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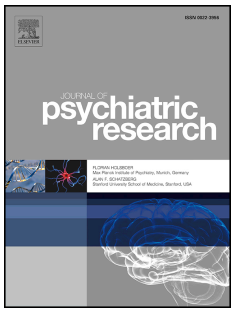

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Improving the physical health of overweight/obese people suffering from severe mental disorder: what is the role of antipsychotic drugs and of lifestyle psychosocial interventions?

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Improving the physical health of overweight/obese people suffering from severe mental disorder: what is the role of antipsychotic drugs and of lifestyle psychosocial interventions?

Abstract

People with severe mental disorders experience premature mortality compared with the general population. Several factors contribute to the mortality gap, including the adoption of unhealthy lifestyle behaviours, poor screening for physical illnesses, difficulties in accessing healthcare facilities, specific clinical features of mental disorders and some pharmacological treatment such as antipsychotic medications with serious metabolic side effects.

In the present study, carried out in the framework of the LIFESTYLE trial, a funded nationwide multicentric study, we aimed to assess the impact of different antipsychotics in mediating the effectiveness of psychosocial intervention on healthy lifestyle behaviours. The antipsychotics have been grouped in metabolically more problematic (MMP) vs. metabolically less problematic (MLP). The final sample consists of 401 participants with a mean age of 45.6±11.8 years, mainly female (57.1%), **suffering from bipolar disorder (43.4% of cases), schizophrenia spectrum disorders (29.7%) and depressive disorders (26.9% of cases). 36.2% of patients (N=145) received MMP antipsychotics, 32.2% were treated with MLP antipsychotics and 31.6% did not take any antipsychotic medication, but were treated with antidepressants, mood stabilizers and/or benzodiazepines.** At 6-month follow-up, patients receiving the experimental lifestyle intervention and treated with MLP medication reported a significant reduction in BMI (p<0.05).

Our findings clearly indicate that a multilevel, personalized and individualized therapeutic approach for the treatment of patients with severe mental disorders is needed, with the involvement of different physicians and health providers for an appropriate long-term management of patients with severe mental disorders.

Keywords

Severe mental disorders; metabolism; antipsychotics; lifestyle; psychosocial intervention.

Background

Compared to the general population, people with severe mental disorders, including schizophrenia, bipolar disorder and major depressive disorder, have a reduced life expectancy of 15-20 years, defining a significant mortality gap (Thornicroft, 2011; Laursen et al., 2012; Nordentoft et al., 2013; Walker et al., 2015; Siddiqi et al., 2017; Luciano et al., 2022a). The excess mortality is primarily attributed to the higher prevalence in these people of cardiovascular, metabolic, respiratory and infectious comorbidities (De Hert et al., 2011; Reily et al., 2015; Correll et al., 2017; Saxena and Maj, 2017; Afzal et al., 2021; Sampogna et al., 2022a). Other factors contributing to this mortality gap include the adoption of unhealthy lifestyle behaviours, such as lack of physical activity, unbalanced diet and smoking (Jacob et al., 2020; Luciano et al., 2021a), poor screening for physical illnesses, unfavorable socioeconomic conditions, difficulties in accessing healthcare facilities, and stigma. Furthermore, other relevant factors include some specific clinical features of mental disorders (e.g., cognitive deficits and delusions) and some pharmacological treatment with serious metabolic side effects (Manu et al., 2015; Burschinski et al., 2023; Correll et al., 2023). Among these, antipsychotic drugs, which can be grouped into first, second-generation and third-generation compounds based on their pharmacodynamic mechanisms (Orzelska-Górka et al., 2022; Correll et al., 2022; Dragioti et al., 2023), show different patterns of side-effects and tolerability (Casey and Zorn, 2001; Zimmerman et al., 2003; Newcome et al., 2005; Patel et al., 2009; Kessing et al., 2010; Zhang et al., 2013; Bak et al., 2014; Grajales et al., 2019; Huhn et al., 2019; Pillinger et al., 2020; Sneller et al., 2021; Wu et al., 2022; Højlund et al., 2022). **According to the most recent international clinical guidelines (Yatham et al., 2018; National Institute for Health and Care Excellence, 2022; 2023; Lam et al., 2024), these medications are not only used for the management of schizophrenia spectrum disorders but are very effective also in patients suffering from bipolar disorder or depressive disorders with psychotic features. However, using antipsychotic drugs in patients with different mental disorders requires a personalized approach, which is reflected in the use of different dosage for each specific clinical condition.** Recently, Vochoskova et al. (2023) grouped antipsychotics into metabolically more problematic (MMP; including clozapine, olanzapine, sertindole, and quetiapine) and metabolically less problematic (MLP; including flupenthixol, haloperidol, levomepromazine, zuclopenthixol, amisulpride, aripiprazole, cariprazine, lurasidone,

melperone, risperidone, and paliperidone), regardless of the classical pharmacodynamic classification.

Although the etiology of metabolic alterations in people with severe mental disorders remains multifactorial, antipsychotic medications and lifestyle behaviors represent key contributors, together with genetic predisposition and socioeconomic status (Fiorillo and Giordano, 2023). The optimization of antipsychotic treatment by treating physicians seems the most amenable to change and can significantly reduce the mortality gap (Leichsenring et al., 2022; Killaspy et al., 2022).

