Year : 2021

Clinical, environmental and epigenetic moderators of cardiometabolic adverse effects in patients receiving psychotropic treatments

Dubath Céline

UNIL | Université de Lausanne
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et de médecine

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Pharmacienne diplômée de l'Université de Genève

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Faculté de biologie
et de médecine

Ecole Doctorale
Doctorat ès sciences de la vie

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Président·e	Monsieur	Prof.	Werner	**Held**
Directeur·trice de thèse	Monsieur	Prof.	Chin Bin	**Eap**
Expert·e·s	Monsieur	Prof.	Giovanni	**Ciriello**
	Monsieur	Prof.	Mirko	**Trajkovski**

le Conseil de Faculté autorise l'impression de la thèse de

Madame Céline Estelle Dubath

Master en pharmarcie, Université de Genève, Suisse

intitulée

Clinical, environmental and epigenetic moderators of cardiometabolic adverse effects in patients receiving psychotropic treatments

Lausanne, le 28 septembre 2021

pour le Doyen
de la Faculté de biologie et de médecine

Werner Held

Prof. Werner Held

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Acknowledgments

This thesis would not have been possible without the support of many people.

First and foremost, I am heartily grateful to my supervisor, Prof Chin Eap, for his invaluable involvement and guidance in every step of my projects. His immense knowledge, plentiful experience and communicative curiosity always encouraged me to go ahead and invest in my projects. I would like to express my infinite gratitude to him, for giving me the opportunity to work on such varied and exciting topics and for the trust he has placed in me over these four and half years.

I would also like to show gratitude to my thesis committee, including the jury president, Prof Werner Held and the experts, Prof Mirko Trajkovski and Prof Giovanni Ciriello, for having accepted to evaluate the present work and for their valuable and constructive reflections.

I must thank Prof Philippe Conus, Prof Armin von Gunten, Prof Kerstin von Plessen and Dre Alessandra Solida from the University Hospital of Lausanne, Dre Franziska Gamma from the private psychiatric center Les Toises, and Prof Julius Popp, Prof Jerome Fredouille, Dr Othmann Sentissi and Prof Jean-Michel Aubry from the University Hospital of Geneva for supporting the clinical and microbiological studies and for their insightful review of articles. I would like to offer my special thanks to Dre Sara Camporesi for the great collaboration on the microbiota project, for her motivation and unfailing perseverance. Many thanks to Isabelle Chaudet, Annette Cossy, Nadir Mebdouhi, Isabelle Bohren and all the medical and nursing staff who contributed to patient inclusion, and eventually, thanks to all patients who gave their consent to participate in the present studies.

My gratefulness goes also to Dr Mehdi Gholam, for his incredible availability and essential statistical support. I wish to further thank Prof Zoltan Kutalik and Dre Eleonora Porcu for their contribution in the methylation project, for the bright ideas and statistical work.

I take this opportunity to express gratitude to all my colleagues of the Unit of Pharmacogenetics and Clinical Psychopharmacology for their practical help in familiarizing me with the hospital environment, for their constant good mood and their kindness, which meant a lot to me. I would like to extend my sincere thanks to Dre Aurélie Reymond, Dre Anais Glatard, Dre Jennifer Sjaarda, Nermine Laaboub, Claire Grosu and Marianna Piras for the shared work, endless discussions and great moments.

Last but not least, none of this could have happened without Benjamin, my family and my friends. I cannot express enough how much I owe them. I am deeply grateful for their unceasing encouragement, attention, and for their unwavering support and belief in me.

Thank you.

Abbreviations

5-HT	5-hydroxytryptamine, or serotonin
5-HT_{2C}	Serotonin 2C receptor
5-HT_{2A}	Serotonin 2A receptor
AAP	Atypical antipsychotic
AgRP	Agouti-related protein
ATP	National Cholesterol Education Program's Adult Treatment Panel III
BMI	Body mass index
BP	Blood pressure
CRW	Clinically relevant weight gain
CVD	Cardiovascular diseases
D_2	Dopamine D_2 receptor
DNA	Deoxyribonucleic acid
EPS	Extrapyramidal symptoms
EWAS	Epigenome wide association study
FMT	Fecal microbiota transplantation
FRS	Framingham risk score
GABA	γ-aminobutyric acid
GWAS	Genome wide association study
H_1	Histamine H_1 receptors
HDL	High-density lipoprotein cholesterol
IDF	International diabetes federation
LDL	Low-density lipoprotein cholesterol
M_3	Muscarinic M3 receptor
meQTLs	Methylation quantitative trait loci
MetS	Metabolic syndrome
MR	Mendelian randomization
NMDAR	*N*-methyl-D-aspartate receptor
NPY	Neuropeptide Y
POMC	Pro-opiomelanocortin
SCFA	Short chain fatty acid
SCORE	Systematic coronary risk estimation
SES	Socio-economic status
SMI	Serious mental illness
SNP	Single nucleotide polymorphism
SSEP	Swiss socioeconomic position
SSRI	Selective serotonin reuptake inhibitor
T_2D	Type 2 diabetes
TC	Total cholesterol
TDM	Therapeutic drug monitoring
TG	Triglycerides
WC	Waist circumference
WG	Weight gain
α_1, α_2	Alpha α_1, α_2 adrenergic receptors

Abstract

Psychiatric patients display an important prevalence of cardiometabolic disturbances, increasing their risk of developing and dying from cardiovascular diseases. This concerning situation results from a combination of genetic and environmental factors. Besides, the medications indicated to treat mental illnesses, including most antipsychotics, many mood stabilizers and some antidepressants, induce weight gain and metabolic alterations. The aim of the present thesis was to assess the metabolic health of a Swiss psychiatric cohort and to explore clinical, environmental and epigenetic risk factors to improve knowledge of psychotropic drugs' metabolic effects.

In the first study, the probabilities of cardiovascular events and death were estimated in a sample of psychiatric patients and a sample of the general population, revealing a similar level of risk. However, metabolic syndrome prevalence was much higher in the psychiatric cohort, especially in younger individuals (<50 years) and in women. In the second project, the association between socioeconomic status and changes in cardiometabolic parameters was evaluated over one year after the prescription of a psychotropic medication at risk for weight gain. Patients with low compared to high socioeconomic status were three times more likely to develop metabolic syndrome. Validating these observations, educational attainment, a marker of socioeconomic status, was found to be causally related to body mass index in an independent cohort of individuals receiving psychotropic treatments. The last study focused on quetiapine, an atypical antipsychotic, and was able to show that its metabolic adverse reactions depended on the daily dosage. Patients on lower doses developed indeed less side effects. However, the magnitude of this effect was small, and low doses of quetiapine still carried a non-negligible risk. Eventually, preliminary results from an ongoing project have revealed a global increase in DNA methylation levels following psychotropic treatment initiation and suggested that some site-specific modifications may play a role in drug-induced metabolic side effects.

These findings are critical in raising awareness of the poor metabolic health highly prevalent in psychiatry. They provide more insights into the risk factors for metabolic adverse reactions, which can be directly used in clinical practice to benefit care. The results of ongoing studies will provide a better understanding of the mechanisms leading to these adverse events, hopefully enabling development of new strategies to prevent their occurrence, to help identify at risk patients and to guide prescription choices.

Résumé

Les patients psychiatriques présentent une prévalence importante de troubles cardiométaboliques, ce qui augmente leur risque de développer des maladies cardiovasculaires et d'en décéder. Cette situation préoccupante résulte d'une combinaison de facteurs génétiques et environnementaux. Par ailleurs, les médicaments pour traiter les maladies mentales, dont la plupart des neuroleptiques, plusieurs stabilisateurs de l'humeur et certains antidépresseurs, induisent une prise de poids et des perturbations métaboliques. L'objectif de la présente thèse était d'évaluer la santé métabolique d'une cohorte psychiatrique suisse et d'explorer les facteurs de risque cliniques, environnementaux et épigénétiques afin d'améliorer les connaissances sur les effets métaboliques des psychotropes.

Dans la première étude, les probabilités d'événements et de décès cardiovasculaires ont été estimées dans un échantillon de patients psychiatriques et de population générale, indiquant un niveau de risque similaire. Cependant, la prévalence de syndrome métabolique dans la cohorte psychiatrique était largement supérieure, en particulier chez les jeunes (<50 ans) et les femmes. Dans le second projet, l'association entre le statut socio-économique et les changements des paramètres cardiométaboliques a été évaluée sur une période d'un an après la prescription d'un traitement psychotrope à risque de prise de poids. Les patients ayant un statut faible étaient trois fois plus susceptibles de développer un syndrome métabolique que ceux ayant un statut élevé. Validant ces résultats, un lien de cause à effet entre le niveau d'éducation, un marqueur du profil socio-économique, et l'indice de masse corporelle a pu être mis en évidence dans une cohorte indépendante recevant des psychotropes. La dernière étude s'est concentrée sur la quétiapine, un neuroleptique atypique, et a pu montrer que ses effets indésirables métaboliques dépendaient de la dose quotidienne. Les patients prenant des doses plus faibles développaient en effet moins d'effets secondaires. Toutefois, l'ampleur de cet effet était modeste, et les petites doses comportaient tout de même un risque non négligeable. Enfin, les résultats préliminaires d'un projet en cours ont révélé une augmentation globale du niveau de méthylation de l'ADN à la suite d'un traitement psychotrope et suggèrent que certaines modifications spécifiques pourraient contribuer à l'apparition des effets secondaires métaboliques.

Ces résultats sont essentiels pour faire prendre conscience de la mauvaise santé métabolique des patients psychiatriques. Ils fournissent davantage d'informations sur les facteurs de risque des effets secondaires métaboliques, qui peuvent être directement utilisées en pratique clinique au bénéfice des soins. Les résultats des études en cours permettront de mieux comprendre les mécanismes conduisant à ces effets indésirables, de développer de nouvelles stratégies pour les prévenir, d'aider à identifier les patients à risque et d'orienter les choix de prescription.

Résumé large public

Les patients souffrant de maladies mentales, incluant la schizophrénie, les troubles bipolaires et la dépression majeure, ont une espérance de vie réduite par rapport à la population générale. Ces patients ont un plus grand risque de développer des maladies cardiovasculaires en raison de leur patrimoine génétique et de facteurs liés au style de vie, ce qui explique en partie le taux de mortalité élevé. Par ailleurs, les médicaments qui leur sont prescrits, dont la plupart des neuroleptiques, plusieurs stabilisateurs de l'humeur et certains antidépresseurs, favorisent la prise de poids et l'apparition d'un syndrome métabolique. L'objectif de cette thèse était d'évaluer l'état de santé cardiovasculaire d'une cohorte psychiatrique et d'explorer les facteurs de risque conduisant aux effets secondaires métaboliques des psychotropes.

Tout d'abord, des outils ont été utilisés pour prédire l'arrivée d'événements et de décès cardiovasculaires sur 10 ans, révélant un risque similaire entre patients psychiatriques et population générale. Cependant, la prévalence d'un syndrome métabolique était beaucoup plus importante dans la cohorte psychiatrique, surtout chez les jeunes (<50 ans) et les femmes. Dans un second projet, l'impact du statut socio-économique sur les changements des paramètres cardiométaboliques a été évalué sur une période d'un an après la prescription d'un traitement psychotrope à risque de prise de poids. Il a notamment été prouvé que les patients ayant un statut faible étaient trois fois plus susceptibles de développer un syndrome métabolique que ceux ayant un statut élevé. La dernière étude s'est concentrée sur la quétiapine, un neuroleptique largement utilisé en psychiatrie, et a pu montrer que ses effets métaboliques dépendaient de la dose journalière. Enfin, les résultats préliminaires d'un projet impliquant la génétique ont indiqué que les médicaments psychotropes pourraient induire des dérèglements du métabolisme en modifiant l'expression des gènes.

Ces résultats sont essentiels pour faire prendre conscience de la mauvaise santé métabolique des patients psychiatriques. Ils fournissent des informations sur les facteurs de risque menant aux effets indésirables métaboliques, qui peuvent être directement utiles en clinique. Les résultats des études en cours permettront de mieux comprendre les mécanismes conduisant à ces effets secondaires, de développer de nouvelles stratégies pour les prévenir, d'aider à identifier les patients à risque et d'orienter les choix de prescription.

Introduction

Serious Mental Illness (SMI) and metabolic health

Psychiatric disorders result in serious functional impairments. The global burden of these diseases is major with a prevalence exceeding 10% of the population worldwide [1]. In Switzerland, it was reported that 6% of the population received a treatment for a psychiatric condition in 2017 [2]. Patients with severe mental illness (SMI), such as schizophrenia, bipolar disorders or major depressive disorders experience important disability, interfering with their day-to-day life activities and often requiring intensive care from mental health services.

Schizophrenia and bipolar disorders typically occur between late adolescence and early adulthood, while depression can happen at any age. The causes of most mental disorders remain poorly understood and a combination of genetic influences and environmental risk factors are believed to be responsible for the onset of SMI [3, 4]. To date, no biological markers or imaging techniques attesting to the presence of these diseases have been identified, and diagnoses are based on patients' symptoms evaluation [5-8]. Briefly, schizophrenia is characterized by the presence of so-called positive symptoms, mainly hallucinations and delusions, negative symptoms, which include social withdrawal and anhedonia, and cognitive dysfunction. In unipolar depression, patients typically experience weeks of low, sad mood, which may be accompanied by several other symptoms including feelings of worthlessness and despair, decreased energy, reduced appetite and sleep. Bipolar disorder is also a mood disorder, in which patients experience periods of abnormally elevated, expansive or irritable mood, with highly increased energy and activity levels, named mania, or hypomania, with attenuated symptoms, followed by periods of depressed mood. Patients may experience one or several acute episode(s), followed by a lasting remission, although schizophrenia and bipolar disorders are most often characterized by persistent symptoms, requiring lifelong treatments.

SMI often co-occur with other physical illnesses, resulting in a dramatic shortening in life expectancy of around 10 years [9, 10]. More specifically, the susceptibility to develop cardiovascular diseases (CVD) in the psychiatric population is markedly increased as

compared to the general population and carry a great responsibility in the premature death rate reported [11]. Indeed, although suicide is a common cause of death in patients with SMI, excess mortality is primarily due to natural events [9], with CVD-related deaths being much higher than in the general population [11].

A number of modifiable risk factors for CVD are elevated in psychiatric patients, with a high prevalence of obesity, smoking, type 2 diabetes (T_2D), hypertension and dyslipidemia; bipolar patients being 1.5 to 2 and schizophrenia patients 2 to 3 times more prone to suffer from metabolic syndrome (MetS) than people from the general population [12, 13].

Psychiatric patients are particularly vulnerable to develop metabolic alterations due to their psychiatric symptoms, to poor lifestyle habits, including smoking, unhealthy diet, alcohol abuse and physical inactivity, to their social and economic environment as well as to disparities in the access to and quality of health care [10, 14, 15]. On top of that, there seems to be some genetic predisposition, with common genes favouring psychiatric diseases along with CVD, further related to dysfunctions in inflammation and immune system [16-19]. Chronic low-grade inflammation has indeed been reported to be associated with both obesity [20] and SMI [21, 22] and could be causally related to the development of these diseases. Eventually, many psychotropic drugs, have metabolic side effects that further affect patients' cardiovascular health. Weight gain is commonly reported following treatment introduction, and may be accompanied by dyslipidemia, hypertension and hyperglycemia. The mechanisms underlying psychotropic drug-induced weight gain and metabolic dysregulation are complex and only partially understood. They represent an important and active field of research. Epidemiological studies describing psychiatric populations' metabolic health have helped raising awareness on metabolic side effects of psychotropic drugs [23-25]. Since then, guidelines have been developed to allow adequate follow-up of patients starting a psychotropic treatment [24, 26, 27]. The first project included in this thesis aimed at assessing the cardiometabolic health of a large psychiatric cohort followed-up in Switzerland.

Psychotropic treatment

Medications for long-term treatment of SMI include mainly antipsychotics, mood stabilizers and antidepressants. The discovery of these classes of treatments is the result of a succession of fortuitous findings. Lithium was discovered by chance in the 19th century and is widely used since the 1960s, still representing the first line of treatment, with antipsychotics, for bipolar disorders. Similarly, the first typical antipsychotic, chlorpromazine, and one of the first antidepressant agents, imipramine, were also discovered through serendipitous clinical observations in the early 1950s [28]. Their effectiveness in alleviating symptoms was striking and paved the way to the development of psychopharmacology. The study of their mechanisms of action, although still not fully elucidated, led to a major advance in the understanding of the pathophysiology of SMI and stimulated the research and development of a whole range of psychotropic agents.

Therapeutic and side effects of psychotropic drugs

The therapeutic action of these drugs is based on interference with numerous neurotransmitter-signalling pathways in various areas of the brain. Typical antipsychotics are characterised by potent blockade of the dopamine D_2 receptor (D_2), inhibiting dopamine activity [29, 30]. It is postulated that the inhibition of these receptors in the mesolimbic pathway contributes to the reduction of the positive symptoms of psychosis, namely an improvement in hallucinations and delusions, as shown in Figure 1 [31].

