

# Lifestyle Intervention and Metformin for Treatment of Antipsychotic-Induced Weight Gain

## A Randomized Controlled Trial

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SINCE THEIR INTRODUCTION, atypical antipsychotic (AAP) medications have been used increasingly for the management of patients with a variety of psychotic disorders and severe behavioral disturbances. In the past decade, there has been a growing concern among clinicians and researchers that use of AAP medications may be related to potentially serious adverse metabolic effects, including weight gain, hyperlipidemia, and glucose intolerance.<sup>1-5</sup>

The induction of obesity by antipsychotic agents has been documented since the introduction of chlorpromazine in the mid-1950s.<sup>6</sup> According to a recent study, 78.8% of patients receiving antipsychotic agents increased their baseline weight by more than 7%.<sup>7</sup> Clinical studies indicate that AAP medications may have a greater potential for inducing weight gain than conventional antipsychotic medications and vary in their propensity to induce weight gain. Clozapine and olanza-

**Context** Weight gain, a common adverse effect of antipsychotic medications, is associated with medical comorbidities in psychiatric patients.

**Objective** To test the efficacy of lifestyle intervention and metformin alone and in combination for antipsychotic-induced weight gain and abnormalities in insulin sensitivity.

**Design, Setting, and Patients** A randomized controlled trial (October 2004-December 2006) involving 128 adult patients with schizophrenia in the Mental Health Institute of the Second Xiangya Hospital, Central South University, China. Participants who gained more than 10% of their predrug weight were assigned to 1 of 4 treatment groups.

**Interventions** Patients continued their antipsychotic medication and were randomly assigned to 12 weeks of placebo, 750 mg/d of metformin alone, 750 mg/d of metformin and lifestyle intervention, or lifestyle intervention only.

**Main Outcome Measures** Body mass index, waist circumference, insulin levels, and insulin resistance index.

**Results** All 128 first-episode schizophrenia patients maintained relatively stable psychiatric improvement. The lifestyle-plus-metformin group had mean decreases in body mass index (BMI) of 1.8 (95% confidence interval [CI], 1.3-2.3), insulin resistance index of 3.6 (95% CI, 2.7-4.5), and waist circumference of 2.0 cm (95% CI, 1.5-2.4 cm). The metformin-alone group had mean decreases in BMI of 1.2 (95% CI, 0.9-1.5), insulin resistance index of 3.5 (95% CI, 2.7-4.4), and waist circumference of 1.3 cm (95% CI, 1.1-1.5 cm). The lifestyle-plus-placebo group had mean decreases in BMI of 0.5 (95% CI, 0.3-0.8) and insulin resistance index of 1.0 (95% CI, 0.5-1.5). However, the placebo group had mean increases in BMI of 1.2 (95% CI, 0.9-1.5), insulin resistance index of 0.4 (95% CI, 0.1-0.7), and waist circumference of 2.2 cm (95% CI, 1.7-2.8 cm). The lifestyle-plus-metformin treatment was significantly superior to metformin alone and to lifestyle plus placebo for weight, BMI, and waist circumference reduction.

**Conclusions** Lifestyle intervention and metformin alone and in combination demonstrated efficacy for antipsychotic-induced weight gain. Lifestyle intervention plus metformin showed the best effect on weight loss. Metformin alone was more effective in weight loss and improving insulin sensitivity than lifestyle intervention alone.

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pine produce the most weight gain, quetiapine and risperidone produce intermediate weight gain, and ziprasidone and aripiprazole produce the least weight gain.<sup>8-12</sup>

This antipsychotic-related adverse effect has lately become a major concern in the treatment of psychosis because weight gain not only influences adherence with drug treatment but also is associated with substantial medical morbidity and mortality.<sup>13</sup> Recent studies<sup>14,15</sup> suggest that people with severe mental illness die up to 3 decades earlier than the general population. Heart disease is a leading cause of death in these patients. One of the major risk factors for heart disease and early death in these patients is weight gain.

The mechanism underlying weight gain resulting from antipsychotic drugs has not been fully understood, although it might be associated with central histamine H<sub>1</sub> antagonism and increased appetite or with direct impairment of metabolic regulation and alteration of insulin sensitivity.<sup>16,17</sup> A combination of genetic, environmental, and lifestyle factors could likely play a role in the high rate of weight gain and metabolic dysregulation in patients taking antipsychotics.

Lifestyle intervention has demonstrated efficacy for weight loss in obese persons and has been shown to prevent or delay the development of type 2 diabetes by 40% to 60% in different populations in controlled studies.<sup>18,19</sup> In patients with schizophrenia, several lifestyle interventions have been used to reduce obesity or to prevent weight gain induced by AAP medications.<sup>20-23</sup> Preliminary evidence has suggested that behavioral interventions are effective in weight gain control for patients who had weight gain induced by antipsychotics.<sup>7,24</sup>

Metformin, which inhibits hepatic glucose production, is well tolerated and prevents continual weight gain while it decreases measures of insulin resistance. Some studies find that metformin can reduce body weight in patients with type 2 diabetes and in obese individuals who do not have diabetes.<sup>25,26</sup>

Metformin can also reduce weight gain induced by antipsychotic agents.<sup>27,28</sup> However, Baptista et al<sup>29</sup> reported that metformin did not improve weight gain induced by antipsychotic agents.

To our knowledge, no double-blind, placebo-controlled studies have directly compared lifestyle intervention and metformin alone or in combination for weight gain induced by antipsychotic medications among patients with schizophrenia. In this article, we report on a 12-week randomized, double-blind, placebo-controlled trial that tested the efficacy of lifestyle intervention and metformin alone and in combination to reduce weight gain and abnormalities of insulin sensitivity induced by antipsychotic medications in patients with schizophrenia.

