Charles University

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Prague, 2024 MUDr. Kristýna Vochosková

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Metabolic changes in first episode of psychosis:
Effects of antipsychotic medications

Metabolické změny u první epizody psychotického onemocnění:
Vliv antipsychotické medikace

Supervisor: prof. MUDr. Tomáš Hájek, Ph.D.

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Abstract

Background: Most people with schizophrenia die from cardiovascular causes closely related to metabolic syndrome/obesity. To better understand the development of metabolic alterations early in the course of illness, we quantified daily medication exposure in the first days of the first hospitalization for psychosis and related it to changes in weight and metabolic markers.

Study design: We recruited participants with first episode psychosis (FEP, N=173) during their first psychiatric hospitalization and compared them to controls (N=204). We prospectively collected weight, body mass index, metabolic markers, and daily medication exposure at admission and during hospitalization. In detailed medication analysis, we calculated the trajectory of polypharmacy and tried to identify additional predictors within collected and quantified prescription patterns that influence BMI changes, such as polypharmacy and adjustments in antipsychotic medication that impact body weight.

Study results: Individuals with FEP gained on average 0.97±2.26 BMI points or 3.46±7.81 kg of weight after an average of 44.6 days of their first inpatient treatment. Greater antipsychotic exposure was associated with greater BMI increase, but only in people with normal/low baseline BMI. Additional predictors of weight gain included type of medication and duration of treatment. Medication exposure was not directly related to metabolic markers, but higher BMI was associated with higher TGC, TSH, and lower HDL. During hospitalization, participants with FEP had significantly higher BMI, TGC, prolactin, and lower fT4, HDL than controls. In the detailed medication analysis, among the potential predictors, only baseline BMI was associated with weight gain.

Conclusion: During their first admission, participants with FEP, especially those with normal/low baseline BMI, showed a rapid and clinically significant weight increase, which was associated with exposure to antipsychotics, and with metabolic changes consistent with metabolic syndrome. These findings emphasize weight monitoring in FEP and suggest a greater need for caution when prescribing metabolically problematic antipsychotics to people with lower BMI.

Abstrakt

Úvod: Velké množství jedinců s diagnózou schizofrenie v současné době umírá na komplikace kardiovaskulárních onemocnění, které jsou úzce spojené s metabolickým syndromem a obezitou. Pro lepší porozumění vztahu antipsychotik k časným změnám hmotnosti a metabolických parametrů jsme se zaměřili na pacienty s FEP v prvních dnech jejich hospitalizace a systematicky kvantifikovali jejich denní expozici antipsychotické medikaci (AP) v prostředí českých psychiatrických nemocnic.

Metody: Do studie jsme zařadili pacienty s první epizodou psychózy (FEP, N=173) během jejich první psychiatrické hospitalizace a porovnali je se zdravými kontrolami (N=204). V prospektivním sledování jsme sbírali data o hmotnosti, BMI, metabolických parametrech a denní expozici AP při přijetí a během výzkumné vizity v průběhu téže hospitalizace. Při detailní analýze léčby jednotlivých pacientů jsme prostřednictvím kvantifikace různých léčebných scénářů hledali další potenciální faktory, které by mohly mít vliv na změny BMI.

Výsledky: Během prvních 44,6 dnů hospitalizace jsem u pacientů s FEP zaznamenali průměrný příbytek na váze o 0,97 ± 2,26 BMI bodů/ 3,46 ± 7,81 kg. Vyšší expozice AP byla spojena s vyšším přírůstkem BMI, avšak pouze u osob s normálním/nižším výchozím BMI. Dále byly identifikovány další faktory ovlivňující nárůst hmotnosti, jako druh užívaného AP a délka léčby. Nebyla nalezena přímá asociace mezi expozicí AP a metabolickými parametry, nicméně vyšší BMI bylo spojeno s vyššími hladinami TCG, TSH a nižšími hladinami HDL cholesterolu. Hospitalizovaní pacienti vykazovali významně vyšší BMI, TAG a hladiny prolaktinu a nižší hladinu fT4 a HDL cholesterolu v porovnání s kontrolní skupinou. Při detailní analýze AP léčby pomocí kvantifikace medikačních trajektorií bylo zjištěno, že výchozí BMI zůstává nejlepším prediktorem přírůstku na váze.

Závěr: Během první hospitalizace pacientů s FEP jsme rychle zaznamenali významný nárůst hmotnosti, který byl spojen s užíváním antipsychotik, zejména u těch se vstupně nižším nebo normálním BMI. Naše pozorování zdůrazňují důležitost zejména pravidelného monitorování hmotnosti u jedinců s FEP a potřebu opatrnosti při předepisování antipsychotik s prometabolickým efektem osobám s nižším BMI.

List of Abreviations

AP - antipsychotics

BMI - body mass index

BP - blood preasure

CRP - C-reactive protein

DIP - duration of inpatient treatment

FEP - first episode of psychosis

fT3 - free T3, tri-iodothyronine

fT4 - free T4, thyroxine

GLP-1RA - glucagon-like peptide-1 receptor agonists

HC - healthy controls

HDL - high-density lipoprotein cholesterol

HDL - high-density lipoprotein cholesterol,

HOMA-IR - Homeostatic Model Assessment of Insulin Resistance

HPA - hypothalamus-pituitary-adrenal

Chlpz - chlorpromazine equivalent

LDL - low-density lipoprotein cholesterol

MARTA - multi acting receptor targeting antipsychotics

MLP - metabolically less problematic

MMP - metabolically more problematic

OLZ/SAM - olanzapine/samidorphan

PANSS - Positive and Negative Symptom Scale

RCT - randomized controlled trial

SCZ - schizophrenia

SD - standard deviation

T1 - Time 1, admission

T2 - Time 2, research visit

TCG - triglycerides

TSH - thyrotropin

WHR - waist-to-hip ratio

Content

1. Introduction

1.1 Studied disorder - definition, epidemiology

Schizophrenia (SCZ) is a severe mental disorder that impacts approximately 1% of the global population. It is characterized by psychotic symptoms of hallucinations, delusions, and disorganized speech, by negative symptoms such as decreased motivation and diminished expressiveness, and by cognitive deficits involving impaired executive functions, memory, and speed of mental processing (Kahn et al., 2015; Marder & Cannon, 2019). Symptoms start early and vary in the patient population, but overall, schizophrenia is among the top 10 global causes of disability and contributes to 13.4 million years of life lived with disability to burden of disease globally (Charlson et al., 2018; Immonen et al., 2017; Marder & Cannon, 2019). Individuals with schizophrenia experience significant decrease and negative impact on social and professional functioning, quality of life, but also excess morbidity and shortened life expectancy (Cowman et al., 2023; Harvey et al., 2022; Taipale et al., 2020; Whiteford et al., 2013). One of the key issues which contributes to a range of negative outcomes in schizophrenia is comorbity with metabolic alterations.

1.2 Metabolic alterations in FEP and schizophrenia – epidemiology

Compared to the general population, individuals with schizophrenia have from 2.8 to 3.5 times higher risk of obesity and up to 2.8 times higher risk of dyslipidemia (Afzal et al., 2021; Coodin, 2001; Saari et al., 2004). The prevalence of type 2 diabetes is about a third higher in patients with schizophrenia than in the general population (Papanastasiou, 2013). Importantly, the onset of metabolic alterations in psychotic disorders starts early in the course of illness. About one-fifth of people with the first episode of psychosis suffer from overweight/obesity, low HDL-cholesterol, or hypertriglyceridemia. Both diabetes and pre-diabetes appear uncommon in the early stages, especially in drug-naive patients (Misiak et al., 2017; Mitchell, Vancampfort, De Herdt et al., 2013; Mitchell et al., 2013). The high prevalence of metabolic alterations in schizophrenia impacts medical, but also psychiatric outcomes.

1.3 Impact of metabolic alterations on mortality in individuals with schizophrenia

Excess mortality is experienced by patients with all severe mental disorders across all age groups, including premature mortality in people with schizophrenia (Brink et al., 2019). Individuals with schizophrenia, on average, experience a 20-year reduction in life expectancy and have a 2.5-3-fold increase in mortality (Brown, 1997; Bushe et al., 2010; Kilbourne et al., 2009; Laursen et al., 2014). Approximately 60% of these excess deaths are associated with concurrent physical illnesses, particularly chronic conditions such as type 2 diabetes mellitus, cardiovascular disease, respiratory diseases, stroke, and malignancies. Cardiovascular disease have the highest mortality rate of all disease groups, accounting for approximately one-third of all natural deaths (Olfson et al., 2015) in people with schizophrenia. Heart and vascular diseases are the main reason for excess mortality in schizophrenia (Kilbourne et al., 2009; Olfson et al., 2015).

We need to better understand and address these cardiovascular risk factors before we can reduce the mortality gap in psychiatry, which in contrast to many other specialties, is increasing. The adjusted hazard ratios for mortality in individuals with schizophrenia showed a gradual increase from 2004 to 2010, at a rate of 0.11 per year, after 2010, the increase in mortality rates accelerated significantly, reaching a rate of 0.34 per year (Hayes et al., 2017). One could argue that the impact of metabolic alterations on mortality in schizophrenia is an issue for internal medicine not for psychiatry, but there are also many psychiatric outcomes related to obesity/metabolic alterations.

1.4 Consequences of metabolic alterations in individuals with schizophrenia

1.4.1 Metabolic alterations and cognition

Metabolic abnormalities have been shown to negatively impact the somatic health of individuals with schizophrenia. Additionally, they can also exacerbate progression of the psychiatric disease and impair cognitive functions. Solid evidence has demonstrated that obesity is negatively associated with cognitive functions in a variety of cognitive domains

in non-SCZ individuals, including the adolescent population (Elias et al., 2003; Gunstad et al., 2010; Meo et al., 2019; Prickett et al., 2015). The literature revealed impairments in obese adults across almost all cognitive domains investigated, e.g. complex attention, verbal and visual memory, decision making (Prickett et al., 2015). Even in non-SCZ populations, people with obesity and related metabolic alterations are at risk of developing Alzheimer's disease and all other types of dementia (Gudala et al., 2013; Ma et al., 2020; Norton et al., 2014). According to Beydoun and collaborating authors, around 12% of dementia (all subtypes) risk was attributed to obesity. Separately for Alzheimer's disease, the population attributable risk was even higher, 21.1% (Beydoun et al., 2008).

There is also evidence for a significant relationship between cognitive impairment in schizophrenia and each of the components of metabolic syndrome including hypertension, dyslipidemia, abdominal obesity and diabetes (Bora et al., 2017) that can potentially contribute to functional decline observed in some patients with schizophrenia throughout the course of illness (Hagi et al., 2021). This finding is vital together with results of study of Veronese *et al.,* who found conversely that intentional weight loss in overweight or obese people was associated with improvements in performance across various cognitive domains (Veronese et al., 2017) and obesity reduction therefore is one of potentially modifiable risk factors for cognitive dysfunction and dementias in the population of SCZ patients as well as the both general non-psychiatric and psychiatric population.

1.4.2 Metabolic alterations and brain changes

Current neuroimaging evidence indicates that obesity not only contributes to cognitive decline but also to changes in brain structure and accelerated brain aging. Large-scale studies and meta-analyses provide compelling evidence from non-psychiatric populations that obesity and body mass are significantly linked to reduced gray matter volume in brain regions critical for executive control. Both high BMI and WHR may represent important risk factors for gray matter atrophy (García-García et al., 2019; Hamer & Batty, 2019).

Similarly, elevated BMI has been found to be associated with reduced regional gray matter volumes in individuals experiencing their first psychotic episode, suggesting that obesity

contributes to neurostructural changes in this population (Kolenic et al., 2018). Brain alterations in psychosis are manifest early during the first episode and over time, higher baseline BMI was found to predict accelerated brain aging in FEP over time (Hajek et al., 2019; McWhinney et al., 2021).

A recent study has also identified widespread associations between BMI and brain structure in individuals diagnosed with schizophrenia. It is likely that individuals with both obesity and schizophrenia will exhibit more pronounced brain alterations compared to those with only one of these conditions (McWhinney et al., 2022).

1.4.3 Noncompliance and worse treatment outcomes

Importantly, metabolic abnormalities in individuals with schizophrenia can also influence the risk and occurrence of relapses and rehospitalizations through medication non-compliance (Ayuso-Gutiérrez & del Río Vega, 1997; Gilmer et al., 2004; Sullivan, 1995). Previous research have consistently reported that a significant proportion of schizophrenia patients, ranging from 50% or more, exhibit non-compliance with their prescribed medications at some point during their illness (Bebbington, 1995; Oehl et al., 2000; Semahegn et al., 2020) although, continuous antipsychotic treatment has been found to provide the lowest risk of rehospitalization or death among patients with schizophrenia (Tiihonen et al., 2018).

Nevertheless, studies identified a significant association between metabolic side effects, such as weight gain, and medication non-compliance. For instance, Weiden *et al.* (2004) found that obese patients were more than twice as likely to discontinue their medication compared to patients with normal BMI, primarily due to distress over weight gain. Similar findings were reported in the CATIE study, where more patients discontinued olanzapine, despite its lower overall discontinuation rate, due to weight gain (Lieberman et al., 2005; Manschreck & Boshes, 2007). Weight gain, as identified in the expert consensus guideline on medication adherence in serious psychiatric illnesses, was also recognized as a potential factor leading to non-adherence. The experts recommended the customization of interventions to address poor adherence in order to mitigate the impact of weight gain on medication compliance (Velligan et al., 2009).

1.5 Metabolic alterations in FEP and schizophrenia – common etiological and risk factors

The etiology of obesity and other metabolic alterations in first-episode psychosis and schizophrenia remains incompletely understood and is likely complex and multifactorial in nature. There are prenatal common risk factors for obesity and schizophrenia implicated in this phenomenon, along with a multitude of additional shared abnormalities relevant to both obesity and schizophrenia, like genetic underpinnings, the HPA axis activity, heightened noradrenergic tone, neuroinflammation, or mitochondrial dysfunction. Moreover, schizophrenia itself serves as a contributor to obesity due to its symptoms, subsequent lifestyle changes, and antipsychotic treatment (Manu et al., 2015).

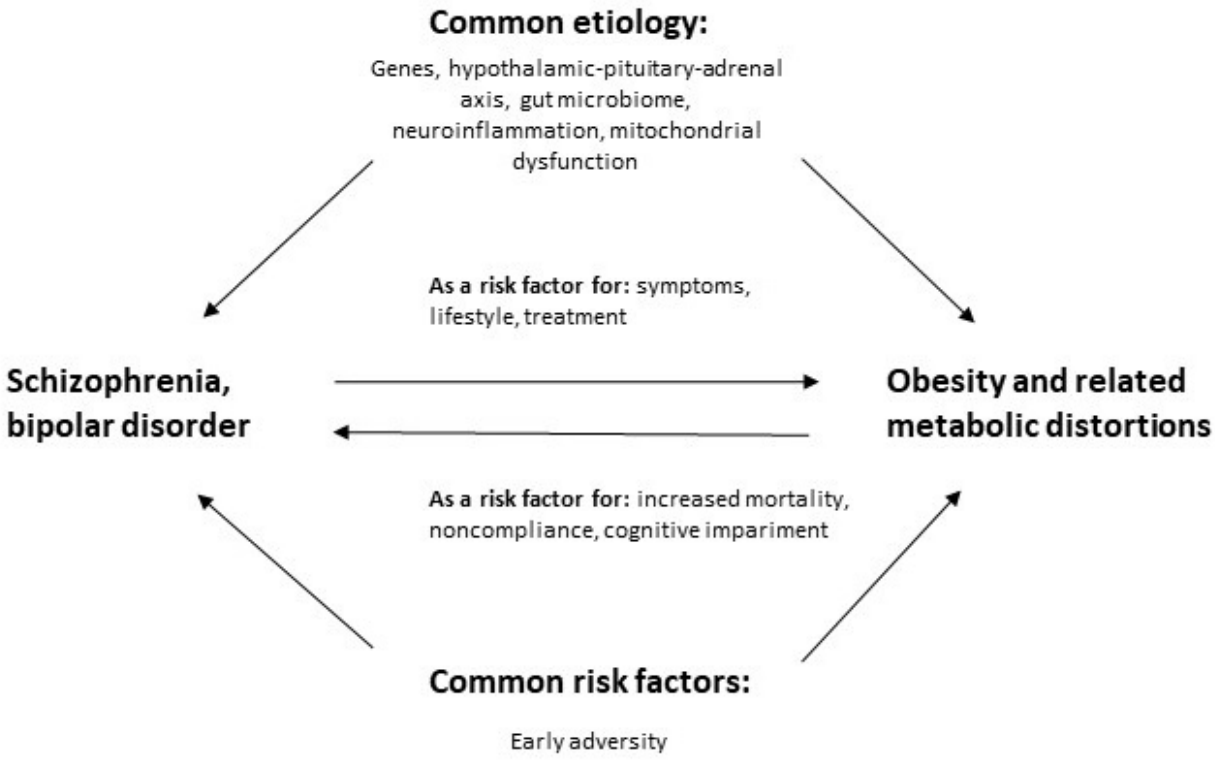


Figure 1 The schematic diagram illustrating the established links between obesity and schizophrenia through shared risk factors, mutual etiological factors, and both obesity and schizophrenia serving as risk factors themselves, created for the purpose of this thesis based on the structural framework presented in the introduction of this work.

