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Olanzapine-induced weight gain plays a key role in the potential cardiovascular risk: evidence from heart rate variability analysis

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Patients with schizophrenia have a higher risk for cardiovascular disease (CVD) than the general population. Research has suggested that autonomic imbalance is a common pathway to increased morbidity and mortality for CVD. Heart rate variability (HRV) analysis is a non-invasive method that assesses autonomic imbalance, and low HRV is correlated with high cardiovascular risk. Olanzapine, a widely used antipsychotic drug, is considered to have good cardiac safety because of not causing significant corrected QT-interval (QTc) prolongation; however, it is still unclear whether olanzapine affects HRV. We recruited 83 patients with schizophrenia who were medication-free for at least 1 month and tested their HRV at the baseline and 4 weeks after treatment with olanzapine. We found that patients who had substantial weight gain (EWG) manifested significantly lower HRV than those who had non-substantial weight gain (NWG) and that HRV decrease was positively correlated to an increase in body mass index (BMI) and weight gain. Our results indicate that olanzapine-induced weight gain may play an important role in its potential cardiovascular risk. Since olanzapine has a very high potential for weight gain compared with other antipsychotics, further research is needed to explore its cardiovascular safety profile, specifically long-term cardiac safety.

Patients with schizophrenia have a mortality risk that is two to three times higher as that of the general population[1]. Despite the high risk for unnatural death including suicide, accidents, violence and substance abuse, most of the extra deaths are due to natural causes, specifically cardiovascular disease (CVD)[1–4]. Furthermore, growing evidence indicates that both typical and atypical antipsychotics may increase cardiovascular risk[5–7]. Autonomic imbalance is associated with various pathological conditions and may be a final, common pathway to increased morbidity and mortality in CVD[8]. Heart rate variability (HRV) analysis is a non-invasive method that can be used to assess autonomic imbalance and the risk for sudden cardiac death and arrhythmia[9,10]. Low HRV, which is mainly characterized by hyperactive sympathetic and/or hypoactive parasympathetic activity, has been observed in patients with schizophrenia, and its severity can be influenced by the psychotic state and duration of the disease[11–14].

Studies have also shown that certain antipsychotics, particularly clozapine, can aggravate autonomic dysregulation[15,16]. However, it is not clear whether olanzapine, a widely used atypical antipsychotic that has a chemical structure and receptor affinity profile that is similar to clozapine, has a similar influence on HRV[17–19]. In addition, overweight or obesity, a common side effect of olanzapine, is also an important cardiovascular risk factor[20–23]. Because even modest short-term weight gain can lead to changes in cardiac autonomic balance[21], we hypothesized that patients with schizophrenia and medicated with olanzapine would display a reduction in HRV that is correlated with weight gain; that is, patients who have substantial weight gain would have lower HRV. As early weight gain may be a predictor of substantial weight gain in the future[24], HRV changes caused by olanzapine-induced weight gain should be observed in early treatment stages. In this study, we divided 83 olanzapine-medicated patients with schizophrenia into two groups according to their changes in body mass index (BMI) after 4 weeks of treatment and examined differences in HRV as well as the correlation between HRV changes and BMI.

Table 1 | Demographic and baseline heart rate variability indicators of patients with schizophrenia (SCZ) and healthy controls (HC). Continuous data are presented as the means ± the standard deviation (SD)

