The Bidirectional Relationship between Weight Gain and Cognitive Function in First-Episode Schizophrenia: A Longitudinal Study in China

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Posted Date: 29 February 2024

doi: 10.20944/preprints202402.1680.v1

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Article

The Bidirectional Relationship between Weight Gain and Cognitive Function in First-Episode Schizophrenia: A Longitudinal Study in China

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Abstract: In patients with schizophrenia, metabolic syndrome is associated with cognitive impairments. We carried out a second analysis of data from a longitudinal trial to examine the relationship between weight gain and cognitive function in patients with first-episode schizophrenia (FES) over the first 6-month antipsychotic treatment. Baseline and 6-month endpoint measurements were taken for both cognitive function and body weight. Linear and logistic regression analyses were applied to investigate the bidirectional relationship between weight gain and cognitive function. Clinically relevant weight gain (CRW) was defined as an increase in body weight exceeding 7%. The final analysis included 337 participants. Lower baseline scores in processing speed (OR=0.837, p=0.007), working memory and attention (OR=0.889, p=0.043), and executive function (OR=0.863, p=0.006) domains were significantly associated with CRW at the 6-month endpoint. After adjusting for confounders, CRW was found to be associated with improvement in the Brief Visuospatial Memory Test (p=0.036). The findings suggest that patients with lower baseline cognitive performance experienced more substantial weight gain. Conversely, weight gain was correlated with cognitive improvements, particularly in the domain of visual learning and memory. This suggested a potential bidirectional relationship between weight gain and cognitive function in patients with first-episode schizophrenia.

Keywords: schizophrenia; weight gain; cognitive function; first episode; China

1. Introduction

Individuals living with schizophrenia have higher prevalence of obesity compared to the general population [1,2]. Weight gain contributes to elevated risk of cardiometabolic diseases, such as type 2 diabetes mellitus, coronary artery disease, dyslipidemia, and hypertension [3–5], which are major factors leading to higher mortality rates and reduced life expectancy in schizophrenia [6]. Weight gain in schizophrenia is attributed to an interaction between lifestyle factors and treatment effects [7]. Particularly, first-episode schizophrenia (FES) patients may experience rapid and substantial weight gain in the early phase of antipsychotic treatments, highlighting the susceptibility of this population and the importance of early intervention[8,9].

Cognitive impairment is a prominent feature in schizophrenia which negatively impact patients' prognosis and social interact, therefore contributes to the disabling nature of schizophrenia [10,11]. Most patients experience both broad cognitive impairments as well as impairments in specific domains including learning, memory, attention, processing speed, and executive function [12]. Premorbid generalized cognitive impairment is identified to persist throughout the course of illness [13]. Though the course of these deficits is not fully clear, general evidences suggest there are relationships between cognitive deficits and negative symptoms [14]. Second-generation

 doi:10.20944/preprints202402.1680.v1

antipsychotics are believed to slightly improve patients' cognitive function, while none of them are found to have a satisfactory profile [15].

Emerging evidences suggest that metabolic disturbances are related to cognitive impairments [16,17]. Some studies have reported the correlation between obesity and cognitive impairments in patients suffered from schizophrenia [18,19], while others have presented contradictory results [20,21]. In a recent 12-month longitudinal study, weight gain is found to be correlated with improvements of the overall cognitive function, particularly in the working memory domain, in patients with first-episode schizophrenia spectrum disorders [22]. Cognitive deficits are considered a risk factor for weight gain, as they influence the self-control in eating behaviors [23,24]. Bond et al. have reported that poorer baseline cognitive function could predict weight gain over a 12-month period in patients suffered from bipolar disorder [25]. Few studies have explored the relationship between baseline cognitive function and weight gain in patients with schizophrenia.

There is a scarcity of longitudinal studies exploring the relationship between weight gain and cognitive function in patients with schizophrenia. Therefore, we conducted a second analysis of the data from the Chinese First-Episode Schizophrenia Trial (CNFEST) to examine the relationship between weight gain and cognitive function over the first 6-month antipsychotic treatments. We hypothesized that baseline cognitive function might be linked to weight gain during treatment, and conversely, weight gain might be associated with changes in cognitive function as well.