1.5.1 Schizophrenia as a risk factor for obesity

1.5.1.1 Symptoms and lifestyle

The significant increase in the worldwide rates of overweight and obese subpopulations has been related to changes in diet composition, increased caloric intake, and modifications of the gut microbiome (Ng et al., 2014). The most basic explanation for weight gain leading to obesity is a prolonged imbalance between energy expenditure and caloric intake. However obesity results from a chronic positive energy balance regulated by a complex interaction between endocrine tissues and the central nervous system where various previously mentioned factors can impact the final outcome (Bosy-Westphal & Müller, 2021; Skolnik & Ryan, 2014). In recent years, the excess energy intake and its conversion into fat storage has been linked to the consumption of sugary beverages and the increased availability of calorie-dense foods (Skolnik & Ryan, 2014)

The dietary regimen and nutrition of individuals with schizophrenia fall short of optimal standards even considering the worsening general population dietary changes. Schizophrenia patients have higher intake of total calories, high consumption of saturated fat and low intake of fruit and dietary fiber per kilogram of body weight. (Tsuruga et al., 2015) finds these nutritional irregularities and also vitamin deficiencies persisted per-kilogram basis, thus remaining independent of BMI and did not correlate with the type of antipsychotic (Dipasquale et al., 2013; Nunes et al., 2014; Tsuruga et al., 2015). Decreased caloric expenditure with inadequate exercise and smoking are common due to the social isolation or unemployed status. Nearly half of individuals with schizophrenia reported that they do not participate in any vigorous physical activity (Brown et al., 1999; Heald et al., 2017).

Symptoms of schizophrenia are diverse, and are often classified into three main categories: 'positive,' 'negative,' and 'cognitive'. Negative symptoms characterize what is known as the amotivational syndrome, encompassing traits such as social withdrawal, affective flattening, anhedonia, and diminished initiative and energy (Kahn et al., 2015). While this particular set of symptoms may seem to play a significant role in contributing to obesity,

current findings are not definitive. Poor social functioning was one of the main factors associated with weight gain in long term perspective. Those patients with no deficits at 3 years follow-up gained a mean of 9.4 kg compared to 14.5 kg of those patients with deficits in social function (Perez-Iglesias et al., 2014). The WAIST Study revealed an alarming excessive sedentary lifestyle of around 13 hours, excluding the time spent not wearing the monitoring device during sleep, as recorded by actigraphy. However, this study did not find any conclusive link between sedentary behaviors and psychiatric symptoms evaluated with PANSS scales or BMI. Although, the lack of associations between sedentary behavior and psychiatric symptoms may be due to a ceiling effect for sedentary behavior (Janney et al., 2013). In prospective longitudinal study on cohort of 170 first-episode psychosis patients, the lack of clinical response was also a significant predictor of weight gain. The lack of response for negative symptoms was positively associated with weight gain ($\beta = 0.197$; $t = 1.989$; $p < 0.049$). On the other hand, the subgroup of patients classified as non-responders for positive symptoms gained significantly less weight at the end of the 3 years follow-up ($\beta = -0.301$; $t = -3.525$; $p < 0.001$). These results suggest that individuals with more severe negative symptoms may engage in fewer physical and social activities, potentially placing them at a higher risk of weight gain. Additionally, the observation that patients with more severe positive symptoms gained significantly less weight might be partially attributed to the fact that only 52% of non-responding patients demonstrated good adherence (Perez-Iglesias et al., 2014). In other studies and case reports have indicated that individuals with schizophrenia who exhibit an obese metabolic phenotype tend to have reduced negative symptoms (Koga & Nakayama, 2005; Wang et al., 2020). The existing literature does not provide a clear consensus on symptom categories, but it does highlight the role of poor social functioning, reduced physical activity and sedentary lifestyle in connection to schizophrenia (Heald et al., 2017; Janney et al., 2013; Perez-Iglesias et al., 2014).

1.5.1.2 Antipsychotic medication

Medications are a well established factor contributing to weight gain already in early stages of schizophrenia. Several studies on patients experiencing their first episode of psychosis have shown that over half of the weight gain occurs within the initial 12 weeks of treatment (Addington et al., 2003; Lieberman et al., 2003; Patel et al., 2009; Schooler et al., 2005; Zipursky et al., 2005). During this period, individuals with schizophrenia treated with atypical

antipsychotics gained between 2.2 and 4.5 kg on average. In studies lasting up to 12 weeks in FEP, the weight gain was approximately 3.22 kg, with a corresponding BMI increase of 1.44 points. Additionally, in studies involving medication-naive individuals, most of which lasted less than 12 weeks, the weight gain was around 4.85 kg, with a BMI increase of 1.97 (Huhn et al., 2019a; Tarricone et al., 2010; Tek et al., 2016). Although almost all antipsychotics lead to some level of weight gain, the disposition of various antipsychotics to cause weight gain vary largely (Bak et al., 2021a; Pillinger et al., 2020). Zotepine, clozapine, olanzapine induce the most severe weight gain, in contrast to ziprasidone, aripiprazole, haloperidol and lurasidone, which seems to be the most weight neutral one, see Figure 2 (Huhn et al., 2019a; Pillinger et al., 2020; Sabé et al., 2023a)

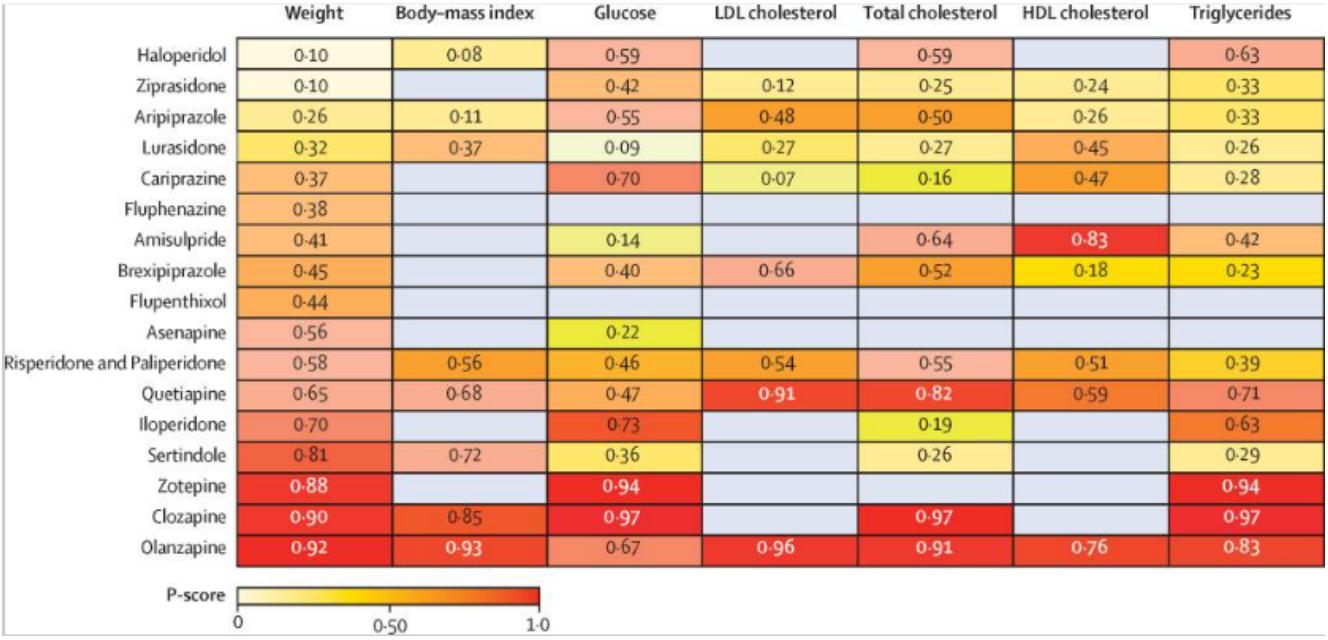


Figure 2 Heat map of antipsychotic drugs ranked according to associated degree of alteration in bodyweight, body-mass index, and metabolic parameters. Numbers reflect P-score, which rank antipsychotics on a continuous scale from 0 to 1. A higher P-score indicates a greater increase in the metabolic parameter, with the exception of HDL cholesterol, for which a higher P-score indicates a smaller increase. Grey squares indicate that data were not available (Pillinger et al., 2020).

Studies based on nationwide registries have revealed that a high cumulative exposure to antipsychotic medications poses a similar hazard ratio of cardiovascular mortality to not receiving any antipsychotic treatment for schizophrenia at all. Furthermore, this high

cumulative exposure is associated with an increased risk of cardiovascular mortality (Torniainen et al., 2015). In the general population, for every 1 kg increase in body weight, there is a 3.1% increase in the risk of cardiovascular disease. Additionally, for every 1 kg/m2 increase in BMI, the risk of heart failure increases by 5-7%, and the risk of type 2 diabetes increases by 8.4%. Furthermore, a 1 mmol/L increase in triglyceride concentrations is associated with a 32-76% increased risk of cardiovascular disease. Therefore, approximately 6 to 7 weeks of treatment with antipsychotic medications such as olanzapine and clozapine, which can lead to an approximate 3 kg increase in body weight, a 1 kg/m2 increase in BMI, and a 1 mmol/L increase in triglyceride levels, may result in significant elevations in the risk of cardiovascular disease (Pillinger et al., 2020). The propensity of antipsychotic medications to cause weight gain, the early changes in BMI observed in patients treated with antipsychotics, and the impact of each individual kilogram gained on metabolic risk factors underscore the critical importance of making informed treatment choices.

We can only speculate about all the precise mechanisms underlying the effect of AP medications on obesity. Several mechanisms have been proposed to explain the general appetite-stimulant weight gain propensity of antipsychotics. Namely, their affinity to specific receptors, e.g. including 5-HT(2A) and 5-HT(2C) serotonin receptors, H(1)-histamine receptors, alpha(1)- and alpha(2)-adrenergic receptors, and M3-muscarinic receptors and subsequent regulation of food intake via the appetite stimulation (Kroeze et al., 2003; Roerig et al., 2011). Antipsychotics also enhance food intake via altering appetite control neuropeptides e.g. increase leptin, ghrelin or decrease adiponectin serum levels (Atmaca et al., 2003; Hosojima et al., 2006; Roerig et al., 2011). Furthermore, later in the thesis is mentioned several polymorphisms that might render genetically predisposed patients more susceptible to weight gain from specific types of antipsychotic medications. In drug-naive adolescents with FEP on olanzapine, risperidone or quetiapine in monotherapy in one year follow-up was also found increased resting energy expenditure/fat-free mass ratio and decreased resting energy expenditure/ kilograms body mass measured with indirect calorimetry and bioelectrical impedance, suggesting a drug induced hypometabolic state. This mechanism might also play a role in prometabolic side effects in AP treated patients (Cuerda et al., 2011).

1.5.2 Schizophrenia and obesity – common risk factors

Extensive research has been conducted on obstetric complications and other prenatal and perinatal risk factors as potential contributors to the risk of psychosis in adulthood (Cannon et al., 2002; Davies et al., 2020). Similar conclusions have been published regarding obesity separately, where it was found that maternal infection during pregnancy is associated with an increased risk of offspring developing obesity (Li et al., 2020). However, recent studies bring indirect evidence suggesting that early life events, represented by an indirect marker of the intrauterine milieu such as birth weight, as a common epiphenomena of both schizophrenia and metabolic disturbances. Work of Ziauddeen *at al.* From 2016 found a significant association between lower birth weight and higher adiposity in treatment resistant individuals with schizophrenia treated with clozapine. Interestingly, this link was not observed in drug-naive patients and healthy volunteers. This suggests early intrauterine development may have negative prometabolic effects, which are noticeable only after exposure to an additional factor, like antipsychotic treatment, and modulates the degree of weight gain and fat distribution in response to the treatment (Ziauddeen et al., 2016). Another recent study discovered the impact of birth weight on a different aspect. In the sample of young FEP patients (23.51 ± (5.8) years), it was observed that lower birth weight is associated with elevated glucose levels, which implies a potential risk for these patients to develop glucose-related abnormalities as time progresses (Garcia-Rizo et al., 2022).

1.5.3 Schizophrenia and obesity – common etiology and links

1.5.3.1 Genes

A substantial body of evidence supports the possibility of genetic overlap of cardiometabolic abnormalities and schizophrenia. Firstly, prevalence of cardiometabolic dysfunction was increased in the otherwise healthy first-degree relatives of individuals with psychosis, which suggests a molecular connection between schizophrenia and metabolic syndrome that could have reciprocal influences, partly from shared genetic factors (Mothi et al., 2015). Secondly, multiple genome-wide association analysis studies have identified common genetic loci associated with both schizophrenia and metabolic disturbances. Study from 2019 identified five genomic regions with evidence of colocalising schizophrenia and type 2 diabetes signals, three containing known loci for both diseases, and 29 genes associated with both (Goh et al., 2022;

Hackinger et al., 2018; Lin & Shuldiner, 2010). The hypothesis suggests that genetic predisposition of individuals with SCZ to psychoneuroendocrine irregularities might also elevate their susceptibility to metabolic distortions like type 2 diabetes and metabolic syndrome. So *et al.* (2019) found tentative polygenic associations of SCZ with glucose metabolism abnormalities, adverse adipokine profiles, increased waist-to-hip ratio and visceral 21erformer, also suggesting susceptibility to cardiometabolic abnormalities independent of medication side effects (So et al., 2019). It is proposed that genes of the prolactin-pathway may be implicated in the comorbidity of these disorders. This shared genetic risk for both schizophrenia and metabolic syndrome potentially contributes to the underlying connection between these two pathways (Postolache et al., 2019).

Nevertheless, several polymorphisms like 5-HT(2C), b3-Receptors (64 Arg allele and 825 T allele), or Leptin (LEPR) Q223R were associated with weight gain specifically in some group treated with antipsychotic medications (Roerig et al., 2011). Further work in this area, particularly utilizing genome-wide association studies, may help to identify risk levels in different individuals that will be helpful in personalized antipsychotic medication selection.

1.5.3.2 Hypothalamic-pituitary-adrenal axis

As stated in the hypothesis related to the prolactin pathway above, the hypothalamic-pituitary-adrenal axis establishes an additional functional connection between the regulation of energy metabolism of the central and peripheral systems. Perhaps, increased prolactin in people with schizophrenia is not exclusively a result of dopamine blockade caused by antipsychotics, as elevated prolactin concentrations have been detected in antipsychotic-naive individuals with FEP. (Albayrak et al., 2014; Del Cacho et al., 2019; Petrikis et al., 2016). It may also highlight the inherent potential of the dopamine-prolactin pathway, which could play a role in both schizophrenia and metabolic syndrome. Dopamine dysfunction, apart from contributing to positive symptoms, may contribute to the clinical schizophrenia- type 2 diabetes association and other metabolic complications (Gragnoli et al., 2016).

Besides prolactin, higher glucocorticoids levels seems to be also intrinsic to drug-naive FEP patients (Misiak et al., 2021). Cortisol, the most important human glucocorticoid, plays a key natural role in releasing energy sources like glucose, amino acids, and fatty acids, during stress responses. It promotes processes like breaking down muscle proteins, adipose tissue lipolysis,

and hepatic gluconeogenesis all while reducing the utilization of glucose. Long-term exposure to high levels of glucocorticoids alters body composition by increasing central fat deposits, which negatively affects metabolism and the functioning of insulin. This intricate interplay ultimately leads to insulin resistance and lipid disturbances (Geer et al., 2014).

1.5.3.3 Gut microbiome

The gut microbiota is considered on of related factors that play a significant role. The bidirectional communication between the gut microbiota and brain development and function, known as the microbiota-gut-brain axis, is a well-recognized concept within the field of psychiatry (Cryan & De Wit, 2019). It plays a significant role due to its interaction with central nervous 22erfor through neural, immunological, and neuroendocrine pathways (Nguyen et al., 2021; Rogers et al., 2016). However, it‘s important to note that our understanding of differences in microbiome diversity in relation to schizophrenia spectrum disorders is still somewhat limited (Nikolova et al., 2021). Recent evidence suggests that an imbalance in the gut microbiota, known as dysbiosis, may also have a notable role in the onset of obesity. The gut microbiome is vital for maintaining normal metabolic and immunological functions, and perturbations in the gut microbiota been perturbations in the gut microbiota have been reported to be linked to the pathogenesis of obesity by influencing glucose tolerance, insulin resistance, lipid metabolism and low-grade inflammation (Baothman et al., 2016).The potential link between the microbiome, obesity, and schizophrenia is related to low-grade neuroinflammation (Müller et al., 2015). Dysbiosis in the gut microbiota may trigger the release of proinflammatory cytokines into circulation, some of which might pass the blood-brain barrier, leading to neuroinflammation. This process, including microglia proliferation, is associated with changes in neural substrates in both schizophrenia and obesity (He et al., 2018).

1.5.3.4 Increased noradrenergic tone

At the turn of the 19th and 20th centuries, Emil Kraepelin described extensive autonomic alterations in patients with schizophrenia, including increased heart rates, altered pupillary function, increased sweating and salivation, as well as temperature changes (Bär et al., 2015). More recently, a number of hypotheses have been proposed to explain the etiology

of schizophrenia, including a lesser known theory is that heightened norepinephrinergic signaling could be also one of the causal factors in schizophrenia (Stahl, 2018). While most current antipsychotic medications primarily target dopamine D2 receptors as antagonists or partial agonists/antagonists, some second-generation antipsychotics also influence α-adrenergic receptors (AR), as seen with medications like risperidone or clozapine (Miyamoto et al., 2005). In schizophrenia, 23erfo generally thought that blocking α1-Ars suppresses positive symptoms, while blocking α2-Ars relieves negative and cognitive symptoms (Maletic et al., 2017; Svensson, 2003). The clinical advantages of these receptor interactions remain theoretical and are primarily supported by evidence from preclinical experiments or case reports (Maletic et al., 2017; Nagamine, 2020). Increased noradrenergic tone has been also widely studied in obesity and other metabolic syndrome components in non-psychiatric population with findings of elevated whole body norepinephrine spillover accompanied by increased muscle sympathetic nerve activity (Grassi et al., 2005; Huggett et al., 2004; Straznicky et al., 2005). Multiple theories and findings have emerged that potentially establish a link between metabolic syndrome and the noradrenergic system in individuals with schizophrenia. These connections may arise from heightened and persistent stress responses associated with psychiatric illness contributing to weight gain, and shared genetic risk factors (Cheng et al., 2012; Liu et al., 2010; Luca et al., 2011). Therefore, it is of considerable interest to understand the role that NE antagonism may play in metabolic abnormalities in schizophrenia individuals.