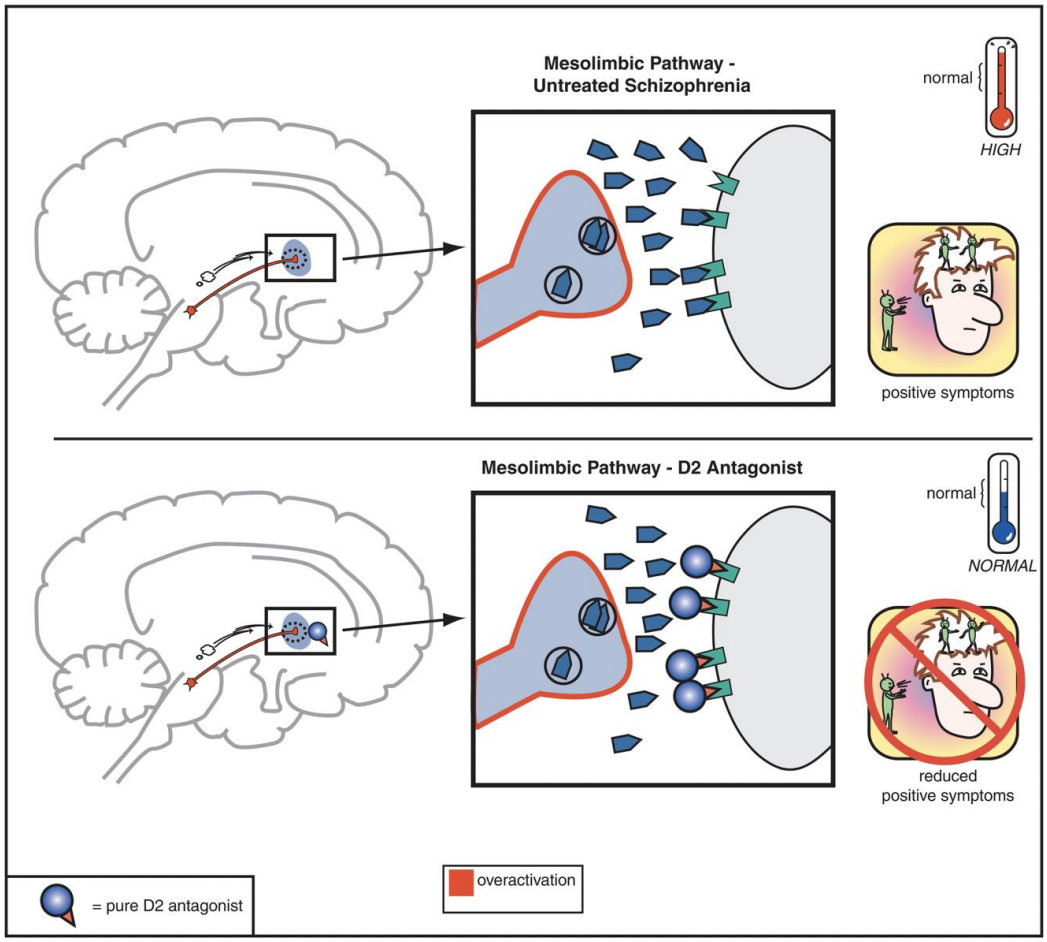

Figure 1. Mesolimbic dopamine pathway and D_2 antagonists (adapted from: Stahl's Essential Psychopharmacology, 2013)

Antagonism of dopamine is however not specific to this pathway, and blockade of D_2 with these medications happens in all brain regions, leading to adverse effects. Thus, classical antipsychotics also act on the mesocortical dopamine pathway, which is already hypoactive in schizophrenia and thought to be responsible for the cognitive and negative symptoms. This activity partly explains why these symptoms are not alleviated by classical antipsychotics and sometimes even get worse. In addition, important motor side effects, known as extrapyramidal symptoms (EPS), often arise when the nigrostriatal dopamine pathway is impaired, resembling the movement disorders seen in Parkinson's disease. When used chronically, antipsychotics can lead to tardive dyskinesia, a movement disorder involving involuntary, repetitive movements of the face and extremities [32]. Eventually, dopamine is also a key regulator of plasma prolactin levels, and the blockade of the tuberoinfundibular pathway may result in

hyperprolactinemia. This condition remains asymptomatic in some cases, but often causes adverse effects on gonadal function, such as galactorrhea, amenorrhea, infertility and sexual disorders [31]. Besides their shared action on D_2, classical antipsychotics also bind to other receptors in the brain, with differing profiles. Side effects thus vary from one agent to another, depending on the binding affinities to these other receptors. Frequent adverse effects such as drowsiness and sedation are, for example, the result of antagonism at histamine H_1 receptors (H_1) and to a lesser extent at alpha α_1 adrenergic receptors (α_1). These side effects are highly debilitating and often responsible for poor quality of life. Treatment adherence is hard to maintain in such conditions, and adverse drug reactions often result in medication discontinuation.

Atypical antipsychotics (AAP), also known as second-generation antipsychotics, have been developed with the aim of treating schizophrenia, with enhanced safety. Their pharmacological profile is based on a lower affinity for D_2 and greater interaction with other neurotransmitters, such as histamine, acetylcholine or noradrenaline with a putative key role of serotonin (5-HT) receptors modulation [33]. Figure 2 displays the various binding profiles of a range of AAPs relevant to their antipsychotic action mechanism.

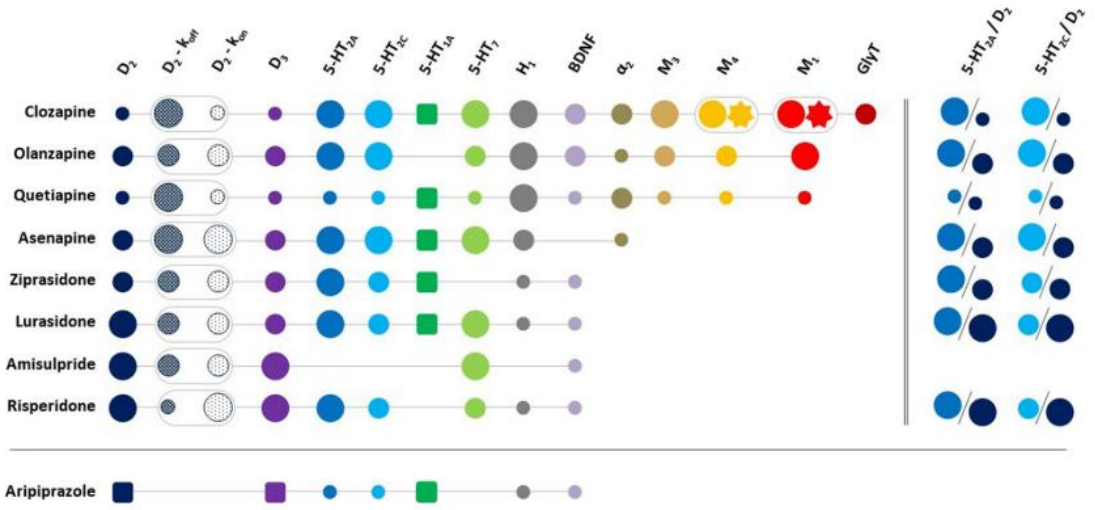

Fig. 1. Molecular targets of AAPs. List of the most relevant targets involved in the mechanism of action of AAPs based on receptor occupancy. Values are reported as high (●), medium (●) and low (●). ●, ■ and ✹ represent receptor antagonism, partial agonism and positive allosterism, respectively. ⊗ and ○ represent k_{off} and k_{on} values for the D_2 receptor and ● represents BDNF production, while ✹ represents positive allosterism by the clozapine metabolite, norclozapine, at M_1 and M_4 receptors. Aripiprazole is shown at the bottom for its different mechanism of action. Finally, the 5-HT_{2A}/D_2 and 5-HT_{2C}/D_2 receptor affinity ratios are included on the right. Clozapine covers a wide-range of molecular targets among all AAPs, while risperidone and amisulpride are mostly limited to just a few, and this might explain clozapine's superiority among AAPs.

Figure 2 : Molecular targets of atypical antipsychotics (adapted from: Aringhieri et al., Pharmacology and Therapeutics, 2018)

Of note, accumulating evidence support a role of glutamatergic system alterations in the pathophysiology of schizophrenia [34]. More precisely, hypofunction of the *N*-methyl-D-aspartate receptors (NMDAR) on γ-aminobutyric acid (GABA)-ergic interneurons in the cortex prevents adequate GABA release and inhibition of glutamatergic pyramidal neurons. Excessive glutamate release in the ventral tegmental area is then thought to be responsible for mesolimbic and mesocortical dopamine pathways abnormalities. Current antipsychotic agents do not target directly the glutamatergic system, although a reduction in glutamate metabolites following treatment introduction has been repeatedly observed, likely occurring secondary to antagonism on the $5HT_{2A}$ receptor. It was thus postulated that glutamatergic reduction may correlate with treatment response and take part in the therapeutic action of some antipsychotics [35].

In terms of efficacy, there is very limited difference between antipsychotics (including typical and atypical antipsychotics), except for clozapine, that shows a clear superiority for treatment of refractory patients [36-38]. The choice of treatment is thus based on the side effect profile, which is far more variable from one drug to another. Figure 2 highlights that each AAP harbours unique characteristics. All AAPs have reduced motor-related side effects, representing a major improvement in the treatment of patients. To one end, clozapine and quetiapine, which have the lowest affinity for D_2, seldom cause drug-induced parkinsonism, while risperidone to the other end has a D_2 occupancy resembling typical antipsychotics and is more likely to induce EPS [33]. A major drawback to AAPs is their propensity to cause weight gain and induce metabolic side effects [39]. The extent of metabolic dysregulation induced by antipsychotics is consistently reported to be highest with clozapine and olanzapine, and lowest with aripiprazole, brexpiprazole, cariprazine or lurasidone [40, 41]. Mechanisms through which antipsychotics cause weight gain and metabolic side effects seem multifactorial and may be partially related to their activity on neuroreceptors. Antagonism at H_1 and $5\text{-}HT_{2C}$ are the most cited candidates, with putative synergistic roles of other receptors modulation, including dopaminergic, muscarinic and adrenergic receptors [42-44].

Implication of brain receptors in metabolic side effects of psychotropic drugs

Patients often report an increased appetite following treatment initiation [45, 46]. Antipsychotics, interfering with central brain receptors, are thought to induce a modification in hunger sensation and a change in feeding behaviour, leading to higher food intake [47]. Regulation of appetite and control of food intake is orchestrated in the hypothalamus, which integrates inputs from different areas of the brain, as well as from peripheral messengers such as the hormones leptin and ghrelin. In this brain region, the expression of neuropeptide Y (NPY) and Agouti-related protein (AgRP) has an orexigenic effect, promoting food intake, while the expression of pro-opiomelanocortin (POMC) produces the opposite effect. Hypothalamic H_1 antagonism is thought to stimulate appetite and counter leptin's anorexiant effect, while antagonism at the serotoninergic receptor 5-HT_{2C} likely increases NPY levels and decreases POMC secretion, and may also interfere with the signaling pathway of leptin [48]. Olanzapine and clozapine display a strong affinity for these two receptors, which favors the hypothesis of their role in weight gain.

Metabolic disturbances have also been reported in the absence of hyperphagia and central H_1 blockade may promote fat accumulation in white adipose tissue. In addition, it may be responsible for reduced energy expenditure, through a reduction in brown adipose tissue thermogenesis, and possibly through its sedative effect [49].

The role of dopamine receptors blockade is less clear. Some evidence, based on agents displaying weight gain liability and selective binding to D_2, suggest that prolactin elevation following dopamine antagonism might be in cause [50]. Besides, a synergistic effect of D_2 and serotoninergic receptors blockade might be a key factor in antipsychotic-induced weigh gain. Other hypotheses postulate a direct effect on food seeking behavior related to a decreased sensitivity of the reward circuit or to an interference with leptin's effect on food intake.

Data on the implication of muscarinic and adrenergic receptors M_3, α_1- and α_2 are lacking, but interaction with these receptors is likely contributing to an altered control of glucose plasma levels and insulin resistance [50]. In addition, anticholinergic agents often affect oral health,

with dry mouth being very frequently reported [51]. Patients tend to drink more to relieve this unpleasant symptom, and when they are used to high-calorie sugar-sweetened beverages, the increase in energy intake is exacerbated.

Besides antipsychotics, antidepressants, mainly mirtazapine and tricyclics as well as the mood stabilizers lithium and valproate also carry a notable potential to induce weight gain [23, 52]. While mood stabilizers' effects on neurotransmission pathways are still unclear, antidepressants with important anti-histaminergic activity have the greatest propensity to cause weight gain, incriminating again H_1 antagonism [53].

Psychotropic drugs' interaction with central neuroreceptors seems responsible for dysregulation of appetite and satiety signalling pathways, which results in increased food intake and, combined with a reduction in energy expenditure, eventually leads to weight gain and metabolic abnormalities.

However, hypotheses solely based on the binding affinities to neuroreceptors fail to explain some differences in the extent of side effects observed between molecules. Besides, although dyslipidemia, hypertension and insulin resistance are driven by obesity and may arise with psychotropic drugs secondary to weight gain, dysregulations following psychotropic treatment have also been observed without or with only slight weight gain, suggesting the implication of other mechanisms [54, 55].

Implication of peripheral mechanisms in metabolic side effects of psychotropic drugs

As mentioned earlier, leptin is an essential hormone in the regulation of food intake. It is primarily produced by adipocytes proportionally to fat stores. The levels of circulating leptin have been shown to be affected by the introduction of antipsychotics, with a quick rise following treatment start [56]. As summarised in a recent review [57], this increase could occur following weight gain, but some authors observed elevation in leptin plasma levels, independently of body weight change. Notably, some studies suggested a direct action of antipsychotics on adipocytes, inducing leptin secretion. The abnormally elevated levels of leptin likely lead to a

decreased sensitivity and eventually to leptin resistance. The anorexic effect of leptin is thus decreased although patients exhibit high leptin plasma levels. Ghrelin, a hormone produced by enteroendocrine cells in the gastrointestinal tract that acts in opposition to leptin, might also play a role as abnormal levels were reported after antipsychotics treatment [58]. Other hormones secreted by the adipocytes are also likely affected by antipsychotics. Adiponectin for instance, which displays anti-inflammatory and anti-apoptotic properties, aside from its role in energy homeostasis where it stimulates fatty acid oxidation in skeletal muscle and inhibits gluconeogenesis in the liver, was reported to be reduced in treated patients [59, 60].

The effect of antipsychotics on adipocytes is not restricted to the modification of their endocrine secretions. Indeed, an increased lipogenesis as well as a decrease in adipose tissue lipolysis have been described when exposed to antipsychotics, resulting in an enlargement of adipose tissue [60]. The synthesis of lipids seems also increased in the liver, with accumulation of cholesterol in hepatocytes being reported both in in vitro and in vivo studies. These effects, occurring independently of body weight, contribute to the occurrence of dyslipidemia [60]. Regarding hyperglycemia and insulin resistance, often observed shortly after antipsychotics introduction, various mechanisms have been identified [55]. Antipsychotics have shown an activity on hepatocytes, inhibiting glycogen synthesis through interference with serotonin signalling, and enhancing gluconeogenesis through H_1 antagonism [55]. They are also thought to affect cellular glucose uptake in skeletal muscle, inhibiting glucose transporters and thus decreasing glucose entry from the circulation [60]. Besides, insulin secretion in response to glucose was found to be disturbed. Serotonin, dopamine and acetylcholine receptors present on pancreatic β-cells modulate, along with others, insulin release in the blood stream. Antipsychotics may directly affect pancreatic β-cells function in binding to these mediators receptors and lead to an impaired control of glucose level [55].

Inter-individual variability and clinical risk factors for metabolic side effects of psychotropic drugs

Mechanisms of antipsychotic-associated weight gain and metabolic alterations are complex and evidence show an effect on various cell types in different tissues. Surprisingly, there is a high inter-individual variability in the occurrence of metabolic side-effects. Some patients, although compliant to their medication will not experience body weight gain nor other metabolic changes. Certain clinical features have already been identified pointing out that young patients, low body mass index (BMI), non-Caucasian ethnicities, family history of obesity and first episode of psychosis seem to be the most important risk factors to develop the side effects [24]. Other factors such as polypharmacy, higher dosages or male sex have also been reported to increase patient risk although with inconsistent results [24, 40, 61-63]. The importance of reporting side effects and characterizing risk profiles is paramount as the prescription of psychotropic drugs is rising [64]. This observation is particularly worrying regarding the increase in off-label prescriptions, for which the efficacy and safety have not been thoroughly assessed. Quetiapine, for example, was reported to be the most frequently prescribed antipsychotic in Denmark, and its use at low dosages in individuals without diagnoses relevant to antipsychotic treatment is very common [64]. One of the project included in this thesis aimed precisely at evaluating the dose effect of quetiapine on weight and metabolic parameters. Adding more evidence on the safety of low doses of quetiapine use will hopefully help to move towards a better prescribing practice.

Through clinical trials and observational studies, some risk factors as the ones cited above, have been highlighted for the development of metabolic side effects. Our research group has tried to further evaluate the risk profiles of psychotropic drugs, and has notably shown that patients who gained more than 5% (>4% in adolescents) of their initial body weight during the first month of treatment were at higher risk to gain substantial weight over a 3 to 12 month period [65, 66]. This observation was further replicated in an independent cohort of depressed patients being prescribed antidepressants [67]. Similarly, patients whose lipid levels increased by more than 5% during the first month had a greater risk to develop subsequent dyslipidemia

in the longer term [68]. The identification of additional early predictive markers of metabolic disturbances would enable clinicians to offer tailored adjunctive therapies (medication and/or lifestyle interventions). These findings demonstrate the usefulness of a close follow-up and the importance of reacting quickly, following an unfavorable evolution of the body weight and metabolic parameters.

In the same line, recent studies conducted in our research group investigated metabolic side effects with a focus on more vulnerable populations. While old age patients undergo physiological changes, their tolerance to psychotropic drugs might be altered. Using a pharmacokinetic/pharmacodynamics analysis, elderly patients treated with amisulpride were shown to have a reduced clearance and were thus likely exposed to plasma concentrations above the reference range [69]. Increased susceptibility to face side-effects was expected, but fortunately, amisulpride concentration was not associated with body weight increase after a period of 3-months of treatment. On the other hand, young patients are particularly at risk of metabolic worsening following treatment, as age was consistently reported to be linked with side effects. As most studies are conducted in adults, data specifically addressing the metabolic outcomes in this population are lacking. Nevertheless, the prescription of psychotropic treatment is increasing in children and adolescents and because many psychotropic drugs are prescribed off-label [70, 71], more studies are greatly needed. A meta-analysis recently synthetized the current evidence in young patients and confirmed poor quality of data on safety of psychotropic drug use [72]. They could however conclude that antipsychotics and mood stabilizers were most frequently associated with weight gain among other side effects. Our research group also reported important cholesterol deteriorations in adolescents receiving a mix of antipsychotics [73], and highlighted that women patients seemed more prone to develop lipid disturbances. Besides, early deteriorations were also linked to a lasting and more pronounced cholesterol worsening.

It is therefore crucial that metabolic follow-up is implemented in clinical practice to adequately monitor young patients who start such treatments.

Research focused on the variability in the predisposition to metabolic side effects, investigating other risk factors such as environmental influences, gut microbiota composition as well as patients' genetic and epigenetic characteristics is needed to further explain the mechanisms implicated. There is a substantial part of the mechanisms leading to metabolic abnormalities that are linked to individual characteristics and might be, at least to some extent, modifiable. Understanding the role of each of these parameters is essential to find strategies to avoid or at least minimize the occurrence of metabolic side effects. In addition, better knowledge on the shared mechanisms common to the diverse psychotropic treatments as well as on the specificities of each molecule is needed to personalise treatment options according to the patients' profile. These advances will hopefully support the development of the next generation of psychotropic treatments.