Parameter	SCZ (n = 83)	HC (n = 46)	Statistics	*P*-value
Age (year)	35.02 ± 5.55	35.78 ± 6.53	$t = 0.698$	0.486
Gender (M/F)	28/55	17/29	$\chi^2 = 0.135$	0.713
$BMI_{baseline}$ (kg/m^2)	22.09 ± 2.65	21.63 ± 2.80	$t = 0.923$	0.358
$Weight_{baseline}$ (kg)	60.22 ± 8.54	59.72 ± 8.23	$t = 0.323$	0.747
Education (years)	10.60 ± 3.21	10.48 ± 2.89	$t = 0.218$	0.828
Smoker/Non-smokers	24/59	16/30	$\chi^2 = 0.476$	0.490
$FPG_{baseline}$ (mmol/L)	5.28 ± 0.28	5.23 ± 0.31	$t = 0.892$	0.374
Handedness (R/L/M)	65/7/11	38/4/4	$\chi^2 = 0.599$	0.741
$SDNN_{baseline}$ (ms)	88.11 ± 13.76	99.61 ± 19.91	$t' = 3.484$	**0.001**
$LFn_{baseline}$ (n.u)	52.42 ± 8.74	46.49 ± 8.81	$t = 3.676$	**0.000**
$HFn_{baseline}$ (n.u)	42.43 ± 8.70	47.64 ± 8.56	$t = 3.272$	**0.001**
$LF/HF_{baseline}$	1.38 ± 0.83	1.04 ± 0.45	$t' = 2.964$	**0.004**

M: male; F: female; R: right; L: left; M: mixed; BMI: body mass index; FPG: fasting plasma glucose; SDNN: standard deviation of the NN interval; LFn: normalized low frequency power; HFn: normalized high frequency power; n.u.: normalized unit.

Results

Baseline data from patients with schizophrenia and healthy controls. Participants were 83 patients with schizophrenia and 46 healthy controls. As shown in Table 1, there was no significant difference between the patients with schizophrenia (SCZ, n = 83) and healthy controls (HC, n = 46) in demographic variables, including age, gender, smoking status, years of education, handedness, and baseline BMI and weight (All $P > 0.05$). When HRV measurements were tested, the standard deviation of the NN interval (SDNN) and the normalized high frequency power (HFn) of the SCZ group were significantly lower than the HC group (both $P = 0.001$) at baseline, whereas the normalized low frequency power (LFn) and LF to HF ratios (LF/HF) were higher in the SCZ group than the HC group ($P = 0.000$ and 0.005, respectively).

Non-HRV data from the substantial early weight gain group (EWG) and the non-substantial weight gain group (NWG). The 83 patients with schizophrenia were divided into two groups according to the degree of BMI changes after the 4 weeks of treatment[24], i.e., substantial early weight gain group (EWG, n = 25) and the non-substantial weight gain group (NWG, n = 58). Demographic data and illness factors are displayed in Table 2. Independent-samples *t*-tests and chi-square tests showed that there were no significant group differences for all variables except for BMI and weight at week 4 (BMI_{week4} and $Weight_{week4}$). The BMI_{week4} and $Weight_{week4}$ of the EWG was significantly higher than the NWG group (23.88 ± 2.38 vs. 22.44 ± 2.78, $P = 0.026$, and 65.80 ± 7.44 vs. 60.88 ± 9.06, $P = 0.012$, respectively). The results indicated that both groups had significant reductions in Positive and Negative Syndrome Scale (PANSS) scores and increases in BMI and weight (All $P < 0.05$) when compared with baseline values via paired-samples *t*-tests.

HRV data for the substantial early weight gain group (EWG) and the non-substantial weight gain group (NWG). As shown in Table 3, there was no significant difference between the EWG and NWG groups for all four HRV indicators at baseline (All $P > 0.05$). However, when re-tested after the 4-week olanzapine treatment, independent-samples *t*-tests showed that all indicators were significant (All $P < 0.05$). Specifically, the EWG group had lower SDNN and HFn and higher LFn and LF/HF ratio compared with the NWG group, which indicated a lower HRV. Similarly, there was a significant decrease in SDNN and HFn, and increase in LFn and LF/HF ratio in the EWG group as shown by paired-samples *t*-tests (All $P < 0.05$), whereas only the HFn decrease was significant in the NWG group ($t = 3.628$, $P = 0.001$).