2. Materials and Methods

2.1. Participants and Setting

CNFEST was a multicenter, randomized clinical trial conducted in several psychiatric hospitals nationwide from 2008 to 2010 [26]. The trial was registered on ClinicalTrials.gov (No. NCT01057849) and approved by the ethics committees of the Ethics Committee of Peking University Sixth Hospital. Written informed consent was obtained from all participants. Participants were 18-45 years old with a diagnosis of schizophrenia which was confirmed by the Structured Clinical Interview for DSM-IV [27]. Their illness duration were less than three years, with continuous antipsychotic treatment less than four weeks. Participants with comorbid other major physical or mental health problems (including alcohol and substance abuse), exposed to long-acting antipsychotic injections, or contraindicated to antipsychotics were excluded. Eligible participants were randomly assigned to an aripiprazole (15-30mg/day), risperidone (3-6mg/day), or olanzapine (10-25mg/day) tretament group. Participants who showed little benefit from the initial treatment were allowed to undergo an antipsychotic switching after first four weeks. Besides, oral benzhexol (2–6 mg/day), promethazine (25–75 mg/day), or lorazepam (0.5–1.5 mg/day) could be prescribed to minimize the drop-outs.

2.2. Assessments

Three psychiatrists who completed consistent training for all instruments conducted clinical assessments at each study center. Psychopathology was measured by the Positive and Negative Syndrome Scale (PANSS)–Chinese Version [28]. Three other psychiatrists who were certified by the HIV Neurobehavioral Research Center of the University of California at San Diego performed cognitive assessments at each center [29]. Ten neuropsychological tests from a battery were administered to measure participants' cognitive functioning at baseline (T1) and at 6-month follow-up endpoint (T2). The clinical validity and test-retest reliability of the battery among patients with schizophrenia and healthy controls in China were verified [30]. The tests assessed six main cognitive function domains, namely processing speed [tested by Trail Making Test–part A (TRAIL A), Stroop Color and Word Test, Animal Naming Test, and Color Trail Test-1], verbal learning and memory [tested by Hopkins Verbal Learning Test-Revised (HVLT-R)], visual learning and memory [tested by Brief Visual-Spatial Memory Test-Revised (BVMT-R)], working memory and attention [tested by Paced Auditory Serial Addition Task (PASAT)], executive function [tested by Color Trail Test-2 and the Stroop Test-unconscious], and fine motor function [tested by Grooved Pegboard Test–dominant hand and Grooved Pegboard Test—nondominant hand (PEG-SD and PEG-SN)] [31].

Body weight was measured at baseline and 6-month follow-up. Participants removed overcoats and shoes and weighed themselves on the same calibrated electronic scale. Body mass index (BMI) was calculated as body weight in kilograms (kg) divided by height in meters squared (m2). Clinically

 doi:10.20944/preprints202402.1680.v1

relevant weight gain (CRW) was defined as an increase in body weight exceeding 7% from baseline to post-treatment [32].

2.3. Statistical analysis

Data were analyzed using SPSS software version 25.0 (IBM Corp., Armonk, New York, US). We conducted logistic regression analyses to evaluate the influence of baseline cognitive function on weight gain. All raw scores of cognitive tests were transformed into scale scores, with a mean of 10 and a standard deviation of 3 [33]. Scores of cognitive domains were calculated by the average scale scores of all included tests. The composite cognitive scores which represented global cognitive function were calculated by averaging scale scores of all cognitive tests. We further conducted linear regression analyses to explore the effect of CRW on changes in cognitive function, with the change rates of cognitive test scores as the dependent variables and CRW as the independent variable. Since scale scores cannot be used for comparison at different time points, raw scores of each cognitive test were used in this analysis. Odds ratios (OR) and 95% confidence intervals (CI) were used to quantify the extent of the effect. All statistical tests were 2-tailed, with p-value less than 0.05 considered significant.

