfort, D. *et al.* Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry* **14**, 339–347 (2015).
- Zhang, X. Y. *et al.* Glucose disturbances in first-episode drug-naïve schizophrenia: relationship to psychopathology. *Psychoneuroendocrinology* **62**, 376–380 (2015).
- De Hert, M., Detraux, J., van Winkel, R., Yu, W. & Correll, C. U. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat. Rev. Endocrinol.* **8**, 114–126 (2011).
- Ho, P. I., Ortiz, D., Rogers, E. & Shea, T. B. Multiple aspects of homocysteine neurotoxicity: glutamate excitotoxicity, kinase hyperactivation and DNA damage. *J. Neurosci. Res.* **70**, 694–702 (2002).
- Shirafuji, N. *et al.* Homocysteine Increases Tau Phosphorylation, Truncation and Oligomerization. *Int. J. Mol. Sci.* **19**, 891 (2018).
- Moustafa, A. A., Hewedi, D. H., Eissa, A. M., Frydecka, D. & Misiak, B. Homocysteine levels in schizophrenia and affective disorders-focus on cognition. *Front Behav. Neurosci.* **8**, 343 (2014).
- Song, X. *et al.* Serum levels of BDNF, folate and homocysteine: in relation to hippocampal volume and psychopathology in drug naïve, first episode schizophrenia. *Schizophr. Res.* **159**, 51–55 (2014).
- Uhlhaas, P. J. & Singer, W. The development of neural synchrony and large-scale cortical networks during adolescence: relevance for the pathophysiology of schizophrenia and neurodevelopmental hypothesis. *Schizophr. Bull.* **37**, 514–523 (2011).
- Zhou, S. J. *et al.* Prevalence and clinical-demographic correlates of hyperhomocysteinemia in inpatients with bipolar disorder in a Han Chinese population. *Psychiatry Res.* **259**, 364–369 (2018).
- Canevar, L. *et al.* The evaluation of folic acid-deficient or folic acid-supplemented diet in the gestational phase of female rats and in their adult offspring subjected to an animal model of schizophrenia. *Mol. Neurobiol.* **55**, 2301–2319 (2018).
- Petronijević, N. D. *et al.* Plasma homocysteine levels in young male patients in the exacerbation and remission phase of schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **32**, 1921–1926 (2008).
- Muntjewerff, J. W., Kahn, R. S., Blom, H. J. & den Heijer, M. Homocysteine, methylenetetrahydrofolate reductase and risk of schizophrenia: a meta-analysis. *Mol. Psychiatry* **11**, 143–149 (2006).
- Ayesa-Arriola, R. *et al.* Homocysteine and cognition in first-episode psychosis patients. *Eur. Arch. Psychiatry Clin. Neurosci.* **262**, 557–564 (2012).
- Levine, J. *et al.* Homocysteine-reducing strategies improve symptoms in chronic schizophrenic patients with hyperhomocysteinemia. *Biol. Psychiatry* **60**, 265–269 (2006).
- Chang, Y. *et al.* The prevalence of hypertension accompanied by high homocysteine and its risk factors in a rural population: a cross-sectional study from Northeast China. *Int. J. Environ. Res. Public Health* **14**, 376 (2017).
- Liu, W., Wang, T., Sun, P. & Zhou, Y. Expression of Hcy and blood lipid levels in serum of CHD patients and analysis of risk factors for CHD. *Exp. Ther. Med.* **17**, 1756–1760 (2019).