## METHODS

### Participants

Patients aged 18 through 45 years with a first psychotic episode of schizophrenia diagnosed in accordance with criteria set out in the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV)* were eligible for our study.<sup>30</sup>

The diagnosis of schizophrenia was determined by the Structured Clinical Interview of *DSM-IV* Axis I Disorders, Clinical Version,<sup>31</sup> during the screening phase. Other enrollment criteria included that participants gained more than 10% of their predrug body weight within the first year of treatment with a targeted antipsychotic agent—clozapine, olanzapine, risperidone, or sulpiride—and were either discharged from inpatient units or first seen in the clinic in the 12 months before enrollment so their weight and antipsychotic treatment were documented; had to have relatively stable improvement (the total score of Positive and Negative Symptom Scale [PANSS]  $\leq 60$ ); and be taking only 1 antipsychotic agent, whose dose had not changed by more than 25% over the past 3 months. We used the criterion of gaining more than 10% of predrug body weight as our target group because a more than 10% weight gain is often considered excessive.<sup>32</sup>

All participants had to be under the care of their parents or another adult caregiver who monitored and recorded food intake, exercise activity, and medication intake each day of the trial to monitor adherence. Participants were recruited from the schizophrenia outpatient clinic of the Mental Health Institute of the Second Xiangya Hospital, Central South University, China, between October 2004 and December 2006.

Patients were excluded from the study if during the screening they had evidence of liver or renal dysfunction, cardiovascular disease, or diabetes mellitus; were pregnant or lactating; or had conditions that limited their ability to perform the lifestyle modifications, such as arthritis, pulmonary disease, or neurological or dietary restrictions. Patients were also excluded if they had received a psychiatric diagnosis other than schizophrenia or had a history of substance abuse.

The study was approved by the ethics committee of the Second Xiangya Hospital, and all participants provided written informed consent in accordance with National Health and Medical Research Council guidelines.

### Study Design

Eligible participants were randomized to 1 of 4 treatment groups in a balanced 2 × 2 factorial design for 12 weeks: metformin alone (750 mg/d), placebo alone, lifestyle intervention plus metformin (750 mg/d), or lifestyle intervention plus placebo. The 750-mg/d dosing of metformin was based on safety and efficacy findings for Chinese obese nondiabetic population.<sup>33</sup>

Participants were randomized through a computer-generated table in blocks of 8 to ensure approximately equal numbers of participants in each group. Assignment was determined after completing all screening assessments and being accepted into the study. To ensure concealment of the treatment assignment, randomization was conducted independently of the investigators by a research pharmacist at

a separate facility and medication was provided in coded containers of identical-appearing capsules of metformin or placebo supplied by the manufacturer.

### Pharmacological Intervention

Metformin treatments were administered in a double-blind placebo-controlled fashion. For the first 4 days, participants took 250 mg of metformin or placebo at their evening meal, after which a second and third dose were added before breakfast and lunch, respectively, for another 80 days. Each participant was given a record sheet to log the number of trial medications taken daily.

The antipsychotic medications remained at a fixed dose as baseline levels throughout the course of treatment. Only trihexyphenidyl for extrapyramidal symptoms or lorazepam for insomnia or agitation were allowed as needed.

The participants' adherence to metformin treatment for each visit was defined as taking more than 80% of the study drug dosage prescribed for that interval. If a participant was nonadherent, both patient and caregiver were counseled on the importance of taking the prescribed amount of study medication.

### Lifestyle Intervention

The lifestyle interventions included psychoeducational, dietary, and exercise programs.

The psychoeducational program focused on the roles of eating and activity in weight management. Topics included healthful weight management techniques, such as benefits of nutrition, physical fitness, and available behavioral techniques. The psychoeducational program was administered to patients in both lifestyle groups at baseline and at weeks 4, 8, and 12.

For the dietary intervention, the American Heart Association (AHA) step 2 diet was prescribed. It allows less than 30% of total calories from fat (<7% saturated fat and <200 mg of cholesterol); 55% from carbohydrates; and more than

15% from protein daily with an increase in fiber intake to at least 15 g per 1000 kcal. Before initiating the dietary intervention, each participant was asked to keep a 3-day diet record that was analyzed by the dietitian who would provide dietary advice on the patient's current diet. In general, there were no changes of total daily caloric intake, but diets were adjusted to follow the AHA plan. During the study, participants maintained 3-day food records before each follow-up visit. The dietitian reviewed the food records, compared them with the prescribed AHA diet, and discussed with each patient concerns about adherence to the AHA diet.

For the first week of the study, exercise sessions were directed by an exercise physiologist. Participants performed endurance exercise (walking or jogging) on a treadmill 7 times a week for 30 minutes at each session. Exercise was designed to attain 70% of heart rate reserve [ $0.7 \times (\text{maximum heart rate} - \text{resting heart rate}) + \text{resting heart rate}$ ]. Heart rate reserve was estimated from the maximum and resting heart rates observed at baseline maximal aerobic capacity ( $\dot{V}O_{2\text{max}}$ ) for each individual. After the first week, exercise was home-based without supervision by investigators. Therapists and patients collaboratively developed individual programs of gradual assignment of exercise. A range of different types of exercise and various levels of intensity was offered, varying from light exercise (increase walking and decrease sedentary activities, particularly time spent watching television or sleeping) to moderate exercise for at least 30 minutes per day. Common moderate-to-vigorous physical exercise included walking at a moderate or very strenuous intensity, bicycling, resistance training, skiing, jogging, ball games, and lifestyle activities, such as chopping wood or clearing brush.

Branching treadmill tests were performed under supervision at each follow-up visit. Good exercise adherence was defined as an increased  $\dot{V}O_{2\text{max}}$  of at least  $1.5 \text{ mL} \times \text{kg}^{-1} \text{ min}^{-1}$  at 4, 8, and 12 weeks compared with baseline.<sup>34</sup>

Participants and their caregivers were instructed to keep records of their exercise activity and heart rate. This information was also used to estimate adherence.