Implication of environmental and socio-economic related risk factors in metabolic side effects of psychotropic drugs

The environment in which a patient grows up plays certainly a role in the susceptibility to drug-induced side effects. The living or working environment can have dramatic influences on an individual's health, related to the ambient noise [74], to air pollution [75], or to the neighbourhood construction in itself, with the presence of green spaces or fast foods having a different impact on individual behaviours [76, 77]. Besides, people with the same socio-economic level tend to cluster together and their lifestyle habits influence each other [76]. The environment thus shapes the events an individual is likely to face, which has lasting effects on health and disease across the life-course. Socio-economic factors such as educational attainment or income level among others have already been associated with both mental health and obesity in the general population [78, 79]. A patient with a precarious situation who starts a treatment with a high risk to induce weight gain might thus be more prone to develop metabolic disturbances. Lifestyle choices surely contribute to these inequities, but not solely [80]. People from lower socio economic backgrounds often suffer from a lack of awareness of symptoms, they are less likely to engage in care and have less money to spend on their health. Other mediators, such as adverse childhood experiences for example are influenced by socio economic status (SES), whereby children and adolescents with lower status are at increased risk of experiencing maltreatment [81]. Childhood trauma has also been associated with obesity in adulthood in the general population [82] as well as in the psychiatric population [83, 84]. Notably, research conducted in our unit has shown that waist circumference increase after psychotropic treatment initiation was more important in patients who experienced a psychological trauma in adolescence [85]. The influence of SES in psychotropic drug-induced weight gain and metabolic changes is further evaluated in a specific project included in the present thesis.

Implication of genetics and epigenetics in metabolic side effects of psychotropic drugs

In the general population, genetics is known to account for inter-individual variability in obesity and metabolic syndrome. Genome Wide Association Studies (GWAS) have identified many loci associated with metabolic traits such as BMI or lipid levels [86-88]. Because of their genetic background, some people are thus more prone to be obese and suffer from metabolic diseases than others. Genetic variability can also contribute to inherited differences in drug tolerability in terms of metabolic side effects. Some GWAS focusing specifically on antipsychotic-induced metabolic disturbances were also conducted in the psychiatric population (i.e. on weight gain [89-93]). The limited number of participants included in these studies did not allow the identification of implicated single nucleotide polymorphisms (SNPs).

However, significant findings were obtained considering the effects of SNPs located on specific genes, chosen based on hypotheses driven approaches [94, 95]. Notably, recent studies conducted in our laboratory have shown that a combination of these SNPs, with other variants that had been associated with BMI, T_2D or dyslipidemia in the general population discovered through GWAS approaches, could predict weight gain or lipid changes in patients following a psychotropic treatment [96, 97]. Thus, polymorphisms in various genes have been shown to impact metabolic traits evolution. Further research to discover the various SNPs implicated is necessary. In the near future, the use of polygenic scores in combination with clinical data to predict patients at high risk of developing side effect might become common in clinical routine. Implementation of systematic genotyping of patients before treatment start would enable a personalized approach of care and improve the safety of treatments.

Epigenetics, integrating genetic susceptibilities and environmental influences, might contribute to further explain the occurrence of metabolic side effects. Briefly, DNA methylation, which is the best understood epigenetic modification to date, is a reversible process involving the covalent binding of a methyl group to the 5-carbon position of a cytosine residue within CpG dinucleotide as shown in Figure 3 [98, 99].

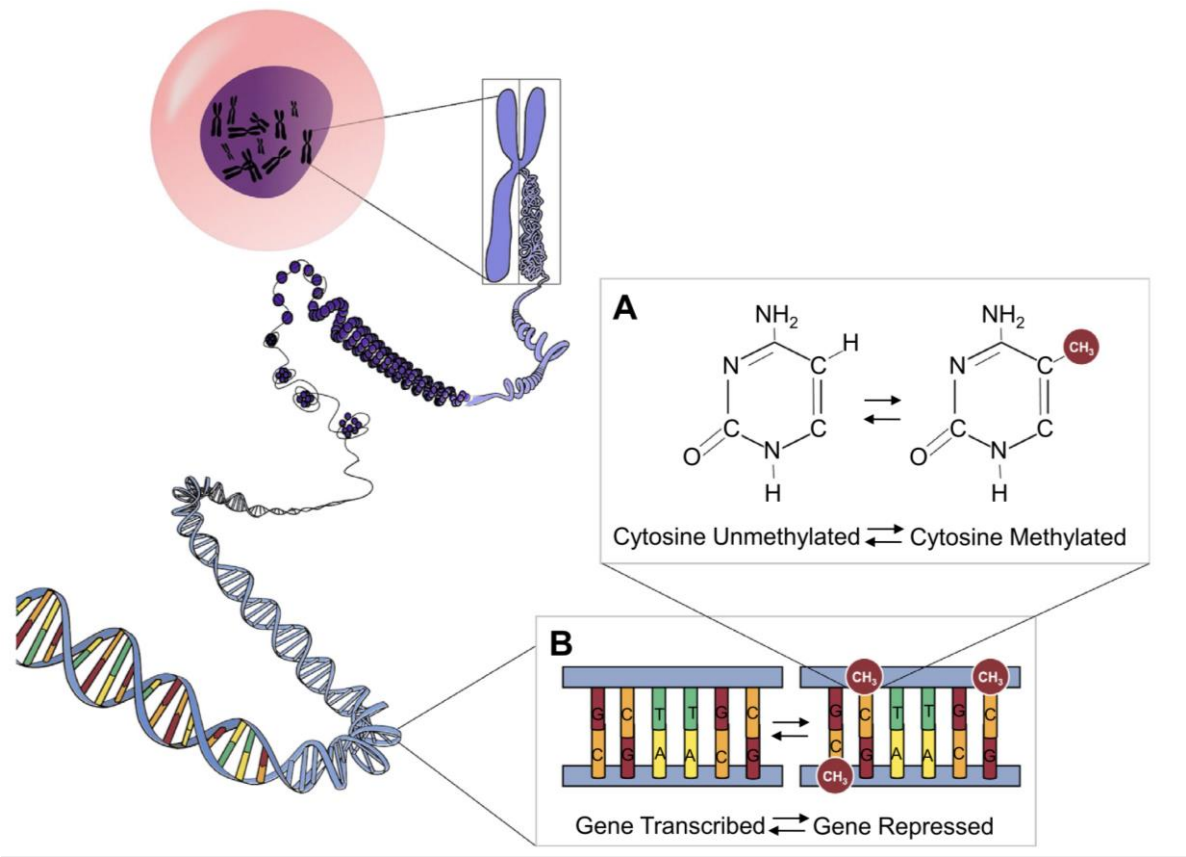

Figure 3. Cytosine methylation within CpG dinucleotide promotes gene silencing (adapted from: Gillespie et al., Nursing Outlook, 2019)

DNA methylation has an impact on gene expression, with hypermethylation being typically linked to lasting transcriptional repression and hypomethylation favouring gene expression.

Individual genetic profiles affect the methylation signature, as many studies reported associations between SNPs and variations in DNA methylation level (i.e. methylation quantitative trait loci, meQTLs) in different tissues, such as in adipose tissue [100, 101] and blood cells [102-105]. In addition, DNA methylation evolves over time, with a trend towards an increase in methylation with age [106]. Environmental factors have also been shown to affect DNA methylation and altered profiles have been associated with disease states including obesity [107, 108].

Administration of psychotropic drugs may induce modifications in DNA methylation, profoundly influencing DNA regulation and expression [109-111]. Although this molecular mechanism is now extensively studied in relation to treatment response, pharmacoepigenetics of

psychotropic drug-induced metabolic side effects remains underexplored [112-116]. In the general population, some differentially methylated sites within the genome have already been reported to be causally linked to CVD [117]. It is thus highly probable that psychotropic drugs act through epigenetic mechanisms to increase CVD risks.

There are a few authors who worked on this field, opening a very promising area of research. Burghardt et al assessed global methylation in relation to atypical antipsychotic treatment and metabolic parameters using peripheral blood samples [118, 119] and skeletal muscle samples [120]. The first study, which included 133 schizophrenia patients, yielded no conclusive results [118], while the second one, which focused on 115 patients with bipolar disorders, showed that atypical antipsychotic use as well as insulin resistance were both significantly associated with a lower global methylation [119]. In the third study, patients with bipolar disorders treated with atypical antipsychotics (n=16) had higher methylation levels compared to patients treated with mood stabilizers (n=12) or healthy controls (n=13) [120]. In this latter study, a positive correlation between methylation levels and insulin resistance was also highlighted.

These preliminary results point towards an effect of psychotropic drugs on global methylation levels mediating metabolic side effects, but gives no information on differentially methylated regions or genes that may drive these associations. In a candidate gene approach, some authors focused their epigenetic analyses on genes or genetic pathways with a highly probable role in the development of MetS induced by psychotropic medications. Thus, DNA methylation of catechol-O-methyl transferase (COMT) gene [121] and insulin growth factor 2 (IGF2) gene [122] were measured in peripheral blood-originated samples of psychiatric patients. These studies did not lead to conclusive results, as no significant relationships between epigenetic variability and metabolic parameters or atypical antipsychotic use were found. Nonetheless, we have previously shown an association between changes of methylation level of CREB-regulated transcription coactivator 1 (CRTC1) gene and early weight gain following psychotropic treatment initiation [123]. Besides, Burghardt et al found a hypermethylation of protein kinase B (AKT1 and AKT2) in skeletal muscle samples of a small group of bipolar

patients treated with atypical antipsychotics compared to patients treated with mood stabilizers [124]. Furthermore, they observed a positive trend for an increased methylation of AKT2 associated with insulin resistance in patients treated with atypical antipsychotics, while the opposite correlation was revealed in mood stabilizers users.

Hypothesis-driven studies may help to reveal how modulation of genes lead to metabolic side effects, but given the mixed results obtained to date, they might also fail to capture the true effect of psychotropic drugs in targeting only specific sites. To overcome this limitation, epigenome-wide association studies (EWAS) can help to further investigate the role of epigenetics in psychotropic drug-induced metabolic side effects. The only studies to date that used this technique allowed to discover a differentially methylated site in fatty acyl CoA reductase 2 (FAR2) gene which was associated with insulin resistance in patients with bipolar disorders treated with atypical antipsychotics and/or lithium [125], and another site in cadherin-like 22 (CDH22) gene, which was associated with metabolic syndrome in a schizophrenia population treated with atypical antipsychotics [126].

These very promising results tend to confirm a role of epigenetic modulation in psychotropic drug-induced metabolic alterations. Further studies are needed to validate these findings, investigate other candidate regions and maybe discover new mechanisms.

Implication of gut microbiome in metabolic side effects of psychotropic drugs

An exponential increase in publication was seen in the past decade unravelling the link between the gut microbiome, human health and various diseases including obesity and CVD [127-130]. Dysbiosis of the gut microbiota composition, with an unusually high abundance of certain bacterial species, an imbalance in the relative levels of different species, or even the loss of beneficial bacteria, seems associated with a number of diseases. Mechanisms explaining the influence of gut microbiome on metabolism and weight control include the regulation of energy uptake from diet, the interaction with signaling molecules involved in host metabolism, the production of bioactive metabolites (such as short-chain fatty acids [SCFA]),

the interaction with the enteric nervous system and the vagus nerve, the increase of gut membrane permeability and the activation of inflammatory pathways [127, 128, 131, 132].

In conventional studies associations can be observed, but it is hard to elucidate whether weight gain causes a change in microbiota composition / diversity / richness or whether an altered microbiota favors an increased body weight. One remarkable study, led by Ridaura et al [133], was able to demonstrate the causal role of gut microbiota in metabolic dysregulation using human microbiota-associated rodents. They exploited this model to observe the metabolic effect of fecal microbiota sampled from twins discordant for obesity transplanted into recipient germ-free mice. One of the major difficulty in working with microbiota communities lies in its substantial variability between unrelated individuals. In twin donors, who share genetics and most environmental exposures, the source of variability is reduced and differences between gut bacteria can be attributed to disease state with more confidence. Through their study, they nicely showed that adiposity phenotype was transmissible, with the adipose mass increase following transplantation being greater in mice that received a co-twin's obese microbiota than in animals receiving the lean twin fecal sample.

Following this rising interest in the gut microbiota and its involvement in metabolism, scientists started to study its implication in psychotropic induced weight gain and metabolic dysregulations. Interestingly, Maier & al. [134] screened a large panel of human targeted drugs for inhibition of commensal bacterial strains in vitro and showed an important antibiotic activity of many antipsychotics. They observed a surprisingly high similarity in the species affected by these drugs, higher than expected from their chemical structures. Notably, they outlined that Akkermansia muciniphila, whose protective effect against obesity has been repeatedly demonstrated [135], was significantly more sensitive than all other screened strains to antipsychotics. This finding implies that antipsychotics may promote a dysbiosis that could contribute to the metabolic side effects shared across psychotropic drugs.

Evidence from rodent studies, restricted to the effect of olanzapine and risperidone, suggest that gut microbes are affected by antipsychotic treatment and further demonstrate that the

presence of micro-organisms is necessary for the occurrence of weight gain side effect [136, 137]. These studies have consistently shown an increased ratio of the Firmicutes / Bacteroidetes phyla secondary to the use of antipsychotics, which had also been associated with obesity [138]. Only few studies have been conducted in humans and the relationship between metabolic worsening and microbiota alterations after antipsychotic treatment is less clear [139]. The latest one to date has been performed in China by Yuan et al [140]. In this study, 41 first episode schizophrenia patients have been followed up for 24 weeks after they were started on risperidone treatment. The authors observed significant changes in both metabolism and microbiota and found that the copy numbers of fecal *Bifidobacterium* spp. increased with weight gain and BMI. Unfortunately, they focused their analysis on only 5 types of bacteria that had previously been associated with metabolic diseases and could not describe the modifications on the whole microbiota community.

Based on the current findings, Figure 4 summarizes the various routes of communication between gut microbiota and its host, which could be involved in psychotropic drug-induced metabolic side effects.

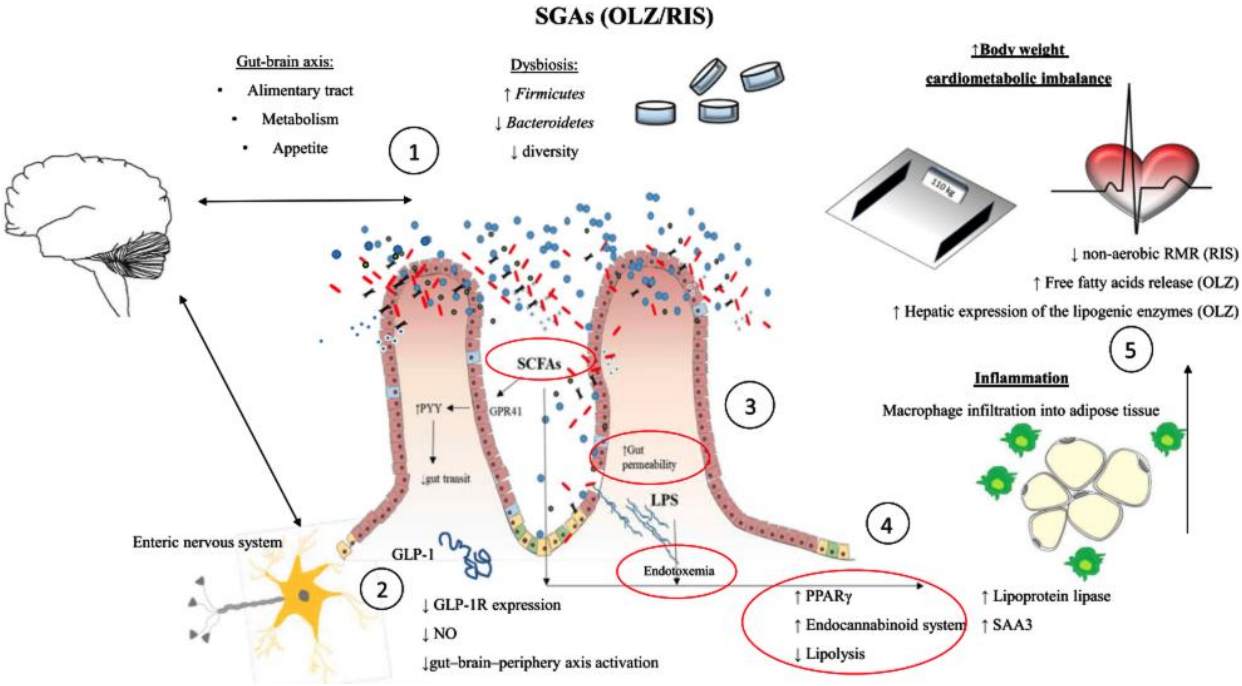

Figure 4. Possible mechanisms of metabolic disturbances secondary to antipsychotic treatment acting through the gut microbiota (adapted from: Skonieczna-Zydecka et al. Psychopharmacology 2018)

The effect of psychotropic drugs on microbiota could also explain the higher susceptibility to metabolic side-effects observed in young patients. Indeed, their microbiota was shown to be less diverse than adults' microbiota. The bacterial composition continuously evolves throughout childhood and adolescence and tends to stabilize when reaching adulthood [141, 142]. It is thus likely that young individuals have a gut microbiota which is more easily influenced and modulated by xenobiotics [141, 143].

Besides, when continuously exposed to psychotropic drugs, commensal bacteria might acquire resistance and the antibiotic-like effect may be attenuated in chronically treated patients [144].

Further research is warranted to better define which bacteria are affected by antipsychotics, to identify which change is beneficial and/or detrimental and confirm the implication of gut microbiota in metabolic adverse reactions. Characterization of each patients gut microbiota could help identifying patients at risk of side effects, and guide choice of medication. Besides, modulation of the gut microbiota using pre- and/or probiotics could be considered to prevent dysbiosis [145].

Brief summary of results

In the projects briefly presented below, I collaborated with PhD students, postdoctoral researchers, biostatisticians, clinicians and advanced researchers, under the supervision and with the support of my thesis director, Prof Chin Bin Eap. I participated in the study design elaboration and ethics approval process, in patients' recruitment and data collection. Through discussions, help and critical feedbacks, I was then able to prepare the databases, perform most of the analyses and, for the closed projects, write the articles' manuscripts. The first three projects have been completed and the articles full version is available in the appendix, while the three other ones are still in progress.

The results presented throughout this thesis were primarily based on data from participants included in PsyMetab and PsyClin studies. Briefly, PsyMetab is an ongoing observational cohort study, recruiting participants receiving psychotropic drugs known to induce weight gain, followed-up in Lausanne and Geneva, Switzerland. Consent is obtained for the use of clinical data collected as part of routine care, and for additional analyses performed on blood samples. PsyClin study aims at similar goals and benefits from clinical data collected between 2007 and 2015 in the Department of Psychiatry of the Lausanne University Hospital. Patients consent was not required because of the non-interventional post hoc analysis design of PsyClin. Both protocols were approved by the ethics committee of the canton of Vaud (CER-VD).