Another relevant strategy to challenge the morbidity and mortality in people with severe mental disorders is represented by the adoption of healthy lifestyle through specific psychosocial interventions (Luciano et al., 2021b). **Several psychosocial approaches are now available (Barber and Thornicroft, 2018), differing in terms of setting, involved professionals, duration and model (e.g., motivational interviews, psychoeducation and/or practice of moderate physical exercise) (De Rosa et al., 2017; Oliveira et al., 2022; Levrat et al., 2024; Gurusamy et al., 2024; Barlati et al., 2024; Hoogervorst et al., 2023; Browne et al., 2024). In the recent years, the field of lifestyle psychiatry (Firth et al., 2020) has been enriched by innovative approaches such as the GILL eHealth intervention led by nurses (Hoogervorst et al., 2023), with a focus on lifestyle promotion and somatic screening, or the PeerFIT approach, consisting of an in-person group lifestyle intervention augmented with mobile health technology (Browne et al., 2024). These are just some examples of recently introduced innovations, which highlights the need for defining appropriate and effective psychosocial interventions targeting lifestyle behaviours in people with severe mental disorders.** Lifestyle psychosocial interventions are effective in reducing weight and abdominal circumference, in preventing weight gain over time, and in improving glucose and lipid metabolism (Bradley et al., 2022; Luciano et al., 2024; Davidson et al., 2022).

A recent meta-analysis showed a nonsignificant improvement in managing antipsychotic-induced weight gain in people receiving lifestyle psychosocial interventions (Mohanty et al., 2024). However, the specific impact of antipsychotic drugs on weight gain and their role on modifying the impact of psychosocial interventions has been rarely explored. On these premises, our study aims to: 1) evaluate the metabolic profile in a sample of real-world patients with severe mental disorders receiving a lifestyle psychosocial intervention; 2) explore the impact of various antipsychotic medications on the effectiveness of the psychosocial intervention.

Methods

This is a secondary analysis of a large multicentric randomized controlled trial funded by the Italian Ministry of University and Research on the effectiveness of a new psychosocial group intervention aimed at improving lifestyle behaviours in patients suffering from severe mental disorders (Sampogna et al., 2018). The trial has been carried out in six Italian university centers (Bari, Campania "Luigi Vanvitelli", Genoa, L'Aquila, Pisa, and Rome "Tor Vergata"), coordinated by University of Campania "Luigi Vanvitelli" in Naples.

Participants

Patients were considered eligible if they fulfilled the following inclusion criteria: 1) age between 18 and 65; 2) a diagnosis of bipolar disorder, major depression, or schizophrenia spectrum disorder according to the DSM-5 criteria (American Psychiatric Association, 2013) and confirmed by the Structured Clinical Interview for DSM-5 (First et al., 2015); 3) written informed consent; 4) BMI≥25 kg/m^2; 5) in charge at the local mental health center for at least three months. Patients were excluded if they: 1) were not able to perform moderate physical activity (e.g., walking at least 150 minutes per week, or practicing vigorous exercises for 75 minutes twice a week); 2) were pregnant or in breastfeeding; 3) suffered from intellectual disability or cognitive impairment; and/or 4) experienced a serious clinical worsening or hospital admission in the three months preceding the recruitment period.

The decision to incorporate a BMI≥25 kg/m^2 among inclusion criteria is due to the need to select real-world patients for which the experimental intervention could be beneficial and in order to detect the impact of the intervention on a metabolic easy-to-assess outcome.

Eligible patients obtained detailed information about study's protocol and procedures by researchers involved in the LIFESTYLE trial. Thereafter, eligible patients were asked to provide their informed consent to take part to the study. Recruited patients were subsequently randomly allocated to the experimental or the control group. The randomization has been performed by a statistician working at the Coordinating Centre using a 1:1 approach, based on center, age, gender and level of education.

The whole recruitment procedure is described in detail in Sampogna et al. (2018).

Assessment

The LIFESTYLE trial included six time point assessments: at baseline (time point zero: T0), after two (time point one: T1), four (time point two: T2), six (T3), 12 (T4), and after 24 months (T5). For the aims of the current paper, only data collected at baseline (time point zero - T0) and at six months (time point 3 - T3) are included in the analyses.

Information on sociodemographic characteristics, medical history and pharmacological treatments was collected at baseline. Weight, height, abdominal circumference, blood pressure, heart rate values, blood levels of glucose, insulin, triglycerides, total cholesterol, LDL and HDL cholesterol were collected at both T0 and T3. The HOMA index was calculated based on glycemia and plasma insulin levels in order to estimate insulin resistance (Matthews et al., 1985). Current and 10-year Framingham risk scores were calculated based on age, sex, smoking, total cholesterol, HDL cholesterol, systolic blood pressure, any anti-hypertensive medications in order to assess cardiovascular risk (Wilson et al., 1998).

Psychopathological status was evaluated by the 24-item Brief Psychiatric Rating Scale (BPRS), a semi-structured interview consisting of 24 items assessing positive, negative, depressive-anxiety and manic-hostility symptoms (Lukoff et al., 1986). Cognitive performance was assessed through the MATRICS Consensus Cognitive Battery, including Trail Making Test, Symbol Coding and Category Fluency – Animal Naming (Kern et al., 2008; Nuechterlein et al., 2008). Quality of life was evaluated by the 17-item Manchester Short Assessment of Quality of Life (Priebe et al., 1999); patients' global functioning was assessed through the 100-point scale Personal and Social Performance Scale (Morosini et al., 2000).

Interventions

Participants were randomly allocated into two arms in order to compare the efficacy of two different lifestyle interventions**.**

Participants in the experimental arm received the LIFESTYLE Psychosocial Group Intervention, carried out for five months. Group sessions were delivered every 7-10 days providing participants with information on healthy habits (balanced diet, physical activity, smoking cessation, medication adherence, risky behaviors management, and circadian rhythms), motivational interviews and problem-solving strategies. The intervention also included 20 minutes of moderate exercise at the end of each session.