Table 2 | Demographic and illness factors for the substantial early weight gain group (EWG) and the non-substantial weight gain group (NWG). Data are presented as the means ± the standard deviation (SD)

Parameter	EWG (n = 25)	NWG (n = 58)	Statistics	*P*-value
Age (year)	34.56 ± 5.81	35.22 ± 5.47	$t = 0.498$	0.620
Gender (M/F)	9/16	19/39	$\chi^2 = 0.082$	0.774
Education (year)	10.08 ± 3.59	10.83 ± 3.04	$t' = 0.910$	0.369
Smoker/Non-smoker	8/17	16/42	$\chi^2 = 0.166$	0.793
Handedness (R/L/M)	18/3/4	47/4/7	$\chi^2 = 0.931$	0.630
Illness duration (month)	36.48 ± 25.67	33.17 ± 18.00	$t = 0.672$	0.504
Olanzapine dose (mg/d)	14.70 ± 4.10	14.91 ± 3.34	$t = 0.489$	0.626
Illness Subtype (P/D/U)	17/2/6	43/5/10	$\chi^2 = 0.513$	0.774
$PANSS_{baseline}$	96.96 ± 7.41	96.03 ± 10.27	$t' = 0.462$	0.646
$PANSS_{week4}$	75.80 ± 4.81①	74.86 ± 7.39①	$t' = 0.687$	0.495
$BMI_{baseline}$ (kg/m^2)	22.35 ± 2.42	21.98 ± 2.75	$t = 0.580$	0.564
BMI_{week4} (kg/m^2)	23.88 ± 2.38①	22.44 ± 2.78①	$t = 2.269$	**0.026**
$Weight_{baseline}$ (kg)	61.57 ± 7.47	59.64 ± 8.96	$t = 0.947$	0.346
$Weight_{week4}$ (kg)	65.80 ± 7.44①	60.88 ± 9.06①	$t' = 2.585$	**0.012**
$FPG_{baseline}$ (mmol/L)	5.30 ± 0.26	5.27 ± 0.28	$t = 0.451$	0.653
FPG_{week4} (mmol/L)	5.33 ± 0.27	5.31 ± 0.30	$t = 0.409$	0.684

M: male; F: female; R: right; L: left; M: mixed; P: paranoid; D: disorganized; U: undifferentiated; PANSS: Positive and Negative Syndrome Scale; BMI: body mass index; FPG: fasting plasma glucose.
①compared with baseline values using a paired-samples *t*test, *P*-value < 0.05.

Table 3 | Heart rate variability measurements for the substantial early weight gain (EWG) and non-substantial weight gain groups (NWG). Data are presented as the means ± the standard deviation (SD)

Variable	EWG (n = 25)	NWG (n = 58)	*P*-value*	Statistics	*P*-value#
$SDNN_{baseline}$ (ms)	85.04 ± 12.14	89.43 ± 14.30	0.180	$t' = 1.431$	0.158
$SDNN_{week4}$ (ms)	78.68 ± 11.36①	88.84 ± 14.50	0.103	$t' = 3.430$	**0.001**
$LFn_{baseline}$ (n.u.)	52.68 ± 9.43	52.30 ± 8.52	0.309	$t = 0.179$	0.859
LFn_{week4} (n.u.)	57.77 ± 8.74①	53.34 ± 7.63	0.255	$t = 2.324$	**0.023**
$HFn_{baseline}$ (n.u.)	42.35 ± 9.67	42.47 ± 8.34	0.166	$t' = 0.055$	0.957
HFn_{week4} (n.u.)	35.94 ± 8.00①	40.99 ± 7.87①	0.475	$t = 2.664$	**0.009**
$LF/HF_{baseline}$	1.39 ± 0.71	1.38 ± 0.88	0.638	$t = 0.065$	0.948
LF/HF_{week4}	1.76 ± 0.74①	1.41 ± 0.63	0.115	$t' = 2.057$	**0.046**

SDNN: standard deviation of the NN interval; LFn: normalized low frequency power; HFn: normalized high frequency power; n.u.: normalized unit.
①compared with baseline using a paired-samples *t*test, *P*-value < 0.05;
**P*-value of Levene's test for equality of variances;
#*P*-value of independent-samples *t*test.