1.5.3.5 Neuroinflammation

The possible link between schizophrenia and metabolic abnormalities is low-grade systemic inflammation (Müller et al., 2015; O'Rourke, 2009; Vachharajani & Granger, 2009). Systemic inflammation, characterized by altered cytokine production and the activation of inflammatory signaling pathways throughout the body, is being actively investigated to determine its role in obesity-related insulin resistence, where adipose tissue serves as a significant site of inflammation in obesity (Wellen & Hotamisligil, 2005). Recent work found robust and biologically plausible evidence for ten colocalized shared genetic variations that may at least in part contribute toward the comorbidity between schizophrenia, inflammation, and cardiometabolic disorders (Perry et al., 2022).

1.5.3.6 Mitochondrial dysfunction

A possible connection of schizophrenia and obesity via systemic inflammation might play the role of mitochondrial dysfunction. Mitochondria have a vital function in controlling cellular processes such as energy production, maintaining calcium levels, managing oxidative signals, and orchestrating programmed cell death. Additionally, mitochondria are indispensable for numerous aspects of neurodevelopment and the functioning of neurons (Rajasekaran et al., 2015). Mitochondrial uncoupling caused by the processing of excess fatty acids in adipocytes can result in an enhanced production of reactive oxygen species and further proinflammatory state (Gregor & Hotamisligil, 2007; Vachharajani & Granger, 2009; Wojtczak & Schönfeld, 1993).

Within this part of introduction, I provide a comprehensive review of the many etiological factors contributing to obesity in schizophrenia. However, while many of these factors are challenging to quantify or directly address in a clinical setting, the selection and optimization of antipsychotic treatment remain in the control of treating physician. Consequently, my research primarily focuses on the impact of antipsychotic medications on obesity, as it is so far the most actionable and controllable factor for clinicians, which might help to reduce this common comorbidity. Monitoring obesity is crucial not only for cardiovascular outcomes but also for psychiatric outcomes and brain health. Focusing on risk factors associated with obesity allows for the prevention of structural brain changes and cognitive deficits that are closely linked to obesity. By understanding and managing the effects of AP medications, psychiatrists can make more informed decisions that better support overal outcomes of patients with FEP.

1.6 Current solutions for metabolic alterations

Solutions for addressing obesity and other metabolic disturbances in patients with schizophrenia spectrum disorders can be categorized into non-pharmacological and pharmacological approaches, with an emphasis on non-pharmacological interventions as the initial step.

1.6.1 Non-pharmacological interventions

Non-pharmacological interventions include education and motivation support for adopting a healthier lifestyle, smoking cessation, healthier dietary choices, and regular exercise. These interventions include educating individuals to reduce calorie intake and increase expenditure through dietary modifications and regular physical aktivity (Jensen et al., 2014). Weight reduction interventions along with strategies to prevent weight gain, have been extensively studied in the general population. Evidence suggests that such interventions can lead to significant weight loss and decrease all-cause mortality in individuals with obesity (Ma et al., 2017). However, the overal success of lifestyle interventions for weight loss in individuals with schizophrenia is a question. Meta-analyses conducted by Naslund and Caemmerer indicated that lifestyle and behavioral interventions can effectively prevent or reduce antipsychotic-induced weight gain and associated cardiometabolic issues (Caemmerer et al., 2012; Naslund et al., 2017). However, the observed effects were relatively small compared to the weight gain observed in this patient population. Additionally, among the six trials reviewed by Naslund et al., only two demonstrated significant positive effects on weight loss at the 12-months visit (Naslund et al., 2017). In second metaanalysis, weight and BMI were significantly improved only in outpatient trials but not in inpatient or mixed samples (Caemmerer et al., 2012). Notably, studies such as the CHANGE trial and STEPWISE indicated that these interventions were not clinically effective or cost-effective or both (Holt et al., 2019; Speyer et al., 2016). Furthermore, weight loss programs designed specifically for individuals with schizophrenia have encountered challenges, including low attendance or limited interest. In one study, only half of the overweight or obese individuals chose to enroll in the program, and those who did enroll attended sporadically in approximately one-fourth of the program (Niv et al., 2014).

1.6.2 Pharmacological and invasive surgical interventions

Pharmacological interventions for weight gain management in a psychiatric inpatient and outpatient setting include switching from a higher-risk antipsychotic to one with lower metabolic risks or augmenting with another medication. In cases where additional metabolic abnormalities, such as hypertension, dyslipidemia, or glucose metabolism disorders, are identified, referral to a specialist for management is recommended (De Hert et al., 2009). In cases of non-response, there is limited data on the effectiveness of bariatric care, as reported by (Shelby et al., 2015). It is important to consider the fact, that medications with weight loss effects seem to act more as a means of minimizing harm, as none of the agents are likely to completely reverse the weight gain induced by antipsychotic medications (Mizuno et al., 2014).

The decision to switch antipsychotic medications to a lower-risk antipsychotic is an evidence-based approach, however should take into account the patient‘s overall psychiatric and physical health, and pharmacological profiles of both their current and proposed medications (Correll, 2010). The CATIE trial in schizophrenia confirmed that weight gain did not yield clinically significant efficacy advantages and switching to lower risk antipsychotics associated with weight loss resulted in similar efficacy outcomes compared to switching to agents that promoted weight gain (Hermes et al., 2011). The most promising weight loss outcomes were achieved through switching to ziprasidone and aripiprazole, which proved beneficial for some, though not all, metabolic measures. Importantly, this switch carried minimal risk of exacerbating psychopathological symptoms. From studies focusing on the effectiveness of switching antipsychotics for antipsychotics induced weight fain, we know that changing to an antipsychotic with a better metabolic profile is a promising and effective strategy for improving weight gain and metabolic parameters in long term. The majority of these studies evaluated promising weight loss outcomes after 12-52 weeks (Mukundan et al., 2010; Newcomer et al., 2008; Stroup et al., 2011; Weiden et al., 2008). In studies with a one-year follow-up, we observed the effectiveness of switching to ziprasidone from olanzapine and risperidone, resulting in reductions in weight from baseline by 9.8 kg ($p<0.001$) and 6.9 kg ($p<0.005$), respectively (Weiden et al., 2008). In a one-year randomized study involving patients with schizophrenia or bipolar disorder who were predominantly previously treated with risperidone, quetiapine, and olanzapine, the switch to either ziprasidone or aripiprazole was

shown to be effective in improving overall metabolic health. After a 6-week follow-up, body weight reductions from baseline were 2.27 kg (baseline mean 98.47 kg; mean at the 6-week follow-up: 96.20 kg) for aripiprazole and 3.17 kg (baseline mean 98.42 kg; 6-week follow-up mean: 95.25 kg) for ziprasidone (Chen et al., 2012).

When switching to a lower-risk antipsychotic is not an option, medications can also be added to counteract antipsychotic-related cardiometabolic adverse events. In a metaanalysis of 40 trials and 19 unique interventions were included in this meta-analysis. Metformin was the most promising drug in regard to body weight, the mean difference amounting to -3.17 kg compared to placebo. Pooled effects for topiramate, sibutramine, aripiprazole, and reboxetine were also different from placebo. Furthermore, metformin and rosiglitazone improved insulin resistance, while aripiprazole, metformin, and sibutramine decreased blood lipids (Mizuno et al., 2014). Older metaanalysis of 32 studies, including 15 different medications for almost 1500 individuals with any diagnosis who had gained weight with antipsychotics, metformin had the greatest weight loss (-2.94 kg). Besides metformin, other medications with weight loss efficacy in comparison to placebo were: d-fenfluramine (2.60 kg), sibutramine (2.56 kg), topiramate (2.52 kg) and reboxetine (1.90 kg). Importantly, metformin was effective only after weight gain occurred, in prevention of weight gain when started concomitantly with antipsychotics was not effective.

Recent research also introduced the combination drug olanzapine/samidorphan (OLZ/SAM), sold under the brand name Lybalvi. The combination of olanzapine with samidorphan, an opioid receptor antagonist, was developed to prevent olanzapine-associated weight gain while maintaining its therapeutic effects. So far, studies indicate that the combination results in modest reductions in weight gain, blood pressure, and the risk of metabolic syndrome compared to olanzapine alone, it shows no significant impact on glucose or lipid levels (Correll et al., 2023). In study on early psychosis patients under 4 years since symptom onset, percent weight change was significantly lower with OLZ/SAM versus olanzapine 4.91% vs 6.77%; (LSM -1.87%, SE 0.75; p=0.012). However, in those patients who experienced the strongest weight gain (≥10%) in both groups, the difference was not statistically significant (Kahn et al., 2023). So far it seems that olanzapine/samidorphan offers some advantages, it is not a comprehensive solution for all metabolic side effects associated with olanzapine and for all FEP patients. It was recently approved for medical use in the United States (May 2021). Curently, it is not yet available in the Czech Republic.

A recent review highlights a crucial point concerning the disparity between psychiatric and non-psychiatric guidelines regarding the management of obesity (Lee et al., 2022). While there is consensus in the importance of monitoring cardiometabolic risk factors and adopting a stepwise approach, beginning with conservative interventions, e.g. lifestyle changes, diet, exercise, before considering pharmacological treatment or more invasive options such as bariatric surgery, they diverge in their choice of medications for pharmacological intervention (Lee et al., 2022). Psychiatric and psychiatric-related societies, such as The American Psychiatric Association Practice Guideline, frequently advocate metformin as the primary pharmacological choice for addressing antipsychotic-induced obesity in conditions like schizophrenia and bipolar disorder (Cooper et al., 2016; Keepers et al., 2020). Conversely, authorities in the field of obesity management for the general population, like the National Institute for Health and Care Excellence (NICE) and the Endocrine Society, support exclusively only licensed medications in weight management and do not entertain off-label alternatives like metformin (Apovian et al., 2015; National Clinical Guideline Centre (UK), 2014). Consequently, the psychiatric approach, by favoring unlicensed medications, deviates from the strategies employed by cardiologists and endocrinologists in managing obesity and its associated cardiometabolic risks. In addition, there is a notable absence of prescribing information specifying the appropriate utilization of metformin (Fitzgerald et al., 2022).

Among licensed weight loss medications, former exclusively T2DM medications from the class of glucagon-like peptide-1 receptor agonists (GLP-1RA) show promising results. There is solid and robust evidence of anti-obesity effect in non-psychiatric population without T2DM (Iqbal et al., 2022). Liraglutide has demonstrated statistically significant improvements in weight, body mass index, and waist circumference also among individuals with schizophrenia, with no adverse impact on psychiatric symptoms (Lee et al., 2022). Available research on the efficacy on metabolic disturbances in obese individuals with schizophrenia spectrum disorders treated with AP medications is not broad yet. Hovewer, recent metanalysis of 4 RCTs on glucagon-like peptide-1 receptor agonists (liraglutide and exenatide) showed promising results. GLP-1RA treatment compared to control resulted in a significantly greater reduction in body weight by 3.8 kg (MD = −3.80, 95% CI; −6.35 to −1.24, I^2 = 64%, p = 0.004). And it appear to be an efficacious treatment option for weight management in individuals with obesity related to antipsychotic drugs, also improving glycemia and lipid profile parameters. The effect appears to be similar in subjects with and without concomitant psychotic disorder (Patoulias et

al., 2023). Recently, reports emerged suggesting a potential increased risk of suicidality in patients treated with GLP-1 receptor agonists. The FDA conducted detailed reviews of reports of suicidal thoughts or actions received in the FDA Adverse Event Reporting System. However, recent analyses and regulatory conclusions by both the FDA and the European Medicines Agency indicate that there is no causal link between GLP-1 receptor agonists and an increased risk of suicidal and self-injurious thoughts and actions (Europen Medicines Agency, n.d.; *Update on FDA's Ongoing Evaluation of Reports of Suicidal Thoughts or Actions in Patients Taking a Certain Type of Medicines Approved for Type 2 Diabetes and Obesity*, n.d.). Moreover, meta-analyses of clinical trials suggest that GLP-1 receptor agonists may reduce depressive symptoms and further exclude suicidality (X. Chen et al., 2024). The impact of GLP-1RAs is expected to expand significantly as the currently high prices decrease, making the treatment more accessible for other indications.

1.7 Current state and potential remedies

As treatment of obesity is difficult in general and especially in people with severe mental illnesess, prevention of weight gain seems to be of great importance. None of the non-pharmacological or pharmacological interventions seem to be able to entirely reverse weight gain and other related metabolic issues in AP-treated patients. At present, no treatment has sufficient evidence to recommend for broad clinical usage (Maayan et al., 2010). There have been attempts by several international societies to develop guidelines for screening and monitoring metabolic consequences of psychosis. The aim of such procedures is to reduce those modifiable factors associated with the risk of cardiometabolic conditions among patients affected by schizophrenia. It is well known that when applied, these guidelines appear to improve the metabolic outcome of patients with severe mental illnesess. For a number of reasons, including the lack of consensus over who should take responsibility for the general healthcare needs of patients with mental illness, we continue to fail in providing appropriate services and these recommendations have been poorly followed and employed in the clinical settings (De Hert et al., 2009; Ventriglio et al., 2015).

During the early stages of schizophrenia, medications are a well-recognized factor contributing to weight gain (Huhn et al., 2019b; Lieberman et al., 2003; Patel et al., 2009; Schooler, et al., 2005; Tarricone et al., 2010; Tek et al., 2016; Zipursky et al., 2005).

Although many guidelines discuss the varying risk of weight gain associated with different types of antipsychotics, the guidelines do not generally mention possible predictors of weight gain nor recommendations for treatment choice in FEP in specific groups of patients, even though the first year of antipsychotic treatment is an especially critical period for development of obesity and metabolic abnormalities (Patel et al., 2009; Verma et al., 2009). International guidelines, such as National Institute for Health and Care Excellence (NICE) (National Collaborating Centre for Mental Health (UK), 2014), Guidelines for the Pharmacotherapy of Schizophrenia in Adults, Canada (Remington et al., 2017), or APA guidelines (American Psychiatric Association, 2021) do not recommend specific medications in individuals with FEP, but only advocate for consideration of side effects. In contrast, Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for early psychosis (Galletly et al., 2016) and Swiss guidelines for early psychosis (Premier Épisode Psychotique - Choix de l'antipsychotique, n.d.) treatment caution against olanzapine as the first-choice medication, recommending it only as a second-line option.

2. Aims, objectives, hypotheses

Higher rates of obesity and metabolic alterations in SCZ are of multifacorial complex etiology, partialy related to shared genetic risk factors, as well as the lifestyle changes due to the disorder symptoms itself, but those factors are very difficult to address. A key contributor and the one which is under control of clinicians is the selection of antipsychotic medications. Despite the well-known replicated knowledge of antipsychotic medication-related metabolic changes and the high prevalence of obesity in individuals with schizophrenia, the effect of antipsychotic medication on these pathologies remains not fully understood and researched. Better understanding of the antipsychotics-caused contribution to obesity and other metabolic abnormalities could help to minimize the iatrogenic metabolic disturbances and thus decrease the somatic problems and increase life and health span of individuals with schizophrenia.

We have a wealth of information from clinical trials (Foley & Morley, 2011), but these results may not generalize to everyday psychiatric practice. Most of our current knowledge comes from randomized controlled trials on cohorts of patients taking antipsychotics as a monotherapy, although the initial treatment of the first episode of psychosis often involves the use of multiple antipsychotic medications or their frequent changes. Moreover, the available studies typically did not quantify daily medication exposure and mostly evaluated changes in metabolic parameters only after at least 3 months of treatment. Also, most of the studies focused on metabolic changes in schizophrenia related disorders are performed on individuals in their chronic stages and FEP controlled trials might not fully cover all the population with psychotic disordes because of the narrow spectrum of selected well collaborating participants.

This research aims to fill some knowledge gaps in naturalistic, inpatient setting. Collaboration with large psychiatric hospitals provided access to a consecutive group of individuals during their first hospitalization for psychosis. Inpatient setting allowed us to maximize adherence, precisely quantify daily exposure to medication, and gain a pragmatic snapshot of everyday psychiatric practice. Moreover, inpatient treatment to a large degree standardized diet, sleep and physical activity and limited adverse lifestyle factors, such as substance abuse. This study focuses on people hospitalized for the first time for psychotic illness, as the first weeks of the first hospitalization are a particularly critical period for development of metabolic alterations, with the main interest to describe the trajectory of weight and metabolic alterations during early

stages of treatment in a naturalistic setting and in relation to precisely quantified antipsychotic exposure.