Patients allocated to the control group received a brief psychoeducational group intervention for 2 months. Group sessions were delivered weekly focusing on information

about healthy lifestyle, early detection of clinical relapses, management of medication side effects, stress management and problem-solving techniques.

Further details of both interventions can be found elsewhere (Sampogna et al., 2018).

Ethical approval

This research was carried out in accordance with the Declaration of Helsinki (World Medical Association, 2013) and local regulations. The study protocol was approved by the Ethics Committee of University of Campania “Luigi Vanvitelli”, Naples, in January 2017 (n. 64; trial registration number: 2015C7374S).

Statistical analyses

Sociodemographic, clinical and metabolic characteristics at T0 were obtained through descriptive statistics. Data were presented as means (M) and standard deviations (SD), or as percentages (%) and frequencies (N), as appropriate.

Patients were categorized in two groups: those receiving clozapine, olanzapine, sertindole, or quetiapine were included in the metabolically more problematic (MMP) group; patients taking flupenthixol, haloperidol, levomepromazine, zuclopenthixol, amisulpride, aripiprazole, cariprazine, lurasidone, melperone, risperidone, or paliperidone were allocated to the metabolically less problematic (MLP) group. **This classification is based on the study by Vochoskova et al. (2023), who grouped antipsychotics according to their effects on weight and metabolic markers (Wu et al., 2022; Pillinger et al., 2020; Arango et al., 2014). Using a distinction based on evidence-based ranking of medications can shed light on the impact of different antipsychotics on the metabolic profile of treated patients with severe mental disorders in ordinary clinical practice.**

Univariate analyses were used to compare MMP and MLP groups in terms of sociodemographic, clinical and metabolic characteristics at T0. In particular, Student t-test was performed to compare mean values of continuous variables between the subsets, while Chi-square test allowed a comparison in the case of categorical variables.

Once stratified according to type of antipsychotics, patients who had received the LIFESTYLE intervention were compared to controls at T3 in order to test differences in terms of metabolic condition.

Linear regression was performed for assessing the impact of using MMP or MLP antipsychotics and receiving the LIFESTYLE experimental intervention on the variation of BMI at T3, adjusting for several confounding variables, such as mean abdominal

circumference, mean systolic pressure, mean diastolic pressure, mean plasmatic levels of glucose, insulin, triglycerides, LDL, HDL and **different diagnostic categories**.

Logistic regression was performed to identify predictors of using MMP antipsychotics at baseline, including gender, age, mean values of BPRS domains (depressive/anxiety, negative, positive, manic symptoms, and hostility), duration of being in charge to the mental health centre, total duration of the illness**, type of diagnostic category,** mean plasma levels of glucose, insulin, triglycerides, LDL, and HDL, systolic pressure, diastolic pressure, and presence of metabolic syndrome.

Logistic regression was performed to identify predictors of different levels of obesity at baseline, including gender, age, mean values of BPRS domains (depressive/anxiety, negative, positive, manic symptoms, and hostility), duration of being in charge to the mental health centre, total duration of the illness**, type of diagnostic category**, mean plasma levels of glucose, insulin, triglycerides, LDL, and HDL, systolic pressure, diastolic pressure, presence of metabolic syndrome, and use of MMP antipsychotics.

Statistical analyses were performed using the IBM Statistical Package for Social Science (SPSS), Version 26. The level of statistical significance was set at $p<.05$.

Results

The global sample consisted of 401 participants, with a mean age of 45.6±11.8 years, mainly female (57.1%), single (52.4%) and unemployed (61.8%). 43.4% of patients suffered from bipolar disorder, 29.7% from schizophrenia spectrum disorder and 26.9% from depression. Mean duration of illness was 15.6±11.3 years, with a mean number of 2.3±4.3 previous voluntary hospitalizations.

Patients reported mild-moderate symptoms, with a mean score of 7.7±3.1 at the BPRS negative symptom subscale and of 5.4±2.0 at the positive symptom subscale (Table 1), and a poor level of functioning (PSP total score: 65.7±15.2). 59.6% of patients were receiving atypical antipsychotics, and 21.2% typical antipsychotics. Almost half of the global sample were receiving second-generation antidepressants (46.4%; N=186) and benzodiazepines (46.6%; N=187), 54.9% of patients received mood stabilizers. According to the type of antipsychotic compound, 145 patients were treated with MMP, while 129 patients with MLP. No significant differences were found in in the two MMP or MLP groups in terms of socio-demographic and clinical variables, apart from the Category Fluency – Animal naming of the MATRICS Consensus Cognitive Battery ($p<.01$) (Table 1).

Anthropometric and metabolic parameters at T0

In the majority of cases, patients were obese (63.2%), with a mean weight of 91.4±17.4 kilograms, with a mean BMI of 32.5±5.5 kg/m^2, and a mean abdominal circumference of 109.2±14.0 centimeters. More than half of participants (N=214) suffered from metabolic syndrome. Mean glycemia was 95.4±27.0 mg/dl, insulin plasma levels were 17.4±18.3 mcU/ml; mean blood levels of triglycerides were 171.2±129.6 mg/dl; mean total cholesterol was 189.9±40.9 mg/dl, and plasmatic LDL and HDL cholesterol levels were 119.2±34.9 mg/dl and 46.0±14.6 mg/dl, respectively. Mean blood pressure was 125.6±13.5 mmHg (systolic) and 80.8±9.0 mmHg (diastolic); heart rate was 77.2±12.2 bpm. Current and 10-year cardiovascular risks were calculated by using Framingham scores, whose mean values were 9.8±4.5 and 9.3±7.5, respectively. No significant differences were found between experimental and control groups.