Correlations between BMI and HRV. We considered olanzapine dosage and the PANSS reduction rate to be confounding factors in the correlations between changes in BMI and changes in HRV indicators. For the SCZ group, BMI change ($\Delta BMI = BMI_{week4} - BMI_{baseline}$), which reflects normalized weight gain or loss, was positively correlated with LFn and LF/HF ratio changes, and negatively correlated with SDNN and HFn changes. Subgroup analyses revealed a similar pattern in the EWG group, whereas there was a marginal negative correlation between changes of BMI and HFn in the NWG group (Table 4). Figure 1 shows the linear regression model of changes in BMI and HRV indicators for the SCZ, EWG and NWG groups.

Correlations between weight gain and HRV. Similar to the ΔBMI, we examined the correlations between changes in weight gain ($\Delta Weight\% = (Weight_{week4} - Weight_{baseline})/Weight_{baseline} \times 100\%$) and changes in HRV indicators using a partial correlation analysis. The results indicated a relationship between ΔWeight% and HRV indicators that was similar to the ΔBMI for the SCZ, EWG and NWG groups (Table 5).

Discussion

In the present study, we explored the association between olanzapine-induced weight gain and HRV. Our results suggest that patients with schizophrenia and substantial early weight gain also showed decreased SDNN and HFn values and increased LFn and LF/HF ratios, which are responsible for reductions in HRV and, thus, may lead to an increased risk of cardiovascular disease.

Impaired HRV has been observed in patients with schizophrenia at both of their first episode and drug-free status[13,25]. Consistent with previous results[13,25], we found that patients with schizophrenia exhibited a significantly lower HRV than healthy controls. Research has suggested that HRV change is associated with psychotic severity as determined by clinical measures, such as PANSS[11,14]. In our study, patient groups significantly improved after 4 weeks of olanzapine treatment, according to changes in PANSS scores, and were therefore expected to have amelioration in HRV. Surprisingly, the EWG group showed reductions of SDNN and HFn, and increases in LFn and the LF/HF ratio, whereas the NWG group had a decrease in HFn. This suggests that olanzapine may harm HRV, which may be correlated to the weight-gain side effect, despite not causing clinically significant corrected QT interval (QT_C) prolongation[17].

Thus far, several studies have found inconsistent results related to the impact of olanzapine on HRV or vagal function[17–19]. Slike et al.[19] compared acute HRV changes after antipsychotic agent administration, including risperidone, thioridazine and olanzapine via a randomized cross-over design in 16 healthy male volunteers, and found that after taking a single dose of olanzapine (10 mg), the HRV indicators after 12 hours Holter recording were significantly increased compared to a placebo. This result indicated that olanzapine may have direct effects on HRV even after a single dose, which could be caused by its high binding affinity to muscarinic receptors and adrenergic α1 receptors. This result is in contrast to the findings from the present study, and may be due to dosage and medication duration differences. A single administration of olanzapine is not sufficient to cause apparent weight gain, which may exert indirect effects on HRV. Furthermore, it is important to consider differential response-patterns to the drug between healthy people and patients with schizophrenia because they differ from each other in many ways. Interestingly, in the Slike et al. study[19], thioridazine, another antipsychotic that also has high binding affinities with muscarinic receptors and adrenergic α1 receptors, significantly decreased HRV. This suggests that the direction (i.e., positive or negative) of antipsychotics' effects on HRV is unlikely determined by their receptor blinding profiles, hence; is difficult to explain the between-group differences of HRV in the present study. Mann et al.[17] conducted a study on patients with schizophrenia who displayed predominantly negative symptoms and found that their LF/HF ratio increased during sleep after 4 weeks of olanzapine treatment when compared with baseline values. However, additional time-domain and frequency-domain indicators only slightly changed, and the total HRV was not altered, thus, they supported its cardiac safety profile because olanzapine did not cause significant changes in the QT_C interval. However, another study[18] used a nonlinear detection method to find that despite little impact on QT variability, heart rate complexity significantly decreased in patients with schizophrenia after olanzapine treatment, which suggested decreased cardiac vagal function and increased risk for cardiac mortality. The inconsistent results of previous studies suggest that research needs to account for the direct and the indirect effects of olanzapine on HRV. In the present study, we found that HRV changed little in the NWG group but substantially decreased in the EWG group. Because the average olanzapine dose, illness