The different projects aimed at increasing awareness on the metabolic adverse effects of psychotropic treatments, and investigated specific risk factors associated with side effects. The results have been used in our department to educate clinicians on the importance of monitoring their patients' metabolic parameters and to promote approaches that include the least metabolic risk. I hope the clinical messages, conveyed through the articles, will reach a wide audience and will be used broadly to improve metabolic health care in psychiatry.

Completed projects

Project 1: Evaluation of cardiometabolic risk in a large psychiatric cohort and comparison with a population-based sample in Switzerland

Dubath C, Delacrétaz A, Glatard A, Vollenweider P, Preisig M, Richard-Lepouriel H, Hasler R, Gamma F, Solida A, Thonney J, Fassassi S, von Gunten A, Conus P, Eap CB

Published in the Journal of Clinical Psychiatry (2020); DOI: 10.4088/JCP.19m12796

In this project, we assessed the cardiometabolic health of patients under psychotropic treatments, included in PsyMetab and PsyClin studies (n=1216). The cardiovascular risks to develop a cardiovascular disease (Framingham risk score [FRS]) or die from a cardiovascular event (Systematic coronary risk estimation [SCORE]) were computed and the prevalence of MetS (International diabetes foundation [IDF], and adapted National Cholesterol Education Program's Adult Treatment Panel III [ATP]) was measured. These parameters were then compared in a cross-sectional analysis with those of a large population-based sample (CoLaus|PsyCoLaus cohort, n=6733). Estimated risks were relatively low and reached a similar level in the compared samples. Notably, 10.7% and 12.3% of the psychiatric and population-based sample, respectively, were at high risk (≥5%) of dying from a cardiovascular disease, while 0.1% and 0.9% were at high risk (≥20%) of experiencing a cardiovascular event. Nonetheless, MetS prevalence was higher in the psychiatric sample than in the population-based cohort, and this difference was more pronounced in younger individuals (aged 35-49 years), especially in women. MetS per IDF definition was indeed reported in 25.6% of them, whereas it was found in only 8.0% of women from the population-based sample. Interestingly, the proportion of these women who received appropriate medication to treat their metabolic condition was half as high in the psychiatric sample.

This project highlighted important differences in cardiometabolic health between psychiatric patients and individuals from the general population, appearing already at a young age.

Project 2: Socio-economic position as a moderator of cardiometabolic outcomes in patients receiving psychotropic treatment associated with weight gain: results from a prospective 12-month inception cohort study and a large population based cohort

Dubath C, Gholam-Rezaee M, Sjaarda J, Levier A, Saigi-Morgui N, Delacrétaz A, Glatard A, Panczak R, Correll CU, Solida A, Plessen KJ, von Gunten A, Kutalik Z, Conus P, Eap CB

Published in Translational Psychiatry (2021); DOI: 10.1038/s41398-021-01482-9

This project focused on the association of socio-economic status with cardiometabolic side effects in patients taking psychotropic drugs known to induce weight gain. Weight and metabolic parameters of patients included in PsyMetab and PsyClin studies were monitored over time. Socio-economic status was defined based on the Swiss socio-economic position (SSEP) index and integrated four neighbourhood-based parameters, namely: income, education, occupation and housing condition. Occurrence of metabolic side effects within 6 months following treatment initiation was found to be modulated by SSEP, whereby adult patients with lower status had a higher BMI, experienced more weight gain and had a more pronounced increase in waist circumference. Interestingly, after stratifying patients according to the potency of the prescribed psychotropic medication to induce weight gain, a greater effect was observed in patients on high risk therapy, with a difference in BMI between patients with low compared to high SSEP of 0.86 kg/m^2. Moreover, the risk of developing MetS (per IDF definition) one year after treatment start was three times higher in patients with low compared to high SSEP.

To validate these findings, cross-sectional data from a population-based sample were used (UKBiobank). An association between educational attainment (one of the four criteria included in the SSEP) and BMI was found, which was significantly stronger in participants receiving psychotropic medications with a high risk of weight gain. Benefitting from genetic data, a Mendelian randomization (MR) analysis was performed on participants using psychotropic drugs and confirmed a causal impact of education on BMI. Again, this causal effect was slightly more pronounced in patients being prescribed high metabolic risk psychotropic medications.

The results of this project showed that when patients are being prescribed psychotropic medications, socio-economic status is partly responsible for inequalities in metabolic side effects, and its influence seems to increase with the drug's propensity to induce weight gain.

Project 3: Effect of quetiapine, from low to high dose, on weight and metabolic traits: results from a prospective cohort study

Dubath C, Piras M, Gholam M, Laaboub N, Grosu C, Sentissi O, Gamma F, Solida A, von Gunten A, Conus P, Eap CB

Accepted in Pharmacopsychiatry (01.06.2021); DOI: 10.1055/a-1525-2820

This clinical project aimed to define whether the weight gain induced by quetiapine treatment is dose-dependent. Quetiapine is a second generation antipsychotic prescribed for various official and off-label indications. The dosage regimen varies accordingly and covers a range of 12.5 to >800 mg per day, higher doses than 800 mg/day being prescribed despite it is the highest authorized dose. Weight and metabolic parameters of patients included in PsyMetab and PsyClin cohorts who started a treatment with quetiapine were recorded over time.

Significant metabolic alterations were observed, even at low doses. Daily dose was slightly associated with weight gain, and higher dosages increased the risk of clinically relevant weight gain (>7% from baseline weight). Quetiapine dose was associated with a change in plasma levels of cholesterol as well as with increased odds of developing hypertriglyceridemia, total and low-density lipoprotein (LDL) hypercholesterolemia. No impact of a dose increase on plasma glucose level and blood pressure was found.

These findings emphasize the importance of looking for the minimal effective dose. However, the effect size of a dose increase on metabolic worsening seems low and thus the potential harm of low-dose quetiapine use should not be omitted.

On-going projects

Changes of DNA methylation following psychotropic drug treatment

Within the current study, we aimed to explore methylation modifications associated with metabolic alterations, using an EWAS hypothesis-free strategy while we also addressed the relationship between site or gene-specific DNA methylation patterns and metabolic side effects. Unlike previous studies that highlighted associations present in samples of patients at a given time, we wished to capture the effects of psychotropic drugs occurring with treatment onset and chose to follow a longitudinal design, analysing samples collected at treatment start and after one month of therapy. We then sought to investigate whether baseline methylation and changes of methylation were associated with increased weight and alterations of metabolic parameters.

This project is soon finished. All analyses have been performed and the first draft of the manuscript is in progress. The main results will be briefly presented here.

An EWAS was performed on a cohort of 78 psychiatric patients starting a psychotropic treatment with known metabolic side-effects (9 different molecules represented), using the Illumina Infinium Methylation EPIC BeadChip, which interrogates over than 850,000 methylation sites per sample at single-site nucleotide resolution. Half of the included patients gained ≥5% of their baseline weight during the first month of treatment (IQR: 5.8-10.9, considered as “cases”), while the other half had no or a slight weight gain (IQR: 0-1.4, considered as “controls”).

Globally, we found a significant hypermethylation between the 2 timepoints with a global methylation at T0 of 61.78% and 61.97% at T1 ($p<2.2*10^{-16}$), with the mean difference of methylation being larger in patients who did not gain weight ($p<2.2*10^{-16}$). More specifically, we found 52 probes that showed a significant methylation evolution after correcting for multiple testing ($p<5*10^{-8}$). When looking separately at cases and controls, we could identify 1

methylation site, cg12209987, which displayed a significant hypermethylation after one month of treatment in cases only ($p = 3.81*10^{-8}$). In multivariate analyses, correcting for baseline BMI, smoking status, sex, age, psychotropic treatment propensity to induce weight gain (ranked from 1 to 3) and the first three components of methylation data assessed by principal component analysis, the difference in methylation level at this site was still significantly associated with weight gain (p=0.004). This site is located upstream of the pseudogene PSMC1P5, which had already been associated with adiposity in GWAS studies [146, 147].

At the genome level, we searched for associations between weight gain and methylation, correcting for the same covariables listed above (EWAS) and obtained one significant result. Methylation level after one month of treatment at the CpG site cg06329892 revealed a positive association with weight gain ($p = 3.9*10^{-8}$). This methylation site is located on chromosome 10, downstream of the non-coding gene RP11.388P9.2.

For a subpart of the participants with available data, we repeated this analysis for blood metabolic parameters including changes in glucose level, triglycerides level and total, high density lipoprotein (HDL) and LDL cholesterol level (n=25, 39, 38, 38, 37, respectively). No probe reached genome wide significance level ($p > 5.9 \times 10^{-8}$ for all) for association with any of the metabolic traits analyzed.

We then tried to detect whether the most significant results from the EWAS could be causally related to metabolic disturbances, using data from the UKBiobank and running MR analyses. More precisely, we searched for meQTLs for the ten sites most associated with metabolic traits alterations, using data published by Bonder et al [148], to be used as instrumental variables. We identified 29 sites with meQTLs and among those, only 10 were associated with a minimum of 2 SNPs enabling to perform the MR analysis. These 10 CpG sites had been identified in the EWAS conducted on change of weight, waist circumference, triglyceride, glucose, HDL- and LDL-cholesterol levels. Thus, MR analyses were conducted on the according phenotype in the UKBiobank (n=350'000). Interestingly, baseline methylation level of one CpG site, namely cg11622362, which showed a negative association with plasma glucose level evolution in the psychiatric sample, was shown to be causally related to glucose level in the UKBiobank

(p=0.00015). This site is located downstream the APIP gene on chromosome 11. APIP gene was recently discovered to be implicated in cardio-protection against myocardial infarction [149], and it was also shown to play a key role in the methionine salvage pathway which is involved in inflammation among other biological functions [150].

We then carried out different hypothesis driven analyses:

First, we selected 315 methylation sites, based on the literature [117, 151, 152], that had been shown to be associated with either BMI, adiposity or other metabolic traits in the general population. We specifically looked at the association of methylation level at these sites with our metabolic data, but no result remained significant after correcting for multiple testing. Nevertheless, a trend of association between a decrease in LDL cholesterol plasma level during treatment and an increase in cg03649429 methylation level was observed (p_{corr} = 0.10). This methylation site, is located on COL4A3BP gene, upstream of the gene POLK, on chromosome 5, and had been shown to affect LDL-cholesterol plasma levels [117].

The second approach was based on the genetics of antipsychotic induced weight gain. We selected SNPs that were shown to be significantly associated with weight gain in a recent meta-analysis [94], and identified 48 loci whose methylation levels were related to 7 of these SNPs [148]. We examined the association of methylation at these sites with weight change in our data, but found no significant results.

We then followed a similar hypothesis and selected SNPs associated with BMI in the general population, identified through GWAS [153]. We found 466 CpG sites, whose methylation levels were associated with 88 of these SNPs [148]. The analysis of association between the methylation sites and metabolic parameters evolution in our cohort gave no significant results.

Alternatively, a MR approach combining SNPs from GWAS on BMI and expression quantitative traits loci (eQTLs) was applied to identify genes whose expression is associated with BMI [154]. CpGs sites located on / nearby those genes were then tested for association with weight change in our cohort. We obtained a trend for a negative association between weight gain and

baseline methylation level of cg01264379 (p_{corr} = 0.08), a site located downstream of ZC3H4 gene.

Eventually, the last strategy was based on in vitro evidence of the effect of psychotropic drugs on gene expression. For this, the Connectivity Map (CMap) catalog developed by the Broad Institute of MIT and Harvard was used [155]. Briefly, this database gives genome-wide genetic perturbation scores for more than 1300 FDA-approved small molecules on various cell-types. Genes were considered perturbed with a score > +/- 2. Focusing the analyses on adipose tissue, liver and central nervous system, clozapine, mirtazapine, quetiapine risperidone and valproate were found to affect the expression of 1039 genes. Methylation level of CpG sites located on / nearby 3 of these genes were significantly increased in the psychiatric sample after the treatment (ttest, $p < 5.9 \times 10^{-8}$), but no association with weight was revealed.

The various analyses that have been conducted on our methylation data gave insights into a putative causative effect of the treatment on methylation levels as a mechanism leading to metabolic dysregulations. To the best of our knowledge, we are the first study that looked at methylation data before and after the introduction of a psychotropic drug treatment on such a short period. The non-statistically significant results we obtained in certain analyses prevent us to conclude on the role of methylation variations. In future studies, a larger sample size may be required to provide greater statistical power and identify EWAS hits. It may also be useful to include a control psychiatric group, not taking psychotropic treatment, to capture the “normal” evolution of methylation patterns. In addition, the effect on methylation might differ from one medication to another. Thus, if future research is to attempt to replicate our results, the specific effect of each molecule should also be studied. Eventually, it could also be interesting to follow the evolution of the methylation profile using a third blood sample, in order to detect whether the observed changes remain stable over the course of treatment, continue to evolve in the same direction or return to baseline.

Clinical study on gut microbiota

The aim of this study is to explore how the gut microbiota is influenced by antipsychotics and evaluate whether the altered gut microbiota contributes to metabolic side effects. In- and out-patients were recruited in Lausanne University Hospital (CHUV), in Geneva University Hospital (HUG) and in a private psychiatric center in Lausanne (centre des Toises). Included patients underwent two visits: the first one at treatment initiation or discontinuation, and the second one after a period of one month. The longitudinal design should allow to capture any change following treatment modification (start or stop), as each patient represents his own “control”. Stool samples for microbiota analyses, blood samples for glucose and lipid levels measurements (and additional analyses) and urine for metabolomic analysis were collected at each visit as well as measures of weight, waist circumference, blood pressure, and information on demographic parameters and dietary habits. For a subpart of the cohort, an analysis of body composition (DEXA analysis) was performed. This exam allows the determination of the fat and lean body weight and gives the fat mass localization (visceral or not), giving a more accurate indication of cardio-vascular risk than BMI measure.

The inclusion of patients and collection of data has ended in December 2020. Stool samples for 51 patients have been collected at the two timepoints and metagenomic analyses, based on 16S rRNA, are ongoing. Final data should be available in automn 2021.

Fecal microbiota transplantation (FMT)

The clinical study evaluating the effect of antipsychotics on gut microbiota aims to establish whether an antipsychotic altered gut microbiota contributes to metabolic side effects. Observational studies suffer from unavoidable bias and even when every known parameter affecting metabolic traits is measured, it is difficult to delineate the effect of each isolated factor and establish the role of the gut microbiota. One strategy to overcome this limitation is to transplant human fecal microbiota into recipient germ-free mice.

Taking advantage of the longitudinal design of our cohort study, we are conducting FMT with patients’ samples collected at the time of antipsychotic treatment onset (T0-sample) and after

one month (T1-sample) into separate groups of recipient mice. Five participants who either underwent significant weight gain following treatment start or lost weight following treatment stop were selected as donors. Differences in body weight and metabolic phenotypes occurring 4 weeks post colonization are then compared between the two groups of mice. For this study, wild type germ-free C57BL/6 male mice are used. This strain represents a suitable model to reproduce susceptibility to antipsychotic-induced weight gain [137, 156] and also to study metabolic alterations linked to gut microbiota [133, 157, 158]. The project is performed in collaboration with Professor Hapfelmeier from the University of Bern. Germ free mice require an aseptic environment until colonization and a controlled one for the conduct of the study to ensure the maintenance of the transplanted microbiota. Professor Hapfelmeier's laboratory members are used to conducting such experiments and are equipped with the necessary infrastructure. Of note, another PhD student from our research group, with expertise and license in animal handling (Ms Marianna Piras) is also involved in this part of the study. The experiments are conducted with 12 mice in parallel who are randomly assigned to receive either the T0- or the T1-sample. The first experiment started mid-April 2021, and the following ones are still ongoing (expected end of experiments: autumn 2021). Figure 5 illustrates the experimental plan.

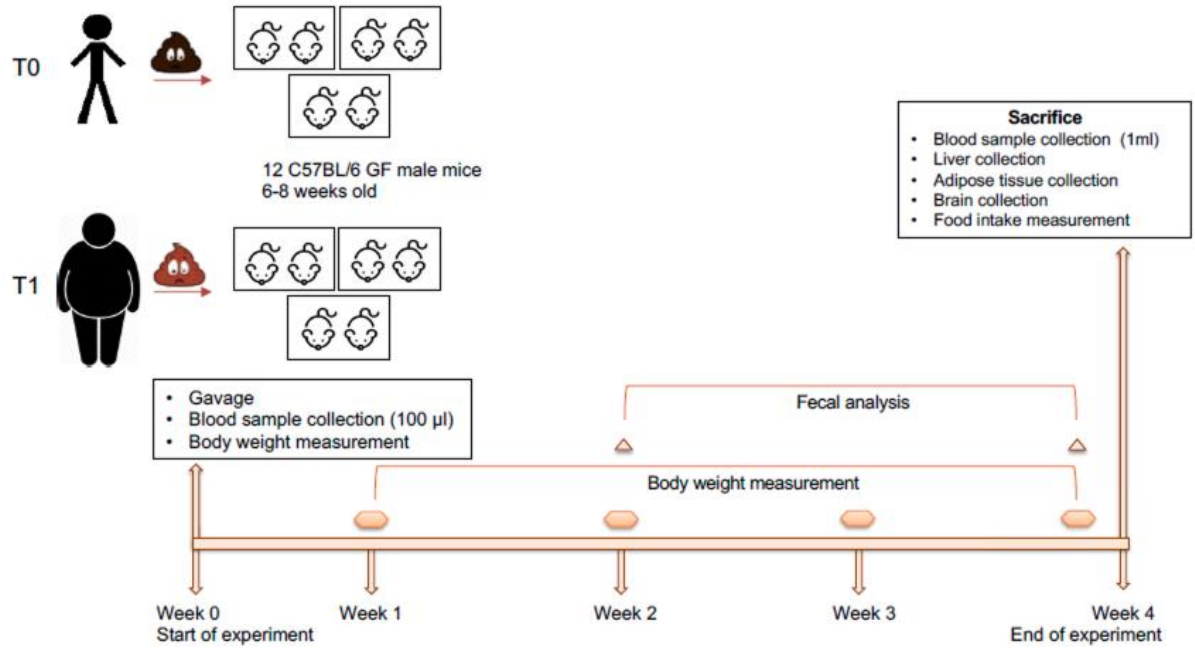

Figure 5. Study plan of FMT experiment

Fecal samples are collected from each mouse at week 2 and 4 post colonization to ensure good engraftment of the human microbiota. Mice are weighed every week and adipose tissues as well as blood samples are collected to measure metabolic parameters (glucose, cholesterol and triglycerides, and a panel of hormones / markers of inflammation) at the end of the experiment.