### Measures

Baseline assessments include demographics, a comprehensive medical history, physical examination including anthropometric measurements (weight, height, and waist circumference, and laboratory examinations). PANSS<sup>35</sup> and Treatment Emergent Symptom Scale (TESS)<sup>36</sup> were also used for monitoring psychiatric symptoms and adverse effects. The research nurses who performed all assessments were blinded to the treatments that the patients were receiving and were not involved in implementing any aspects of the intervention.

The laboratory examinations at baseline included fasting glucose and insulin, lactic acid, liver and renal function, blood counts, and electrocardiogram. At each follow-up visit, all baseline evaluations including physical examination, anthropometric measurements, laboratory examinations, and TESS were repeated. PANSS and lipid levels were reevaluated at week 12.

The primary outcomes included the changes of weight; body mass index (BMI), calculated as weight in kilograms divided by height in meters squared; waist circumference; fasting glucose; fasting insulin level; and insulin resistance index (IRI), which was calculated based on formula of homeostasis assessment for insulin resistance model:  $\text{fasting insulin (10}^3 \text{ } \mu\text{IU/L)} \times \text{fasting glucose (mg/dL)} / 404.45$  ( $\text{fasting insulin (10}^3 \text{ } \mu\text{IU/L)} \times \text{fasting glucose [mmol/L]} / 22.5$ ).<sup>37</sup> The major secondary outcomes included the change in PANSS total scores and adverse effects.

### Statistical Analysis

The analyses designed to compare treatments were performed separately for those who completed the treatment, and for all randomized patients with at least

1 follow-up test (intention-to-treat [ITT] analysis) using the last-observation-carried-forward method included 127 of the 128 patients.

All analyses were conducted by using the Statistical Package for Social Sciences, version 11.5 (SPSS Inc, Chicago, Illinois). Continuous variables were described by using summary statistics such as means and 95% confidence intervals (CIs). Categorical variables were described by using frequencies and percentages. We used *t* tests,  $\chi^2$  analysis, and analysis of variance (ANOVA) as appropriate. For comparison of the 4 treatment groups at baseline, ANOVA was used to compare all continuous variables and  $\chi^2$  analysis was used for categorical variables.

Because the follow-up data were all continuous measures, the main strategy we used was analysis of covariance, with corresponding baseline values as covariates. To compare the difference among the 4 treatment groups, data were first examined by

omnibus testing; when omnibus analyses revealed statistically significant differences, post hoc tests (least-significant-difference procedure) were used to compare the specific treatment between groups. All the data were normally distributed. The difference was considered statistically significant if a 2-tailed *P* value was less than .05.

The relationship between initial body weight and weight loss at 12 weeks was assessed using Pearson correlation.

Sample size was determined based on mean reductions in BMI from the first generation studies testing metformin and lifestyle intervention (reviewed above), and estimates for interaction effects were based on the study by Menza et al.<sup>38</sup> The completer sample size provided at least 85% power (with *P* < .05) to detect treatment differences reflecting effect sizes of 0.30, and at least 80% power to detect interaction effects with effect sizes as small as 0.25 to ensure detection of differences between the 4 groups.

## RESULTS

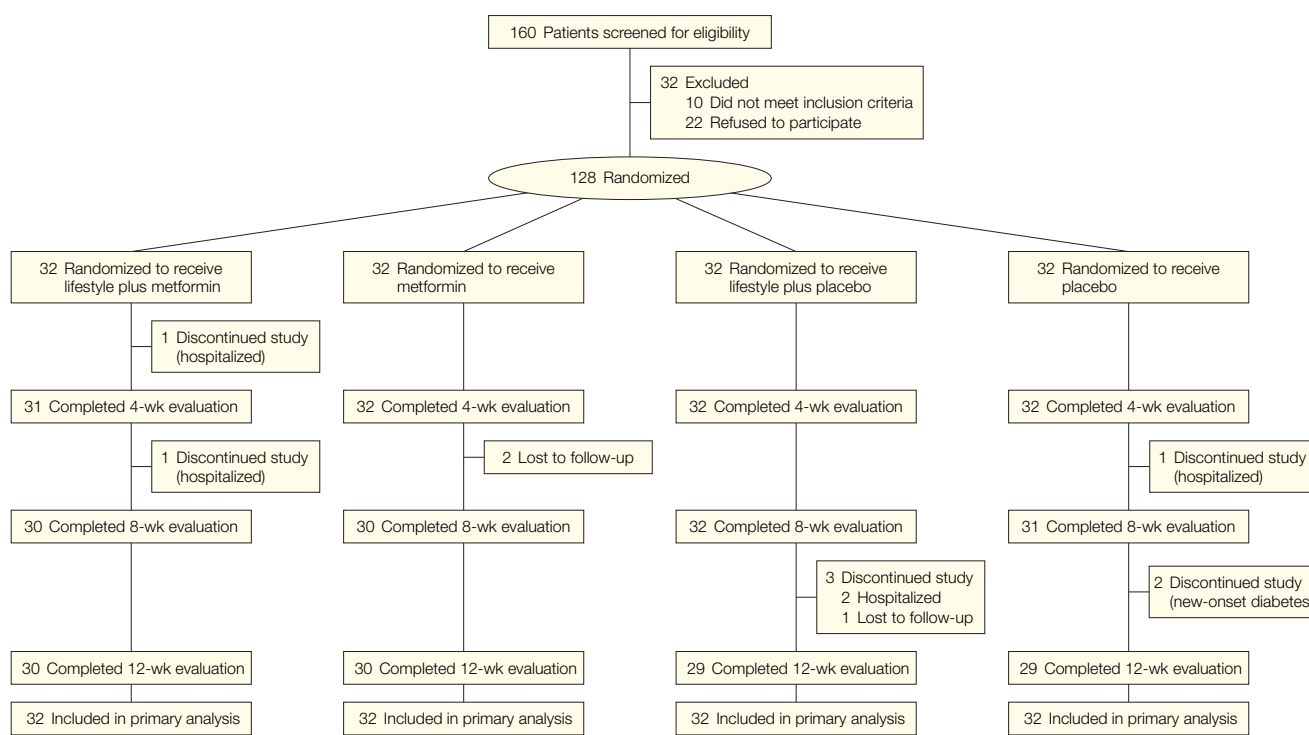
### Randomization and Patients Characteristics