- Nakazato, M. *et al.* Relation of body mass index to blood folate and total homocysteine concentrations in Japanese adults. *Eur. J. Nutr.* **50**, 581–585 (2011).
- Fu, L., Li, Y. N., Luo, D., Deng, S. & Hu, Y. Q. Plausible relationship between homocysteine and obesity risk via MTHFR gene: a meta-analysis of 38,317 individuals implementing Mendelian randomization. *Diabetes Metab. Syndr. Obes.* **12**, 1201–1212 (2019).
- Wang, Y. *et al.* Central but not general obesity is positively associated with the risk of hyperhomocysteinemia in middle-aged women. *Nutrients* **11**, 1614 (2019).
- Ji, C. Y., Chen, T. J. & Working Group on Obesity in China (WGOC). Empirical changes in the prevalence of overweight and obesity among Chinese students from 1985 to 2010 and corresponding preventive strategies. *Biomed. Environ. Scis* **26**, 1–12 (2013).
- Elshorbagy, A. K. *et al.* Homocysteine, cysteine, and body composition in the Hordaland Homocysteine Study: does cysteine link amino acid and lipid metabolism. *Am. J. Clin. Nutr.* **88**, 738–746 (2008).
- Ganji, V., Kafai, M. R. & Third National Health and Nutrition Examination Survey. Demographic, health, lifestyle, and blood vitamin determinants of serum total homocysteine concentrations in the third National Health and Nutrition Examination Survey, 1988–1994. *Am. J. Clin. Nutr.* **77**, 826–833 (2003).
- Elci, E., Kaya, C., Cim, N., Yildizhan, R. & Elci, G. G. Evaluation of cardiac risk marker levels in obese and non-obese patients with polycystic ovaries. *Gynecol. Endocrinol.* **33**, 43–47 (2017).
- Lewis, S. J. *et al.* The methylenetetrahydrofolate reductase C677T genotype and the risk of obesity in three large population-based cohorts. *Eur. J. Endocrinol.* **159**, 35–40 (2008).
- Lima, A., Ferin, R., Bourbon, M., Baptista, J. & Pavão, M. L. Hypercysteinemia, a potential risk factor for central obesity and related disorders in Azores, Portugal. *J. Nutr. Metab.* **2019**, 1826780 (2019).
- Foscolou, A. *et al.* The association between homocysteine levels, Mediterranean diet and cardiovascular disease: a case-control study. *Int. J. Food. Sci. Nutr.* **70**, 603–611 (2019).
- Liu, J., Quan, J., Li, Y., Wu, Y. & Yang, L. Blood homocysteine levels could predict major adverse cardiac events in patients with acute coronary syndrome: A STROBE-compliant observational study. *Medicine (Baltimore)* **97**, e12626 (2018).
- Fan, N. *et al.* Effect of risperidone on serum homocysteine levels in first-episode, drug-naïve patients with schizophrenia. *Neurosci. Lett.* **650**, 168–173 (2017).
- Cheng, L. S., Prasad, A. N. & Rieder, M. J. Relationship between antiepileptic drugs and biological markers affecting long-term cardiovascular function in children and adolescents. *Can. J. Clin. Pharmacol.* **17**, e5–46 (2010).
- Bhalodia, Y., Sheth, N., Vaghasiya, J. & Jivani, N. Role of fenofibrate alone and in combination with telmisartan on renal ischemia/reperfusion injury. *Ren Fail.* **32**, 1088–1094 (2010).
- Park, S. B. & Georgiades, A. Changes in body composition predict homocysteine changes and hyperhomocysteinemia in Korea. *J. Korean Med. Sci.* **28**, 1015–1020 (2013).