3. Results

3.1. Demographic and clinical characteristics of study participants

A total of 337 participants (167 males and 170 females) completed both the baseline and the 6-month follow-up assessments, with an average age of 25.03±7.16 years at entry. Median duration of untreated psychosis was 7 months. Mean baseline PANSS total score was 85.54±14.60, and mean baseline BMI was 21.05±3.07 kg/m2. 34.8% of the participants were treated with risperidone, 37.6% with olanzapine, and 27.6% with aripiprazole, with an average daily antipsychotic dose of 15.0 mg in olanzapine equivalent[34]. The raw scores of cognitive tests and body weight at baseline (T1) and the 6-month follow-up endpoint (T2) were presented in Table 1. Except for Animals-Naming and HVLT-R tests, other tests showed significant improvements during the follow-up period (all $p<0.05$). The average weight gain was 6.3kg during the 6-month antipsychotic treatment period, corresponding to an average rate of weight gain of 10.8%. 214 patients (64.3%) experienced clinically relevant weight gain (CRW).

Table 1. Comparisons of cognitive tests raw scores and body weight at baseline (T1) and at the 6-month follow-up endpoint (T2)

N=333	Baseline Mean (SD)	6-month follow-up Mean (SD)	t	*p*
Processing speed				
TRAIL A	49.82 (23.26)	40.01 (16.77)	9.613	**<0.001**
CTT1	57.21 (29.34)	46.89 (27.64)	6.764	**<0.001**
Animals-Naming	17.02 (5.58)	17.00 (5.58)	0.085	0.932
Stroop Word	79.39 (21.30)	82.43 (18.18)	-3.221	**0.001**
Stroop Color	54.00 (16.91)	56.58 (14.48)	-3.734	**<0.001**
Vocabulary learning and memory				
HVLT-R Learning (total 3 trials)	22.16 (6.41)	22.52 (5.35)	-1.054	0.293
HVLT-R delayed recall	7.57 (2.93)	7.49 (2.70)	0.454	0.650
Visual learning and memory				
BVMT-R Learning (total 3 trials)	22.18 (7.50)	24.01 (6.89)	-5.039	**<0.001**

 doi:10.20944/preprints202402.1680.v1

BVMT-R delayed recall	8.97 (2.94)	9.41 (2.45)	-2.949	**0.003**
Working memory and attention				
Spatial Span	14.98 (3.81)	16.05 (3.48)	-5.911	**<0.001**
PASAT	31.01 (11.00)	37.16 (9.52)	-12.162	**<0.001**
Executive function				
CTT2	119.58 (58.24)	95.63 (36.53)	8.850	**<0.001**
Stroop Unconscious	31.34 (11.33)	34.01 (10.06)	-5.605	**<0.001**
Fine motor function				
Peg-SD	85.46 (28.65)	77.52 (17.25)	5.860	**<0.001**
Peg-SN	95.02 (32.64)	90.02 (24.85)	3.164	**0.002**
Body Weight	58.54 (11.18)	64.89 (11.14)	-21.147	**<0.001**

TRAIL A: Trail Making Test Part A, *CTT1*: Color Trails Test 1, *CTT2*: Color Trails Test 2, *HVLT-R*: Hopkins Verbal Learning Test-Revised, *BVMT-R*: Brief Visuospatial Memory Test-Revised, *Spatial Span*: Wechsler Memory Scale-spatial span subtest, *PASAT*: paced auditory serial addition test, *Peg-SD*: Grooved Pegboard Test dominant hand, *Peg-SN*: Grooved Pegboard Test non-dominant hand.