Table 4 | Partial correlations between changes in BMI and changes in HRV measurements controlling for olanzapine dose and PANSS reduction rate

Group		ΔSDNN (ms)	ΔLFn	ΔHFn	ΔLF/HF
SCZ (n = 83)	*r*-value	−0.516	0.441	−0.657	0.462
	P-value	**0.000**	**0.000**	**0.000**	**0.000**
EWG (n = 25)	*r*-value	−0.584	0.489	−0.636	0.538
	P-value	**0.003**	**0.018**	**0.001**	**0.008**
NWG (n = 58)	*r*-value	−0.125	0.022	−0.263	0.046
	P-value	0.361	0.874	0.050	0.734

ΔSDNN: average change in the standard deviation of the NN interval; ΔLFn: average change of normalized low frequency power; ΔHFn: average change of normalized high frequency power; ΔLF/HF: average change of the LF to HF ratio.

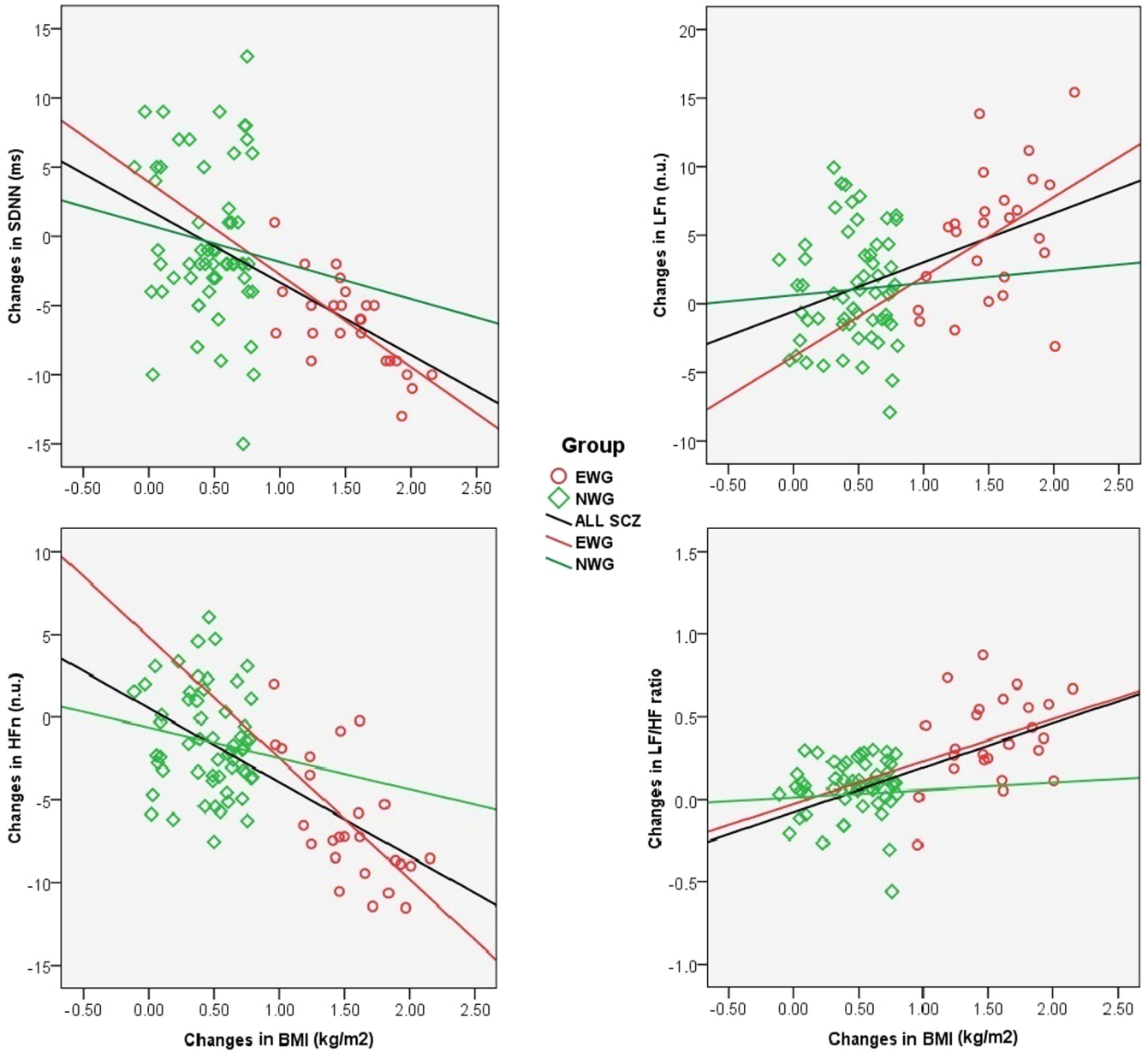

Figure 1 | Correlations among changes in body mass index and HRV measurements for the SCZ, EWG and NWG groups. The change in body mass index (ΔBMI) is positively correlated with the change in the normalized low frequency power LFn (ΔLFn) and the LF/HF ratio (ΔLF/HF) and negatively correlated with the change in the standard deviation for the NN interval (ΔSDNN) and normalized high frequency power (ΔHFn) in both the SCZ and EWG groups (All $P < 0.05$). There is only a marginal negative correlation between ΔBMI and ΔHFn ($P = 0.05$) for the NWG group.

Table 5 | Partial correlations between changes in Weight gain (ΔWeight%) and changes in HRV measurements controlling for olanzapine dose and PANSS reduction rate

Group		ΔSDNN (ms)	ΔLFn	ΔHFn	ΔLF/HF
SCZ (n = 83)	*r*-value	−0.534	0.437	−0.646	0.452