Of the 128 eligible patients, 32 patients were randomly assigned to each of the treatment groups (FIGURE). One hundred eighteen patients (92.2%) completed the 12-week treatment: 30 (93.8%), lifestyle intervention plus metformin; 30 (93.8%), metformin alone; 29 (90.6%), lifestyle intervention plus placebo; and 29 (90.6%), placebo alone. The demographic or clinical characteristics and baseline measurements did not differ significantly among groups (TABLE 1).

### Intervention Adherence

Based on measures at each follow-up visit, between 86% and 100% of patients in the lifestyle-plus-metformin group took 80% or more of their medication, between 68% and 84% consumed less than 30% of their total calories from fat, and between 50% and 57% had  $\dot{V}O_{2\max}$  results that demonstrated adherence to exercise. Between 88% and

**Figure.** Flowchart of Participation in the Study



100% of those in the metformin-alone and placebo-alone groups took 80% of their medication. Between 61% and 74% of those in the lifestyle-plus-placebo group consumed less than 30% of their calories from fat and between 55% and 60% had good adherence to the exercise protocol. There were no group differences in metformin treatment and lifestyle intervention adherence. The metformin treatment and dietary adherence were based on patient self-report.

### Changes in Weight, BMI, and Waist Circumference Over Time

Intention-to-treat analysis showed that those in the lifestyle-plus-metformin group had significant mean decreases in weight, BMI, and

waist circumference at each follow-up session. Those in the lifestyle-plus-placebo group had significant mean decreases in weight and BMI levels at each follow-up session, but their mean waist circumference decreased significantly only at the first follow-up session but not at weeks 8 and 12. Those in the placebo group had a significant increase in weight, BMI, and waist circumference at each follow-up session (TABLE 2). Over the 12-week study period, patients in the placebo group continued to gain weight by 4.8% compared with baseline (mean, 3.1 kg; 95% CI, 2.4-3.8 kg), whereas, compared with baseline, weight decreased in the treatment groups: lifestyle plus metformin by 7.3% (mean, 4.7 kg; 95% CI, 3.4-5.7 kg);

metformin alone by 4.9% (mean, 3.2 kg; 95% CI, 2.5-3.9 kg); and the lifestyle alone by 2.2% (1.4 kg; 95% CI, 0.7-2.0 kg). Similarly, the mean BMI decreased by 1.8 (95% CI, 1.3-2.3) in the lifestyle-plus-metformin group, 1.2 (95% CI, 0.9-1.5) in the metformin-alone group, and 0.5 (95% CI, 0.3-0.8) in the lifestyle-plus-placebo group while it increased by a mean of 1.2 (95% CI, 0.9-1.5) in the placebo group (TABLE 3).

There were no significant correlations between initial weight and weight changes at 12 weeks for the lifestyle-plus-metformin group ( $r_{31}=0.104$ ,  $P=.57$ ), metformin-alone group ( $r_{31}=0.013$ ,  $P=.94$ ), lifestyle-plus-placebo group ( $r_{31}=0.019$ ,  $P=.92$ ), or the placebo group ( $r_{31}=0.219$ ,  $P=.23$ ).

**Table 1.** Demographic and Clinical Characteristics of 128 Participants Across Treatment Groups at Baseline<sup>a</sup>