Compared with the MLP group, participants taking MMP antipsychotics had significantly alteration in metabolic profile, in terms of higher plasma levels of LDL cholesterol, diastolic pressure (p<.05), and heart rate (p<.05), compared to those patients receiving MLP drugs (Table 2).

Impact of MMP/MLP antipsychotics on metabolic parameters and BMI at the end of the intervention

At T3, patients treated with MMP reported no significant differences in terms of metabolic parameters compared to T0 both in the experimental and in the control groups. On the contrary, patients receiving MLP antipsychotics had a significant reduction in BMI (31.6±4.3) compared to the control group (35.1±6.4; p<.05) after receiving the LIFESTYLE intervention (**Figure 1**).

HDL cholesterol plasma levels (B: .018; p<.05), diastolic blood pressure (B: -.032; p<.05), use of MLP antipsychotics (B: .570; p<.05) and abdominal circumference (B: .293; p<.000) predicted a significant reduction of BMI at T3.

There were no significant differences between the experimental and the control group taking MMP medications (Table 4).

Discussion

The mortality gap in patients with severe mental disorders requires urgent actions from an ethical and health perspective (Fiorillo and Sartorius, 2021; Dumas, 2022; Freeman,

2022). The premature mortality in these patients is a complex phenomenon resulting by the interaction of several factors. Among the modifiable risk factors, lifestyle behaviours and types of medications are the most amenable to change following simple actions by treating physicians and patients according to a shared decision-making approach (Puschner et al., 2010; Luciano et al., 2022b). Several studies have highlighted that psychosocial interventions aiming to improve lifestyle are highly effective in reducing physical parameters (such as the BMI and cardiovascular risk), increasing patients' physical activity (Luciano et al., 2022c; Sampogna et al., 2022b) and improving patients' adherence to pharmacological treatments (Sampogna et al., 2023).

Robust evidence shows that people with severe mental disorders are at higher risk compared to the general population to become overweight or obese (Afzal et al., 2021). A recent meta-analysis found that lifestyle interventions are effective in reducing the waist circumference, weight, and BMI in persons with severe mental disorders, as shown from changes of obesity parameters of in the intervention group compared to control group. These findings should be considered in ordinary clinical practice in order to help health care providers to manage obesogenic environmental and metabolic risk factors among patients with severe mental disorders (Mohanty et al., 2024).

In this study, we have explored the impact of antipsychotic drugs on the achievement of metabolic improvement among real-world patients receiving an innovative psychosocial group intervention compared with patients receiving a brief psychoeducational intervention. Our findings show that patients treated with MMP antipsychotics, such as clozapine, olanzapine, sertindole, and quetiapine (Vochoskova et al., 2023), experience a reduced effectiveness of psychosocial interventions.

Our results are in line with those by Conventry et al. (2019) and Looijmans et al. (2019), who found no significant differences in weight loss, controlling for different categories of antipsychotics based on metabolic side effects. In particular, in the STEPWISE intervention (Holt et al., 2019), patients receiving clozapine and olanzapine did not report any significant improvement in weight reduction.

At baseline, patients receiving MLP drugs reported a BMI significantly higher compared to those in the MMP group. This finding confirms the complexity of the inter-relationship between the metabolic impact of drugs, the individual liability to metabolic side effects and the role of lifestyle behaviours. Other variables, such as dosage of drugs, number of drugs previously taken, presence of familiarity for metabolic disorders, may have a significant role on the metabolic outcomes and on

the improvement in lifestyle behaviours. Thus, real-world, long-term, observational studies which take into account such variables may help to better understand this complex interplay.

Metabolic alterations in people with severe mental disorders are multifactorial, and are due to the interaction of genetic predisposition, socioeconomic status, lifestyle behaviors and antipsychotic medications. Although many guidelines discuss the varying risk of weight gain associated with different types of antipsychotics, none of them recommend considering the baseline BMI as a significant predictor of greater weight gain following antipsychotic treatment. Our results, in line with those by Vochoskova et al. (2023), suggest caution when prescribing MMP medications in people with severe mental disorders, in particular for those with a low BMI. Moreover, weight gain should be closely monitored during treatment, given its role as a proxy measure of the metabolic changes.

Looking at other metabolic indexes, such as HDL, LDL and lipid metabolism, no significant differences were observed between patients treated with MMP and MLP groups both in the LIFESTYLE and in the control group. It is well established that second-generation antipsychotics are associated with a greater alteration of lipid metabolism, although the exact mechanism has not been clarified yet. Recently, a key role for gut microbiota and composition of the intestinal microflora has been proposed, but it requires further confirmation (Chen et al., 2023). However, it confirms the complex interplay between genetic, biological psychological and physical factors underlying the metabolic alterations in people with severe mental disorders, according to the biolopsychosocial model of complex diseases (Fiorillo and Giordano, 2023). Further real-world studies are needed to fully understand the role of psychosocial lifestyle interventions and the importance of selecting psychotropic drugs less problematic from a metabolic profile for the recovery of patients with severe mental disorders.

At the regression analyses, when adjusting for the LIFESTYLE treatment, MLP antipsychotics predicted a significant BMI reduction at 6 months. This finding is in line with the hypothesis that antipsychotics with a low metabolic impact, when combined with psychosocial lifestyle interventions, significantly improve patients' physical health. Abdominal circumference resulted to predict BMI, confirming prior robust evidence of correlation (Wilmet et al., 2017; Ross et al., 2020). Furthermore, lower diastolic blood pressure was found associated with reduced BMI, as it was a non-significant trend captured by the univariate analysis in the group of patients receiving LIFESTYLE and taking MLP.