The strength of the current design lies in its use of fecal samples from the same donor collected at two time-points. Each human donor will represent his own control, reducing variability, with the comparative evaluation of the effect of fecal samples collected with or without treatment. Results from this study will help improve our understanding on the complex interplay leading to metabolic disorders in the psychiatric population. If the gut microbiota is involved, and if we can identify how, it would open a new area of possibilities to improve patients' outcome, targeting the gut microbiota.

Collaborations

I have been involved in the realization of other projects, all of which were performed using data of patients included in PsyMetab and PsyClin cohorts. For these projects, I have thus contributed to patients' inclusions, data acquisition and data quality management, discussions regarding working hypotheses and conducted analyses and eventually I shared comments and thoughts and provided support for the writing of the manuscripts. To date, 6 of these projects are already published, one has just been accepted for publication and others are still ongoing. The abstracts of the published and submitted articles are included at the end of the thesis, in the appendix.

Discussion

Severe mental illnesses are most often chronic, with a lifelong impact on patients. The burden of psychiatric diseases is further increased with the occurrence of cardiovascular problems, responsible for a worrying morbidity and mortality.

With the growing use of psychotropic drugs, prescribed at an increasingly younger age, awareness on medication-induced weight gain and metabolic abnormalities needs to be raised. Psychiatrists should better evaluate their patients' metabolic risks, as part of their routine assessments, and perform adequate follow-up over time. Although recommendations and guidelines have been published several years ago [12, 24, 159-161], suboptimal follow-ups are still documented [162-165], which is also in line with our personal observations in different settings and hospitals in Switzerland. The causes for the poor monitoring practices are likely a combination of patients and practitioner characteristics. There might be a lack of effective communication between mental health and primary care services in defining the responsibility of who should screen patients, probably accompanied by insufficient consideration of or resources dedicated to this aspect of health. Interestingly, patients already diagnosed with a metabolic disease were reported to be more often tested [165, 166]. Besides, regardless of the healthcare system, some patients might be reluctant to engage in care, partly due to their psychiatric symptoms, attend fewer appointments, and thus be less likely to undergo appropriate metabolic screening. It has precisely been shown that a low general functioning was associated with lower likelihood of blood testing [165].

In the first project included in this thesis, we could confirm a difference in metabolic health between psychiatric patients and people from the general population. The proportion of patients receiving appropriate care for their metabolic disturbances was low, highlighting the need for better screening and treatment. It must be mentioned that the population-based sample most likely included participants suffering from mental illnesses, which may have underestimated the differences between healthy subjects and psychiatric patients. The risks of a CVD event or death, estimated with Framingham and SCORE algorithms, were comparable between the two samples. The risk scores used in our study were chosen based on the most commonly and easy to compute available ones [167, 168]. However, a recent

work has shown that the algorithms developed to date, including the ones with psychiatric predictors (PRIMROSE or QRISK3), likely underestimated the risk in psychiatric populations, especially for young patients [169]. In our analysis, we have not been able to compare metabolic health between our psychiatric cohort and the general population for individuals younger than 35 years, as Colaus|PsyColaus study only recruited participants aged 35-75 years. Nonetheless, we have highlighted that the difference in metabolic health was particularly striking for younger participants, with an important proportion of psychiatric patients with metabolic syndrome. This indicates that metabolic health is already impacted at an early stage. The need for screening and metabolic health management is paramount and should start with the first signs of psychosis. Yet, the tools used to predict patients' risk, developed for the general population, are not informative for these patients.

Based on this observation, a research group recently developed a new algorithm (PsyMetRiC) to predict the occurrence of MetS in up to 6 years, specifically in young people with psychosis (aged 16 to 35 years) [170]. It would be very interesting to validate PsyMetRiC in our psychiatric cohort. Estimating patients' risk could influence psychiatrists' practice with respect to medication selection, lifestyle changes counseling and referral to dieticians. We could investigate in a pilot study whether its use at the time of prescription would improve patients' outcomes when compared to the standard of care.

For patients with available data, we could also update the model and evaluate whether including genetic risk scores or socio-economic variables would improve the accuracy of the prediction. Early increases in weight and plasma lipids (>5% after a 1-month treatment) could further be added to the model as these factors were shown to be good predictors of longer-term metabolic alterations [65, 68]. An important predictor included in their model is the prescription of an antipsychotic with a risk for weight gain. This improves the risk prediction of a first episode drug-naïve patient, but implies that it needs to be recalculated at each modification of treatment. Switching from one antipsychotic to another is quite frequent when patients are not responding to their treatment or when they experience important side effects [171]. In addition, medication adherence is also hard to ensure over the long term, especially

in first episode patients [172]. The authors who developed PsyMetRiC did not mention this issue nor did they precise whether the participants enrolled in their study were maintained on the same treatment over the years of follow-up. It would thus be a nice add-on to evaluate the performance of the algorithm selecting only patients who remained on their initial treatment for the entire duration between baseline measurement and final outcome evaluation, and compare the adequacy of predicted against observed risk selecting patients with baseline assessment and outcome measure, with no information on medication history in between.

In the second project included in this thesis, we have been able to demonstrate that patients' socio-economic status impacts their propensity to gain weight. This observation outlines the importance of modifiable risk factors, and points to new avenues of intervention. Not only psychiatrists should provide closer follow-ups for these patients and insist on lifestyle habits, but policy makers should also address and manage this issue of social inequity.

As mentioned earlier, the integration of individuals socio-economic attributes should be included in risk prediction algorithms to better identify patients with the highest risk profile. It was already shown that socio-economic status was a moderator of treatment effectiveness, indicating the need to account for this factor in future studies [173]. Based on our findings, we believe it should also be added as a covariate in the various studies investigating new risk factors for psychotropic-induced metabolic side effects.

The SSEP used in our study is an index developed with data collected in 2000. Although the spatial repartition of neighborhood socio-economic level has shown to be relatively stable over time in the city of Lausanne [174], the validity of the SSEP might be decreasing. Alternatively, individual socio-economic factors might be used as proxies of the global SSEP, such as income, occupation or educational attainment as we did in our study. This would have the advantage of enabling the inclusion of homeless participants or those living in psycho-social institutions. Individual data might however be harder to gather, and studies may be subject to much more missing data (in our study, we could indeed only include 119 participants in the adult population using educational attainment, against 526 using the SSEP) [175]. Besides,

the indices based on geographic areas have generally a greater effect on health over individual characteristics [176]. This might explain the non-statistically significant effect of educational attainment on BMI in our study, not to mention the loss of power. There is therefore a need to validate the index with new data or to update it and build a new version. Dr Radek Panczak, who was involved in the development of the SSEP, is precisely working on these improvements, and an article presenting these results should be soon published.

In the last project included in this study, we aimed to address a recurrent clinical question: when patients treated with quetiapine gain weight, would a reduction of the dose avoid further worsening? Or, is it safe to prescribe quetiapine at low doses to treat insomnia or anxiety? The answer to this question is not straightforward, as conflicting results have been reported. We observed a statistically significant effect of a dose increase on metabolic parameters change indicating that patients prescribed lower dosages are less likely to develop side effects. However, the magnitude of this effect being small, we can state that low doses of quetiapine still display a non-negligible risk. Based on these data, dose lowering is not recommended as a strategy to counter weight gain. To date, lifestyle interventions, switching medication to agents with relatively neutral effect on weight and, when these options have not proven effective or are not feasible, addition of metformin or another drug to counteract weight gain and metabolic adversities would instead be recommended [177, 178].

The present findings confirmed previous works that reported the detrimental effect of low doses of quetiapine [179, 180]. However, a recent study comparing low dose quetiapine users to antidepressant users (selective serotonin reuptake inhibitors – SSRI) in a cohort of >800'000 participants found no difference in the incidence of T_2D [181]. The incidence rates in both groups were nevertheless higher than among the general population. The authors of this study conclude that the increased risk of T_2D may either result from an equivalent risk conveyed by SSRI and quetiapine low-doses or be caused by the psychiatric illness itself, rather than being induced by medication. This outlines the difficulty of choosing an appropriate and informative control group for such studies as SSRIs have been reported to increase the risk of T_2D, but

with conflicting results [182, 183]. The authors support the second hypothesis by citing the high prevalence of T_2D in patients with depression, regardless of medication. Nevertheless, the off-label use of low-dose quetiapine, such as in anxiety or insomnia, has also been frequently associated with increased risk of T_2D and CVD [184-187]. In our study, we could not highlight a dose effect of quetiapine on glucose plasma levels, nor on the odds ratio of hyperglycemia onset, suggesting an equivalent risk no matter the dose. We however focused only on the first 3 months of treatment, which is too short to assess the onset of T_2D. If we had had the follow-up data for a longer period, we might have observed a dose effect. In addition, we have not included any control group, as we could not find an appropriate one, with the same characteristics as our sample who started a treatment with quetiapine. An alternative, applied in a recent study, would have been to collect biological measures up to 3 months before the start of the treatment [188]. In this analysis, a stable or even declining body weight before the introduction of antipsychotics was nicely shown, followed by a rapid increase in the first 6 weeks of treatment, which then stabilized or continued to increase slightly.

More studies are thus needed to delineate the effect of the drug from the effect of the disease and be able to conclude whether the metabolic worsening observed with low doses results from the natural history of the disease or is drug-induced. Nonetheless, metabolic monitoring should be performed no matter the dose, as we observed notable worsening of the measured parameters. Non-medicinal approaches should be preferred for insomnia or anxiety management and, when this is not possible, the choice of a drug should be based on the molecule with the most favorable profile.

Eventually, the three projects that are still ongoing are digging deeper into the mechanisms of psychotropic drug-induced weight gain. Effects on DNA methylation and gut microbiota are still largely unknown and these projects, benefitting from longitudinal designs, are very promising.

The findings presented throughout this thesis need to be interpreted in light of certain limitations. First, a mix of first episode drug-naïve and chronic patients were included in the three projects. Very little information was available on this characteristic and it was difficult to identify if the treatment for which a patient was followed-up in the presented studies was the first prescribed treatment or the second, third, or the umpteenth treatment received. Medical history influences the metabolic side effects that patients are likely to experience, with drug-naïve patients being much more vulnerable [189]. There is a great value in conducting studies that include both patient profiles and do not limit investigations to a single population; however, additional efforts should be made to record and account for prior treatments patients received before entering a study. This element is also essential in the clinical context, where a good knowledge of previous treatments, their efficacy or the side effects experienced, will guide future prescription choices. Better monitoring of previous treatments will thus benefit research and have a direct impact on clinical care. Second, lifestyle habits were not measured and thus no information regarding diet, physical exercise or sleep quality could be integrated into our models. We also did not have access to information on potential interventions to counteract metabolic side effects. Since interventions on lifestyle are one of the first strategies to minimize the development of metabolic disorders, some patients may have received advice and implemented certain changes without our knowledge. For a long time, collecting this data was complicated, but digitalization has greatly improved the accuracy and precision of lifestyle measurements. While objective measures, such as the number of daily steps, can be now easily recorded, electronic questionnaires may also be less subject to social desirability bias than those completed with a medical staff member. Future studies should attempt to incorporate the use of mobile apps for the purpose of collecting lifestyle data and could also serve as a tool for health interventions [190-192].

In spite of these limitations, the major strength of our investigations lies in the representativeness of the psychiatric population. Because data used in the different projects were collected as part of routine clinical care, participation in the studies was not demanding for patients. Projects aiming to include many more variables (data-intensive studies) are

generally less well received by patients, who more easily refuse to participate. Such studies suffer from unavoidable bias where the most severely ill patients are not represented. Thus, in the three projects presented, a great number of patients, with various diagnoses and psychotropic treatments were included in a naturalistic study design, enabling to strengthen the clinical validity of the findings. Many observational studies, as the first one included in this thesis, report associations based on cross-sectional data comparing a psychiatric with a control population. In the two last projects, the longitudinal designs with multiple metabolic parameters monitored regularly over the time were key to respond to the issues raised. The difficulty of following psychiatric patients and gathering their data over time in hospital and ambulatory settings makes these studies valuable.

To conclude, intense research into psychotropic induced weight gain and metabolic disturbances is ongoing. Findings reported to date help guiding prescriptions but the road to personalized medicine is still long. More work needs to be done to support implementation of metabolic monitoring. More generally, psychiatrists should consider metabolic side effects when prescribing antipsychotics, mood stabilizers and antidepressants, give thorough information and prescribe lifestyle changes referring their patients to dieticians, and / or physiotherapists, with a special focus on patients most at risk. Future research will hopefully improve the identification of these patients through a better characterization of risk factors and integration of the use of genetic, epigenetic and microbiological data. Prevention is paramount, since in the case of weight gain or other metabolic disorders, strategies for reversing side effects or at least minimizing further worsening are limited. The range of options will certainly be expanded in the future, with the development of targeted microbiota modulations, for example, or with hormonal cues to reduce food craving and restore satiety feeling, or with other as yet unknown approaches that upcoming research will reveal.

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Appendix

Project 1: Evaluation of cardiometabolic risk in a large psychiatric cohort and comparison with a population-based sample in Switzerland

Dubath C, Delacrétaz A, Glatard A, Vollenweider P, Preisig M, Richard-Lepouriel H, Hasler R, Gamma F, Solida A, Thonney J, Fassassi S, von Gunten A, Conus P, Eap CB

Published in the Journal of Clinical Psychiatry (2020); DOI: 10.4088/JCP.19m12796

Original Research

Evaluation of Cardiometabolic Risk in a Large Psychiatric Cohort and Comparison With a Population-Based Sample in Switzerland

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ABSTRACT

Background: Psychiatric patients are known to be at high risk of developing cardiovascular diseases (CVDs), leading to an increased mortality rate.

Objective: To assess the CVD risk (presence of metabolic syndrome [MetS] and calculated 10-year CVD risk) in a Swiss psychiatric cohort taking weight gain–inducing psychotropic drugs, compare the findings to a Swiss population-based cohort, and evaluate the prevalence of participants treated for metabolic disruptions in both cohorts.

Methods: Data for 1,216 psychiatric patients (of whom 634 were aged 35–75 years) were obtained between 2007 and 2017 from a study with metabolic parameters monitored during psychotropic treatment and between 2003 and 2006 for 6,733 participants from the population-based CoLaus|PsyCoLaus study.

Results: MetS as defined by the International Diabetes Federation (IDF) was identified in 33% of the psychiatric participants and 24.7% of the population-based subjects. Specifically, prevalence per the IDF definition was more than 3 times higher in the psychiatric cohort among women aged 35 to 49 years (25.6% vs 8.0%; $P < 10^{-4}$). The psychiatric and population-based cohorts, respectively, had comparable predicted CVD risk (10-year risk of CVD event > 20%: 0% vs 0.1% in women and 0.3% vs 1.8% [$P = .01$] in men; 10-year risk of CVD death > 5%: 8.5% vs 8.4% [$P = .58$] in women and 13.4% vs 16.6% [$P = .42$] in men). No difference was observed among the proportion of participants with MetS treated for metabolic disturbances in the two cohorts, with the exception of women aged 35–49 years, for whom those in the psychiatric cohort were half as likely to receive treatment compared to participants in CoLaus|PsyCoLaus (17.8% vs 38.8% per the IDF definition; $P = .0004$).

Conclusions: These findings emphasize the concern that psychiatric patients present an altered metabolic profile and that they do not receive adequate treatment for metabolic disruptions. Presence of metabolic disturbances should be routinely assessed, and adequate follow-up is needed to intervene early after illness onset.

J Clin Psychiatry 2020;81(3):19m12796

To cite: Dubath C, Delacrétaz A, Glatard A, et al. Evaluation of cardiometabolic risk in a large psychiatric cohort and comparison with a population-based sample in Switzerland. *J Clin Psychiatry.* 2020;81(3):19m12796.

To share: https://doi.org/10.4088/JCP.19m12796

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People with mental disorders have a high morbidity and mortality rate with a reduced life expectancy compared to the general population.[1] Studies diverge on the estimated mortality gap; however, a recent review[1] of 22 studies reported a median of 10 years' reduced life expectancy, with evidence that this difference is increasing over time. Although suicides are one main concern in this population, natural causes account for approximatively two-thirds of these premature deaths. Indeed, people with mental disorders tend to have adverse health behaviors, including tobacco and substance use, physical inactivity, and unhealthy diets. In addition, they often have poor access to appropriate care and develop chronic diseases, mainly cardiovascular diseases (CVDs). Furthermore, patients treated with psychotropic drugs, including atypical and conventional antipsychotics, mood stabilizers (eg, valproate and lithium), and antidepressants (eg, mirtazapine), are exposed to metabolic side effects, increasing their risk of developing CVD.[2–5] Unfortunately, preventive strategies remain a low priority for psychiatric patients among clinicians, and a large majority of psychiatric patients are not treated for their metabolic conditions.[6–9]

In the general population, CVD is among the leading causes of death worldwide.[10] Many scoring systems have been developed to evaluate CVD risk. The Framingham Risk Score (FRS), which gives an estimation of the 10-year risk of a CVD event, is widely used[11–13] but does not adequately predict CVD risk when applied to populations with lower CVD incidence. In Europe, the Systematic Coronary Risk Estimation (SCORE),[14] proposed by the European Society of Cardiology, is preferred as it is based on European epidemiologic studies. This score provides an estimate of the 10-year risk of fatal CVD and is recommended to help clinicians evaluate their patients' risks and make decisions on which treatment strategy

Clinical Points

- Cardiometabolic health is a great concern in psychiatric patients, especially those initiating a psychotropic treatment known to induce metabolic side effects.
- Prevalence of metabolic syndrome is much higher in psychiatric patients than in the general population, with marked differences highlighted already in young patients.
- Careful monitoring of metabolic profile is warranted in psychiatric patients, as is supporting these patients in engaging in weight control strategies.

to adopt.[15] These two risk scores have been calibrated for the Swiss population, using national CVD death rate and an estimation of the number of events based on the Vaud-Fribourg MONICA study.[16] Validation of these calibrated scores in the CoLaus study in the Lausanne area has shown them to be strong predictors of CVD events[17] and CVD deaths,[18] respectively.

CVD risk can also be estimated by assessing for the presence of metabolic syndrome (MetS).[19] MetS is defined by the combined presence of metabolic disorders such as central obesity (ie, according to high waist circumference), raised triglycerides, reduced high-density lipoprotein (HDL) cholesterol, raised blood pressure, and/or raised fasting glycemia. Although the precise definition has been a matter of debate, this clustering is associated with the risk of developing CVD and type 2 diabetes.[20,21] MetS is more predictive of CVD events than the sum of isolated risk factors and is thus widely used as an early diagnostic tool to help decision making regarding treatment interventions.[22,23]

The psychiatric population is well known to be at higher risk of CVD compared to the general population; however, these differences are poorly understood and not well characterized. The first aim of the present study was to compare the prevalence of MetS between a Swiss cohort treated with weight-gain–inducing psychotropic drugs and a population-based sample. In addition to the presence of MetS, the CVD risk was further quantified using the FRS and SCORE, calibrated for the Swiss population. Additionally, this study sought to evaluate the proportion of patients receiving treatments for their metabolic disturbances (antihypertensive, lipid-lowering, or antidiabetic drug prescription) and assess whether it differed from that in the population-based sample.