3.2. The relationship between baseline cognitive function and CRW at the follow-up endpoint

When comparing the baseline parameters, significant differences were observed in several factors between participants with CRW and those without CRW. These factors include age (p=0.016), baseline BMI (p<0.001), treated with olanzapine (p=0.003), domain scores in baseline processing speed (p=0.034), working memory and attention (p=0.084), and executive function (p=0.017) (Table S1). Gender showed a marginal significance (p=0.079). Therefore, we conducted logistic regression analyses with above three baseline cognitive domain scores as independent variables and CRW as the dependent variable, controlling for age, gender, baseline BMI, and treatment group. Our results indicated that worse performances in all three cognitive domains at baseline [processing speed (OR=0.837, p=0.007), working memory and attention (OR=0.889, p=0.043), and executive function (OR=0.863, p=0.006)] were associated with CRW at the 6-month follow-up endpoint (Table 2).

Table 2. Logistic regression models of the relationships between baseline cognitive function and CRW.

	OR	95% CI	*p*
Model 1			
Processing speed T1	0.837	(0.735, 0.954)	**0.007**
Gender	0.703	(0.417, 1.183)	0.185
Age	0.972	(0.936, 1.008)	0.129
BMI T1	0.769	(0.702, 0.844)	**<0.001**
Treated with olanzapine	2.884	(1.648, 5.050)	**<0.001**
Model 2			
Working memory and attention T1	0.889	(0.794, 0.996)	**0.043**
Gender	0.771	(0.462, 1.285)	0.318
Age	0.985	(0.951, 1.021)	0.402
BMI T1	0.769	(0.701, 0.844)	**<0.001**
Treated with olanzapine	2.851	(1.632, 4.981)	**<0.001**

 doi:10.20944/preprints202402.1680.v1

Model 3			
Executive function T1	0.863	(0.777, 0.958)	**0.006**
Gender	0.724	(0.430, 1.218)	0.223
Age	0.969	(0.933, 1.006)	0.099
BMI T1	0.768	(0.699, 0.843)	**<0.001**
Treated with olanzapine	2.831	(1.622, 4.943)	**<0.001**

T1: baseline, *BMI*: Body Mass Index

3.3. The relationship between CRW and cognitive improvements during the 6-month treatment

When comparing the cognitive improvements over the course of 6 months, participants who achieved CRW exhibited more improvements in BVMT-R delayed recall (p=0.042) and Spatial Span tests (p=0.031) (Table S2). Therefore, we conducted linear regression analyses with the change rates of BVMT-R delayed recall and Spatial Span tests as dependent variables and CRW as the independent variable, controlling for age, gender, education, treatment (types and doses of antipsychotics), symptom improvements, and baseline symptom severity. Since there were no significant differences in baseline cognitive test scores between participants with CRW and those without CRW (p>0.05), we chose not to include baseline cognitive test scores as confounding variables. CRW showed significant association with improvements in the BVMT-R delayed recall test (β=0.121, t=2.101, p=0.036), and a marginal association with improvements in the Spatial Span test (β=0.099, t=1.707, p=0.089) (Table 3).

Table 3a. Linear regression model of the relationship between CRW and improvement in BVMT-R delayed recall test during 6-month treatment

ΔBVMT-R Delayed Recall	Standardized Beta-coefficient	T	*p*
CRW	0.121	2.101	**0.036**
Gender	0.081	1.415	0.158
Age	-0.019	-0.333	0.740
Education years	-0.071	-1.258	0.209
ΔPANSS Total scores	-0.222	-2.146	0.033
PANSS Total scores T1	-0.122	-1.151	0.250
Treatment groups	0.143	1.464	0.144
Antipsychotic dose (in olanzapine equivalent)	0.140	1.606	0.109

BVMT-R: Brief Visuospatial Memory Test-Revised, CRW: clinically relevant weight gain, PANSS: Positive and Negative Syndrome Scale

Δ was calculated by (T2 scores-T1 scores)/T1 scores.