| Characteristics                                       | Total<br>(N = 128)  | Lifestyle +<br>Metformin<br>(n = 32) | Metformin<br>(n = 32) | Lifestyle<br>(n = 32) | Placebo<br>(n = 32) | Test<br>Statistics <sup>b</sup> | P<br>Value |
|-------------------------------------------------------|---------------------|--------------------------------------|-----------------------|-----------------------|---------------------|---------------------------------|------------|
| Age, y                                                | 26.3 (25.5-27.1)    | 26.1 (24.3-27.8)                     | 26.8 (25.2-28.3)      | 26.4 (24.8-28.1)      | 25.8 (24.1-27.6)    | 0.245                           | .86        |
| Men, No. (%)                                          | 64 (50.0)           | 15 (46.9)                            | 16 (50.0)             | 17 (53.1)             | 16 (50.0)           | 0.250                           | .97        |
| Patient smoking currently,<br>No (%)                  | 10 (7.8)            | 3 (9.4)                              | 2 (6.3)               | 2 (6.3)               | 3 (9.4)             | 0.434                           | .93        |
| Patient with family history<br>of diabetes, No. (%)   | 9 (7.0)             | 2 (6.3)                              | 3 (9.4)               | 2 (6.3)               | 2 (6.3)             | 0.359                           | .95        |
| Duration of schizophrenia,<br>mo                      | 9.0 (8.6-9.5)       | 8.9 (7.8-10.0)                       | 9.3 (8.4-10.2)        | 9.0 (8.0-10.0)        | 8.9 (8.1-9.8)       | 0.162                           | .92        |
| Current antipsychotic<br>agent, No. (%)               |                     |                                      |                       |                       |                     |                                 |            |
| Clozapine                                             | 40 (31.3)           | 10 (31.3)                            | 11 (34.4)             | 9 (28.1)              | 10 (31.3)           | 1.173                           | .99        |
| Olanzapine                                            | 33 (25.8)           | 8 (25.0)                             | 8 (25.0)              | 10 (31.3)             | 7 (21.9)            |                                 |            |
| Risperidone                                           | 28 (21.9)           | 7 (21.9)                             | 7 (21.9)              | 6 (18.8)              | 8 (25.0)            |                                 |            |
| Sulpiride                                             | 27 (21.1)           | 7 (21.9)                             | 6 (18.8)              | 7 (21.9)              | 7 (21.9)            |                                 |            |
| Duration of current<br>antipsychotic treatment,<br>mo | 7.7 (7.3-8.2)       | 7.6 (6.5-8.6)                        | 8.1 (7.2-8.9)         | 7.7 (6.7-8.7)         | 7.7 (6.8-8.5)       | 0.254                           | .86        |
| Daily dose of antipsychotic<br>agents, mg             |                     |                                      |                       |                       |                     |                                 |            |
| Clozapine                                             | 115.0 (107.6-122.4) | 122.5 (97.9-147.0)                   | 106.8 (98.9-114.7)    | 119.4 (100.8-138.1)   | 112.5 (99.8-125.1)  | 0.949                           | .43        |
| Olanzapine                                            | 5.9 (5.4-6.4)       | 6.3 (4.7-7.8)                        | 5.6 (4.6-6.6)         | 6.0 (5.1-6.9)         | 5.7 (4.6-6.8)       | 0.319                           | .81        |
| Risperidone                                           | 2.7 (2.5-2.9)       | 2.8 (2.3-3.3)                        | 2.7 (2.3-3.2)         | 2.8 (2.4-3.3)         | 2.5 (2.1-2.9)       | 0.619                           | .61        |
| Sulpiride                                             | 562.9 (540.6-585.3) | 542.8 (470.1-615.6)                  | 566.7 (512.5-620.9)   | 585.7 (550.8-620.7)   | 557.1 (507.7-606.5) | 0.681                           | .57        |
| Weight, kg                                            | 64.6 (63.6-65.7)    | 64.6 (62.4-66.7)                     | 64.7 (62.6-66.9)      | 64.7 (62.7-66.8)      | 64.6 (62.4-66.7)    | 0.018                           | .99        |
| BMI                                                   | 24.5 (24.4-24.8)    | 24.6 (24.1-25.0)                     | 24.6 (24.2-25.1)      | 24.6 (24.1-24.9)      | 24.5 (24.2-24.9)    | 0.026                           | .99        |
| Waist circumference, cm                               | 83.7 (82.8-84.5)    | 83.9 (82.3-85.9)                     | 83.8 (82.1-85.8)      | 83.6 (81.5-85.1)      | 83.5 (81.7-84.9)    | 0.033                           | .98        |
| Fasting glucose, mg/dL                                | 95.5 (93.7-95.5)    | 95.5 (93.7-97.3)                     | 97.3 (93.7-99.1)      | 95.5 (91.9-97.3)      | 91.9 (88.3-95.5)    | 1.663                           | .18        |
| Insulin, $\mu$ U/mL                                   | 25.9 (24.4-27.1)    | 25.7 (22.8-28.6)                     | 26.2 (23.3-29.1)      | 25.7 (22.8-28.7)      | 25.3 (22.6-28.0)    | 0.068                           | .98        |
| Insulin resistance index                              | 6.2 (5.7-6.6)       | 6.2 (5.3-7.1)                        | 6.4 (5.5-7.3)         | 6.2 (5.3-7.1)         | 5.8 (5.1-6.5)       | 0.303                           | .82        |
| Total score of PANSS                                  | 46.1 (40.0-52.2)    | 47.1 (41.0-53.2)                     | 45.1 (39.0-51.2)      | 45.9 (39.8-52.0)      | 46.4 (40.3-52.5)    | 0.382                           | .77        |

Abbreviations: BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; PANSS, Positive and Negative Symptom Scale.

SI conversions: To convert glucose from mg/dL to mmol/L, multiply by 0.0555; insulin from  $\mu$ U/mL to pmol/L, multiply by 6.945.

<sup>a</sup>Data are presented as mean (95% confidence interval) unless otherwise indicated. Percentages may not sum to 100 due to rounding.

<sup>b</sup>Test statistic:  $\chi^2$  for categorical variables and analysis of variance for continuous variables.

### Changes in Fasting Glucose, Insulin, and IRI Over Time

Intention-to treat analysis showed that the mean fasting glucose, insulin levels, and IRI levels decreased significantly in the lifestyle-plus-metformin group, metformin-alone group, and the lifestyle-plus-placebo group during weeks 4, 8, and 12. In the placebo group, however, there was a significant increase in insulin and IRI levels during the 3 follow-up sessions (Table 2). During the 12 weeks of follow-up, the mean IRI value decreased by 3.6 (95% CI, 2.7-4.5) in the lifestyle-plus-metformin group, 3.5 (95% CI, 2.7-4.4) in the metformin-alone group, and 1.0 (95% CI, 0.5-1.5) in the lifestyle-plus-placebo group, whereas it increased by 0.4 (95% CI, 0.1-0.7) in the placebo-alone group.

### Mean Changes of Outcomes Between the Treatment Groups

Table 3 summarizes analyses for mean changes of all outcomes across the 4 treatment groups for all randomized patients. Specific pairwise comparisons of the treatments indicate (1) lifestyle-plus-metformin was significantly superior to metformin on weight, BMI, and waist circumference; was significantly superior to lifestyle plus placebo on weight, BMI, waist circumference, insulin, and IRI; and was significantly superior to placebo on weight, BMI, waist circumference, fasting glucose, insulin, and IRI; (2) metformin was significantly superior to lifestyle plus placebo and placebo alone on weight, BMI, waist circumference, fasting glucose, insulin, and

IRI; and (3) lifestyle plus placebo was significantly superior to placebo on weight, BMI, waist circumference, fasting glucose, insulin, and IRI.