All these findings show that lifestyle interventions, including motivational interviewing, problem-solving strategies, and physical activity, are particularly effective in those patients taking metabolic less problematic antipsychotics. **Moreover, the present findings contribute to the increasing evidence in the field of lifestyle psychiatry (Firth et al., 2020), showing that the promotion of healthy lifestyle behaviours can help to prevent the onset of severe mental disorders, as well as to promote the long-term recovery of people already suffering from those disorders. The present findings can be specifically useful for informing clinicians to the need of implementing some physical evaluations, such as measurement of body weight, BMI and other metabolic parameters in their ordinary routine practice.** Thus, choosing the right medication for the right patient may lead to the improvement of physical health outcomes, according a personalized and integrated approach (Maj et al., 2020; Maj et al., 2021; McCutcheon et al., 2022; McIntyre et al., 2022; Ostuzzi et al., 2022; Galderisi, 2023; Leucht et al., 2023). Moreover, implementing and disseminating lifestyle psychosocial strategies as an add-on treatment is strongly supported by international scientific associations, such as the European Psychiatric Association (Stubbs et al., 2018) and the World Psychiatric Association (Wasserman et al., 2023; Wasserman, 2023; Sunkel, 2022). After one year from the intervention, improvements in BMI, weight, abdominal circumference and psychopathological domains were still present in the global sample (Luciano et al., 2024). This is why the LIFESTYLE intervention is now being disseminated throughout Italy in order to challenge patients' physical and mental unmet needs (Sampogna et al., 2021).

A relevant innovation of the LIFESTYLE trial is the adoption of a transdiagnostic approach for evaluating the effectiveness of a new psychosocial intervention on lifestyle behaviours in people with severe mental disorders. Although people suffering from schizophrenia present specific deficits and difficulties which are different from those reported by people suffering from affective unipolar or bipolar disorders, one common element to these mental disorders is the unacceptable mortality gap compared to the general population, partially due to the adoption of unhealthy lifestyle behaviour. Moreover, our statistical analyses have confirmed the validity of the transdiagnostic approach, since the effect of the experimental intervention has been controlled for the impact of the different diagnostic categories.

The following limitations should be considered. First, the present study is focused only on the impact of antipsychotic medications on patients' metabolic profile. The decision to tailor our analyses on the impact of antipsychotics on the metabolic profile is due to the large

evidence on the relationship between antipsychotics and metabolic side effects. However, a systematic review (Sepúlveda-Lizcano et al., 2023) has highlighted that not only drugs such clozapine, olanzapine, and risperidone are linked to weight gain and lipid profile alterations, but also some antidepressants and mood stabilizers. Therefore, it is essential to closely monitor medications' side effects, also considering that the metabolic effects caused by psychopharmacological medications may vary depending on patients' age. Another limitation is the short follow-up period considered, i.e., six months. It should be that this time frame did not allow us to detect other metabolic changes in the long term.

Another possible limitation is related to the mild-moderate levels of severity of clinical symptoms as well as to the poor level of patients' personal functioning. It should be that these clinical aspects have limited the effectiveness of the interventions, or that doses of pharmacological drugs have been defined according to the severity of patients' clinical status. However, the inclusion in the study of "clinically stable" patients only, evaluated as proxy measure by the absence of any hospitalization in the previous three months, could have reduced such source of variability. However, further real-world studies, including patients regardless the severity of their clinical conditions, might be useful. Finally, we did not collect data on dosages of antipsychotics (evaluated as chlorpromazine equivalent); future studies might be carried out to identify the impact of the different dosages of the same drug on patients' metabolic profile.

Conclusions

Patients suffering from severe mental disorders experience premature mortality and high levels of physical comorbidities in comparison with the general population. Metabolic side effects of antipsychotics contribute to weight gain and glucose and lipid metabolism alterations. Patients receiving an innovative psychosocial intervention focused on healthy lifestyle behaviours reported a significant BMI reduction compared to controls, especially when they were treated with less metabolic problematic antipsychotics.

Our findings clearly indicate that a multilevel, personalized and individualized therapeutic approach is needed, with the involvement of different physicians and health providers for an appropriate long-term management of patients with severe mental disorders (Kestel, 2022; Steger, 2022; Roe, 2022).

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Table 1. Participants' socio-demographic and clinical characteristics at T0.

	Global sample (N = 401)	**Metabolically More Problematic (MMP) Group (N = 145)**	**Metabolically Less Problematic (MLP) Group (N=129)**
Gender, female, % (N)	57.1 (229)	48.3 (70)	51.9 (67)
Age, M (SD)	45.6 (11.8)	45.0 (10.5)	44.0 (12.0)
Living situation, % (N)			
Single	52.4 (210)	60.0 (87)	62.0 (80)
Married/with partner	28.7 (115)	24.8 (36)	23.3 (30)
Separated/Divorced	14.0 (56)	11.0 (16)	11.6 (15)
Widowed	5.0 (20)	4.1 (6)	3.1 (4)
Years of education, M (SD)	11.7 (2.9)	12.1 (2.9)	11.6 (2.6)
Employed, yes, % (N)	38.2 (144)	30.2 (42)	35.0 (42)
Diagnosis, % (N)			
Depression	26.9 (108)	9.7 (14)	11.6 (15)
Bipolar disorder	43.4 (174)	47.6 (69)	45.7 (59)
Schizophrenia spectrum disorder	29.7 (119)	42.8 (62)	42.6 (55)
Charge to the mental health service, years, M (SD)	5.9 (6.9)	6.7 (6.8)	7.0 (7.8)
Duration of illness, years, M (SD)	15.6 (11.3)	17.9 (11.0)	17.1 (11.0)
Number of voluntary hospitalizations, M (SD)	2.3 (4.3)	2.8 (3.8)	2.8 (5.1)
Number of compulsory hospitalizations, M (SD)	0.5 (1.5)	0.7 (1.3)	0.7 (2.0)
Number of suicide attempts, M (SD)	1.8 (1.6)	2.09 (2.0)	1.5 (1.0)
Treated with LIFESTYLE intervention, yes, % (N)	51.4 (206)	50.3 (73)	56.6 (73)
BPRS, Positive Symptoms, M (SD)	5.4 (2.0)	5.6 (2.1)	5.8 (2.5)
BPRS, Negative Symptoms, M (SD)	7.7 (3.1)	7.5 (3.1)	7.6 (3.0)
BPRS, Depressive/anxiety symptoms, M (SD)	8.8. (3.1)	8.8 (3.3)	8.3 (3.2)
BPRS, Manic symptoms, M (SD)	4.7 (1.9)	4.8 (1.8)	4.8 (1.9)
BPRS, Hostility, M (SD)	4.0 (1.9)	4.4 (2.1)	4.4 (2.1)
MANSA, total score, M (SD)	4.1 (1.0)	4.1 (1.1)	4.2 (1.0)
B-MCCB, Symbol coding, M (SD)	34.5 (13.8)	33.4 (12.2)	30.7 (12.2)
B-MCCB, Animal naming, M (SD)	17.9 (5.4)	**18.0 (5.7)**	**16.2 (4.7)****
B-MCCB, Trail making test A,	52.4 (28.7)	53.0 (24.3)	59.9 (37.0)