We generated the following hypotheses:

For cross sectional analyses:

1) There are significant metabolic changes in total cholesterol, HDL, LDL, and triacylglycerols in drug-naive patients with a first episode of psychosis compared to healthy controls or previously medicated FEP patients in research visit (Time 2). Drug-naive FEP patients exhibit lower levels of these abnormalities than previously medicated FEP patients but higher levels than controls

In a prospective follow-up:

2) There will be significant weigth gain in patients between two measurements which will be directly proportional to the overall exposure to antipsychotics and more pronounced in those treated with metabolically problematic antipsychotics (olanzapine, clozapine, quetiapine).

3) We will identify additional predictors within collected and quantified prescription patterns that influence BMI changes, such as baseline characteristics, polypharmacy, and adjustments in antipsychotic medication that impact body weight.

In following sections, parts of Chapter 3, 4 and 5 interpolates my two research articles 'Weight and Metabolic Changes in Early Psychosis: Association with Daily Quantification of Medication Exposure during the First Hospitalization' (Vochoskova et al., 2023) and 'Trajectories of daily antipsychotic use and weight gain in people hospitalized for first episode of psychosis' (Vochoskova et al., 2024).

3. Materials and methods

3.1 Sample description

Between 2016 and 2021, the Early Stages of Schizophrenia study (ESO) recruited participants from 10 psychiatric hospitals in the Czech Republic. Most of our patients (83%) came from Psychiatrická nemocnice Bohnice, large psychiatric hospital with 1135 beds serving the Prague and Central Bohemian regions. We focused on individuals with FEP, who met the following inclusion criteria: a) were undergoing their first psychiatric hospitalization, b) had the ICD-10 diagnosis of SZ (F20), or acute and transient psychotic disorders (F23) made by a psychiatrist according to Mini-International Neuropsychiatric Interview (Dv et al., 1998), c) had < 24 months of untreated psychosis, and d) were 18–35 years old. We wanted to recruit participants at the early stages of illness, to minimize the effects of illness and medications. Thus, participants who were hospitalized before meeting the duration criteria for schizophrenia were included in the study and received the working diagnosis of acute and transient psychotic disorders, which is congruent with DSMIV brief psychotic disorder. This approach is in keeping with other studies of FEP (Fusar-Poli et al., 2016; Mitchell, Vancampfort, De Herdt, et al., 2013).

Healthy controls, 18–35 years old, were recruited via advertisement, using the following exclusion criteria: 1) lifetime history of any psychiatric disorders, 2) psychotic disorders in first or second-degree relatives.

All participants provided written informed consent for the study protocol approved by the Ethics committee at the National Institute of Mental Health, Klecany. The treating psychiatrist evaluated the patient's capacity to provide informed consent before they were approached by the study team (Vochoskova et al., 2023,2024).

3.2 Study procedures

Participants were assessed using the Positive and Negative Symptom Scale (PANSS). Healthy volunteers were evaluated through a Mini-International Neuropsychiatric Interview (M.I.N.I). Weight, height, hip, waist circumferences and blood pressure were measured at the time of assessment by trained clinicians. Specifically, the mid abdominal waist circumference was measured at the midpoint between the subcostal and suprailiac landmarks using an inelastic plastic fiber tape. Blood pressure was measured with participants in a seated position, using a certified sphygmomanometer. Three readings were taken with a 1-minute interval between measurements. The mean value of the three measurements was calculated and recorded by the study examiner. BMI was calculated using the standard formula: BMI = weight (kg)/height (meters)2. We systematically asked about smoking as well as the use of other drugs in the previous 12 months. During the first research visit, we also collected 15-milliliter fasting venous blood samples and measured the following markers: glucose, LDL-cholesterol, HDL-cholesterol and triglycerides, TSH, fT3, fT4, prolactin, and CRP in a single, licensed medical lab using standard methods. Subsequently, using the inpatient charts, we collected data from the time of admission, including BMI, glucose, LDL-cholesterol, HDL-cholesterol, and triglycerides and calculated the duration of inpatient treatment (DIP), i.e. the interval between admission and research visit in days. Using the daily chart notes, we recorded daily medication exposure and calculated the total and average daily dose between admission (Time 1, T1) and research visit (Time 2, T2).

For reasons related to statistical power, sample size, extent of exposure and the number of comparisons, it was not possible to compare across all 14 different medications used in this study. Thus, antipsychotics were divided into two groups - metabolically more problematic (MMP; clozapine, olanzapine, sertindole, and quetiapine) and metabolically less problematic (MLP; flupenthixol, haloperidol, levomepromazine, zuclopenthixol, amisulpride, aripiprazole, cariprazine, lurasidone, melperone, risperidone, paliperidone) (Arango et al., 2014; Borison et al., 1996; Pillinger et al., 2020; Taylor & McAskill, 2000; Wu et al., 2022; J.-P. Zhang et al., 2013; Zipursky et al., 2005). This grouping was based on the most recent ranking of antipsychotics according to their effects on weight and metabolic markers (Pillinger et al., 2020; Huhn et al., 2019a; Sabé et al., 2023b) and resulted in the most balanced subgroups in terms of sample size and extent of exposure, see Table 2, Figure 3.

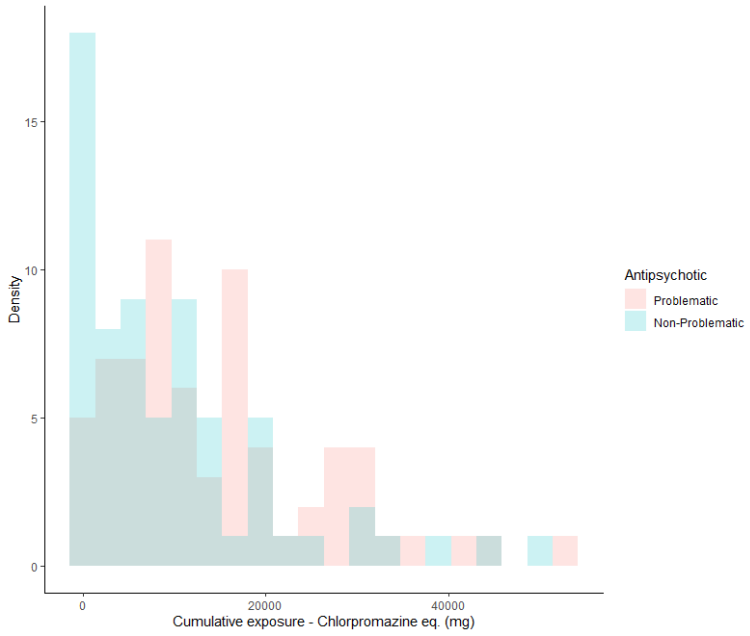


Figure 3: Histogram of cumulative exposure to antipsychotic medication separately for metabolically more problematic and metabolically less problematic medications (Vochoskova et al., 2023).

We calculated cumulative and average daily dose of MMP and MLP antipsychotics for each subject in milligrams of chlorpromazine equivalent (chlpzE).

For the purposes of detailed medication analysis (3rd hypothesis), we ranked AP medications according to their degree of alteration in body weight using whole numbers from 1 to 12 according to most recent metaanalyses (Huhn et al., 2019a; Pillinger et al., 2020; Sabé et al., 2023a). Then, we calculated the trajectory of AP polypharmacy by plotting the rank of medication (*y*-axis) over time in days (*x*-axis), with points at the time of prescription and termination of each medication (Figure 4). The rank of subsequent medications in plotting was summed with the rank of any that were active at the time of their prescription or termination. Termination of medications was noted with an additional point at the summed rank of all remaining medications, see Figure 4. A regression line was fitted through these points, and the intercept and slope were extracted as a measure of the metabolic impact of the initial prescription, and the change in metabolic impact throughout treatment, respectively. In order to separately account for the dose of medications, we repeated the above described procedure using the average standardized daily dose, instead of rank, for each medication. Even if medications were used short time or as needed, we accounted for them when quantifying the medications related slopes and intercepts. The result was an intercept and slope for each

of medication rank and dose. These four measures were used as predictors of change in weight or BMI (Vochoskova et al., 2023,2024).

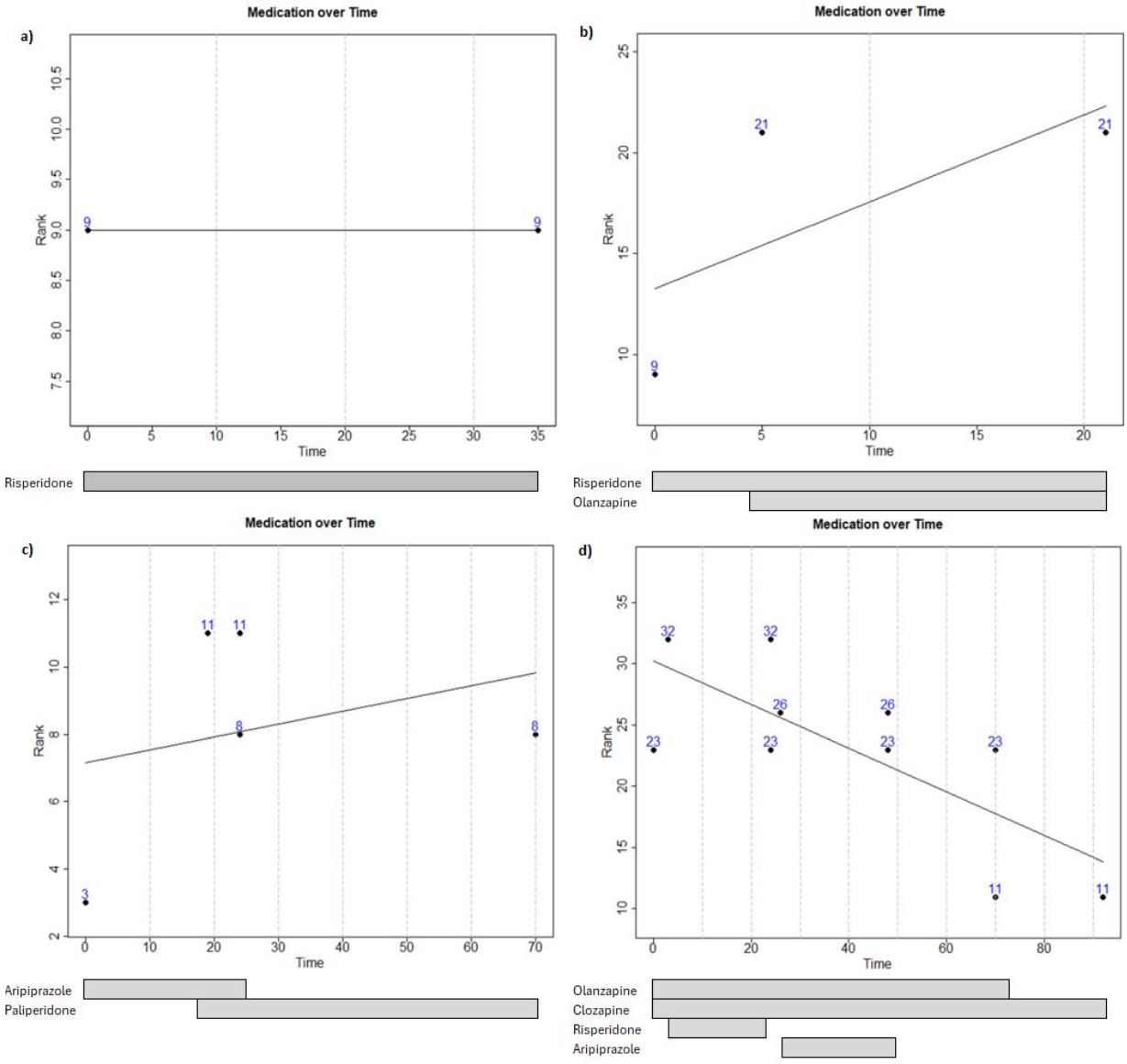


Figure 4 Sample polypharmacy plots for four subjects, showing the summed ranks of all active medications at the time of their prescription and termination as described in the Study procedures above. a) shows a 35day follow-up of an individual with FEP on risperidone monotherapy (rank 9); b) shows a 20day follow-up of an individual with FEP on risperidone during the initial 5 days of hospitalization, olanzapine (rank 12) was added on the 5th day; c) shows a 70day follow-up of an individual with FEP initially prescribed aripiprazole (rank 3) from days 1 to 24, on day 19, paliperidone (rank 8) was added until day 70, the cumulative rank (11) is the sum of ranks 3 and 8; d) 92day follow-up of an individual with FEP, olanzapine was administered between days 1 to 70, clozapine between days 1 to 92, risperidone between days 3 to 24, and aripiprazole between days 26 to 48 (Vochoskova et al., 2024).

3.3 Statistical Analyses

Statistical modeling was completed using the package lme4 in R version 4.1.1. (Bates et al., 2015) Marginal means were estimated using the package emmeans (https://CRAN.R-project.org/package=emmeans).

Among participants with FEP, we tested for changes in BMI or weight between T1 and T2. We also tested for differences in the rates of changes between groups (medication-naïve or previously medicated participants) using an interaction between time point and group, while controlling for DIP as well as a random effect of subject to control for repeated measures. We provided the estimated marginal means and their standard errors for weight, BMI at each time point, as well as the actual mean and SD for the difference between the 2 time points, marked as ΔBMI and Δweight.

Any significant changes in BMI over time were tested for association with the cumulative or average daily dosage of antipsychotics (one model for each, in chlorpromazine equivalent mg), BMI at T1, and an interaction between the two. The average daily dose controlled for DIP. In both models, we tested for partial effects of MMP and MLP antipsychotics. We lastly tested for an association between the DIP and the change in BMI over time, or BMI at T2.

For cross sectional analyses, we compared the 3 groups (medication naive at T2, previously medicated at T2, and control participants), using either BMI or metabolic markers as dependent variables, while controlling for age, sex, and BMI in case of metabolic markers. Admission bloodworks often did not contain key metabolic markers. Therefore, we had to compare control participants to those with FEP at T2, when we systematically collected all of the measures. We performed post-hoc testing using Tukey's HSD between groups. For any metabolites with significant group differences, we tested for associations with BMI while controlling for group, age, and sex. We used chi-square testing to compare the proportion of abnormal metabolite findings in participants with normal weight relative to those who were overweight or obese.

For any metabolic markers that differed between the three groups, we tested in participants with FEP whether concentrations were associated with BMI at T2, antipsychotic dosage (problematic or non-problematic), and symptoms (PANSS positive, negative, or global). For all models we confirmed that multicollinearity was negligible using the Variance Inflation Factor (VIF) and used QQ plots to confirm that all model residuals were normally distributed

and reported FDR-adjusted p-values to control for multiple comparisons (Vochoskova et al., 2023).

For the purposes of detailed medication analysis (3rd hypothesis), we used linear multiple regression modeling to test whether baseline BMI or change in BMI over time, were associated with a number of predictors. Baseline BMI was tested for association with the intercept of medication rank and dose. Change in BMI was tested for association with the slope and the intercept of both the medication rank and dose, as well as baseline BMI, and treatment duration. We controlled for age and sex in all of the models. We used linear regression modeling to test for associations between change in BMI with PANSS scores (positive, negative, and global) while controlling for age, sex, duration of treatment, and medication dose intercept. Residuals were confirmed as normally distributed using the Kolmogorov-Smirnov test for normality, as well as visually using QQ plots. Multicollinearity was tested by calculating the variance inflation factor (VIF) among all predictors in a model and was negligible. Lastly, participants were split into those whose change in BMI was in the top or bottom 33%, and the two groups were compared in demographic and clinical variables using either pairwise two-tailed t-tests for continuous variables or Chi-square testing for categorical variables. This same procedure was completed to compare participants with a positive medication rank slope relative to those with a negative slope. In addition, to check for regression to the mean, we performed a median split based on the baseline BMI and compared the BMI change in each subgroup. We performed a retrospective power analysis for each effect shown in Table 7, using an effect size as calculated from the t-statistic for the respective effects, a confidence level of 0.95, and a power level of 0.80. In each case, we determined the number of observations required to achieve this power and confidence level given the present effect size (Vochoskova et al., 2024).

4. Results

4.1 Sample

The sample included 377 participants (204 controls, and 173 individuals with FEP, 61 of whom were medication-naïve), see Tables 1, 2.

	Controls N=204	**FEP**		**Difference**
		Prior medicated N=112	**Drug-naïve N=61**	
Age - Mean (SD)	25.79 (4.35)	24.92 (4.94)	24.97 (4.77)	F(2,374)=1.60, p=0.204
Sex - M (%)	89 (43.6)	73 (65.2)	45 (73.8) *	$\chi 2$=24.02, p<0.001
Baseline BMI **BMI<25** **BMI=25-30** **BMI>30, N (%)**	 157 (77.3) 38 (18.7) 8 (3.9)	 25 (78.1) 5 (15.6) 2 (6.3)	 37 (72.5) 10 (19.6) 4 (7.8)	$\chi 2$=1.72, p=0.787
Systolic BP (mm Hg)- Mean (SD)	119.44 (15.02)	110.88 (12.20)	112.54 (11.39)	F(2,91)=3.66, p=0.029
Diastolic BP (mm Hg) - Mean (SD)	82.40 (8.88)	77.23 (10.32)	76.46 (7.55)	F(2,91)=3.25, p=0.043
Prior medicated vs Drug Naïve: $\chi 2$=21.86, <0.001, there were no other significant differences between these two groups.				

Table 1 Sample characteristics for controls and individuals with FEP at T2 (Vochoskova et al., 2023).