	P-value	**0.000**	**0.000**	**0.000**	**0.000**
EWG (n = 25)	*r*-value	−0.546	0.352	−0.555	0.558
	P-value	**0.007**	0.099	**0.006**	**0.006**
NWG (n = 58)	*r*-value	−0.250	0.054	−0.241	0.021
	P-value	0.063	0.694	0.074	0.878

ΔSDNN: average change of the standard deviation for the NN interval; ΔLFn: average change of normalized low frequency power; ΔHFn: average change of normalized high frequency power; ΔLF/HF: average change of LF to HF ratio.

severity, baseline HRV parameters and demographic factors were all comparable between the two groups, we believe that the between-group difference of HRV is due to differences in olanzapine-induced weight gain. In other words, we believe that the degree of weight gain after olanzapine treatment may be the major contributor to changes in HRV parameters, after accounting for other factors, including psychotic state and HRV detection method. Previous studies have found that existing obesity and short-term weight gain, similar to the EWG in our study, will lead to impairments in HRV; but the accompanied increases of insulin, leptin and adiponectin were not consistently correlated with changes in HRV[21,22]. We tested the fasting plasma glucose (FPG) of patients with schizophrenia at baseline and follow-up, and failed to find a correlation with HRV.

Given the results presented above, we hypothesized that olanzapine-induced weight gain may have an important effect on HRV. Thus, we explored the correlations between the change in BMI