M (SD)			
PSP, Total score, M (SD)	65.7 (15.2)	61.7 (16.1)	64.7 (14.3)
Typical antipsychotics, yes, % (N)	21.2 (85)	**25.5 (37)**	**37.2 (48)***
Atypical antipsychotics, yes, % (N)	59.6 (239)	**100 (145)**	**71.3 (92)******
First generation antidepressants, yes, % (N)	5.7 (23)	4.8 (7)	8.5 (11)
Second generation antidepressants, yes, % (N)	46.4 (186)	33.8 (49)	33.3 (43)
Benzodiazepines, yes, % (N)	46.6 (187)	46.2 (67)	47.3 (61)
Mood stabilizers, yes, % (N)	54.9 (220)	60.7 (88)	56.6 (73)

*$p < 0.05$; ** $p < 0.01$, **** $p < 0.0001$

Table 2. Participants' metabolic parameters at T0.

	Global sample (N = 401)	**MMP Group (N = 145)**	**MLP Group (N = 129)**
Weight (kilograms), M (SD)	91.4 (17.4)	93.8 (18.2)	91.5 (15.3)
Height (meters), M (SD)	1.68 (0.1)	**1.70 (0.1)**	**1.67 (0.1)***
Abdominal circumference, M (SD)	109.2 (14.0)	111.1 (15.7)	110.3 (11.8)
BMI, M (SD)	32.5 (5.5)	32.5 (5.8)	32.7 (5.0)
Overweight/obesity degree, % (N):			
Overweight (BMI: 24.9-29.9 kg/m^2)	35.9 (144)	36.6 (53)	31.0 (40)
Obesity, class 1 (BMI: 30.0-34.9 kg/m^2)	35.2 (141)	33.1 (48)	40.3 (52)
Obesity, class 2 (BMI: 35.0-39.9 kg/m^2)	19 (76)	18.6 (27)	20.9 (27)
Obesity, class 3 (BMI $\geq$ 40.0 kg/m^2)	9 (36)	10.3 (15)	7.8 (10)
Metabolic syndrome, yes, % (N)	53.4 (214)	62.1 (90)	51.2 (66)
Glycemia, M (SD)	95.4 (27.0)	94.5 (19.3)	92.0 (20.3)
Insulin plasm. levels, M (SD)	17.4 (18.3)	17.2 (14.6)	18.5 (23.2)
HOMA index, M (SD)	4.9 (11.62)	5.7 (17.4)	4.5 (6.2)
Triglycerides plasm. levels, M (SD)	171.2 (129.6)	185.7 (113.6)	158.9 (118.7)
Total cholesterol plasm. levels, M (SD)	189.9 (40.9)	190.4 (39.8)	181.7 (37.8)
LDL plasm. levels, M (SD)	119.2 (34.9)	**121.6 (33.8)**	**112.9 (32.1)***
HDL plasm. levels, M (SD)	46.0 (14.6)	42.9 (12.4)	45.7 (15.1)
Systolic pressure, (mmHg), M (SD)	125.6 (13.5)	127.1 (13.8)	126.4 (12.5)
Diastolic pressure, (mmHg), M (SD)	80.8 (9.0)	**82.5 (9.9)**	**80.3 (8.3)***
Heart rate (bpm), M (SD)	77.2 (12.2)	**80.4 (13.2)**	**76.9 (11.3)***
Framingham risk score, M (SD)	9.8 (4.5)	9.8 (4.5)	9.6 (4.4)
Framingham risk score 10 years, M (SD)	9.3 (7.5)	10.0 (8.7)	8.9 (6.7)

*$p < 0.05$

Table 3. Participants' metabolic parameters at the end of intervention, stratified according to MMP or MLP antipsychotics.