Table 3b. Linear regression model of the relationship between CRW and improvement in Spatial Span test during 6-month treatment

ΔSpatial Span	Standardized Beta-coefficient	T	*p*
CRW	0.099	1.707	**0.089**
Gender	-0.023	-0.393	0.694
Age	0.090	1.578	0.116
Education years	-0.044	-0.769	0.442

 doi:10.20944/preprints202402.1680.v1

ΔPANSS Total scores	0.143	1.369	0.172
PANSS Total scores T1	0.215	2.005	0.046
Treatment groups	-0.030	-0.309	0.757
Antipsychotic dose (in olanzapine equivalent)	-0.008	-0.090	0.929

Spatial Span: Wechsler Memory Scale-spatial span subtest, *CRW:* clinically relevant weight gain, *PANSS*: Positive and Negative Syndrome Scale

Δ was calculated by (T2 scores-T1 scores)/T1 scores.

4. Discussion

To the best of our knowledge, this study was one of the largest longitudinal studies investigating the relationship between weight gain and cognitive function in patients with first-episode schizophrenia. Our results revealed a bidirectional relationship. On one hand, poorer baseline cognitive performance, especially in the processing speed, working memory and attention, and executive function domains were related to clinically relevant weight gain (CRW) over the first 6-month antipsychotic treatment. On the other hand, CRW was associated with cognitive improvements in the visual learning and memory domain, which was independent from psychopathology improvement.

Our results demonstrated significant improvements in nearly all cognitive function domains together with significant weight gain during the first 6-month treatment in patients with first-episode schizophrenia, which were consistent with previous studies [35,36]. We found that poorer baseline performance in processing speed, working memory and attention, and executive function were correlated with clinically relevant weight gain during the 6-month treatment period. Previous studies conducted in healthy population and patients with bipolar disorder also have reported unanimous correlation [25,37]. Similarly, Jakobsen et al. have revealed that higher baseline cognitive function might predict a more advantageous metabolic profile in patients with schizophrenia spectrum disorders [38]. The effect of cognitive function on weight gain may be mediated by eating behavior [39,40]. People with schizophrenia have been observed to exhibit significantly unhealthy dietary habits [41]. Disordered eating behaviors are believed to be associated with impaired frontal lobe function[42], which is prominent in the pathophysiology and cognitive impairment in schizophrenia [43,44]. Individuals with lower working memory tend to choose less healthy foods and face a higher likelihood of failure in dietary interventions [45]. In contrast, those with superior working memory experience quicker satisfaction from stimuli [46]. Conversely, individuals with poor executive function often struggle with delaying gratification, leading to ineffective restraint in eating behaviors [47].

Research evidences indicate a relationship between psychopathology improvement and weight gain induced by antipsychotics [48,49]. Notably, our results demonstrated that the correlation between weight gain and cognitive enhancement persisted after accounting for psychotic symptom improvements. We proposed several possible explanations for this result. Firstly, 5-HT receptors, which are targets for atypical antipsychotics, are involved in both cognitive function and weight gain [50,51]. Secondly, the physiological effects of insulin in the central nervous system include the regulation of striatal dopamine levels, peripheral glucose homeostasis, body weight, and cognitive performance [52]. Thus, insulin regulation may play a role in the correlation between cognitive improvements and weight gain[53]. Thirdly, patients with better treatment compliance experience greater improvements in cognitive function during treatment [54]. Consequently, individuals with better treatment compliance may also receive higher doses of antipsychotics or undergo longer treatment durations, potentially leading to increased antipsychotic-induced weight gain [55].

Several studies have reported the association between obesity and compromised cognitive function [56,57], which is inconsistent with our results. All the aforementioned studies are cross-sectional, preventing the investigation of the longitudinal relationship between weight gain and cognitive improvements. We found only one prospective cohort study in this field. Luckhoff et al. discovered that as their BMI increased, patients with first-episode schizophrenia spectrum disorders exhibited improved working memory function and overall cognitive function over a 12-month

 doi:10.20944/preprints202402.1680.v1

treatment period [22], aligning with our findings. However, it is crucial to note that this correlation may change as the disease progresses and treatment persists [58]. It is plausible that the adverse effects of metabolic syndrome accumulate to a threshold, ultimately resulting in cognitive impairments [59].