39. Williams, K. T. & Schalinske, K. L. New insights into the regulation of methyl group and homocysteine metabolism. *J. Nutr.* **137**, 311–314 (2007).
40. Gallistl, S., Sudi, K. M., Erwa, W., Aigner, R. & Borkenstein, M. Determinants of homocysteine during weight reduction in obese children and adolescents. *Metabolism* **50**, 1220–1223 (2001).
41. Momin, M. *et al.* Relationship between plasma homocysteine level and lipid profiles in a community-based Chinese population. *Lipids Health Dis.* **16**, 54 (2017).
42. Lee, J. M. *et al.* BRD7 deficiency leads to the development of obesity and hyperglycemia. *Sci. Rep.* **9**, 5327 (2019).
43. Kannan, S., Srinivasan, D., Raghupathy, P. B. & Bhaskaran, R. S. Association between duration of obesity and severity of ovarian dysfunction in rat-cafeteria diet approach. *J. Nutr. Biochem.* **71**, 132–143 (2019).
44. Hermes, E. *et al.* The association between weight change and symptom reduction in the CATIE schizophrenia trial. *Schizophr. Res.* **128**, 166–170 (2011).
45. Janney, C. A. *et al.* Sedentary behavior and psychiatric symptoms in overweight and obese adults with schizophrenia and schizoaffective disorders (WAIST Study). *Schizophr. Res.* **145**, 63–68 (2013).
46. Ascher-Svanum, H., Stensland, M. D., Kinon, B. J. & Tollefson, G. D. Weight gain as a prognostic indicator of therapeutic improvement during acute treatment of schizophrenia with placebo or active antipsychotic. *J. Psychopharmacol.* **19**, 110–117 (2005).
47. Hui, L. *et al.* Obesity correlates with fewer symptoms in schizophrenia treated with long-term clozapine: gender difference. *Psychiatry Res.* **225**, 741–742 (2015).
48. Kemp, D. E. *et al.* Associations among obesity, acute weight gain, and response to treatment with olanzapine in adolescent schizophrenia. *J. Child. Adolesc. Psychopharmacol.* **23**, 522–530 (2013).
49. Kang, S. H. & Lee, J. I. Metabolic disturbances independent of body mass in patients with schizophrenia taking atypical antipsychotics. *Psychiatry Investig.* **12**, 242–248 (2015).
50. Meltzer, H. Y., Perry, E. & Jayathilake, K. Clozapine-induced weight gain predicts improvement in psychopathology. *Schizophr. Res.* **59**, 19–27 (2003).
51. Brobakken, M. F. *et al.* A comprehensive cardiovascular disease risk profile in patients with schizophrenia. *Scand. J. Med. Sci. Sports* **29**, 575–585 (2019).
52. Jung, U. J. & Choi, M. S. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *Int. J. Mol. Sci.* **15**, 6184–6223 (2014).
53. Pickens, C. A., Vazquez, A. I., Jones, A. D. & Fenton, J. I. Obesity, adipokines, and C-peptide are associated with distinct plasma phospholipid profiles in adult males, an untargeted lipidomic approach. *Sci. Rep.* **7**, 6335 (2017).
54. An, H. *et al.* Obesity, altered oxidative stress, and clinical correlates in chronic schizophrenia patients. *Transl. Psychiatry* **8**, 258 (2018).
55. Subramaniam, M. *et al.* Body mass index, obesity, and psychopathology in patients with schizophrenia. *J. Clin. Psychopharmacol.* **34**, 40–46 (2014).
56. Veghari, G. *et al.* The correlation between educational levels and central obesity in the north of Iran: an epidemiologic study. *ARYA Atheroscler.* **9**, 217–222 (2013).
57. Garriga, M. *et al.* Antipsychotic-induced weight gain and birth weight in psychosis: a fetal programming model. *J. Psychiatr. Res.* **115**, 29–35 (2019).
58. Huhn, M. *et al.* Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* **394**, 939–951 (2019).
59. Yang, F. *et al.* Sex difference in the association of body mass index and BDNF levels in Chinese patients with chronic schizophrenia. *Psychopharmacology* **236**, 753–762 (2019).

Acknowledgment

This study was supported by the Affiliated Brain Hospital of Guangzhou Medical University. We would like to thank all the psychiatrists and nurses associated with this study for their hard work and important contributions to the study.

Author contributions

All authors contributed to the study design and data interpretation. F.C.W. and X.Y.Z. were responsible for management and oversight of the study. Y.Y.H., K.Wu and H.H.L. were responsible for general omnibus data analyses and were keys contributing author of the manuscript. Y.L. and J.H.L. were responsible for all research interviews and clinical chart reviews associated with this study. J.Z. and D.S.X. provided guidance on design of primary analyses. X.H. and Z.L.P. assisted with all data collection, analysis, and writing of the manuscript. All authors revised drafts and approved the final version of the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (NSFC; 31771074, 81802230), the Science and Technology Plan Project of Guangdong Province (2018B030335001, 2019B030316001), the Science and Technology Program of Guangzhou (2017A040405059, 201804010259, 201704020168, 201704020113, 201807010064, 201803010100, 201903010032), and the Science and Technology Project of Liwan District (201804011).

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to F.W. or X.Y.Z.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2020