	MMP		**MLP**	
	LIFESTYLE (N=38)	**Controls (N=36)**	**LIFESTYLE (N=30)**	**Controls (N=19)**
Weight (kilograms), M (SD)	93.3 (16.9)	91.5 (18.4)	88.3 (15.8)	95.1 (15.2)
Abdominal circumference, M (SD)	110.5 (13.8)	108.3 (15.6)	107.6 (13.2)	111.9 (10.4)
BMI, M (SD)	31.8 (4.7)	31.9 (6.3)	**31.9 (4.3)**	**35.1 (6.4)***
Glycemia, M (SD)	98.5 (29.8)	92.1 (13.8)	96.7 (28.0)	91.4 (14.6)
Insulin plasm. levels, M (SD)	18.7 (16.4)	25.5 (32.3)	14.1 (16.1)	18.7 (11.2)
Triglycerides plasm. levels, M (SD)	200.2 (101.1)	164.7 (80.3)	139.1 (73.9)	154.2 (76.5)
Total cholesterol plasm. levels, M (SD)	189.1 (36.9)	192.1 (41.8)	180.9 (29.4)	184.7 (39.4)
LDL plasm. levels, M (SD)	119.5 (40.3)	128.0 (40.0)	143.7 (170.7)	116.0 (34.3)
HDL plasm. levels, M (SD)	43.2 (15.9)	46.7 (19.4)	47.1 (10.6)	46.9 (11.8)
Systolic pressure, (mmHg), M (SD)	124.3 (12.1)	123.9 (10.2)	125.4 (13.6)	127.8 (14.3)
Diastolic pressure, (mmHg), M (SD)	82.1 (7.1)	78.3 (14.1)	77.6 (7.7)	80.6 (9.3)

*$p < 0.05$

Table 4. Predictors of variation in BMI at T3.

Variables	B	Sign.	95% Confidence Interval
MMP antipsychotics	-.115	.426	-.400 – .169
MLP antipsychotics	.016	.908	-.261 – .294
Treated with LIFESTYLE intervention	.306	.127	-.088 – .700
Abdominal circumference	.010	.194	-.005 – .025
Glycemia	.006	.096	-.001 – .014
Plasmatic levels of insulin	.001	.849	-.010 – .012
Plasmatic levels of triglycerides	.000	.886	-.001 – .002
Plasmatic levels of LDL	.000	.969	-.006 – .006
Plasmatic levels of HDL	**.018**	**.015**	**.004 – .033**
Systolic pressure	-.005	.589	-.024 – .014
Diastolic pressure	**-.032**	**.034**	**-.061 – -.002**

Table 4. Predictors of BMI at T3.

Variables	B	Sign.	95% Confidence Interval
MMP antipsychotics	-.001	.997	-.569 – .566
MLP antipsychotics	**.570**	**.044**	**.016 – 1.123**
Treated with LIFESTYLE intervention	**-.997**	**.001**	**-.784 – .787**
Abdominal circumference	**.293**	**.000**	**.262 – .323**
Glycemia	.000	.956	-.015 – .016
Plasmatic levels of insulin	.004	.733	-.018 – .026
Plasmatic levels of triglycerides	.002	.435	-.003 – .006
Plasmatic levels of total cholesterol	-.009	.462	-.034 – .015
Plasmatic levels of LDL	.013	.313	-.012 – .037
Plasmatic levels of HDL	.021	.256	-.015 – .056
Systolic pressure	.026	.171	-.011 – .064
Diastolic pressure	**-.077**	**.011**	**-.135 – -.018**

Table 5. Predictors of using MMP antipsychotic

Variables	B	Sign.	95% Confidence Interval
Gender	-.035	.905	.548 – 1.702
Age	.005	.740	.975 – 1.036
BPRS, Depressive/anxiety symptoms	.075	.128	.979 – 1.187
BPRS, Negative Symptoms	-.053	.311	.856 – 1.051
BPRS, Positive Symptoms	-.064	.417	.804 – 1.094
BPRS, Manic symptoms	-.024	.788	.821 – 1.161
BPRS, Hostility	.016	.848	.860 – 1.202
Duration of charge to the mental health service	.000	.854	.996 – 1.003
Duration of illness	.005	.749	.975 – 1.035
Glycemia	.003	.669	.989 – 1.018
Plasmatic levels of insulin	-.005	.493	.981 – 1.009
Plasmatic levels of triglycerides	.001	.457	.998 – 1.004
Plasmatic levels of LDL	.007	.083	.999 – 1.015
Plasmatic levels of HDL	-.015	.220	.985 – 1.009
Metabolic Syndrome	.121	.711	.594 – 2.145
Systolic pressure	-.012	.373	.962 – 1.015
Diastolic pressure	.032	.086	.995 – 1.071