(ΔBMI) and the changes in HRV measurements using a partial correlation analysis. After controlling for confounding variables, such as medicine dose and psychotic state, data from SCZ or were in the EWG group indicated that BMI change was positively correlated with a decrease in SDNN and HFn and an increase in LFn and the LF/HF ratio, which represents sympathetic hyperactivity and/or parasympathetic hypoactivity and autonomic imbalance, i.e., HRV impairment. However, for the NWG group, there was only a marginal negative correlation between BMI change and HFn, with *P*-values of 0.05. We found similar relationships between ΔWeight% and HRV changes. Although we based the cutoff-point for dichotomizing subjects into the EWG and NWG groups on the results of a previous study[24], our results demonstrated the negative impact of obesity or inappropriate weight gain on autonomic function. The findings also suggest that the HFn may be more sensitive to BMI change than other indicators, including the SDNN, LFn and LF/HF ratio. Olanzapine has a very high potential for weight gain compared with other antipsychotic drugs[23], and the most significant olanzapine-induced weight gain ever reported raised BMI by 58%[26]. Therefore, olanzapine may exert a negative impact on HRV for patients who are sensitive to its weight-inducing effect, thus, it is important to attend to their risk for cardiovascular disease. Fortunately, research has found that adverse HRV changes are reversible by weight loss[21,22], and the risk of substantial weight gain or BMI increase for olanzapine-treated patients can be predicted by early weight gain and baseline characteristics[24,27]. In addition, there are many prevention interventions for drug-induced obesity[23]. However, further studies are needed to evaluate cardiovascular risk for olanzapine.

There are several limitations in the present study. First, the criteria used to dichotomize subjects into EWG and NWG groups were based on a single study[24], thus, results should be interpreted with caution. Second, we did not study the direct effects of olanzapine on HRV, or changes in lipids or C-reactive protein, which may have affected HRV. Therefore we cannot attribute all of the effects of olanzapine on HRV to weight gain. Finally, because we only explored HRV changes over a 4-week period of olanzapine use in patients with schizophrenia, cardiovascular safety is not clear for long-term use. There is a need for additional, long-term longitudinal studies that have large sample sizes.

Taken together, despite some limitations, our study indicates that olanzapine-induced weight gain is correlated with increased risk of cardiovascular disease for patients with schizophrenia. Further research is needed to explore its cardiovascular safety profile, specifically long-term cardiac safety.

Methods

Participants. Inpatients with schizophrenia without CVD were recruited between October 2012 and March 2014 from the Wuxi Mental Health Center, China. The inclusion criteria were as follows: 1) meeting Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria; 2) Chinese Han aged from 18 to 65 years, with a baseline body mass index (BMI, kg/m^2) of less than 30; 3) an initial total Positive and Negative Syndrome Scale (PANSS) score more than 70; 4) not medicated with any antipsychotics or antidepressants for the past 1 month; and 5) received neither electroconvulsive therapy (ECT) nor vagus nerve stimulation therapy (VNS) before. Subjects were excluded if they suffered from serious physical illnesses that could influence cardiac autonomic nervous system (ANS) functions, such as diabetes, hyperthyroidism and hypothyroidism, or met the DSM-IV criteria for current or lifetime substance-related disorders. A total of 83 subjects who met the criteria were recruited. Forty-six healthy Chinese Han from hospital staff and community residents, matched to participants by age, gender and smoking status, were recruited as the healthy control group (HC). All participants were provided with a written informed consent protocol that was approved by the ethics committee of the Wuxi Mental Health Center. Study methods were conducted in accord with the approved guidelines. Demographic data and other information are presented in Table 1.

All patients were treated with olanzapine at an initial dose of 5 mg per day with the highest dose of 20 mg per day, and neither other antipsychotic nor physical therapy was permitted as combination or augmentation. The dosage for each patient was based on clinical efficacy and her or his tolerance. For those with severe anxiety or insomnia, appropriate use of benzodiazepines, but not β-blockers, were allowed. During treatment, coffee, wine or other alcoholic beverages were restricted, and smokers were allowed no more than 10 cigarettes per day. After the 4-week treatment, changes in BMI (ΔBMI, calculated as the BMI of week-4 minus BMI of baseline) for each patients was calculated. According to a previous study by Lipkovich et al[24], the extent of early weight gain after olanzapine treatment can be used to predict the risk for substantial weight gain in long-term treatment. Their analysis of BMI changes for 669 participants suggested that approximately 84.7% of patients who gained less than 0.83 kg/m^2 in BMI by week 4 would gain less than 3 kg/m^2 in BMI after 28–30 weeks of olanzapine treatment. Therefore, to explore HRV differences between patients with and without significant weight gain, we defined those who had a ΔBMI more than 0.83 kg/m^2 as the substantial early weight gain group (EWG, n = 25), and all others were in the non-substantial weight gain group (NWG, n = 58).