	Prior medicated FEP N=112	Drug-naïve FEP N=61	Difference
Diagnosis – Schizophrenia (N, %)/ Acute polymorphic psychotic disorder (N, %)	45 (40.1)/ 67 (59.9)	29 (47.5)/ 32 (52.5)	$\chi2$=0.59, p=0.439
Illness Duration (Months) - Mean (SD)	7.89 (7.12)	4.45 (4.06)	F(1,170)=11.94, p<0.001
Interval (Days) - Mean (SD)	32.34 (22.67)	52.46 (81.52)	F(1,95)=2.20, p=0.142
Duration of treatment prior to admission (months) - Mean (SD)	5.69 (7.06)	-	-
PANSS Positive - Mean (SD)	11.19 (3.79)	11.15 (3.58)	t(168)=0.07, p=0.945
PANSS Negative - Mean (SD)	16.45 (5.79)	16.70 (5.71)	t(168)=0.27, p=0.791
PANSS Global - Mean (SD)	28.22 (7.03)	30.07 (7.94)	t(168)=1.56, p=0.120
PANSS Total - Mean (SD)	55.86 (13.67)	57.92 (14.40)	t(168)=0.92, p=0.360
Antidepressant - Yes (%)	7 (14.9)	19 (31.1)	$\chi2$=2.99, p=0.083
Benzodiazepine - Yes (%)	23 (50.0)	51 (83.6)	$\chi2$=12.35, p<0.001
Mood stabilizer - Yes (%)	2 (4.3)	4 (6.6)	$\chi2$=0.01, p=0.925
Olanzapine, clozapine, quetiapine - Yes (%)	78 (69.6)	39 (66.1)	$\chi2$=2.99, p=0.083
MLP Cumulative dose (chlpzE) - Mean (SD)	9188 (10122)	10414 (11692)	t(66)=0.44, p=0.660
MLP Daily dose (chlpzE) - Mean (SD)	374 (437)	352 (438)	t(66)=0.20, p=0.840
MLP Sample size (monopharmacy only)	10	12	NA
MMP Cumulative dose (chlpzE) - Mean (SD)	11637 (10982)	16674.29 (11597)	t(67)=1.79, p=0.077
MMP Daily dose (chlpzE)- Mean (SD)	302 (179)	379.13 (204)	t(66)=1.57, p=0.120
MMP Sample size (monopharmacy only)	6	6	NA
MMP Specific medication - N	Clozapine - 9, quetiapine - 9, olanzapine – 67		
MLP Specific medication - N	Amisulpride - 9, aripiprazole - 30, chlorprothixen - 1, haloperidol - 21, levopromazine - 8, paliperidon - 10, risperidone - 63, ziprasidone - 3, zuklopenthixol - 3		

Table 2: Clinical and treatment characteristics for each FEP group. Antipsychotic dosages are shown in mg of chlorpromazine equivalent (chlpzE) and separately for metabolically more problematic (MMP) and metabolically less problematic (MLP) medications (Vochoskova et al., 2023).

4.2 Changes over time in participants with FEP

BMI significantly increased from a baseline of 22.45 (SE=1.02) at T1 to 23.41 (SE=1.02, ΔBMI=0.97±2.26) at T2 ($F(1,80)=11.56$, $p=0.005$) on average 44.6 days later, with no difference in rate of increase between previously medicated and medication naïve individuals ($F(1,80)=0.09$, $p=0.836$). Similarly, weight significantly increased from a baseline of 71.9 kg (SE=1.7) to 75.6 (SE=1.67, Δweight=3.46±7.81 kg; $F(1,81)=7.09$, $p=0.009$), with no difference between the groups ($F(1,81)=0.71$, $p=0.402$). The proportion of participants with FEP at baseline who were overweight (18.3%) or obese (7.3%) increased at follow-up to 24.3% and 8.5%, respectively, but not significantly ($\chi2=1.10$, $p=0.577$).

There was a significant interaction between BMI at T1 and medication exposure in predicting change in BMI. Greater medication exposure was associated with greater BMI increase, but this effect was strongest in people with lower baseline BMI and weakest in those with higher baseline BMI. This was true both for cumulative ($F(1,55)=4.43$, $p=0.039$) and average daily ($F(1,54)=6.42$, $p=0.014$) dose of MMP antipsychotics (Figure 4). However, neither the cumulative nor average daily dose of MLP medications were related to change in BMI. Correspondingly, longer DIPs were significantly associated with larger increases in BMI ($t(80)=5.08$, $p<0.001$) and higher BMI at T2 ($t(94)=2.18$, $p=0.032$). Lastly, the MMP /total cumulative dose ratio was not significantly predictive of change in BMI ($F(1,59)=0.05$, $p=0.823$) (Vochoskova et al., 2023).

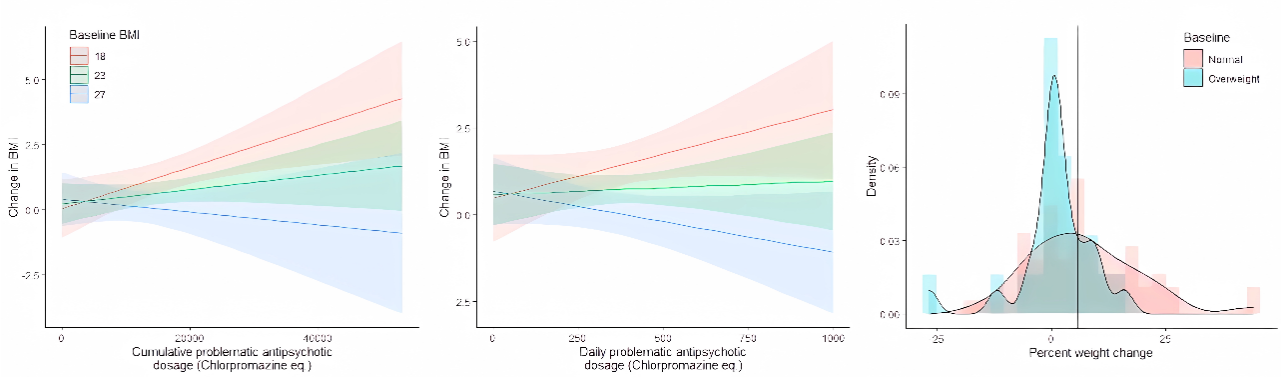


Figure 4 Significant interaction between the cumulative and average daily dosage of metabolically more problematic antipsychotics with baseline BMI in predicting the amount of change in BMI between T1 and T2 (left). Percent body weight change for normal weight (BMI<25) and overweight or obese (BMI 25 or higher) individuals, with 7% gain marked (right). Percent weight gain is standardized by average study visit length (44.6 days) (Vochoskova et al., 2023).

In participants with FEP, the mean percent weight gain in initially normal weight individuals (BMI<25, mean=7.13%, SD=12.19) was higher than for initially overweight or obese individuals (BMI>=25, mean=0.72%, SD=8.59, t(80)=2.25, p=0.029, Figure 4). Moreover, the proportion of participants who experienced clinically significant weight gain (i.e., weight gain of at least 7%) in baseline overweight or obese versus baseline normal weight individuals was 19.0% vs 45.9% ($\chi 2$=3.67, p=0.053) (Vochoskova et al., 2023).

4.3 Differences between FEP and controls

At the time of the research visit, BMI and triglycerides were significantly higher, while TSH was significantly lower in previously medicated participants relative to controls. Both medication-naïve and previously medicated participants with FEP had significantly lower HDL, fT3, fT4, and higher prolactin relative to controls, see Table 3.

	Group difference	Control	Medication-naive (b)	Prior medication (c)
BMI (kg/m^2)	F(2,370)=3.87, p=0.040 *	22.92 (1.01) [c]	22.71 (1.02)	23.91 (1.01)
Cholesterol (mmol/l)	F(2,316)=0.43, p=0.653	4.45 (0.07)	4.52 (0.11)	4.55 (0.08)
HDL (mmol/l)	F(2,316)=8.94, p=0.001 *	1.53 (0.03) [b, c]	1.41 (0.04)	1.36 (0.03)
LDL (mmol/l)	F(2,310)=2.95, p=0.074	2.40 (0.05)	2.61 (0.09)	2.58 (0.07)
TGC (mmol/l)	F(2,316)=3.70, p=0.041 *	1.05 (1.04) [c]	1.04 (1.06)	1.21 (1.05)
Glucose (mmol/l)	F(2,306)=1.98, p=0.170	4.07 (0.04)	3.92 (0.07)	4.00 (0.05)
Insulin (mmol/l)	F(2,324)=0.19, p=0.231	9.30 (0.64)	11.37 (1.07)	10.65 (0.79)
HOMA-IR	F(2,283)=2.13, p=0.201	1.61 (0.15)	2.06 (0.21)	2.02 (0.16)
TSH (mIU/l)	F(2,315)=5.44, p=0.010 *	2.44 (1.04) [c]	2.18 (1.07)	1.98 (1.05)
fT3 (pmol/l)	F(2,289)=15.12, p=0.000 *	5.41 (0.06) [b, c]	4.91 (0.09)	5.02 (0.07)
fT4 (pmol/l)	F(2,290)=7.24, p=0.002 *	14.95 (0.17) [b, c]	13.92 (0.26)	14.13 (0.20)
Prolactin (mIU/l)	F(2,294)=39.66, p=0.000 *	235.63 (1.08) [b, c]	770.34 (1.13) [c]	511.86 (1.10)
CRP (mg/l)	F(2,314)=1.72, p=0.199	0.69 (1.11)	0.95 (1.18)	0.67 (1.13)

Table 3 Group differences in BMI and metabolites (mean (SE)), with significance denoted using asterisks (*, p<0.05). Superscript where means significantly differed from medication-naïve [b] patients or those with prior medication [c]. All models controlled for age and sex. (Vochoskova et al., 2023)

When we categorized these measures using standard clinical thresholds, significantly more participants with FEP were overweight/obese, and had abnormal HDL, TGC, fT4, and prolactin levels relative to controls, see Table 4. Despite significant differences in concentrations, the rates of abnormal TSH and fT3 levels were comparable between the three groups (Vochoskova et al., 2023).

Measure	Clinical threshold for abnormal values	Control	Medication-naïve	Prior medication	Significance
BMI (kg/m^2)	>25	22.6%	36.1%	38.7%	$\chi2$=10.36, p=0.006 *
HDL (mmol/l)	<1.2 (F), <1.0 (M) *	5.2%	21.3%	26.4%	$\chi2$=23.89, p<0.001 *
TGC (mmol/l)	>1.7	11.1%	19.7%	24.5%	$\chi2$=8.37, p=0.015 *
TSH (mIU/l)	<0.55	7.0%	6.7%	6.6%	$\chi2$=0.02, p=0.992
fT3 (pmol/l)	<3.5, >6.5	4.6%	4.9%	5.7%	$\chi2$=0.15, p=0.928
fT4 (pmol/l)	<11.5, >22.7	1.5%	6.6%	13.3%	$\chi2$=12.94, p=0.002 *
Prolactin (mIU/l)	>619 (F), >375.2 (M) *	3.7%	72.1%	58.7%	$\chi2$=118.59, p<0.001 *

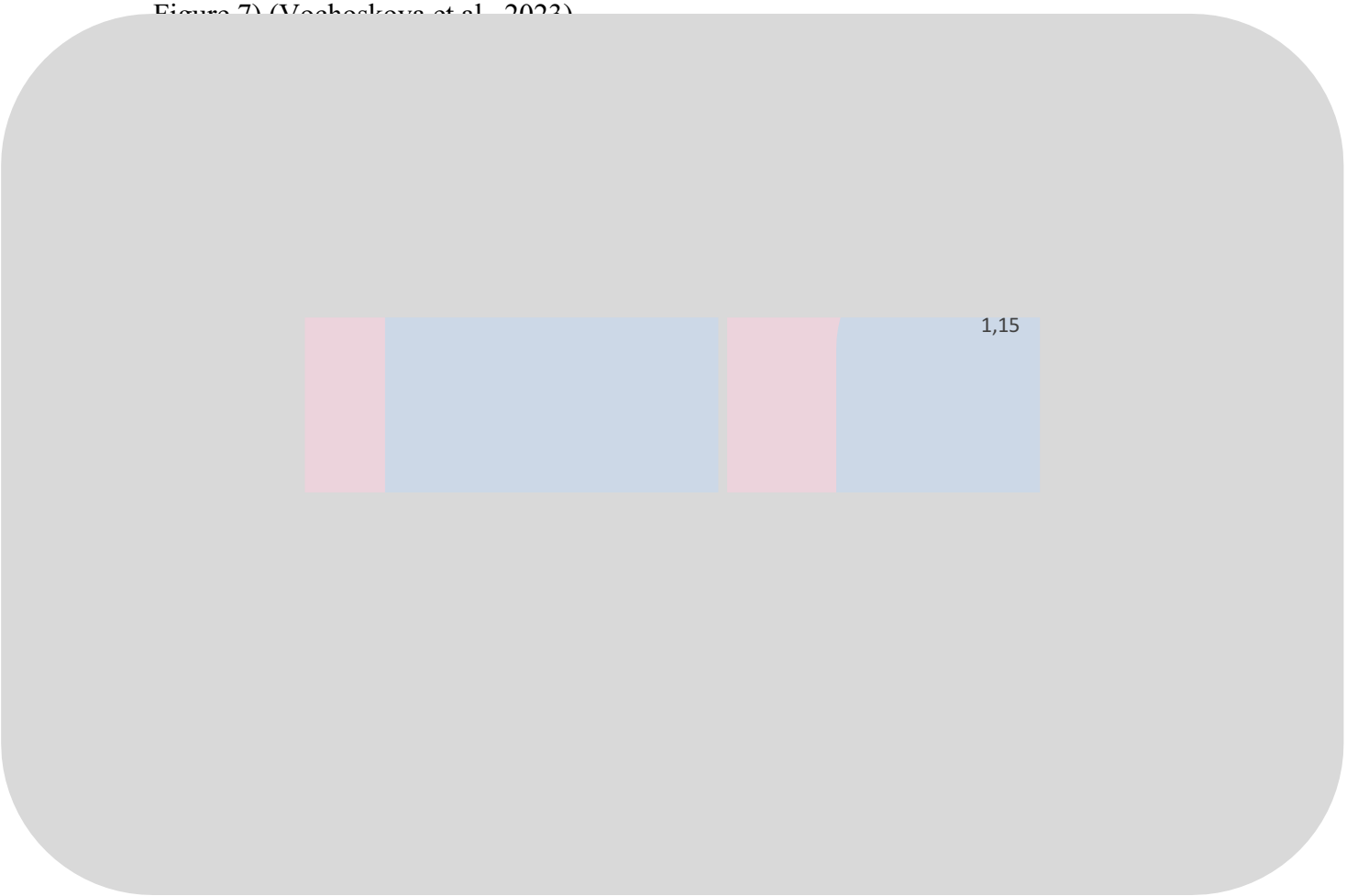
* We provide separate thresholds for females (F) and males (M)

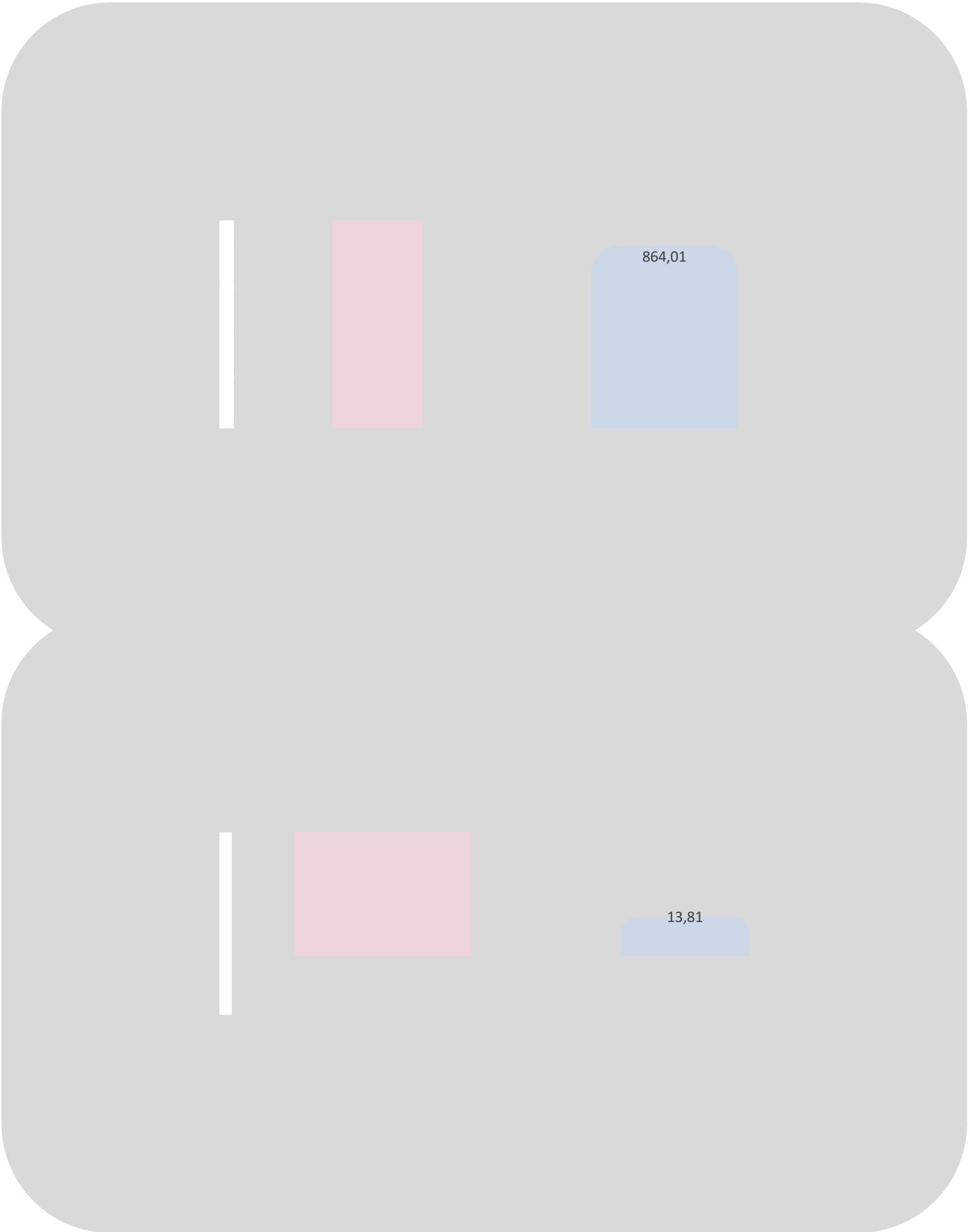
Table 4 Rates of clinically abnormal BMI or metabolite concentrations by group. Significant group differences are shown using asterisks (*, p<0.05) (Vochoskova et al., 2023).