Our findings have considerable clinical implications. Dietary interventions are effective in reducing weight and improving cognitive function in obese population [60]. Previous research indicates that the dietary plan with reduced calorie intake can improve cognitive function and reduce metabolic indicators in patients with schizophrenia [61]. Additionally, there is evidence suggesting that increasing aerobic exercise can effectively enhance cognitive function in patients with schizophrenia [62]. Cognitive behavioral therapy is beneficial in managing weight gain in patients treated with antipsychotics[63]. Thus, we recommend early weight management and cognitive remediation, as they might offer dual benefits for patients with schizophrenia. Healthcare providers should raise awareness about the bidirectional relationship between weight gain and cognitive function and provide appropriate intervention recommendations for patients and their family members. By implementing effective interventions targeting both weight management and cognitive function, healthcare providers can contribute to enhancing the overall well-being and quality of life for patients with schizophrenia[64].

This study had several strengths which contributed to its scientific rigor. The utilization of a longitudinal design, detailed cognitive assessments, and a relatively large sample size enhanced the validity of our findings. Focusing on minimally treated first-episode schizophrenia patients allowed us to control confounding factors including illness duration and complex medication regimens. Nevertheless, several warrant limitations should be taken into consideration. Firstly, the relatively short follow-up duration and the somewhat high drop-out rate might limit us to observe the long-term relationship between weight gain and cognitive function. Secondly, we did not include laboratory metabolic indicators, i.e. blood pressure, glucose level, and lipids profile, which might limit us to provide more objective results. Thirdly, psychosocial factors such as dietary habits and physical activities were not collected in the original study, which might have a significant impact on the relationship between weight change and cognitive function. Addressing these issues in future research will enable us to gain a more comprehensive understanding of the complex interactions between weight gain, cognitive function, and related factors in patients with schizophrenia.

5. Conclusions

In conclusion, our study suggests that patients in their first episode of schizophrenia, with poorer baseline cognitive performance, particularly in the domains of processing speed, working memory and attention, and executive function, tend to experience more prominent weight gain during the first 6-month antipsychotic treatment. Intriguingly, weight gain was found to be associated with cognitive improvements in the visual learning and memory domain. These findings imply a bidirectional relationship between weight gain and cognitive function, suggesting a connection that extends beyond a simple causal link. Further study should delve into the association between metabolic syndrome and cognitive function within the specific context of schizophrenia, considering both its nature and progression.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Table S1: Comparisons of baseline clinical and sociodemographic characteristics between CRW and Non-CRW group; Table S2: Comparison of cognitive improvements between participants with CRW and without CRW.

Author Contributions: Conceptualization: Ke Ma, Tianhang Zhou. Data curation: Chengcheng Pu, Zhang Cheng, Xue Han, Lei Yang. Formal analysis: Ke Ma. Funding acquisition: Xin Yu, Chengcheng Pu. Investigation: Zhang Cheng, Xue Han, Lei Yang. Methodology: Xin Yu. Project administration: Xin Yu. Resources: Xin Yu, Chengcheng Pu. Software: Ke Ma. Supervision: Xin Yu. Validation: Ke Ma, Xin Yu, Tianhang Zhou. Visualization: Ke Ma. Writing—original draft: Ke Ma, Tianhang Zhou. Writing—review & editing: Xin Yu.

Funding: This study was supported by the National Science Fund China (No. 82171500), the Key Program of Beijing Science and Technology Commission (No. D171100007017002), and the Capital's Funds for Health Improvement and Research (CFH, No. 2018-4-4116).

 doi:10.20944/preprints202402.1680.v1

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by Ethics Committee of Peking University Sixth Hospital (protocol code: 2008-002, date of approval: 1 Feb 2008).

Informed Consent Statement: Written informed consent was obtained from all participants in the study.

Data Availability Statement: The data supporting the results of this study are available upon request from the corresponding author.

Acknowledgments: We extend our gratitude to everyone who contributed to the preparation and data collection, including the participants and their families, for their invaluable cooperation and assistance. Furthermore, we express our appreciation to fellow researchers at our collaborating centers for their dedicated work and unwavering support throughout this study.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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