At week 12, the total score of PANSS was 47.6 (95% CI, 41.3-53.9) in the lifestyle-plus-metformin group, 45.3 (95% CI, 39.0-51.6) in the metformin-alone group, 46.2 (95% CI, 39.9-52.5) in the lifestyle-plus-placebo group, and 46.2 (95% CI, 41.3-52.5) in the placebo-alone group ( $P > .20$ ), with no significant changes from baseline.

Completer analyses were also carried out separately to compare changes in weight, BMI, waist circumference, fasting glucose, insulin, and IRI over time as well as mean changes of these outcomes between the treatment groups. They revealed very similar findings to the ITT analysis; thus, we present only the ITT analysis findings above. Ten patients did not complete the 12-week treatment; their data had to be estimated by the last observation carried forward for the ITT analysis.

### Adverse Events

There were no significant differences in the frequency and types of adverse effects reported among 4 treatment groups. TABLE 4 presents adverse events that affected more than 5% in the entire sample. There were 5 serious adverse events that led to withdrawal from the trial. All 5 events were exacerbation of psychosis and resulted in hospital admission. Two patients who were treated with placebo were diagnosed as having diabetes at week 8. No hypoglycemia was reported during the trial.

### COMMENT

This randomized, placebo-controlled study used a balanced  $2 \times 2$  factorial design to test the comparative efficacy of lifestyle intervention and metformin alone and in combination on preventing further weight accretion or causing weight loss in patients with schizophrenia who had experienced substantial weight gain during the first year of treatment with antipsychotic agents.

**Table 2.** Treatment Outcomes for All 128 Randomized Participants

|                                             | Mean (95% Confidence Interval) |                               |                               |
|---------------------------------------------|--------------------------------|-------------------------------|-------------------------------|
|                                             | Week 4                         | Week 8                        | Week 12                       |
| Lifestyle intervention + metformin (n = 32) |                                |                               |                               |
| Weight, kg                                  | 62.8 (62.6-63.0) <sup>a</sup>  | 61.2 (60.6-61.8) <sup>a</sup> | 59.8 (58.9-60.7) <sup>a</sup> |
| BMI                                         | 23.9 (23.6-24.0) <sup>a</sup>  | 23.3 (22.8-23.5) <sup>a</sup> | 22.8 (22.5-23.1) <sup>a</sup> |
| Waist circumference, cm                     | 83.5 (83.2-83.8) <sup>a</sup>  | 82.9 (82.5-83.3) <sup>a</sup> | 84.1 (83.6-84.6) <sup>a</sup> |
| Fasting glucose, mg/dL                      | 90.1 (88.3-91.9) <sup>a</sup>  | 86.5 (84.7-88.3) <sup>a</sup> | 88.3 (86.5-90.1) <sup>a</sup> |
| Insulin, $\mu$ U/mL                         | 19.9 (18.9-20.9) <sup>a</sup>  | 16.3 (14.9-17.7) <sup>a</sup> | 13.2 (9.0-17.4) <sup>a</sup>  |
| IRI                                         | 4.5 (4.2-4.8) <sup>a</sup>     | 3.5 (2.6-4.4) <sup>a</sup>    | 2.8 (1.9-3.7) <sup>a</sup>    |
| Metformin (n = 32)                          |                                |                               |                               |
| Weight, kg                                  | 63.6 (63.2-64.0) <sup>a</sup>  | 62.7 (62.1-63.3) <sup>a</sup> | 61.9 (61.0-62.8) <sup>a</sup> |
| BMI                                         | 24.2 (24.1-24.3) <sup>a</sup>  | 23.8 (23.6-24.0) <sup>a</sup> | 23.5 (23.2-23.8) <sup>a</sup> |
| Waist circumference, cm                     | 83.7 (83.4-84.0) <sup>a</sup>  | 83.3 (82.9-83.7) <sup>a</sup> | 82.7 (82.2-83.2) <sup>a</sup> |
| Fasting glucose, mg/dL                      | 88.3 (86.5-90.1) <sup>a</sup>  | 84.7 (82.9-86.5) <sup>a</sup> | 84.7 (82.9-86.5) <sup>a</sup> |
| Insulin, $\mu$ U/mL                         | 20.1 (19.1-21.1) <sup>a</sup>  | 16.1 (14.7-17.5) <sup>a</sup> | 13.5 (9.3-17.7) <sup>a</sup>  |
| IRI                                         | 4.5 (4.2-4.8) <sup>a</sup>     | 3.4 (2.5-4.3) <sup>a</sup>    | 2.8 (1.9-3.7) <sup>a</sup>    |
| Lifestyle intervention + placebo (n = 32)   |                                |                               |                               |
| Weight, kg                                  | 63.9 (63.4-64.3) <sup>a</sup>  | 63.6 (63.0-64.2) <sup>a</sup> | 63.4 (62.5-64.3) <sup>a</sup> |
| BMI                                         | 24.0 (23.8-24.2) <sup>a</sup>  | 23.5 (23.3-23.7) <sup>a</sup> | 23.1 (22.8-23.4) <sup>a</sup> |
| Waist circumference, cm                     | 83.8 (83.5-84.1) <sup>a</sup>  | 83.7 (83.3-84.1) <sup>a</sup> | 83.7 (83.2-84.2) <sup>a</sup> |
| Fasting glucose, mg/dL                      | 91.9 (90.1-93.7)               | 90.1 (88.3-91.9) <sup>a</sup> | 88.3 (86.5-90.1) <sup>a</sup> |
| Insulin, $\mu$ U/mL                         | 24.3 (23.3-25.4) <sup>a</sup>  | 23.8 (22.4-25.2) <sup>a</sup> | 23.1 (18.9-27.3) <sup>a</sup> |
| IRI                                         | 5.5 (5.2-5.8) <sup>a</sup>     | 4.9 (4.0-5.8) <sup>a</sup>    | 4.2 (3.3-5.1) <sup>a</sup>    |
| Placebo (n = 32)                            |                                |                               |                               |
| Weight, kg                                  | 65.4 (65.0-65.8) <sup>a</sup>  | 66.0 (65.4-66.6) <sup>a</sup> | 67.2 (66.3-68.1) <sup>a</sup> |
| BMI                                         | 24.7 (24.5-24.8) <sup>a</sup>  | 24.9 (24.7-25.1) <sup>a</sup> | 25.4 (25.1-25.7) <sup>a</sup> |
| Waist circumference, cm                     | 84.2 (83.8-84.5) <sup>a</sup>  | 84.7 (84.3-85.1) <sup>a</sup> | 85.5 (85.0-86.0) <sup>a</sup> |
| Fasting glucose, mg/dL                      | 93.7 (91.9-95.5)               | 91.9 (90.1-93.7)              | 93.7 (91.9-95.5)              |
| Insulin, $\mu$ U/mL                         | 26.6 (25.6-27.6) <sup>a</sup>  | 27.3 (25.9-28.7) <sup>a</sup> | 27.6 (23.4-31.8) <sup>a</sup> |
| IRI                                         | 6.1 (5.9-6.4) <sup>a</sup>     | 6.2 (5.3-7.1) <sup>a</sup>    | 6.3 (5.4-7.2) <sup>a</sup>    |