4.4 Metabolite associations with BMI and waist-to-hip ratio

Higher BMI at T2 was significantly associated with higher TGC (t(316)=5.85, p<0.001, Est=0.09), higher TSH (t(315)=2.80, p=0.011, Est=0.06), and lower HDL (t(316)=-4.08, p<0.001, Est=-0.02). However, BMI was not significantly associated with fT3, fT4 or prolactin. Higher waist-to-hip ratio (WHR) was similarly associated with higher TGC (t(146)=4.13, *p*<0.001, Est=6.82) and lower HDL (t(146)=2.39, *p*=0.018, Est=-0.96), but no other metabolites.

Individuals with baseline BMI (<25) showed similar concentrations of HDL ($\chi2$=0.11, *p*=0.737), TGC ($\chi2$=0.28, *p*=0.597), fT4 ($\chi2$=0.09, *p*=0.759), and prolactin ($\chi2$=0.01, *p*=0.909) at T2 when compared with those who were initially overweight or obese (Figure 5, Figure 6, Figure 7) (Vachoskova et al., 2023).

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4.5 Role of medication, symptoms, and substance use

Cumulative exposure to either metabolically more or less problematic medications was not significantly related to the concentration of any metabolite while controlling for symptoms and BMI. More positive symptoms were significantly associated with higher TGC. Notably, even when controlling for medication exposure and symptom load, higher BMI remained significantly associated with higher TGC and lower HDL, see Table 5a and Table 5b. Substance or benzodiazepine use was not associated with weight, see Table 6 (Vochoskova et al., 2023).

Metabolite	**Predictor**	**Estimate (SE)**	**Significance**
HDL	Cumulative AP (Any)	0.00 (0.00)	F(1,60)=0.01, p=0.939
	Cumulative AP (Problematic)	0.00 (0.00)	F(1,60)=0.05, p=0.817
	PANSS Positive	-0.02 (0.01)	F(1,60)=2.04, p=0.397
	PANSS Negative	-0.01 (0.01)	F(1,60)=0.62, p=0.882
	PANSS Global	0.02 (0.01)	F(1,60)=3.69, p=0.148
	BMI	-0.03 (0.01)	F(1,60)=13.87, p=0.002 *
TGC	Cumulative AP (Any)	0.00 (0.00)	F(1,60)=0.25, p=0.773
	Cumulative AP (Problematic)	0.00 (0.00)	F(1,60)=0.18, p=0.817
	PANSS Positive	0.15 (0.04)	F(1,60)=17.69, p=0.000 *
	PANSS Negative	0.00 (0.03)	F(1,60)=0.03, p=0.900
	PANSS Global	-0.04 (0.02)	F(1,60)=4.21, p=0.148
	BMI	0.08 (0.02)	F(1,60)=9.40, p=0.008 *

Table 5a Associations between HDL and TGC that showed significant group differences and cumulative antipsychotic dosage, symptom load, and BMI at T2 (Vochoskova et al., 2023).

Metabolite	Predictor	Estimate (SE)	Significance
TSH	Cumulative AP (Any)	0.00 (0.00)	F(1,56)=0.31, p=0.773
	Cumulative AP (Problematic)	0.00 (0.00)	F(1,56)=2.18, p=0.603
	PANSS Positive	-0.04 (0.05)	F(1,56)=0.68, p=0.546
	PANSS Negative	-0.05 (0.04)	F(1,56)=1.89, p=0.875
	PANSS Global	0.02 (0.03)	F(1,56)=0.72, p=0.569
	BMI	0.02 (0.04)	F(1,56)=0.20, p=0.659
fT3	Cumulative AP (Any)	0.00 (0.00)	F(1,57)=0.68, p=0.773
	Cumulative AP (Problematic)	0.00 (0.00)	F(1,57)=0.06, p=0.817
	PANSS Positive	0.01 (0.03)	F(1,57)=0.22, p=0.639
	PANSS Negative	0.00 (0.02)	F(1,57)=0.02, p=0.900
	PANSS Global	0.00 (0.02)	F(1,57)=0.02, p=0.894
	BMI	0.02 (0.03)	F(1,57)=0.40, p=0.659
fT4	Cumulative AP (Any)	0.00 (0.00)	F(1,57)=0.92, p=0.773
	Cumulative AP (Problematic)	0.00 (0.00)	F(1,57)=1.40, p=0.603
	PANSS Positive	-0.07 (0.09)	F(1,57)=0.61, p=0.546
	PANSS Negative	0.04 (0.06)	F(1,57)=0.40, p=0.882
	PANSS Global	0.04 (0.05)	F(1,57)=0.56, p=0.569
	MI	0.10 (0.07)	F(1,57)=2.05, p=0.263

Table 5b Associations between TSH, fT3 and fT4 that showed significant group differences and cumulative antipsychotic dosage, symptom load, and BMI at T2 (Vochoskova et al., 2023).

Cigarette smoking	$\chi 2 = 0.51$, $p = 0.474$
Alcohol:	$\chi 2 = 1.01$, $p = 0.315$
Marijuana:	$\chi 2 = 0.04$, $p = 0.837$
Amphetamines:	$\chi 2 = 2.13$, $p = 0.145$
Opioids:	$\chi 2 = 0.00$, $p = 1.000$
Hallucinogens:	$\chi 2 = 0.00$, $p = 1.000$
MDMA:	$\chi 2 = 0.22$, $p = 0.636$
Cocaine:	$\chi 2 = 0.00$, $p = 1.000$
Methadone:	$\chi 2 = 3.20$, $p = 0.074$
Benzodiazepines:	$\chi 2 = 3\ .59$, $p=0.450$

Table 6 Associations between substance or benzodiazepine use (Yes/No) and weight category (BMI<25, BMI 25-30, BMI≥30) (Vochoskova et al., 2023).

4.6 Detailed medication analysis (3rd hypothesis)

4.6.1 Sample

The second sample included 92 participants (70.7% male) with a mean age of 25.5 years (SD=4.9). In the rest of the sample from the previous analysis (n=173), we had only limited access to day-by-day medication administration records, so we could not calculate the detailed trajectory of antipsychotic polypharmacy as previously described. The dropouts were random, and there is no indication of selection bias. More than half (59.8%) of participants had never been prescribed antipsychotics before the present hospitalization, and the onset of symptoms was on average 4.58 months prior to the study date (SD=4.60). In participants with prior medication, the average duration of pre-hospitalization treatment with antipsychotics was 4.27 months (SD=6.12). Participants had a mean baseline BMI at hospitalization of 22.84 (SD=4.40), and a mean BMI at follow-up of 23.70 (SD=4.25). Those with BMI recorded at both times experienced a satistically significant average increase of 0.74 (SD=1.84) from hospitalization until the research visit follow-up ($t(77)=3.56$, $p<0.001$) and we observed clinically significant weight gain (≥7%) in 30.4% of participants. Within our sample, none of the participants had a personal history of T2D or hypertension, 1 participant was diagnosed and treated with hypothyroidism, 2 were chronically treated for allergies, 1 was treated for gastroesophageal reflux disease. Additionally, none of the participants exhibited signs of hypertension or diabetes in their bloodwork and blood pressure measurements. Among the participants, 51.2% reported nicotine use, and none had a prior diagnosis or treatment for substance use disorder at the time of admission (Vochoskova et al., 2024).

4.6.2 Prescription patterns

The numbers of people prescribed each of the following medications as their first medication after admission were: risperidone (n=57), olanzapine (n=29), quetiapine (n=3), aripiprazol (n=2), clozapine (n=1). The total number of different medications used was 15 (Mean=2.52 medications per individual, SD=1.68) in the sample. More than half of the individuals (57%) who received risperidone or olanzapine were additionally treated with another AP medication during hospitalization. Less than half of individuals (44/92) remained on their first prescribed medication for the whole duration of follow up (for 33.1 days (SD=17.1), with a median of 31

days). The average duration before the first change of medications (switch or addition of a new medication), was 17.6 (SD=17.9, median =10) days.

One third of individuals (32.6%) remained on a monotherapy for the entire duration of follow up (33.1 (SD=17.1) days, median 31 days). Almost half of individuals (42.4%) had a positive slope for ranking of meds based on metabolic side effects. This was related to switch to a combination treatment: N=12, switch to a metabolically more problematic medication: N=4 and a switch to a combination treatment with a more metabolically problematic medication: N=23. Only 23.9% of individuals (n=22) had a negative slope, i.e. moved from a metabolically more to a metabolically less problematic medication. Relative to those with negative slope, individuals with positive slope had greater PANSS scores for positive and negative symptoms at follow up (Table 8), indicating possibly that people with more symptoms/worse response needed escalation of medication, see Figure 8. 26 of 92 participants (28.2%) were treated with antidepressants, 5 individuals took valproic acid, 1 lithium, 1 modafinil (Vochoskova et al., 2024).

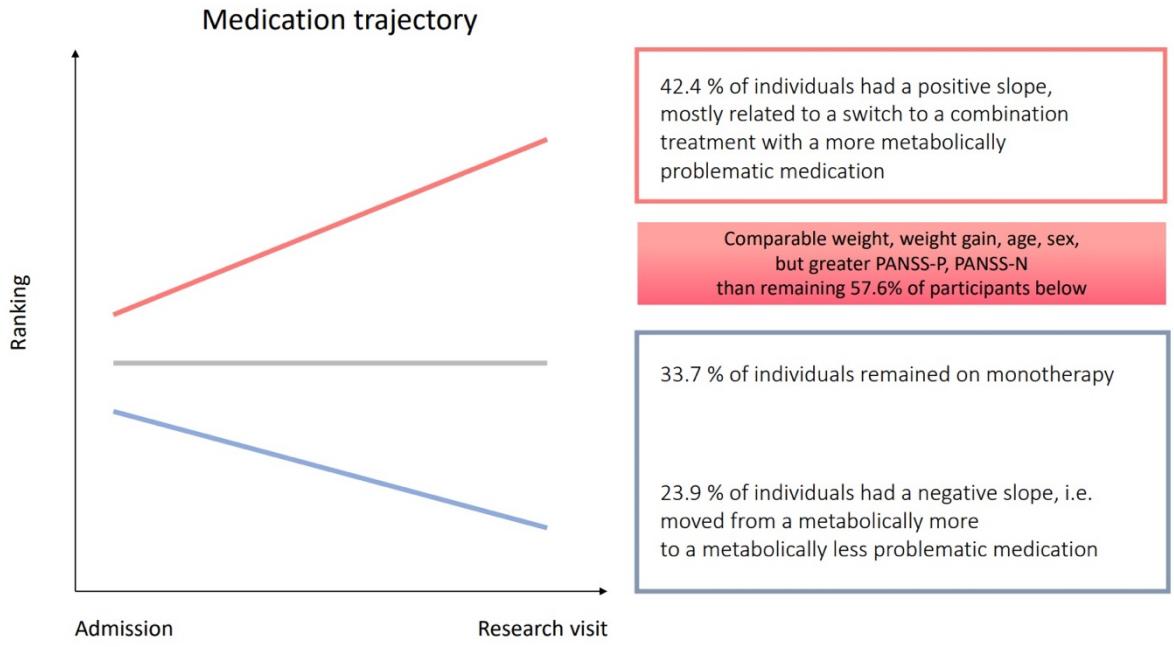

Figure 8: Comparison of AP medication trajectories from admission to the research visit and their characteristics (Vochoskova et al., 2024).

4.6.3 Impact of prescription patterns on baseline weight or weight gain

Baseline BMI was not associated with the slope or intercept of medication ranking or dose, see Table 7, or with the initial dose (t(74)=-1.21, p=0.231) or the initial medication's rank (t(74)=-0.13, p=0.897), suggesting that weight was not a factor in selecting the initial medication. When we jointly analyzed the main predictors of weight gain, age, sex, duration of treatment, baseline BMI with the new measures, including slope and intercept for dose, rank, only low baseline BMI was a predictor of greater BMI increase (Table 7). Sex did not influence the effects of rank slope (F(1,65)=2.39, p=0.127), rank intercept (F(1,65)=0.01, p=0.939), dose slope (F(1,65)=0.49, p=0.485), or dose intercept (F(1,65)=053, p=0.471), on weight gain. Taking a median split on baseline BMI, the lower 50% of participants gained on average 1.53 points (SD=2.28). The higher 50% of participants also gained weight, on average gaining 0.40 points (SD=2.12). Notably, the slope or intercept of medication ranking, or dose were not significantly associated with change in BMI. Retrospective power analysis shows that effects of medication rank would not be significantly associated with change in BMI, even at a much higher sample size, i.e. thousands of participants, thus suggesting this to be a true negative finding, see Table 7. There was a positive association between dose intercept vs rank intercept (t(90)=3.18, *p*=0.002). That is, when treating clinicians used a high dose, they also used a more metabolically problematic medication (Vochoskova et al., 2024).

Outcome	Predictor	Estimate (SE)	Standardized coefficient (SE)	Significance	Sample req. for power 0.80
Baseline BMI	*Rank intercept*	0.080 (0.142)	*0.068 (0.119)*	F(1,74)=0.32, p=0.573	1838
	Dose intercept	0.001 (0.001)	*-0.211 (0.118)*	F(1,74)=3.18, p=0.079	187
	Age	0.232 (0.103)	*0.246 (0.109)*	F(1,74)=5.11, p=0.027 *	117
	Sex (M)	2.961 (1.046)	*0.340 (0.120)*	F(1,74)=8.01, p=0.006 *	75
BMI change	*Medication rank slope*	-0.469 (1.569)	*-0.079 (0.263)*	F(1,69)=0.09, p=0.766	6052
	Medication rank intercept	-0.029 (0.065)	*-0.105 (0.237)*	F(1,69)=0.02, p=0.658	2748
	Dose slope	-0.001 (0.001)	*-0.150 (0.219)*	F(1,69)=0.47, p=0.495	1151
	Dose intercept	0.001 (0.001)	*0.280 (0.307)*	F(1,69)=0.83, p=0.364	651
	Baseline BMI	-0.115 (0.052)	*-0.497 (0.225)*	F(1,69)=4.89, p=0.030 *	113
	Treatment duration	0.007 (0.013)	*0.164 (0.297)*	F(1,69)=0.31, p=0.582	1770
	Age	-0.027 (0.047)	*-0.123 (0.218)*	F(1,69)=0.32, p=0.574	1697
	Sex (M)	0.623 (0.488)	*0.310 (0.243)*	F(1,69)=1.63, p=0.206	334

Table 7 Predictors of baseline BMI, change in BMI, and change in weight (*, $p < 0.05$). The sample size required to achieve a power of 0.80, given the size of each effect, is shown (Vochoskova et al., 2024).

4.6.4 Comparison of extremes

Relative to the third of individuals who gained the least amount of weight (Mean BMI change of -1.02, SD=0.87), the third of individuals who gained the most weight (Mean BMI change of 3.24, SD=2.25) had significantly lower global, positive and negative symptom scores at the end of the follow up, a trend for longer prehospitalization antipsychotic treatment and a trend for greater exposure to medications with the highest potential for weight gain (expressed as weighted medication gain sum, see Table 8). However, when constrained to the same medications, change in BMI was not significantly associated with positive (t(66)=1.28, p=0.205), negative (t(66)=1.80, p=0.077), or global (t(66)=0.04, p=0.968) PANSS scores (Vochoskova et al., 2024).

	Change in BMI		
	Bottom 33%	***Top 33%***	***Significance***
Sample size	26	28	
Age - Mean (SD)	25.10 (4.72)	23.66 (4.09)	t(52)=-1.19, p=0.238
Sex, male - No. (%)	17 (65.4)	24 (85.7)	χ2=2.04, p=0.153
Drug-naive - No. (%)	15 (57.7)	18 (64.3)	χ2=0.05, p=0.828
Baseline BMI - Mean (SD)	23.86 (4.14)	22.01 (4.65)	t(52)=-1.54, p=0.130
Follow-up BMI - Mean (SD)	22.84 (3.82)	25.25 (4.78)	t(52)=2.04, p=0.047 *
Change in BMI - Mean (SD)	-1.02 (0.87)	3.24 (2.25)	t(52)=9.03, p<0.001 *
PANSS Global - Mean (SD)	33.40 (6.92)	26.50 (7.09)	t(51)=-3.58, p=0.001 *
PANSS Positive - Mean (SD)	12.40 (4.13)	10.04 (3.11)	t(51)=-2.37, p=0.022 *
PANSS Negative - Mean (SD)	18.08 (5.26)	14.79 (4.63)	t(51)=-2.43, p=0.019 *
Weighted medication rank sum - Mean (SD)	480.84 (260.64)	603.44 (440.11)	t(48)=1.20, p=0.237
Weighted medication gain sum - Mean (SD)	118.12 (65.32)	170.22 (137.43)	t(48)=1.71, p=0.093
Proportion AP problematic - Mean (SD)	0.60 (0.29)	0.62 (0.30)	t(40)=0.21, p=0.834
Treatment prior to hospitalization - Mean (SD)	1.39 (1.73)	3.36 (4.93)	t(51)=1.92, p=0.060

Table 8 Demographic and clinical characteristics of participants whose change in BMI during treatment was among the lowest and highest 33% (Vochoskova et al., 2024).