METHODS

Study Design

An observational prospective study has been ongoing since 2007 in the Department of Psychiatry of the Lausanne University Hospital, in the Department of Psychiatry of the Geneva University Hospital, and in a private mental health care center (Les Toises; Lausanne, Switzerland), focusing on side effects of psychotropic treatments, approved by the Ethic Committee of the Canton of Vaud (CER-VD). This large study benefits from data and blood samples collected from 2007 to 2017 during routine clinical visits of patients who gave their informed consent. Because of the non-interventional post hoc analysis study design, the Ethic Committee approved the use of clinical data of followed-up patients from 2007 to end of 2015 in the Department of Psychiatry of the Lausanne University Hospital without informed consent.

Only cross-sectional data were used in the present research. The inclusion criterion for the study was the prescription of a psychotropic treatment known to display metabolic side effects, and both inpatients and outpatients not differentiating for early psychosis and chronically ill patients were considered (see Supplementary Appendix 1 for more information). Included patients, who constitute psychiatric sample 1, are noted in Supplementary Figure 1. The presence of MetS was assessed using two of the most commonly used definitions: the International Diabetes Federation (IDF) and the adapted National Cholesterol Education Program's Adult Treatment Panel III (ATP) definitions (Supplementary Table 3).[24,25] The CVD risk was further quantified using the FRS and SCORE, calibrated for the Swiss population.[17,18]

To compare our psychiatric sample with the general population, we used data from the CoLaus|PsyCoLaus study. This study is population-based and included participants aged 35 to 75 years living in Lausanne, Switzerland. Briefly, the CoLaus|PsyCoLaus study assessed cardiovascular risk factors and diseases and collected various genetic variants and biomarkers. The baseline recruitment and medical assessment of the CoLaus|PsyCoLaus sample, which was completed between 2003 and 2006, has already been described in detail.[26] As our psychiatric sample included patients aged 12 to 96 years, we selected a subsample aged 35 to 75 years (psychiatric sample 2) for comparison with the population-based sample (see Supplementary Figure 1).

Statistical Analysis

Descriptive statistics including frequencies and percentages for the categorical variables and median and interquartile range (IQR) for the continuous variables were calculated. Associations of CVD risk scores and MetS with clinical characteristics (age, sex, smoking status, illness duration, diagnosis, and psychotropic medication) were tested using linear and logistic regression models, respectively (see Supplementary Appendix 1 for more information).

Differences between men and women in the psychiatric sample were tested for significance using Pearson χ^2 tests for categorical variables and Wilcoxon Mann-Whitney rank sum tests for continuous variables. For the comparison with the population-based sample, weighted t tests were conducted to account for age difference. The analyses were conducted for both men and women separately and were also stratified by age.

Statistical significance was determined by a P value $\leq .05$. Statistical analyses were performed using Stata 14

Table 1. Demographic and Clinical Characteristics, including Prevalence of Metabolic Syndrome and Quantification of the 10-Year Cardiovascular Disease Risk, in Psychiatric Sample 1 (aged 12–96 years)[a]

Characteristic	Women	Men	Total	*P* Value[b]
Sample size, n (%)	626 (51.5)	590 (48.5)	1,216	
Age, median (IQR), y	45 (32–63)	35 (26–51)	41 (28–56)	**$<10^{-4}$**
Smoker, n (%)	271 (43.3)	377 (63.9)	648 (53.3)	**$<10^{-4}$**
Diagnosis,[c] n (%)				
Psychotic disorders (F20–F24; F28–F29)	113 (18.1)	194 (32.9)	307 (25.3)	**$<10^{-4}$**
Schizoaffective disorders (F25)	40 (6.4)	34 (5.8)	74 (6.1)	.65
Bipolar disorders (F30–F31)	85 (13.6)	71 (12.0)	156 (12.8)	.42
Depressive disorders (F32–F33)	115 (18.4)	49 (8.3)	164 (13.5)	**$<10^{-4}$**
Other	79 (12.6)	51 (8.6)	130 (10.7)	**.03**
Not available	194 (31.0)	191 (32.4)	385 (31.7)	.60
Psychotropic medication,[d] n (%)				
Low risk	112 (17.9)	131 (22.2)	243 (20.0)	.06
Medium risk	386 (61.7)	328 (55.6)	714 (58.7)	**.03**
High risk	128 (20.4)	131 (22.2)	259 (21.3)	.46
BMI, median (IQR), kg/m^2	24 (21–29)	25 (22–28)	25 (21–28)	.13
Waist circumference, median (IQR), cm	88 (78–98)	93 (84–104)	90 (81–101)	**$<10^{-4}$**
A. Central obesity prevalence (IDF), n (%)[e,f]	434 (69.4)	275 (46.8)	709 (58.5)	**$<10^{-4}$**
B. Central obesity prevalence (ATP), n(%)[e,f]	315 (50.6)	170 (29.0)	485 (40.1)	**$<10^{-4}$**
Systolic blood pressure, median (IQR), mm Hg	120 (110–130)	124 (115–136)	120 (110–132)	**$<10^{-4}$**
Diastolic blood pressure, median (IQR), mm Hg	76 (69–85)	80 (70–86)	78 (70–85)	**10^{-4}**
C. Hypertension prevalence, n (%)[e]	153 (24.4)	172 (29.2)	325 (26.7)	.06
Plasma cholesterol				
Total, median (IQR), mmol/L	5 (4.3–5.7)	4.7 (3.9–5.5)	4.8 (4.1–5.6)	**$<10^{-4}$**
LDL, median (IQR), mmol/L	2.9 (2.2–3.5)	2.7 (2.1–3.4)	2.8 (2.1–3.5)	**.004**
HDL, median (IQR), mmol/L	1.5 (1.2–1.7)	1.2 (1.0–1.5)	1.3 (1.1–1.6)	**$<10^{-4}$**
D. HDL hypocholesterolemia prevalence, n (%)[e,f]	209 (33.4)	194 (32.9)	403 (33.2)	.84
Plasma triglycerides, median (IQR), mmol/L	1.1 (0.8–1.6)	1.2 (0.9–1.9)	1.2 (0.9–1.7)	**.0004**
E. Hypertriglyceridemia prevalence, n (%)[e,f]	162 (26.0)	197 (33.4)	359 (29.6)	**.004**
Fasting plasma glucose, median (IQR), mmol/L	5.1 (4.7–5.5)	5.1 (4.7–5.6)	5.1 (4.7–5.5)	.09
F. Raised fasting plasma glucose prevalence, n (%)[e,f]	156 (25.2)	153 (26.0)	309 (25.6)	.73
MetS (IDF) prevalence, n (%)	164 (26.3)	138 (23.4)	302 (24.9)	.24
MetS (ATP) prevalence, n (%)	147 (23.7)	135 (22.9)	282 (23.3)	.76

[a]Clinical characteristics of patients were measured at their first visit, which was at baseline for 48% of the sample, month 1 for 21%, month 2 for 3%, month 3 for 19%, and month 5 or later for the rest of the sample.
[b]Statistical significance for differences between men and women was tested using the Wilcoxon Mann-Whitney test for continuous variables and Pearson χ^2 test for categorical variables. *P* values in bold are significant (≤.05).
[c]Diagnoses were based on *ICD-10* classification. Organic disorders, anxiety, personality disorder, and mental retardation were classified together as "other."
[d]Psychotropic medications were classified according to the risk of weight gain as follows: low risk: haloperidol, pipamperone, flupentixol, asenapine, amisulpride, aripiprazole, and lurasidone; medium risk: zuclopenthixol, levomepromazine, paliperidone, risperidone, quetiapine, lithium, and mirtazapine; high risk: valproate, olanzapine, and clozapine.
[e]Thresholds for metabolic abnormalities: A. waist circumference: men, ≥ 94 cm; women, ≥ 80 cm and/or BMI > 30 kg/m^2; B. waist circumference: men, ≥ 102 cm; women, ≥ 88 cm; C. blood pressure ≥ 130/85 mm Hg or treatment for hypertension; D. HDL hypocholesterolemia: men, ≤ 1.03 mmol/L; women, ≤ 1.29 mmol/L or lipid-lowering treatment; E. triglycerides ≥ 1.7 mmol/L or lipid-lowering treatment; F. glucose ≥ 5.6 mmol/L or type 2 diabetes treatment.
[f]The total n value used in the calculations of percentages for the following variables differs from the values listed for overall sample size due to missing data: A. central obesity (IDF): n = 1,212; B. central obesity (ATP): n = 1,210; D. HDL hypocholesterolemia: n = 1,204; E. hypocholesterolemia: n = 1,214; F. increased fasting plasma glucose: n = 1,204; MetS (IDF): n = 1,212; MetS (ATP): n = 1,210.
Abbreviations: ATP = National Cholesterol Education Program Adult Treatment Panel III, BMI = body mass index, HDL = high-density lipoprotein, IDF = International Diabetes Federation, IQR = interquartile range, LDL = low-density lipoprotein, MetS = metabolic syndrome.

(StataCorp; College Station, Texas) and RStudio version 0.99.879 (RStudio, Inc; Boston, Massachusetts).

RESULTS

Table 1 displays demographic and clinical characteristics of psychiatric sample 1, which includes 1,216 patients. Male patients represented 48.5% of the sample and were significantly younger than female patients. Most of the measured variables showed significant differences between men and women, justifying the stratification by sex. For instance, 43.3% of women and 63.9% of men ($P<10^{-4}$) were smokers. The most commonly prescribed medications were those classified as having a medium potential to induce weight gain; these medications were prescribed to 58.7% of participants.

Central obesity represented the most prevalent metabolic risk factor, as it was present in 69.4% and 46.8% of women and men, respectively, per the IDF definition and in 50.6% and 29.0%, respectively, per the ATP definition ($P<10^{-4}$ for both). Median blood pressure was 120/78 mm Hg (IQR, 110–132/70–85), with men presenting with slightly higher values than women ($P<10^{-4}$), although only a trend was found when comparing hypertension prevalence

Table 2. Clinical Variables and Prevalence of Metabolic Syndrome in Psychiatric Sample 2 and Comparison With the Population-Based Sample (aged 35–75 years)

Variable	Women-Psy	Women-Gpop	*P* Value[a]	Men-Psy	Men-Gpop	*P* Value[a]	Total-Psy	Total-Gpop
Sample size, n (%)	351 (55.4)	3,544 (52.6)		283 (44.6)	3,189 (47.4)		634	6,733
Age, median (IQR), y	49 (43–61)	52 (44–62)	**.02**	49 (41–58)	51 (43–61)	**.002**	49 (42–60)	52 (44–61)
Smoker, n (%)	171 (48.7)	880 (24.8)	**$<10^{-4}$**	171 (60.4)	932 (29.3)	**$<10^{-4}$**	342 (53.9)	1,812 (26.9)
BMI, median (IQR), kg/m^2	25 (22–29)	24 (22-28)	**.004**	26 (23–29)	26 (24–29)	.48	26 (22–29)	25 (23–28)
Waist circumference, median (IQR), cm	90 (81–100)	81 (74–91)	**$<10^{-4}$**	98 (90–107)	95 (88–102)	**.0006**	94 (85–105)	89 (79–98)
A. Central obesity prevalence (IDF), n (%)[b]	265 (75.7)	1,974 (55.7)	**$<10^{-4}$**	166 (59.1)	1,734 (54.4)	.84	431 (68.3)	3,708 (55.1)
B. Central obesity prevalence (ATP), n (%)[b]	199 (56.9)	1152 (32.5)	**$<10^{-4}$**	112 (39.9)	823 (25.8)	**.0006**	311 (49.3)	1975 (29.3)
Systolic blood pressure, median (IQR), mm Hg	120 (110–130)	122 (112–135)	.17	125 (116–138)	130 (120–142)	**$<10^{-4}$**	123 (112–135)	126 (116–139)
Diastolic blood pressure, median (IQR), mm Hg	80 (70–88)	77 (70–84)	**.03**	80 (75–90)	81 (74–88)	.75	80 (71-89)	79 (72–86)
C. Hypertension prevalence, n (%)[b]	97 (27.6)	1,069 (30.2)	.79	106 (37.5)	1,354 (42.5)	**.03**	203 (32.0)	2,423 (36.0)
Treated for hypertension, n (%)[c]	44 (45.4)	660 (61.7)	.07	42 (39.6)	689 (50.9)	.61	86 (42.4)	1,349 (55.7)
Total plasma cholesterol, median (IQR), mmol/L	5.2 (4.5–6)	5.5 (4.9–6.3)	**$<10^{-4}$**	4.9 (4.2–5.7)	5.5 (4.8–6.2)	**$<10^{-4}$**	5.1 (4.4–5.9)	5.5 (4.9–6.2)
Plasma HDL cholesterol, median (IQR), mmol/L	1.5 (1.2–1.8)	1.8 (1.5–2.1)	**$<10^{-4}$**	1.2 (1–1.5)	1.4 (1.2–1.6)	**$<10^{-4}$**	1.4 (1.1–1.7)	1.6 (1.3–1.9)
D. Hypocholesterolemia prevalence, n (%)[b]	114 (32.6)	308 (8.7)	**$<10^{-4}$**	95 (33.6)	394 (12.4)	**$<10^{-4}$**	209 (33.0)	702 (10.4)
Plasma triglycerides, median (IQR), mmol/L	1.2 (0.9–1.7)	1 (0.7–1.4)	**$<10^{-4}$**	1.4 (1–2.1)	1.3 (0.9–1.9)	.81	1.3 (0.9–1.9)	1.1 (0.8–1.6)
E. Hypertriglyceridemia prevalence, n (%)[b]	105 (29.9)	576 (16.3)	**$<10^{-4}$**	121 (42.9)	1,096 (34.4)	**.02**	226 (35.7)	1,672 (24.9)
Treated for hypertriglyceridemia, n (%)[c]	24 (22.9)	26 (4.8)	**$<10^{-4}$**	25 (20.7)	23 (2.3)	**$<10^{-4}$**	49 (21.7)	49 (3.2)
Fasting plasma glucose, median (IQR), mmol/L	5.2 (4.7–5.7)	5.2 (4.9–5.6)	**.047**	5.3 (4.9–5.9)	5.5 (5.2–6)	.30	5.2 (4.8–5.8)	5.4 (5–5.8)
F. Raised fasting plasma glucose prevalence, n (%)[b]	109 (31.2)	931 (26.3)	**.0005**	104 (36.9)	1,596 (50.1)	**$<10^{-4}$**	213 (33.8)	2,527 (37.5)
Diabetes prevalence,[d] n (%)	31 (8.8)	142 (4.0)	**.002**	31 (11.0)	294 (9.2)	.36	62 (9.8)	436 (6.5)
Treated for diabetes, n (%)[c]	17 (54.8)	92 (64.8)	.46	17 (54.8)	183 (62.2)	.64	34 (54.8)	275 (63.1)
MetS (IDF) prevalence, n (%)	110 (31.6)	636 (18.0)	**$<10^{-4}$**	98 (34.8)	1,025 (32.1)	.97	207 (33.0)	1,661 (24.7)
Treated,[e] n (%) [c]	46 (42.6)	370 (58.5)	.21	39 (39.4)	472 (46.1)	.96	85 (41.1)	842 (50.9)
MetS (ATP) prevalence, n (%)	97 (27.9)	530 (15.0)	**$<10^{-4}$**	93 (33.0)	829 (26.0)	**.04**	190 (30.2)	1,359 (20.2)
Treated,[e] n (%) [c]	44 (45.8)	323 (61.6)	.07	36 (40.9)	413 (49.9)	.99	80 (43.5)	736 (54.5)

[a]Statistical significance for difference between the psychiatric and population-based samples was tested using a weighted statistic according to participants' age (2-sample weighted *t* test), except for the age distribution, for which a standard *t* test was used. *P* values in bold are significant (≤ .05).
[b]Thresholds for metabolic abnormalities: A. waist circumference: men, ≥ 94 cm; women. ≥ 80 cm and/or BMI > 30 kg/m^2; B. waist circumference: men, ≥ 102 cm; women, ≥ 88 cm; C. blood pressure ≥ 130/85 mm Hg or treatment for hypertension; D. HDL cholesterol: men, ≤ 1.03 mmol/L; women, ≤ 1.29 mmol/L or lipid-lowering treatment; E. triglycerides ≥ 1.7 mmol/L or lipid-lowering treatment; F. glucose ≥ 5.6 mmol/L or type 2 diabetes treatment.
[c]Percentages are calculated as number of treated patients over number of patients with disease.
[d]Diabetes was defined as glucose > 7 mmol/L or type 2 diabetes treatment.
[e]Treated: prevalence of any CVD medication intervention among MetS participants (ie, antihypertensive, lipid-lowering, or antidiabetic drug prescription).
Abbreviations: ATP = National Cholesterol Education Program Adult Treatment Panel III, BMI = body mass index, CVD = cardiovascular disease, Gpop = population-based sample, IDF = International Diabetes Federation, IQR = interquartile range, MetS = metabolic syndrome, Psy = psychiatric sample.

(29.2% vs 24.4%, respectively; $P = .06$). Concerning lipid traits, women showed higher levels of total cholesterol and HDL cholesterol and lower levels of triglycerides than men (median: total cholesterol = 5.0 mmol/L, HDL cholesterol = 1.5 mmol/L and triglycerides = 1.1 mmol/L vs total cholesterol = 4.7 mmol/, HDL cholesterol = 1.2 mmol/L and triglycerides = 1.2 mmol/L, respectively; all $P \leq .0004$). About one-third of participants reached cutoff values for lipid disturbances: 33.2% had HDL hypocholesterolemia overall, and 26.0% and 33.4% of women and men, respectively, had hypertriglyceridemia ($P = .004$). Elevated fasting plasma glucose level was less prevalent (25.6%) than other risk factors, with a median value of 5.1 mmol/L (IQR, 4.7–5.5). Combining these individual risk factors, 24.9% and 23.3% of participants (with no significant difference between men and women) met IDF and ATP definitions for MetS, respectively.