HRV Assessment and Data Collection. A 24-hour electrocardiogram test was conducted by an ambulatory monitoring system that can collect physiological data via 3 channels with a sampling rate of 512 Hz. Heart rate variability was analyzed by a corresponding analysis software package (BI9000, Biomedical Instruments Co., Ltd, Shenzhen, China). The testing began at 8:00 to 9:00 am and ended at the same time on the next day. Each patient with schizophrenia was tested at baseline and after 4 weeks of treatment, whereas the healthy subjects were only tested once. Premature systoles and other arrhythmias were rejected before HRV analysis. HRV data were analyzed in both time and frequency domains. For the time domain, the standard deviation of the NN interval (SDNN) was calculated, which reflects all of the cyclic components responsible for the variability in the recording period[9]. For the frequency domain, we analyzed the low-frequency power (LF, 0.04–0.15 Hz), the high-frequency power (HF, 0.15–0.40 Hz) and the LF to HF ratio (LF/HF). LF is mediated by both sympathetic and parasympathetic activity, whereas HF is primarily mediated by parasympathetic activity, and the LF/HF reflects the comparative balance of the two branches of the autonomic system[9]. Because the total power (TP) of the spectral signal may greatly differ from individual to individual[28], it has been recommended that LF and HF data be normalized to total TP. Hence, we analyzed the LF using the normalized low frequency power (LFn, LF/(TP – Very Low Frequency)), and the normalized high frequency power for HF (HFn, HF/(TP – Very Low Frequency)).

Clinical Assessment and Data Collection. The Positive and Negative Syndrome Scale (PANSS) was employed to evaluate the patient's psychopathology severity. Scoring was completed by a blinded psychiatrist. A higher score reflects a greater severity. Clinical efficacy was evaluated by the PANSS reduction rate, which was calculated as the baseline score value minus the endpoint score divided by the baseline score value minus 30, i.e., PANSS reduction rate = $(PANSS_{baseline} - PANSS_{week4})/(PANSS_{baseline} - 30) \times 100\%$. The fasting plasma glucose (FPG) for each participant was examined at baseline, and re-examined for patients with schizophrenia on the day of HRV re-testing.

Statistical Analysis. Continuous variables are presented as the mean ± SD (standard deviation). Levene's Test tested the equality of variances. The differences between two groups were compared using an independent-samples *t*-test, and when equality of variances were not assumed ($P < 0.20$). The changes in the HRV indicators within the same group were calculated with a paired-samples *t*-test. Categorical data were compared using the chi-square test (χ^2). When assessing the relationship between the change of BMI (ΔBMI), weight gain percentage (ΔWeight%) and the changes of HRV data (i.e., ΔSDNN, ΔLFn, ΔHFn and ΔLF/HF, all were calculated as week-4 data minus the baseline data), a partial correlation analysis controlling for the average olanzapine dosage and PANSS reduction rate was conducted to minimize the impact of confounding factors such as psychotic state[6,11,14]. All data were analyzed with SPSS 15.0 for Windows (SPSS Inc, Chicago, Illinois, USA). All tests were two-tailed, and differences with $P < 0.05$ were considered statistically significant.

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Author contributions

Z.H.Z. and J.W. planned and designed the study. Y.S.L. and Z.W.X. recruited participants, performed clinical diagnostics and collected the HRV data. F.Q.Z. conducted clinical assessments. J.W. and F.Q.Z. analyzed the data. J.W. and Z.H.Z. wrote the manuscript and prepared all tables and figure 1. All authors discussed the results and reviewed the manuscript.

Additional information

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