4.7 Additional findings

Among the patients included in our prospective analysis, all of whom were hospitalized in one of the ten psychiatric hospitals in the Czech Republic, we found that while bloodworks for serum glucose and anthropometric measurements like weight, height, and BMI are routinely conducted, only 16 of them underwent blood lipid analysis. Furthermore, only 14 from 16 lipid analysis had complete lipid panel screening, which is recommended by all current national and international guidelines, as well as the recommended psychiatric care procedures outlined by the Czech Psychiatric Society (ČLS JEP) and current Summary of Product Characteristics for some antipsychotic medications. Our findings indicate that large portion of the participating hospitals in this study do not routinely include lipid panel screening as part of the initial blood work conducted during patient admission.

5. Discussion

5.1 First and second hypotheses:

Individuals with FEP gained on average ~1 BMI point or 3.46 kg of weight after an average of 44.6 days of their first inpatient treatment, regardless of whether they were medicated or medication naïve prior to admission. Almost two thirds of individuals demonstrated a clinically significant weight gain of >7% of their body weight. The impact of medications on weight gain depended on the baseline weight and type of medication. The dose, as well as total exposure to MMP antipsychotics, were significantly associated with weight gain, but only in people with the lowest baseline BMI. People treated with metabolically less problematic antipsychotics or those with higher baseline BMI did not show association between medication exposure and weight gain. After an average of 44.6 days of inpatient treatment, people with FEP regardless of pre-admission medication status showed lower HDL, FT3, FT4 and higher prolactin than controls, with higher BMI and TGC only in previously medicated FEP participants. Even though medications were not directly associated with these metabolic markers, they were associated with weight gain and people with higher weight showed higher TGC, TSH and lower HDL levels.

While most studies documented that more than half of the weight gain happens in the first 12 weeks of treatment (Addington et al., 2003; Lieberman et al., 2003; Patel et al., 2009; Schooler et al. 2005; Zipursky et al., 2005), we found a significant increase in weight already after an average of 44.6 days of hospitalization. Previous meta-analyses estimated that 10 week weight gain for individuals on atypical antipsychotics ranged from 2.2 to 4.5 kg in established psychosis (Huhn et al., 2019a), while it was 3.22 kg and BMI gain of 1.44 points in studies of up to 12 weeks duration in FEP (Tek et al., 2016), 4.85 kg and BMI gain of 1.97 in studies of medication naive individuals mostly lasting less than 12 weeks (Tarricone et al., 2010). Our findings of an average weight gain of 3.46 kg and average BMI increase of ~1 point, fall right within the same range, but already after ~7 weeks. This could be related to the fact that a significant proportion of participants received antipsychotics for the first time, and all were hospitalized, which ensures regular meals, less physical activity and a greater compliance. It is in keeping with a recent meta-analysis, which observed weight gain of 3.42 kg during up to 6 weeks of treatment with olanzapine (Bak et al., 2014a).

Aside from the duration of treatment, daily and cumulative dose, the extent of weight gain depended on the type of antipsychotic (most pronounced with olanzapine, clozapine, quetiapine), and on the baseline BMI. We found greater weight gain in people with lower baseline BMI, which is in keeping with other studies (Bak et al., 2021a; Brecher et al., 2007; Bushe et al., 2013; Gebhardt et al., 2009; Kinon et al., 2001; Ratzoni et al., 2002; Schimmelmann et al., 2007). Specifically, people with baseline BMI<23 gained the most weight, therefore this effect is not constrained to underweight people (BMI <18.5). Some have argued that weight gain is less of an issue or even beneficial in people with initially lower weight (Allison et al., 1999). These results do not support this suggestion. Almost half of individuals with baseline BMI<25 demonstrated a clinically significant weight gain. In addition, on average 44.6 days into their first hospitalization, individuals with normal baseline BMI were statistically indistinguishable in their metabolic markers (HDL, TGC, FT4) from initially overweight or obese participants.

Greater weight was associated with higher TGC and lower HDL. In keeping with this, people with FEP differed from controls in both of these metabolic markers. Interestingly, HDL was lower both in medication naive and previously medicated individuals, whereas TGC were higher only in previously medicated individuals. Thus, TGC changes may be a more delayed effect of antipsychotic treatment or weight gain, or HDL abnormalities could be more closely related to FEP. These differences are clinically meaningful, as they resulted in a significantly greater proportion of individuals with FEP crossing the threshold to pathological values. On average 44.6 days after admission among previously medication naive individuals, 36% were overweight and about 20% showed abnormal HDL, and TGC. These proportions were even higher among previously medicated individuals, where roughly quarter of participants showed abnormal TGC or HDL. This is concerning, especially considering the average age of 25 years.

While higher TGC and lower HDL were associated with weight and FEP, we did not see significant associations with weight or FEP for glucose or LDL. This is in keeping with studies showing that second generation antipsychotics show more pronounced effects on TGC than total cholesterol, see (Meyer & Koro, 2004) for review. Even though there are reports of diabetic ketoacidosis shortly after initiating antipsychotic treatment (Vuk et al., 2017), dyslipidemia in people exposed to antipsychotics typically develops faster than diabetes (Bernardo et al., 2021; Perez-Iglesias et al., 2014; Vázquez-Bourgon et al., 2020), which is often preceded by a period of glucose intolerance. While we did not measure glucose tolerance,

a more sensitive measure of glucose dysregulation (Pillinger et al., 2017), we did not find abnormalities in insulin in people with FEP relative to controls.

There was no direct association between precisely quantified medication exposure, either daily or cumulative and any metabolic markers. Some studies have described a weight independent effect of antipsychotics on lipids, insulin resistance, or glucose dysregulation (Kowalchuk et al., 2019; Meyer, 2001; Teff et al., 2013). In this work, metabolic alterations (high TGC, low HDL) were more closely related to weight than to exposure to medications, as also demonstrated by others (Kinon et al., 2001; Patel et al., 2009; Vázquez-Bourgon et al., 2020; Zipursky et al., 2005).

Other studies have also documented that early during the treatment, individuals with FEP separate from controls in prolactin, FT3, and FT4. Antipsychotic treatment can impair thyroid function by several mechanisms which are unrelated to obesity, including alterations of iodine capture or induction of thyroid autoantibodies (Bou Khalil & Richa, 2011; Zhang & Li, 2020). Hyperprolactinemia is a common side effect of treatment with dopamine receptor blockers. We found significantly higher prolactin in medication-naïve (1.13) than in previously medicated (1.10) participants with FEP. This may be related to stress induction of prolactin release which may be greater in medication naïve individuals. Alternatively, medication-naïve individuals may require more D2 blockade to control their symptoms. Indeed, the pre-admission medication-naïve cohort had a greater exposure to more potent D2 blockers (amisulpride, risperidone, 374 mg chlorpromazine equivalent) than the previously medicated individuals (352 mg chlorpromazine equivalent). Furthermore, it is also possible that longer term use of antipsychotics leads to upregulation of D2 receptors, thus rendering the system more sensitive to the prolactin inhibiting effects of dopamine (Vochoskova et al., 2023).

5.2 Detailed medication analysis – 3rd hypotheses

Detailed medication analysis provides deeper insights into inpatient treatment of 92 individuals hospitalized with the first episode psychosis in Czech Republic. Most individuals admitted to the hospital for first episode of psychosis start treatment with either risperidone or olanzapine. Less than half of individuals will remain on the same medication throughout their first hospitalization and only a third of people with FEP remain on monotherapy. The first switch or addition of new medication happened within a median of 10 days. Almost half

of individuals (42.4%) experienced an escalation of medications, mostly a switch to a medication with a worse metabolic profile than their initial treatment. De-escalation of medications, i.e. switch to a medication with less propensity for metabolic changes was rare, happened only in about 23.9% of individuals. The medication choices and changes appear to be primarily related to symptoms and are unrelated to baseline BMI. Among the potential predictors, only baseline BMI was associated with weight gain. Slope or intercept for medication rank or dose, which reflect the patterns of medication changes were not related to weight gain and would not be even with thousands of individuals.

This work provides support for two other predictors of weight gain, type of medication and duration of medication treatment. After on average weeks of treatment, the effect of these factors was evident, but only as trend and when comparing extremes of weight change. People who gained the most weight had a trend for greater exposure to metabolically more problematic meds or a longer duration of pre-hospitalization treatment then people who lost weight. This is in line with many previous studies (Bak et al., 2014b; Huhn et al., 2019b; Tek et al., 2016; Zipursky et al., 2005). It is likely that over time the effect of the type of medication and duration of treatment would become more pronounced and would not be evident only when comparing extremes of weight change. This further suggests that baseline BMI is a faster and more general predictor than type of medication or duration of treatment.

In this study, the starting point or trajectory of medication changes was not related to weight gain after an average of 6.3 weeks of treatment. This is in contrast to studies, where transitioning to olanzapine for 3 months to 1 year was associated with significant weight gain (Faries et al., 2008; Godleski et al., 2003). In a before-to-after switch meta-analysis, there was no statistically significant change evident when switching to amisulpride, quetiapine, paliperidone, risperidone, or lurasidone (Siskind et al., 2021). This is similar to our findings. In contrast, a significant increase in weight was noted when switching to olanzapine (+2.7 kg) and clozapine (+2.8 kg) (Siskind et al., 2021), but the mean study duration was 26.3 weeks in comparison to 6.3 weeks in our study. With these longer intervals, we are essentially seeing effect of the prolonged use of the new medication. This is in keeping with our findings, where individuals who experienced the most pronounced weight gain had greater exposure to metabolically more problematic meds than people with the lowest weight gain. We can conclude from this that the switch itself even to a more metabolically problematic medication is not causing weight gain over a relatively short period of time (weeks to months). In the short term, baseline BMI was a more sensitive predictor of weight gain than medications changes.

We can observe an association between weight change and symptoms, such that individuals who gained the most weight showed lower symptoms at follow up then individuals who lost weight. This association was documented in other studies (Ascher-Svanum et al., 2005; Czobor et al., 2002; Leadbetter, 1992; Luckhoff et al., 2019). However, when constrained to the same medications, BMI change was not associated with any symptoms in any model. We only saw this effect in a strict comparison of the top and bottom 33% (Table 8) based on weight gain. However, people in these two groups were not treated with the same medications. So in this study, treatment response to a medication was not associated with weight gain. What we effectively observed was that individuals who gained weight had a trend for greater exposure to metabolically more problematic medications and fewer symptoms at follow up, i.e. a more aggressive treatment led to both a greater weight gain and fewer symptoms. This seems in keeping with the presumably greater efficacy of metabolically more (-ines) vs metabolically less problematic (-oles) medications (Huhn et al., 2019b).

The majority of individuals with FEP in our study initiated treatment with risperidone (n=57), followed by olanzapine (n=29), which in in keeping with the Czech guidelines (*Doporučené Postupy Psychiatrické Péče Psychiatrické Společnosti ČLS JEP*, n.d.). However, this research also shows a difference between clinical practices and guideline recommendations regarding antipsychotic polypharmacy and bloodwork monitoring of metabolic parameters in patients with severe mental disorders, which were not routinely followed in our sample. Approximately two-thirds of individuals in our sample were treated with AP polypharmacy. This is in keeping with some other studies from Europe, Canada and the USA, which have reported polypharmacy rates ranging widely from 19% up to 67% (Barbui et al., 2006; Correll et al., 2007; Faries et al., 2008; Farrell & Brink, 2020; Ganguly et al., 2004; Tiihonen et al., 2019). While there is evidence supporting the potential superiority of antipsychotic cotreatment over monotherapy in certain clinical situations, such as combining aripiprazole with clozapine associated with the lowest risk of rehospitalization (Correll et al., 2009; Tiihonen et al., 2019), the current recommendations for first-line treatment in early psychosis continue to emphasize antipsychotic monotherapy. Despite limited research on polypharmacy and lack of metabolic monitoring in FEP and the consequent absence of guideline recommendations, it appears to remain a frequent pattern in clinical practice (Vochoskova et al., 2024).

5.3 Additional findings

Our additional findings show the insufficient monitoring of metabolic components in individuals with FEP during the first hospitalization in our sample. Despite nearly three decades of using MARTA antipsychotics, strong evidence of their metabolic side effects, and the existence of clinical guidelines advocating for metabolic monitoring both internationally and in the Czech Republic, clinical practice in this area remains insufficent. In our sample, only 8% patients underwent lipid profile screening at the beginning of treatment. Even when considering only those prescribed MARTA antipsychotics as a first-line treatment, where metabolic monitoring is explicitly recommended in the Summary of Product Characteristics (SPC), only 42% of these patients were appropriately monitored.

As a clinician, I observe a significant gap in the surveillance and treatment of metabolic components in patients with schizophrenia compared to individuals with less severe mental illnesses or healthy populations. My percetion of this gap might be attributable to low sample size bias. Alarmingly, research on this topic is limited. However, the limited amount of such studies suggests that our findings are not isolated. Studies indicate that adequate laboratory screening rates for patients with schizophrenia range from only 2% to 30% (Phillips et al., 2015; Saloojee et al., 2014). Existing research also corresponds with our findings, indicating that while the majority of individuals with schizophrenia have their height and body weight monitored within the healthcare system, measurements such as blood pressure, fasting blood glucose, and lipid profiles are evaluated far less frequently (Buckley et al., 2005).

In addition to monitoring, this gap is evident in treatment as well. Patients with severe psychiatric disorders experience significant disparities in care, including screening, preventive interventions, and treatment at all levels. These disparities are not solely linked to patient compliance but also stem from healthcare providers delivering unequal medical care to psychiatric patients. For instance, they are less likely to be prescribed medications to address metabolic abnormalities, such as statins, or to receive invasive procedures for heart disease (Hippisley-Cox et al., 2007; Laursen et al., 2009).

The reasons for this discrepancy are likely multifactorial and findings of inadequate treatment cannot be explained only by factors on the patient's side. From the hospital perspective, financial motivations and other systemic issues may influence practices. In our sample, it was evident that monitoring depended heavily on the established habits and norms of individual psychiatric hospitals and wards. On the side of psychiatrists, awareness of the metabolic side

effects of antipsychotic drugs appears to be high, even 20 years backwards, majority of practicing psychiatrist (97%) considered metabolic side effects of second-generation antipsychotics serious or very serious concern and 86% reported that these adverse effects had influenced their prescribing practices for second-generation antipsychotics (Buckley et al., 2005). However, in practice, as Sullivan et al. (2015) noted, a history of schizophrenia may lower doctors' expectations of patients' treatment adherence and further self-management. This could potentially lead to decreased screening of metabolic issues by health care providers. This combination of patient and provider attitudes, and institutional practices might contribute to the observed gaps in metabolic monitoring. This leads to higher mortality rates, which could be significantly reduced with improved care.

5.4 Clinical implications

These findings have some possible clinical implications which might challenge some of the current practices in psychiatry. Although many guidelines discuss the varying risk of weight gain associated with different types of antipsychotics, most of them do not recommend considering the baseline BMI as a factor. Yet, there is a growing body of evidence showing that low baseline BMI is a significant predictor of greater weight gain following antipsychotic treatment. This weight gain was often clinically significant and resulted in early onset of metabolic abnormalities. Contrary to this, insurance companies in some countries cover medications with a lower propensity for weight gain only in overweight/obese individuals (Vochoskova et al., 2023).

Yet, in this research, people with baseline BMI>25 did not demonstrate an association between medication exposure and weight gain even for MMP antipsychotics. These results suggest that we should be most cautious to prescribe MMP medications in people with low BMI and that perhaps the metabolically less problematic medications should preferentially be used in people with BMI <25, in order to prevent weight gain.

Despite initiating treatment with metabolically problematic medications, in detailed medication analysis, a substantial number of individuals (40/92) experienced an escalation of medications, in 90% of cases an addition of another medication. The main concern with using metabolically less problematic medications may be their presumably lower efficacy (Taylor et al., 2012). This is not necessarily supported by meta-analytical evidence (Crossley et al., 2010; Zhang et al.,

2013). If these medications were less effective, we could expect even more switches if commencing treatment with metabolically less problematic options. However, in this research, early switches did not impact weight gain. While most APs have metabolic side effects, careful selection of antipsychotic following evidence-based ranking of side effects may slow or delay the onset of weight gain and metabolic alterations in FEP. Also, duration of treatment predicted greater weight gain independently of the total antipsychotic dose. As suggested by other studies, individuals who remain on antipsychotics longer will gain more weight regardless of the dose (Bak et al., 2014b, 2021b). So, using low doses may not be sufficient to prevent weight gain in people who need long term treatment with antipsychotics (Vochoskova et al., 2024).

Despite existing guideline recommendations, laboratory screening for metabolic abnormalities, such as dyslipidemia, remains notably low. It raises concerns about the adequacy of patient management in this regard. The influence of medications on metabolic markers appears to be indirect and primarily mediated by weight gain. So, the importance of carefully evaluating BMI and prioritizing metabolically less problematic MLP medications for high-risk patients, particularly those with a low or normal BMI seems reasonable. It might lead to improved clinical practices, regardless of potential barriers such as healthcare according to hidden assumptions or broader systemic issues.