Abbreviations: BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; IRI, insulin resistance index.

SI conversions: To convert glucose from mg/dL to mmol/L, multiply by 0.0555; insulin from  $\mu$ U/mL to pmol/L, multiply by 6.945.

<sup>a</sup>For between each time point and baseline,  $P < .05$ .

In this 12-week study, we found statistically significant decreases in mean weight, BMI, waist circumference, insulin, and IRI among patients in the lifestyle-plus-metformin, metformin-alone, and lifestyle-plus-placebo groups but not among those in the placebo-alone group whose measurements continued to increase. These findings indicate that lifestyle intervention and metformin alone and in combination can improve the weight gain and insulin sensitivity induced by antipsychotic medications. In a large trial of nondiabetic persons, Knowler et al<sup>18</sup> reported that lifestyle changes and treatment with metformin both reduced weight and the incidence of diabetes and lifestyle intervention was even more

effective than metformin. In patients with schizophrenia, several studies<sup>21-23</sup> have reported that the behavioral and nutritional therapy were more effective than control for weight reduction. Three metformin trials have been reported for prevention of weight gain or weight reduction in patients taking antipsychotic medications.<sup>27,28,39</sup> All these studies suggested a significant effect of metformin in reducing weight and improving insulin sensitivity. Our findings are consistent with most of these controlled studies.

In addition, our study showed that lifestyle intervention plus metformin was superior to lifestyle intervention plus placebo in decreasing weight, BMI, waist circumference, insulin, and

IRI. Lifestyle intervention plus metformin was also superior to metformin alone in decreasing weight, BMI, and waist circumference, although these 2 treatment groups did not differ from each other in decreasing insulin and IRI level. These findings suggest that the lifestyle intervention plus metformin could be most effective in reversing the weight gain induced by antipsychotic agents in patients with schizophrenia while metformin alone has the same effect on insulin sensitivity as lifestyle intervention plus metformin. Intention-to-treat analyses revealed that metformin was superior to lifestyle intervention plus placebo in decreasing weight, BMI, waist circumference, fasting glucose, and insu-

**Table 3.** The Difference Between Baseline and End Point of All Treatment Outcomes

| Assessment Levels       | Mean (95% CI)                  |                           |                        |                      | P Value             |                                    |                                    |                                  |                        |                      |                      |
|-------------------------|--------------------------------|---------------------------|------------------------|----------------------|---------------------|------------------------------------|------------------------------------|----------------------------------|------------------------|----------------------|----------------------|
|                         |                                |                           |                        |                      | ANCOVA <sup>a</sup> | Lifestyle + Metformin vs Metformin | Lifestyle + Metformin vs Lifestyle | Lifestyle + Metformin vs Placebo | Metformin vs Lifestyle | Metformin vs Placebo | Lifestyle vs Placebo |
|                         | Lifestyle + Metformin (n = 32) | Metformin (n = 32)        | Lifestyle (n = 32)     | Placebo (n = 32)     |                     |                                    |                                    |                                  |                        |                      |                      |
| Weight, kg              | -4.7<br>(-5.7 to -3.4)         | -3.2<br>(-3.9 to -2.5)    | -1.4<br>(-2.0 to -0.7) | 3.1<br>(2.4 to 3.8)  | <.001               | .02                                | .01                                | <.001                            | .004                   | <.001                | <.001                |
| BMI                     | -1.8<br>(-2.3 to -1.3)         | -1.2<br>(-1.5 to -0.9)    | -0.5<br>(-0.8 to -0.3) | 1.2<br>(0.9 to 1.5)  | <.001               | .01                                | <.001                              | <.001                            | .006                   | <.001                | <.001                |
| Waist circumference, cm | -2.0<br>(-2.4 to -1.5)         | -1.3<br>(-1.5 to -1.1)    | 0.1<br>(-0.5 to 0.7)   | 2.2<br>(1.7 to 2.8)  | <.001               | .03                                | <.001                              | <.001                            | <.001                  | <.001                | <.001                |
| Fasting glucose, mg/dl  | -7.2<br>(-10.8 to -5.4)        | -10.8<br>(-16.2 to -7.2)  | -7.2<br>(-9.0 to -3.6) | 1.8<br>(-1.8 to 3.6) | <.001               | .08                                | .48                                | .006                             | .04                    | <.001                | .04                  |
| Insulin, $\mu$ U/ml     | -13.9<br>(-17.1 to -10.8)      | -12.7<br>(-15.3 to -10.2) | -2.7<br>(-4.3 to -1.1) | 2.1<br>(1.0 to 3.2)  | <.001               | .80                                | <.001                              | <.001                            | <.001                  | <.001                | <.001                |
| IRI                     | -3.6<br>(-4.5 to -2.7)         | -3.5<br>(-4.4 to -2.7)    | -1.0<br>(-1.5 to -0.5) | 0.4<br>(0.1 to 0.7)  | <.001               | .98                                | <.001                              | <.001                            | <.001                  | <.001                | <.001                |

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; IRI, insulin resistance index. SI conversions: To convert glucose from mg/dL to mmol/L, multiply by 0.0555; insulin from  $\mu$ U/mL to pmol/L, multiply by 6.945.