Figure 1. Variation in BMI

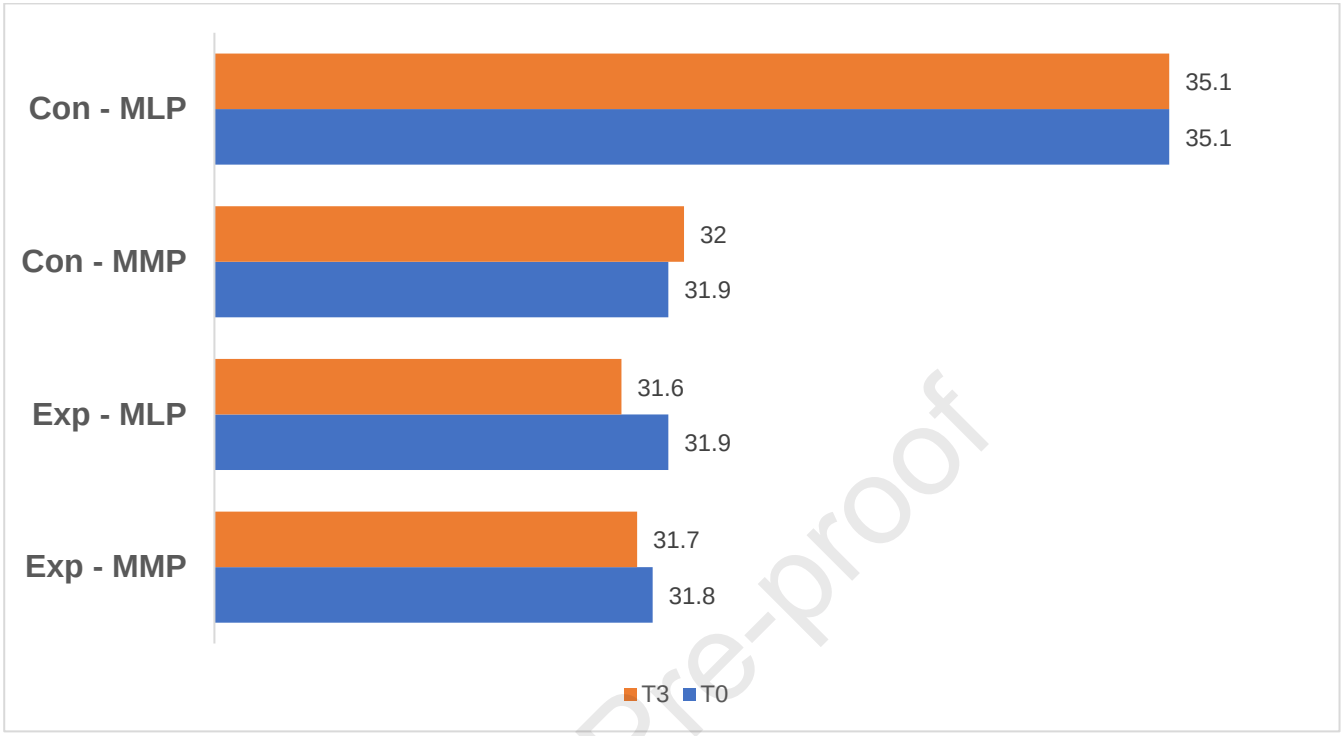

Table 4. Predictors of variation in BMI at T3.

Variables	**B**	**Sign.**	**95% Confidence Interval**
MMP antipsychotics	-.115	.426	-.400 – .169
MLP antipsychotics	.016	.908	-.261 – .294
Treated with LIFESTYLE intervention	.306	.127	-.088 – .700
Abdominal circumference	.010	.194	-.005 – .025
Glycemia	.006	.096	-.001 – .014
Plasmatic levels of insulin	.001	.849	-.010 – .012
Plasmatic levels of triglycerides	.000	.886	-.001 – .002
Plasmatic levels of LDL	.000	.969	-.006 – .006
Plasmatic levels of HDL	**.018**	**.015**	**.004 – .033**
Systolic pressure	-.005	.589	-.024 – .014
Diastolic pressure	**-.032**	**.034**	**-.061 – -.002**

Table 5. Predictors of BMI at T3.

Variables	**B**	**Sign.**	**95% Confidence Interval**
MMP antipsychotics	-.001	.997	-.569 – .566
MLP antipsychotics	**.570**	**.044**	**.016 – 1.123**
Treated with LIFESTYLE intervention	**-.997**	**.001**	**-.784 – .787**
Abdominal circumference	**.293**	**.000**	**.262 – .323**
Glycemia	.000	.956	-.015 – .016
Plasmatic levels of insulin	.004	.733	-.018 – .026
Plasmatic levels of triglycerides	.002	.435	-.003 – .006
Plasmatic levels of total cholesterol	-.009	.462	-.034 – .015
Plasmatic levels of LDL	.013	.313	-.012 – .037
Plasmatic levels of HDL	.021	.256	-.015 – .056
Systolic pressure	.026	.171	-.011 – .064
Diastolic pressure	**-.077**	**.011**	**-.135 – -.018**

Table 6. Predictors of using MMP antipsychotic

Variables	B	Sign.	95% Confidence Interval
Gender	-.035	.905	.548 – 1.702
Age	.005	.740	.975 – 1.036
BPRS, Depressive/anxiety symptoms	.075	.128	.979 – 1.187
BPRS, Negative Symptoms	-.053	.311	.856 – 1.051
BPRS, Positive Symptoms	-.064	.417	.804 – 1.094
BPRS, Manic symptoms	-.024	.788	.821 – 1.161
BPRS, Hostility	.016	.848	.860 – 1.202
Duration of charge to the mental health service	.000	.854	.996 – 1.003
Duration of illness	.005	.749	.975 – 1.035
Glycemia	.003	.669	.989 – 1.018
Plasmatic levels of insulin	-.005	.493	.981 – 1.009
Plasmatic levels of triglycerides	.001	.457	.998 – 1.004
Plasmatic levels of LDL	.007	.083	.999 – 1.015
Plasmatic levels of HDL	-.015	.220	.985 – 1.009
Metabolic Syndrome	.121	.711	.594 – 2.145
Systolic pressure	-.012	.373	.962 – 1.015
Diastolic pressure	.032	.086	.995 – 1.071

Improving the physical health of overweight/obese people suffering from severe mental disorder: what is the role of antipsychotic drugs and of lifestyle psychosocial interventions?

Highlights

- People with severe mental disorders experience premature mortality, mainly due to the high prevalence of cardiovascular, metabolic, respiratory and infectious diseases, to the adoption of unhealthy lifestyle behaviours.
- Some pharmacological treatment such as antipsychotic medications can have serious metabolic side effects.
- Antipsychotic medications can be grouped in metabolically more problematic (MMP) vs. metabolically less problematic (MLP).
- Patients receiving the experimental lifestyle intervention and treated with MLP medication reported a significant reduction in BMI ($p<0.05$).
- A multilevel, personalized and individualized therapeutic approach for the treatment of patients with severe mental disorders is needed, and the selection of less metabolically problematic drugs should be advisable.

Declaration of Interest Statement

All authors have nothing to disclose.