5.5 Limitations

This research has the following limitations. Both analyses were based on data of naturalistic, observational study, not a randomized controlled trial. This leaves room for patient/prescriber bias, and we had no access to all information and can only speculate about the clinical reasons for changes in medication. Since we focused on newly admitted, acutely ill patients, pre-hospitalization factors such as diet, exercise, substance abuse, and socioeconomic factors could not be controlled. Illegal substance use and misuse, as well as alcohol and nicotine consumption, was screened during a clinical assessment, but not by a standardized questionnaire.

Although biochemical measures were analyzed in the same laboratory, blood collection at admission could not be standardized with regards to the duration of fasting. The weight gain during hospitalization with regular diet and limited exercise may be greater than weight gain in an outpatient setting. The distinction between MMP and MLP antipsychotics was based on evidence-based ranking of medications and on statistical considerations, not on any current guidelines or clinical groupings (Vochoskova et al., 2023).

Although the detailed medication analysis provides a detailed and precise description of antipsychotic medication usage day by day, physical measures and psychopathology were assessed only at the end of the study during the research visit, thus limiting more temporal resolution. The metabolic burden of antipsychotics was listed according to an arbitrary ordinary scale (0-12) and the distance between the individual antipsychotics is assumed to be the same. The ordinary scale may not accurately represent the distance between medications. At the same time, it appeared to be the simplest and most conservative method with the fewest assumptions.

Also, the average duration of follow up was relatively short, however, it was sufficient for people to gain weight and allowed to look for the most sensitive, fastest predictor of weight changes.

6. Further directions

There is increasing and replicated evidence suggesting that baseline BMI serves as a predictor of weight gain. Additional research and a heightened focus on this topic, particularly through meta-analyses, could offer deeper insights. Conducting more naturalistic, prospective studies within daily practice and exploring the influence of antipsychotic medication seems to be important. Also, conducting more studies detailing the exact sequence in which these metabolic alterations develop following initiation of antipsychotic treatment, as well as longer terms studies to ensure that the risk of certain metabolic alterations because of short duration of exposure is not misinterpretered.

Critically low is the current knowledge about adherence to clinical guidelines and the recommended monitoring of metabolic syndrome in patients with schizophrenia. and Further research is needed to map approaches across a larger number of psychiatric hospitals to obtain more comprehensive data.

From the clinical point of view, there is very little we can do about duration of treatment or selection of medication, which are mostly determined by severity or type of illness. However, we can screen for people with baseline low BMI and be particularly cautious in treating those, by prescribing them medications with the lowest potential for weight gain.

Besides if obesity worsens psychiatric outcomes, it is also important to ask if treatment of obesity improves psychiatric prognosis. To this goal, I also participated in a systematic literature review "Are the antidepressant effects of insulin-sensitizing medications related to improvements in metabolic markers?" (Toba-Oluboka et al., 2022). We conducted a systematic literature search following the PRISMA guidelines to identify studies investigating the antidepressant effects of insulin-sensitizing medication, with specific focus on examining whether improvements in depressive symptoms were linked to improvements in metabolic dysfunction. We included 15 out of 334 screened studies and majority of the studies (14 out of 15) included in this review reported significant improvement in depressive symptoms following treatment with insulin-sensitizing medications, with clear positive impact on depressive symptoms. However, it appears that the symptom improvement may not be directly related to improvements in metabolic markers or weight loss as 9 out of 15 included studies assessed for a correlation between improvement in symptoms and changes in metabolic markers and only 2 out of 9 studies found such association, with effect sizes ranging from R2 =

0.26-0.38. The metabolic variables, which correlated with improvements in depressive symptoms included oral glucose tolerance test, fasting plasma glucose and glycosylated hemoglobin following treatment with pioglitazone or metformin (Toba-Oluboka et al., 2022). The additional mechanisms contributing to the observed clinical improvement remain unclear.

Moreover, in this review, some of these medications have demonstrated improvements in cognitive performance of participant, including verbal memory index, visual memory index, general memory index, attention, concentration, and delayed memory tasks. (Toba-Oluboka et al., 2022). We have multiple studies suggesting that insulin or insulin-sensitizing medications may indeed enhance cognitive function. In animal studies, medications like liraglutide or metformin have demonstrated the potential to improve cognitive performance and delay progressive memory decline, particularly associated with hippocampal loss, in a mouse model of pathological aging (Hansen et al., 2015; Ying et al., 2015). Human experiments have shown that a high intravenous insulin dose is more effective than a low dose in acutely enhancing the ability to remember word lists in both somatically and psychiatrically healthy volunteers (Kern et al., 2001). These improvements are important also for severe mental illnesses, including schizophrenia and related cognitive symptoms. This has been already support by research and recent meta-analysis on 12 studies found positive trend with better cognitive performances in the Brief Assessment of Cognition in Schizophrenia and PANNS after 24 weeks of metformin treatment in schizophrenic patients (Battini et al., 2023).

Future studies on insulin-sensitizing medications are needed to explore mechanisms of function in symptoms improvement, the connections between changes in metabolic markers and changes in psychiatric symptoms. Additionally, it is crucial to investigate insulin-sensitizing medications not only acute but also prophylactic treatment effects in psychiatric field.

7. Conclusion

In crossectional analysis, formulated hypotheses were partially validated. As hypothesized, we found significant alterations in TGC and HDL, but no significant associations with total cholesterol and LDL. The shifts in TGC were significantly higher in participants with prior medication history compared to the control group. HDL changes were pronounced also in drug-naïve individual. This phenomenon could be related to relatively short time frame after the initiation of antipsychotic treatment with second generation antipsychotics. Additionaly, we found significant changes in BMI and other blood parameters TSH, fT3, fT4, prolactin.

In the prospective measurements, we confirmed our hypothesis regarding weight gain over time. BMI significantly increased from the baseline measurement until the follow-up visit (ΔBMI=0.97±2.26), occuring on average after 44.6 days. Likewise, the body weight of participant significantly increased from the baseline measurement until follow-up (Δweight=3.46±7.81 kg). We did not observe a difference in rate of BMI increase or kilograms of weight gain between previously medicated and medication naïve individuals. Our hypotheses, stating that significant weight gain in patients between the two measurements would be directly proportional to the overall antipsychotic exposure, were not confirmed. However, we found a significant interaction between BMI at T1 and medication exposure predicting change in BMI. Greater exposures to olanzapin, clozapine and quetiapine were associated with greater BMI increase, but this effect was most pronouced in people with lower baseline BMI and weakest in those with higher baseline BMI. This was true both for cumulative and average daily dose of MMP antipsychotics. However, neither the cumulative nor average daily dose of all medications or metabolically less problematic medications were related to change in BMI. Additionaly, we found that longer durations of treatment until research visit were significantly associated with larger increases in BMI and higher BMI at follow-up.

Regarding our third hypothesis, the collected prescription patterns did not predict BMI changes in the comprehensive medication analysis, regardless of how medications changed during the follow-up. We did not find polypharmacy or adjustments in antipsychotic medication that might impact body weight to be predictors of BMI or BMI changes in the early course of treatment. Based on power analyses, these were true negative rather than false negative findings. The primary predictors remained the baseline BMI, duration of medication exposure, and the dose of metabolically problematic antipsychotics.

Additionally, the absence of recommended metabolic monitoring at the beginning of hospitalization in our sample is alarming. This serious gap in patient care clearly needs to be addressed in the future.

In conclusion, we observed a significant weight gain early during the first hospitalization for psychosis. The association between medication exposure and weight gain was moderated by baseline BMI and was especially pronounced in people with low baseline BMI who were treated with medications including clozapine, olanzapine, and quetiapine. The weight gain in people with low to normal baseline BMI was not harmless – it reached clinically significant range in almost half of these individuals within an average 44.6 days into the hospitalization, and made them statistically comparable in TGC, HDL, and FT4 to people who were overweight or obese at admission. In our detailed medication analysis, regardless of how changes in medication during the follow-up, the main predictors remained the baseline BMI, duration of medication exposure, and the dose of antipsychotics with pronouced prometabolic side effects. These findings emphasize weight monitoring in people with FEP and warrant extra caution in prescribing these medications to people with low to normal baseline BMI.

8. Summary

Obesity and metabolic alterations are the primary causes of cardiovascular morbidity and mortality, leading to shortened life expectancy in schizophrenia. This study addresses various potential etiologies and explores the connections between metabolic health and this mental disorder. However, most of these connections remain highly theoretical with limited clinical implications.

The introduction of the thesis also describe several approaches to improving somatic health and combating obesity and other metabolic abnormalities in individuals with schizophrenia. These approaches encompass non-pharmacological interventions, such as education and motivational support, as well as lifestyle changes aimed at weight loss. Non-pharmacological interventions appear to be less clinically and cost-effective than desired due to challenges like low attendance and limited interest among individuals with obesity and schizophrenia. Moreover, questions surround their general accessibility. The pharmacological interventions, such as medication adjustments or the weight loss medications, are also considered. These interventions appear to be more focused on harm reduction, with some showing effectiveness only after weight gain appeared and their clinical implementation often falls short.

So the main focus of this work was to clarify and better understand the links between medication exposure and metabolic changes in people hospitalized for their first episode of psychosis.

In above described study, we analyzed data from 173 patients with first episode psychosis who were hospitalized in one of 10 psychiatric hospitals and wards in the Czech Republic and from 204 healthy controls. We obtained blood samples for metabolic markers, weight, height, body mass index at the time of admission and on average 44.6 days later, while participants were still hospitalized. The inpatient setting allowed us to maximize adherence, standardize other lifestyle factors, and prospectively and precisely quantify daily exposure to medications based on daily chart records. We calculated the total and daily antipsychotic exposure based on daily chart records. In detailed medication analysis, we calculated the trajectory of polypharmacy and tried to identify additional predictors within collected and quantified prescription patterns that influence BMI changes, such as polypharmacy and adjustments in antipsychotic medication that impact body weight.

In our findings, higher daily or cumulative doses of metabolically problematic antipsychotics (olanzapine, quetiapine, clozapine), were associated with weight gain in first-episode psychosis, but only in people with low to normal baseline BMI. Morover, over half of people with initially low to normal BMI experienced clinically significant weight gain of at least 7 percent. Equally significant is the fact that within the on average 44.6 days between measurements, metabolic parameters such as HDL, LDL, TGC, glucose, FT3, and FT4 in patients with initially normal or low BMI became almost ndistinguishable from metabolic markers of individuals who were initially overweight or obese. In the detailed medication analysis, among the potential predictors, baseline BMI remained the earliest predictor of weight gain.

In conclusion, low to normal baseline BMI was a significant predictor of future weight gain on olanzapine, quetiapine, or clozapine. Clinical implications of this work suggest high importance of monitoring BMI in individuals with FEP and clinical cautiousness when prescribing especially metabolically problematic antipsychotics to people with normal to low baseline BMI. Further research and a heightened focus on this topic, particularly through meta-analyses and longer follow-up naturalistic studies, could offer deeper insights into predictors of antipsychotic-induced weight gain.

9. Souhrn

Obezita a další metabolické odchylky jsou hlavními příčinami zvýšené kardiovaskulární morbidity a mortality u pacientů se schizofrenií, přičemž značně zkracují průměrnou délku jejich života a přispívají ke značnému zkrácené střední délky jejich života. Úvod této práce mapuje četná propojení mezi metabolickými odchylkami a schizofrenií prostřednictvím společných rizikových faktorů a dalších etiologických činitelů. Většina těchto souvislostí však zůstává převážně teoretická a s omezenými klinickými výstupy. Dále v úvodu této práce shrnuji možné přístupy k léčbě metabolických odchylek, které spočívají ve farmakologických i nefarmakologických postupech. Nefarmakologické intervence zahrnují edukaci o zdravém životním stylu a specializované programy pro úpravu životního stylu, psychickou podporu a snižování hmotnosti. Současné důkazy však naznačují, že tyto přístupy mohou být méně efektivní z klinického a ekonomického hlediska, přičemž se setkáváme s nízkým zájmem a motivací pacientů a s otázkou reálné dostupnosti těchto programů. Farmakologické intervence, jako jsou změny v léčbě na méně metabolicky problematická antipsychotika nebo přidání antiobezitik, představují spíše sekundární či terciální prevenci. Klinická praxe se také potýká s četnými výzvami včetně kompliance a adherence pacientů či s problémy v navazující péči.

Cílem této práce bylo detailně zmapovat vliv antipsychotické medikace na metabolické změny u pacientů s první epizodou psychotického onemocnění.

Do studie, jež je výše detailně popsána, jsme zařadili 173 pacientů z 10 nemocnic v České republice s první epizodou psychotického onemocnění během jejich první psychiatrické hospitalizace a porovnali je se 204 zdravými kontrolami. V prospektivním sledování jsme sbírali data o tělesné hmotnosti, BMI, denní expozici antipsychotikům od přijetí až do výzkumné vizity v průběhu téže hospitalizace a byly provedeny odběry pro analýzu metabolických parametrů. Průměrná délka sledování mezi vizitami byla 44,6 dne. Hospitalizační sledování alespoň částečně standardizovalo dietní příjem, adherenci k léčbě a další faktory související s životním stylem. V průběhu sledování bylo také přesně kvantifikováno množství ordinované medikace a vypočítána celková a průměrná denní expozice antipsychotikům. Při detailní analýze farmakologické léčby 92 osob s FEP jsme skrze kvantifikaci jednotlivých medikačních trajektorií hledali další možné prediktory (výměna AP medikace na AP s lepším či horším metabolickým profilem, polypragmazie).

Tento výzkum odhalil spojitost mezi vyššími denními i kumulativními dávkami metabolicky problematických antipsychotik (olanzapin, klozapin a kvetiapin) a větším nárůstem BMI. Tato spojitost byla zřetelná pouze u osob s normálním nebo nižším BMI. U více než poloviny pacientů s původně nízkým či normálním BMI jsme zaznamenali klinicky významný přírůstek na váze (7 % a více). U těchto pacientů byly při výzkumné vizitě zjištěny téměř srovnatelné změny v metabolických parametrech (HDL, LDL, TGC, sérová glukoza, FT3 a FT4) jako u pacientů, kteří byli při přijetí k hospitalizaci již obézní. V detailní analýze medikace se z potenciálních prediktorů počáteční BMI ukázalo jako nejranější ukazatel přírůstku na váze.

Nízké či normální BMI z našich dat vychází opakovaně jako prediktor přírůstku na váze při užívání antipsychotik, zejména olanzapinu, klozapinu či kvetiapinu. Naše data podporují důležitost monitorace hmotnosti u osob s FEP a větší opatrnost při předepisování antipsychotik s prometabolickým efektem osobám s nižším BMI. Další výzkum včetně metanalýz a studií s delším intervalem sledování zaměřené na toto téma by mohl přinést upřesnění poznatků důležitých pro klinickou praxi.

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11. Publications of author

Publications in extenso, that constitute the basis of the PhD thesis:

a) with impact factor:

Vochoskova K, McWhinney SR, Fialova M, et al. Weight and metabolic changes in early psychosis-association with daily quantification of medication exposure during the first hospitalization. Acta Psychiatr Scand. 2023;148(3):265-276. doi:10.1111/acps.13594 (IF 6.6)

Vochoskova K, McWhinney SR, Fialova M, et al. Trajectories of daily antipsychotic use and weight gain in people hospitalized for the first episode of psychosis. Eur Psychiatry. 2024;67(1):e59. Published 2024 Sep 26. doi:10.1192/j.eurpsy.2024.176 (IF 6.4)

b) without impact factor: –

Other publications of author in extenso:

a) with impact factor:

Baumann S, Mareš T, Albrecht J, et al. Effects of Transcranial Direct Current Stimulation Treatment for Anorexia Nervosa. Front Psychiatry. 2021;12:717255. Published 2021 Oct 6. doi:10.3389/fpsyt.2021.717255 (IF 3.9)

Toba-Oluboka T, Vochosková K, Hajek T. Are the antidepressant effects of insulin-sensitizing medications related to improvements in metabolic markers?. Transl Psychiatry. 2022;12(1):469. Published 2022 Nov 8. doi:10.1038/s41398-022-02234-z (IF 6.3)

Svancer, P., Capek, V., Skoch, A., Kopecek, M., Vochoskova, K., Fialova, M., Furstova, P., Jakob, L., Bakstein, E., Kolenic, M., Hlinka, J., Knytl, P., & Spaniel, F. (2024). Longitudinal assessment of ventricular volume trajectories in early-stage schizophrenia: evidence of both enlargement and shrinkage. BMC psychiatry, 24(1), 309. https://doi.org/10.1186/s12888-024-05749-5 (IF 4.2)

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Abstracts and posters:

Nosková, E., Vochosková, K., Knop, V., Stopková, P., & Kopeček, M. (2022). Histamine intolerance and anxiety disorders: pilot cross-sectional study of histamine intolerance prevalence in cohort of patients with anxiety disorders. European Psychiatry, 65(Suppl 1), S387–S388. https://doi.org/10.1192/j.eurpsy.2022.980

Vochosková, K, McWhinney, S., Kolenič, M., Španiel, F., Hájek, T. Longitudinal Investigation of Metabolic Changes, Weight Gain, and Medication Exposure in First Episode Psychosis. Society Of Biological Psychiatry Annual Meetenig. San Diego. 27.4.-29.4. 2023.

12. Appendix

Original publications related to the thesis.