<sup>a</sup>P value for the omnibus analysis testing for overall differences between the 4 treatment groups on the continuous variables is based primarily on ANCOVA with baseline levels of the variables as covariates. When the overall omnibus analysis P value was significant, then pair-wise comparisons were performed.

**Table 4.** Adverse Effects by Treatment Group

| Adverse Effect          | No. (%)         |                                |                    |                              |                  | $\chi^2$ Test <sup>a</sup> | P Value |
|-------------------------|-----------------|--------------------------------|--------------------|------------------------------|------------------|----------------------------|---------|
|                         | Total (N = 128) | Lifestyle + Metformin (n = 32) | Metformin (n = 32) | Lifestyle + Placebo (n = 32) | Placebo (n = 32) |                            |         |
| Nausea                  | 19 (14.8)       | 4 (12.5)                       | 6 (18.8)           | 5 (15.6)                     | 4 (12.5)         | 0.680                      | .88     |
| Extrapyramidal symptoms | 30 (23.4)       | 8 (25.0)                       | 6 (18.8)           | 7 (21.9)                     | 9 (28.1)         | 0.871                      | .83     |
| Insomnia and agitation  | 23 (18.0)       | 5 (15.6)                       | 6 (18.8)           | 6 (18.8)                     | 6 (18.8)         | 0.159                      | .98     |
| Somnolence              | 10 (7.8)        | 2 (6.3)                        | 3 (9.4)            | 3 (9.4)                      | 2 (6.3)          | 0.434                      | .93     |
| Headache                | 10 (7.8)        | 3 (9.4)                        | 3 (9.4)            | 2 (6.3)                      | 2 (6.3)          | 0.434                      | .93     |
| Dry mouth               | 10 (7.8)        | 3 (9.4)                        | 3 (9.4)            | 2 (6.3)                      | 2 (6.3)          | 0.434                      | .93     |

<sup>a</sup> $\chi^2$  Test among 4 treatment groups.

lin and IRI levels. Finally, all 3 intervention groups were found to have a significant advantage over placebo in improving weight gain and insulin sensitivity in patients with schizophrenia. Our study verified that metformin treatment is safe and well tolerated in patients with schizophrenia. No major adverse events could be attributed to the study drug in this trial.

To maintain a balanced weight is often very challenging, but especially so for patients with schizophrenia due to their poor diet, sedentary lifestyle, and long-time need for antipsychotic medication. Therefore, developing interventions to fit this patient population is critically important because poorly managed weight not only leads to medical complications, diminished quality of life, and increased mortality but also leads to dramatic increases in health care costs. According to our study results, lifestyle intervention, metformin alone, or their combination could be added to attenuate antipsychotic-induced weight gain in patients with schizophrenia. In particular, we recommend that lifestyle intervention plus metformin be considered first for those with weight gain. If patients cannot tolerate or adhere poorly to lifestyle intervention, they should consider metformin alone.

This study has some limitations. First, this is a 12-week trial, so we do not know whether the improved body weight and insulin sensitivity could be sustained after patients stop taking metformin or engaging in the lifestyle intervention. Second, we could not assess the relative contributions of different components of the lifestyle intervention; thus, we do not know whether dietary or physical exercise would be more effective on weight loss and increasing insulin sensitivity. Third, we did not measure appetite change, so the measures of compliance for lifestyle intervention, particularly the food intake, were mainly reliant on patient or caregiver report. Metformin treatment adherence was based on patient self-report. As a result, the calculation of adherence could be inaccurate.

Fourth, all enrolled patients were taken care of by their parents or caregivers, so they could have better adherence with the interventions than patients living independently with schizophrenia. Fifth, in the study, the doses of antipsychotics were low. In China, stable patients are usually given low doses of antipsychotics as maintenance therapy. However, we required that antipsychotic medications remain fixed at the baseline dose levels throughout the course of treatment. Finally, because we used 750 mg/d of metformin as a fixed dose in the study, we do not know the dose effect of metformin on weight loss or whether it can be generalized to Western populations. As first-episode schizophrenia patients with less than a year of illness, patients in our study were young and few were obese, so we do not know whether these interventions would have the same effect on obese, older, or long-term patients.

Despite these limitations, this is the first placebo-controlled study to examine the effect of lifestyle intervention and metformin alone and in combination on weight gain and insulin sensitivity in first-episode patients with schizophrenia who were treated with a stable dose of antipsychotic monotherapy.

## CONCLUSION

Our study indicated that lifestyle intervention and metformin alone and in combination were effective in weight loss and increasing insulin sensitivity, lifestyle intervention plus metformin had the greatest effect on weight loss, and metformin alone was more effective than lifestyle intervention alone in increasing insulin sensitivity and reversing weight gain in patients with schizophrenia with significant weight gain because of antipsychotic medications.

**Author Contributions:** Dr Zhao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Wu, Zhao.

**Acquisition of data:** Wu, Zhao, Fang, He, Li.

**Analysis and interpretation of data:** Wu, Zhao, Jin, Shao, Guo, Liu, Chen.

**Drafting of the manuscript:** Wu, Zhao.

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**Statistical analysis:** Wu, Zhao.

**Obtained funding:** Zhao.

**Administrative, technical, or material support:** Wu, Shao, He, Chen, Li.

**Study supervision:** Wu, Zhao.

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