Per linear regression models adjusted for age, sex, smoking status, and body mass index (BMI), no association was observed between psychiatric diagnosis and CVD risk scores or between psychotropic medication and CVD risk scores. Age, illness duration, and smoking status showed significant association with MetS ($P < .05$), while sex, psychiatric diagnosis, and psychotropic medication showed no significant association. Indeed, according to IDF criteria, an increase of 10 years of age was associated with a 1.35-fold (95% CI, 1.27–1.48, $P < 10^{-4}$) greater odds of MetS, while chronic compared with early psychosis patients had an

Table 3. Quantification of the 10-Year Cardiovascular Disease Risk in the Psychiatric Sample 2 and Comparison With the Population-Based Sample (aged 35–75 years)[a]

	Women			Men				
Variable	Psy	Gpop	*P* Value[b]	Psy	Gpop	*P* Value[b]	Total-Psy	Total-Gpop
SCORE, median (IQR), %	0.28 (0.12–1.32)	0.36 (0.12–1.34)	.54	0.85 (0.38–2.25)	1.04 (0.43–3.45)	0.14	0.52 (0.19–1.75)	0.63 (0.23–2.18)
Prevalence, n (%)								
High risk (≥ 5%)	30 (8.5)	296 (8.4)	.58	38 (13.4)	528 (16.6)	.42	68 (10.7)	824 (12.3)
Intermediate risk (2.5 ≥ risk < 5%)	26 (7.4)	240 (6.8)	.50	27 (9.5)	476 (15.0)	.18	53 (8.4)	716 (10.7)
Low risk (1.5 ≥ risk < 2.4%)	21 (6.0)	269 (7.6)	.50	34 (12.0)	316 (10.0)	.02	55 (8.7)	585 (8.7)
Very low risk (< 1.5%)	274 (78.1)	2723 (77.2)	.24	184 (65.0)	1,856 (58.4)	.83	458 (72.2)	4,579 (68.3)
FRS, median (IQR), %	0.40 (0.18–0.81)	0.41 (0.17–0.93)	.57	1.72 (0.95–3.39)	2.54 (1.20–5.03)	**$<10^{-4}$**	0.82 (0.33–1.88)	1.00 (0.36–2.72)
Prevalence, n (%)								
High risk (> 20%)	0	2 (0.1)	…	1 (0.3)	58 (1.8)	**.01**	1 (0.1)	60 (0.9)
Intermediate risk (10 < risk ≤ 20%)	0	5 (0.1)	…	7 (2.5)	192 (6.0)	**.0002**	7 (1.1)	197 (2.9)
Low risk (6 < risk ≤ 10%)	3 (0.8)	14 (0.4)	.66	19 (6.7)	376 (11.8)	**.0006**	22 (3.5)	390 (5.8)
Very low risk (≤ 6%)	348 (99.1)	3521 (99.4)	.95	256 (90.5)	2,559 (80.4)	**$<10^{-4}$**	604 (95.3)	6,080 (90.4)

[a]Total n values: SCORE: women: Psy n = 351, Gpop n = 3,528; men: Psy n = 283, Gpop n = 3,176; Total-Psy n = 634; Total-Gpop n = 6,704. FRS: women: Psy n = 351, Gpop n = 3,542; men: Psy n = 283, Gpop n = 3,185; Total-Psy n = 634; Total-Gpop n = 6,727.
[b]Statistical significance for difference between the psychiatric and population-based samples was tested using a weighted statistic according to participants' age (2-sample weighted *t* test). *P* values in bold are significant (≤ .05).
Abbreviations: FRS = Framingham Risk Score, Gpop = population-based sample; Psy = psychiatric sample, SCORE = Systematic Coronary Risk Estimation.

increased risk of MetS, with an odds ratio of 2.3 (95% CI, 1.4–3.7, $P = .001$) and being a current smoker was associated with a 1.62-fold (95% CI, 1.18–2.13, $P = .002$) greater odds of MetS. Consistent findings were observed when using ATP criteria (odds ratios of 1.37 [95% CI, 1.25–1.45, $P < 10^{-4}$], 1.9 [95% CI, 1.1–3.1, $P = .013$], and 1.68 [95% CI, 1.22–2.27, $P = .001$] for age, illness duration, and smoking status, respectively). Notably, BMI and age at treatment initiation were found to be statistically different across medication groups according to their risk of metabolic side effects. Moreover, an effect of the dose of medication was also observed on the probability to display a MetS (see Supplementary Appendix 1 for more details).

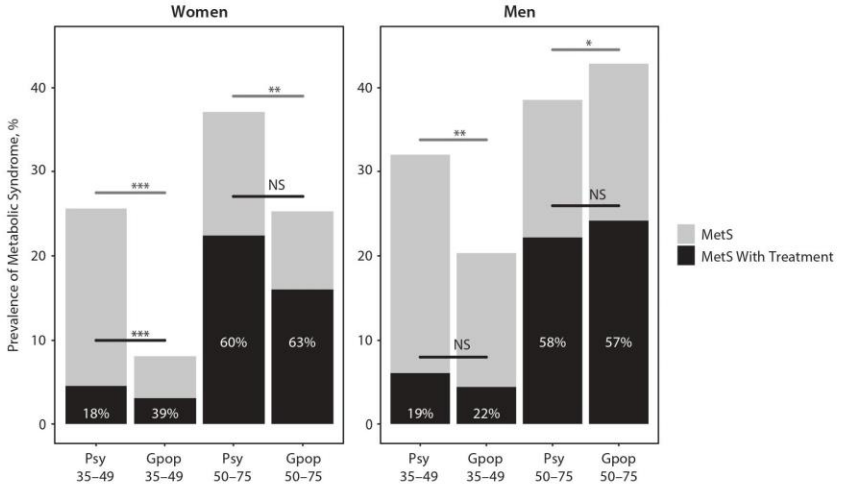
Table 2 shows clinical variables and prevalence of MetS in the subsample of patients aged 35–75 years old (psychiatric sample 2) and in the population-based sample. Notably, the proportion of smokers was twice as high in the psychiatric sample as in the population-based cohort ($P < 10^{-4}$). The psychiatric sample showed generally poorer metabolic health. Indeed, female patients showed a higher prevalence of obesity compared to the population-based sample with both definitions (75.7% vs 55.7% for IDF obesity, $P < 10^{-4}$; and 56.9% vs 32.5% for ATP obesity, $P < 10^{-4}$). Consistent findings were seen in men, but only with the ATP definition (39.9% vs 25.8%, $P = .0006$). For lipid-related traits, psychiatric patients showed greater prevalence of dyslipidemia (HDL hypocholesterolemia prevalence of 33% vs 10.4%, $P < 10^{-4}$; and hypertriglyceridemia prevalence of 35.7% vs 24.9%, $P < .05$). Female patients had a higher prevalence of increased glucose level and diabetes compared to the population-based sample (31.2% vs 26.3%, $P = .0005$; and 8.8% vs 4.0%, $P = .002$, respectively). In contrast, male patients showed a better profile for hypertension prevalence compared to men from the population-based sample (37.5% vs 42.5%, $P = .03$). Men also had a lower hyperglycemia prevalence (36.9% vs 50.1%, $P < 10^{-4}$), although the difference for diabetes prevalence was not statistically significant (11.0% vs 9.2%, $P = .36$). Significant differences in MetS prevalence were observed between the two cohorts, and this observation was more pronounced in women, for whom the prevalence of cases in the psychiatric sample was nearly twice the prevalence in the population-based sample (31.6% vs 18.0%, $P < 10^{-4}$; and 27.9% vs 15%, $P < 10^{-4}$, according to the IDF and ATP criteria, respectively). This difference was lower for men and significant only according to the ATP definition of MetS (33% vs 26%, $P = .04$).

The comparison between the psychiatric and population-based cohort according to the proportion of participants treated for their metabolic disturbances gave mixed results (see Supplementary Appendix 1 for details).

The estimations of cardiovascular risks with the SCORE and the FRS were similar, showing a very low median risk in both cohorts (Table 3). Of note, men from the population-based sample showed a higher risk of CVD events than men from the psychiatric sample (median [IQR] = 2.54% [1.2%–5.03%] vs 1.72% [0.95%–3.39%], $P < 10^{-4}$). The proportion of participants at high risk of developing a CVD in 10 years (FRS > 20%) for the population-based sample versus the psychiatric sample was 0% versus 0.1% in women and 0.3% versus 1.8% ($P = .01$) in men, while the respective proportions of participants at high risk of dying within 10 years from a CVD event (SCORE ≥ 5%) were 8.5% versus 8.4% ($P = .58$) in women and 13.4% versus 16.6% ($P = .42$) in men.

The MetS prevalence, stratified into 2 age groups, is presented in Supplementary Table 4 and in Figure 1. These results highlight that the higher prevalence of MetS in the psychiatric sample was more pronounced among younger adults (aged 35–49 years old). Young female patients were particularly vulnerable, with a MetS prevalence 3 times

Figure 1. Age- and Sex-Stratified Prevalence of Metabolic Syndrome (IDF) and Cardiovascular Disease Medication Intervention in Psychiatric Sample 2 and Comparison With the Population-Based Sample[a,b,c]



[a]Metabolic syndrome defined per the International Disease Federation.
[b]Statistical significance for difference between the psychiatric and population-based samples was tested using a weighted statistic according to participants' age (2-sample weighted *t* test). *P* values are Bonferroni-corrected.
[c]The first bar on the left is to be read as follows: in young women with mental disorders, the prevalence of MetS was 26%, and 18% of these women with MetS received a treatment for their metabolic disorder (corresponding to 5% of the young women with mental disorders). The subsequent bars are to be understood similarly.
*$P \leq .05$.
**$P \leq .005$.
***$P \leq .0005$.
Abbreviations: Gpop 35–49 = population-based sample aged 35–49 years, Gpop 50–75 = population-based sample aged 50–75 years, MetS = metabolic syndrome, MetS with treatment = medication intervention among MetS participants (ie, antihypertensive, lipid-lowering, or antidiabetic drug prescription), NS = not significant, Psy 35–49 = psychiatric sample aged 35–49 years, Psy 50–75 = psychiatric sample aged 50–75 years.

higher than that for young women from the population-based sample (25.6% vs 8.0%, $P < 10^{-4}$; and 21.6% vs 6.8%, $P < 10^{-4}$, according to IDF and ATP definitions, respectively). A significant difference was also observed in younger men (32% vs 20.3%, $P = .004$; and 27.2% vs 15.6%, $P = .004$, according to IDF and ATP definitions, respectively). Conversely, in older subjects, the proportion of male patients with MetS was lower than in the population-based sample (38.5% vs 42.8%, $P = .01$; and 35.6% vs 35.2%, $P = .64$, according to IDF and ATP definitions, respectively). The proportion of psychiatric patients with MetS receiving a CVD treatment was similar to that in the population-based participants for all subgroups except for young female patients. Specifically, among younger women with MetS, the proportion of psychiatric patients treated was roughly 2 times less than that of the population-based sample (17.8% vs 38.8%, $P = .0004$; and 21.1% vs 43.7%, $P = .0005$, according to IDF and ATP definitions, respectively).

DISCUSSION

In the present study, cardiovascular risk was estimated using the SCORE and the FRS. We found very low risk in both a large psychiatric Swiss cohort and a control Swiss population-based cohort. These observations are consistent with previously detected levels of CVD risk in psychiatric populations in Spain, another low–CVD risk European country.[27–29] The comparison between the two cohorts using both scores did not show statistically significant differences. However, the use of these scores applied to a psychiatric sample might underestimate the risk. Indeed, the calibration of the scores was done with data from the general population, and, as has been extensively shown, cardiovascular events and death rates are higher in the psychiatric population.[1,30] New equations have been proposed to more accurately evaluate the risk in this vulnerable population such as the PRIMROSE model,[31] developed specifically for people with severe mental illness, and very recently the QRISK3,[32] which considers the presence of several somatic conditions and mental illness in evaluating a patient's risk. However, these models require international validation in well-characterized cohorts and are not yet suitable for clinical applications. Specifically, the need for additional variables such as use of antidepressants or antipsychotics, severe mental illness diagnosis, history of heavy drinking, socioeconomic factors, family history of CVD events, and other comorbidities make those tools more laborious to use.

In the present study, no difference in MetS prevalence was observed across psychiatric diagnoses or between male and female patients, which is in agreement with previous studies.[33,34] According to our data, the same attention should thus be paid to every psychiatric patient, especially in those taking weight gain–inducing psychotropic drugs, regardless of their sex or diagnosis. It is, however, interesting to note that in the population-based sample, the difference in MetS prevalence between the sexes was striking, especially among younger individuals. This observation is again in line with what is reported in the literature, as mortality rates for CVDs in the general population are higher in males than in females.[35] Also, it is reported that biological and social factors for development of cardiovascular diseases differ between the two sexes.[36] Factors enabling better cardiovascular health in women (as compared to men) in the general population might be missing in women suffering from severe mental illness. Mental illnesses most likely have greater impact regarding cardiovascular health on women than on men. Thus, although MetS prevalence is similar in both sexes, requiring the same care, more investigation is warranted in female patients to understand the substantial difference between them and women from the general population.

In the present psychiatric sample, about 1 in 4 patients displayed MetS, which is slightly lower than reported in previous meta-analyses[19,37] showing MetS rates of 32.5% and 37.3% in schizophrenia patients and in bipolar patients respectively. In their meta-analysis, Vancampfort et al[37] found that the strongest moderator for MetS rate was the region in which the study took place. The lower prevalence that we report in this study most likely reflects, at least in part, the fact that Switzerland is a low-risk country for CVD.[15,35] Consistent with previous studies,[34] we found that psychiatric patients were more susceptible to metabolic disturbances than subjects from the population-based sample, which may be partially due to the illness and/or exposure to antipsychotic and other psychotropic medication.[34,37–39] Unfortunately, data on previous psychotropic treatments were not available for psychiatric patients, preventing us from teasing out the weight of the illness from that of the medication. To note, even if the cohort was heterogeneous in terms of illness duration, the psychiatric condition was severe enough in every patient to require the prescription of a psychotropic drug. Besides medication, smoking is a key risk factor for MetS in the psychiatric population. Smoking has previously been demonstrated to be associated with MetS in the general population,[40] an association further confirmed in the present psychiatric sample. The higher prevalence of smokers in the psychiatric sample (53.9%) as compared to the population-based sample (26.9%) very likely contributes to the difference of MetS observed between the two cohorts. As smoking was also shown to exert an additive risk for CVD events,[41] those patients with MetS who are smokers are at even higher CVD risk.

Notably, older male psychiatric patients presented with a similar or even lower prevalence of MetS than their counterparts in the population-based sample. Nonetheless, this observation might be biased, as the selection process could have led to inclusion of the healthier patients, with male patients with the worst clinical and/or psychiatric conditions lost to or refusing a clinical follow-up. Those patients were thus quite likely underrepresented in the sample described and used for the present analyses. On the contrary, the proportion of young female patients with MetS was particularly high (25.6%, IDF) as compared to women from the population-based sample (8.0%), and they were far less likely to be treated for metabolic disturbances (17.8% vs 38.8%). Of note, the proportion of young female patients treated for their metabolic disorders was similar to that of young male patients (around 20% for both sex groups). This finding is in contrast to the sex difference on health care–seeking behavior assessed in the general population.[42]

Age plays a significant role in this sample for CVD treatment prescription, with the proportion of medication intervention being 3 times as large in the older age group as compared to the younger age group. In the RAISE-ETP study conducted by Correll et al,[9] in first-episode schizophrenia patients with a mean age of 24 years old, only 0.5% of the participants with dyslipidemia received a lipid-lowering treatment. To compare our cohort to the RAISE-ETP study cohort and add evidence for the importance of age in treatment prescription, we selected a subsample from psychiatric sample 1 having the same age distribution as the RAISE-ETP study cohort; when considering those patients (mean = 25 years old, SD = 5, n = 446), a very similar trend was observed, in which only 1.9% of patients with dyslipidemia received a lipid-lowering treatment.

Unfortunately, only CVD drug prescription (ie, antihypertensive, lipid-lowering, or antidiabetic drug prescription) could be assessed, but no information on lifestyle interventions was available. There may have been dietary or physical activity interventions as well as support for smoking cessation or restriction of alcohol intake involved in reaction to metabolic disturbances, especially among the younger age group participants, that could not be accounted for in these analyses. Despite several limitations, it can be assumed that the comparison of the present psychiatric sample with participants from the CoLaus|PsyCoLaus study sheds light on the differences expected between people with mental illness and the general population.

CONCLUSION

The prevalence of MetS was higher in patients with mental illness treated with weight gain–inducing psychotropic drugs than in the general population, especially among young adults. Young female patients seemed to be underdiagnosed and/or undertreated for metabolic traits, and awareness should be raised to detect these cases and give appropriate care. Regular monitoring of metabolic disturbances is of crucial importance in this vulnerable population.

Submitted: February 22, 2019; accepted October 21, 2019.

Published online: March 31, 2020.

Potential conflicts of interest: **Dr Eap** has received honoraria for conferences or teaching CME courses from Forum für Medizinische Fortbildung, Janssen-Cilag, Lundbeck, Mepha, Otsuka, Sandoz, Servier, Sunovion, Vifor-Pharma, and Zeller in the past 3 years and for writing a review article for the journal *Dialogues in Clinical Neurosciences* (Servier). **Dr von Gunten** has received honoraria for a conference or workshop participation from Vifor and Schwabe in the previous 3 years. The other authors have no relevant financial or other relationships, and all authors declare no conflict of interest in relation to the content of the article.

Funding/support: This work has been funded in part by the Swiss National Research Foundation (CBE and PC: 320030-120686, 324730-144064, and 320030-173211). Dr Vollenweiderm received an unrestricted grant from GlaxoSmithKline to build the CoLaus|PsyCoLaus study. The CoLaus study received financial contributions from GlaxoSmithKline, the Faculty of Biology and Medicine of the University of Lausanne, and the Swiss National Science Foundation (33CSCO-122661, 3200BO-111361/2, 3100AO-116323/1,310000-112552).

Role of the sponsor: The funding sources had no role in the writing of the manuscript or in the decision to submit it for publication.

Acknowledgments: The authors thank M. Gholam-Rezaee, PhD (scientific support; Lausanne University Hospital, Lausanne, Switzerland); C. Brogli and C. Darbellay (logistical assistance; Lausanne University Hospital, Lausanne, Switzerland); E. Retamales (bibliographic help; Lausanne University Hospital, Lausanne, Switzerland); and A. C. Aubert, M. Brocard, N. Cochard, M. Delessert, M. Brawand, S. Jaquet, A. Vullioud, G. Viret (sample analysis; Lausanne University Hospital, Lausanne, Switzerland). None have conflicts of interest to declare. The authors thank the nursing and medical staff who were involved in the metabolic monitoring program.

Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Evaluation of Cardiometabolic Risk in a Large Psychiatric Cohort and Comparison With a Population-Based Sample in Switzerland

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DOI Number: https://doi.org/10.4088/JCP.19m12796

List of Supplementary Material for the article

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Appendix 1

METHODS

Study design

An institutional guideline of the Department of Psychiatry of the Lausanne University Hospital requires follow-up to assess metabolic parameters when a psychotropic treatment known to induce metabolic side effect is initiated (complete list of medication in **Supplementary Table 1)**. Inclusion criteria for the study was the prescription of a psychotropic treatment listed in the institutional guideline for metabolic parameters follow-up. Diagnoses were based on the ICD-10 classification (F20.0-F24.9 and F28-F29: psychotic disorders; F25.0-F25.9; schizoaffective disorders; F30.0-F31.9: bipolar disorders; F32.0-F33.9: depression). Anxiety, personality disorders and mental retardation were classified in "other" disorders.

According to the institutional guideline, monitoring for physical health risk factors was performed at baseline, and one month, three months, and one year after treatment initiation. Body measurements (height, weight, waist circumference, blood pressure) were taken along with blood parameters (total cholesterol (TC), HDL cholesterol (HDL-C), triglycerides (TG) and glucose (GLC)). Presence of CVD treatment medication (i.e. lipid-lowering, antidiabetic and antihypertensive treatments, complete list of medication in **Supplementary Table 2**) was collected. The present study gathered data from the clinical follow-up to run a cross sectional evaluation of the metabolic state of the cohort at the start of a new treatment. Because of the non-interventional post-hoc analysis study design, the Ethic Committee approved the use of clinical data of followed-up patients from 2007 to end of 2015 (PsyClin). From 2015 to 2017, included patients gave written informed consent (PsyMetab). Detailed description of the monitoring and of the cohort study can be found elsewhere[1-4]. Only observations with blood samples drawn in fasting conditions were retained for the present analysis.

For some patients, the clinical monitoring could not be conducted as required and some measures were not carried out. For those, we selected the earliest available observation after treatment initiation. Observations included in the present analysis were thus obtained at baseline for 48% of the sample, month 1 for 21%, month 2 for 3%, month 3 for 19% and month 5 or more for the rest of the sample (9%).

Statistical analyses

The analyses considering illness duration could only be conducted on a subset of patients (n=732, 60% of the cohort), as the information was missing for the other participants. We compared the two extreme quartiles of the cohort, to consider early psychosis versus chronic patients (i.e. patients who experienced 13 years of illness or more versus those with 2 years of illness or less), correcting for age and smoking status.

Prescribed psychotropic treatments were categorized into three groups to test associations with CVD risk scores and MetS according to the expected metabolic side effect.[5,6] Thus, psychotropic drugs were classified as follow: low risk: haloperidol, pipamperone, flupentixol, asenapine, amisulpride, aripiprazole, lurasidone; medium risk: zuclopenthixol, levomepromazine, paliperidone, risperidone, quetiapine, lithium, mirtazapine; high risk: valproate, olanzapine, clozapine. Since higher dosage is commonly associated with higher metabolic risk, analyses were also run categorizing patients either as taking low or high dose, according to the median prescribed dose of each medication. These analyses were run considering patients measured after the treatment start (n=614).

RESULTS

Psychotropic Medication

Quetiapine represented 31% of all prescriptions, followed by risperidone, olanzapine, aripiprazole, and amisulpride accounting for 15%, 11%, 10% and 8% respectively (data not shown). BMI and age were found to be statistically different across the three medication groups at baseline, with participants being prescribed high versus low risk drugs showing a lower BMI (2 kg/m^2, 95% CI=0.94-3.7, p=0.001) and being older (7 years older, 95% CI=2-12, p=0.006).

The observation that young patients having a high baseline BMI were more likely to receive a psychotropic medication classified as having a low potential to induce weight gain, suggests that the metabolic secondary effects of drugs seemed to be taken into account in prescription choices. Low risk drugs are thus preferred in young patients but also in patients already presenting an unfavorable metabolic profile. This observation might be specific to this sample's context where awareness has been raised on psychotropic drugs secondary effects for many years. Besides, when considering doses of medication of patients assessed after treatment start, those prescribed a high dose were more susceptible to have MetS using IDF criteria (n=614, OR = 1.5, 95% CI=1.02-2.15, p=0.04). This association was however not statistically significant with ATP definition. (n=614, OR = 1.4, p=0.08).

Cardiovascular Medication

The comparison between the psychiatric and population-based cohort according to the proportion of participants treated for their metabolic disturbances gave mixed results. Specifically, we found a lower rate of antihypertensive drug prescription in psychiatric patients with hypertension as compared to non-psychiatric participants, while patients with dyslipidemia were more often treated with lipid-lowering drugs in the psychiatric sample. No difference was observed in diabetes treatment prescription. Overall, no difference in the prescription of treatment for all risk factors combined was found between the two cohorts among subject diagnosed with MetS.

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Supplementary Table 1. Drugs included in the metabolic follow-up recommendation[a]

ANTIPSYCHOTICS		ANTIDEPRESSANTS		MOOD STABILIZERS
Atypical (second-generation)	**Typical (first-generation)**	**Tricyclic**	**Other**	
Amisulpride **Aripiprazole** **Asenapine** **Clozapine** **Lurasidone** **Olanzapine** **Paliperidone** **Quetiapine** **Risperidone** Sertindole	Chlorprothixene **Flupentixol** **Haloperidol** **Levomepromazine** **Pipamperone** Promazine Sulpiride Tiapride **Zuclopenthixol**	Amitriptyline Clomipramine Doxepine Imipramine Nortriptyline Opipramol Trimipramine	**Mirtazapine**	Carbamazepine **Lithium** **Valproate**

[a]Psychotropic drugs **in bold** indicate which of the treatments included in the institutional guideline were represented in our study sample.

Supplementary Table 2. Lipid-lowering, antidiabetic and antihypertensive treatments considered as CVD medication intervention

Lipid-lowering drugs	antidiabetic	Antihypertensive		
Atorvastatin	Insulin	Enalapril	Amlodipine	Propranolol
Fluvastatin		Lisinopril	Diltiazem	Carvedilol
Pravastatin	Metformin	Perindopril	Felodipine	
Rosuvastatin		Ramipril	Lercanidipine	Furosemide
Simvastatin	Pioglitazone	Trandolapril	Nifédipine	Torasemide
	Rosiglitazone		Verapamil	Amiloride
Fenofibrate		Candesartan		Spironolactone
	Glibenclamide	Irbesartan	Atenolol	Hydrochlorothiazide
Ezetimibe	Gliclazide	Losartan	Bisoprolol	Indapamide
	Glimepiride	Olmesartan	Celiprolol	
		Telmisartan	Metoprolol	Aliskirene
	Sitagliptine	Valsartan	Nebivolol	

Supplementary Table 3. Metabolic syndrome criteria

	Metabolic syndrome (IDF definition)	Metabolic syndrome (NCEP - adapted ATP III)
	A and at least two in B, C, D or E	Three or more of A, B, C, D, or E
A. Central obesity **IDF def** **ATP III def**	waist circumference: male ≥94 cm, female ≥80 cm and/or BMI > 30kg/m² waist circumference: male ≥102cm, female ≥88 cm	
B. Triglycerides	≥ 1.7 mmol/l (≥150mg/dl) or lipid-lowering treatment	
C. HDL-cholesterol	male ≤ 1.03 mmol/l(≤40mg/dl), female ≤ 1.29 mmol/l(≤50mg/dl) or lipid-lowering treatment	
D. Blood pressure	≥ 130/85 mmHg or treatment for hypertension	
E. Glucose	≥ 5.6 mmol/l (≥100mg/dl) or type 2 diabetes treatment	

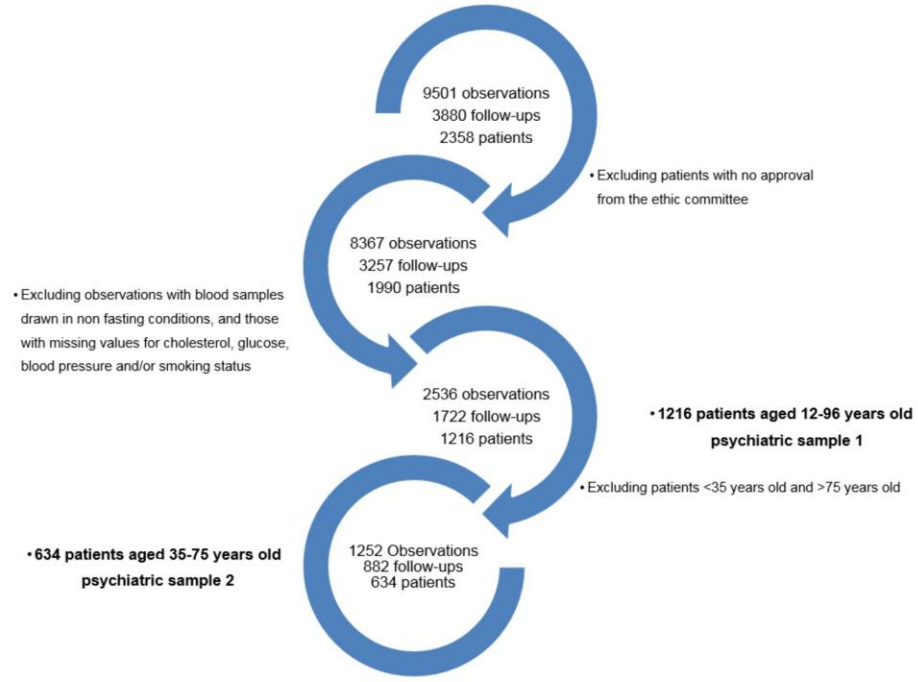
Supplementary Table 4. Prevalence of metabolic syndrome and CVD medication intervention stratified into two age groups in the psychiatric sample 2 and comparison with the population-based sample

Women	Psy	Gpop	p-val[a]
35-49 years old, n	176	1517	
MetS (IDF) prevalence, n(%)	45 (25.6)	121 (8.0)	**$<10^{-4}$**
Treated[b], n(%)	8 (17.8)	47 (38.8)	**0.0004**
MetS (ATP) prevalenc, n(%)	38 (21.6)	103 (6.8)	**$<10^{-4}$**
Treated[b], n(%)	8 (21.1)	45 (43.7)	**0.0005**
50-75 years old, n	170	2025	
MetS (IDF) prevalence, n(%)	63 (37.1)	512 (25.3)	**0.001**
Treated[b], n(%)	38 (60.3)	323 (63.1)	0.42
MetS (ATP) prevalence, n(%)	58 (34.1)	421 (20.8)	**0.0005**
Treated[b], n(%)	36 (62.1)	278 (66.0)	0.35

Men	Psy	Gpop	p-val
35-49 years old, n	147	1511	
MetS (IDF) prevalence, n(%)	47 (32.0)	306 (20.3)	**0.004**
Treated[b], n(%)	9 (19.1)	67 (21.9)	0.77
MetS(ATP) prevalence, n(%)	40 (27.2)	236 (15.6)	**0.004**
Treated[b], n(%)	8 (20.0)	54 (22.9)	0.77
50-75 years old, n	135	1675	
MetS (IDF) prevalence, n(%)	52 (38.5)	717 (42.8)	**0.01**
Treated[b], n(%)	30 (57.7)	405 (56.5)	0.57
MetS(ATP) prevalence, n(%)	48 (35.6)	591 (35.2)	0.64
Treated[b], n(%)	28 (58.3)	359 (60.7)	0.75

[a]Statistical significance for difference between the psychiatric and populations based samples was tested using a weighted statistic according to participants' age (two-sample weighted t-test). P-values significant after Bonferroni correction are in bold (≤0.025)

[b]Treated: prevalence of any CVD medication intervention among MetS participants (i.e. antihypertensive, lipid lowering or antidiabetic drug prescription)
Abbreviations: Gpop= population-based sample; MetS= metabolic syndrome ; psy= psychiatric sample



Supplementary Figure 1. Flow chart of study participants

Project 2: Socio-economic position as a moderator of cardiometabolic outcomes in patients receiving psychotropic treatment associated with weight gain: results from a prospective 12-month inception cohort study and a large population based cohort

Dubath C, Gholam-Rezaee M, Sjaarda J, Levier A, Saigi-Morgui N, Delacrétaz A, Glatard A, Panczak R, Correll CU, Solida A, Plessen KJ, von Gunten A, Kutalik Z, Conus P, Eap CB

Published in Translational Psychiatry (2021); DOI: 10.1038/s41398-021-01482-9

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Socio-economic position as a moderator of cardiometabolic outcomes in patients receiving psychotropic treatment associated with weight gain: results from a prospective 12-month inception cohort study and a large population-based cohort

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Weight gain and metabolic complications are major adverse effects of many psychotropic drugs. We aimed to understand how socio-economic status (SES), defined as the Swiss socio-economic position (SSEP), is associated with cardiometabolic parameters after initiation of psychotropic medications known to induce weight gain. Cardiometabolic parameters were collected in two Swiss cohorts following the prescription of psychotropic medications. The SSEP integrated neighborhood-based income, education, occupation, and housing condition. The results were then validated in an independent replication sample (UKBiobank), using educational attainment (EA) as a proxy for SES. Adult patients with a low SSEP had a higher risk of developing metabolic syndrome over one year versus patients with a high SSEP (Hazard ratio (95% CI) = 3.1 (1.5–6.5), $n = 366$). During the first 6 months of follow-up, a significant negative association between SSEP and body mass index (BMI), weight change, and waist circumference change was observed ($25 \leq$ age < 65, $n = 526$), which was particularly important in adults receiving medications with the highest risk of weight gain, with a BMI difference of 0.86 kg/m^2 between patients with low versus high SSEP (95% CI: 0.03–1.70, $n = 99$). Eventually, a causal effect of EA on BMI was revealed using Mendelian randomization in the UKBiobank, which was notably strong in high-risk medication users (beta: −0.47 SD EA per 1 SD BMI; 95% CI: −0.46 to −0.27, $n = 11{,}314$). An additional aspect of personalized medicine was highlighted, suggesting the patients' SES represents a significant risk factor. Particular attention should be paid to patients with low SES when initiating high cardiometabolic risk psychotropic medications.

Translational Psychiatry (2021)11:360 ; https://doi.org/10.1038/s41398-021-01482-9

INTRODUCTION

In psychiatric populations (comprising schizophrenia, bipolar disorder, major depressive disorder, and their related spectrum disorders) life expectancy is reduced by about ≥10 years versus the general population. Approximately two-thirds of this mortality is attributed to cardiovascular diseases [1]. This increase in cardiometabolic-related health problems is multidetermined, including psychiatric illness, lifestyle, and diet behaviors, resulting in a high prevalence of obesity and other cardiometabolic risk factors [2]. In addition, many psychotropic medications (most antipsychotics, some mood stabilizers, and antidepressants) can worsen weight, body mass index (BMI), waist circumference (WC), lipid, and glucose profiles [2].

Social factors, such as low educational attainment (EA) or low income, have been associated with poor mental health outcomes

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Received: 20 October 2020 Revised: 17 May 2021 Accepted: 7 June 2021
Published online: 26 June 2021

and depression [3]. Some studies also linked socio-economic status (SES) with the risk of or severity of symptoms in schizophrenia and other mental disorders [4, 5]. Moreover, SES is a moderator of obesity in the general population [6]. In the area of Lausanne, Switzerland, geographic clusters of high versus low BMIs were observed, which were influenced by neighborhood-level income [7]. Similar results were reported in another Swiss study, performed on young men using conscription data [8], showing substantial spatial variations in obesity risk, which increased with lower SES. These studies suggest an influence of SES on both mental health and obesity. Nevertheless, associations between SES and cardiometabolic parameters in patients treated with psychotropic medications are under-researched.

One study found that social determinants of health were inversely associated with glycated hemoglobin in first-episode psychosis [9]. However, patients had very short prior psychotropic treatment exposure and the cross-sectional design precluded the investigation of the impact of SES factors on treatment-related metabolic health evolution. Another study conducted in treated bipolar patients revealed an inverse correlation between normal weight, overweight, obesity, or extreme obesity and income level [10]. However, this finding did not remain significant when adjusting for site of inclusion and eating disorder diagnoses. Besides, no other SES factors, such as EA, occupation, or housing condition, were characterized in this study. In a third study, using multivariable modeling, housing condition was significantly associated with weight gain during 6-month olanzapine therapy in patients with schizophrenia and bipolar disorders [11].

To better address the impact of SES, we aimed to longitudinally explore whether and how SES is associated with cardiometabolic variables in a psychiatric cohort treated with psychotropic medications, which can induce weight gain, and explore mediating effects of high-, medium- and low-risk medications. Finally, we sought to validate our epidemiological associations in the UKBiobank (UKB), a very large population-based cohort. Based on the prior literature, we hypothesized that weight gain following psychotropic medication initiation would be inversely related to SES and that this effect would be most pronounced with high cardiometabolic risk medications.

METHODS

Psychiatric population and metabolic outcomes

A departmental guideline, adopted in 2007 in the Department of Psychiatry at Lausanne University Hospital, requires the monitoring of metabolic adverse effects when patients start a psychotropic treatment known to induce weight gain and/or worsen other metabolic parameters. In- and outpatients starting such treatments are thus followed with routine check-ups at baseline and after 1, 2, 3, 6, and 12 months. Body weight, BMI, WC, blood pressure, and plasma levels of glucose and lipids (low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), total cholesterol, and triglycerides) are monitored routinely at these same time points.

Informed consent was obtained from prospectively followed patients between 4/2007 and 10/2016 (PsyMetab, $n = 1093$) as previously described [12]. Because of the non-interventional post-hoc analysis design, the requirement of informed consent was waived for patients routinely assessed as part of clinical care between 4/2007 and 12/2015 (PsyClin, $n = 714$). Data use in both cohorts was approved by the Ethics Committee of the Canton of Vaud. Patients selection is described in Supplementary Fig. 1.

Medication, diagnosis, age at medication onset, smoking status, and sex were extracted from medical files and/or specific questionnaires. Diagnostic groups were established according to ICD-10 classification, and psychotropic medications were classified, independently of daily dosage, according to their risk for inducing weight gain in three categories, i.e., low-risk (e.g., amisulpride, aripiprazole, haloperidol, lurasidone, and flupentixol); medium-risk (e.g., quetiapine, risperidone, paliperidone, lithium, mirtazapine, zuclopenthixol, and levomepromazine), and high-risk (e.g., valproate, olanzapine, and clozapine) as previously described [13].

SES: assignment of the SSEP index

Research conducted in Switzerland aimed to determine individual's SES based on postal address [14]. An area-based index of Swiss socio-economic position (SSEP) was developed, ranging between 0 (most disadvantaged) and 100 (most privileged). The characterization of the SSEP index by place of residency was based on 2000 census data including income, education, occupation, and housing conditions. The validity of the SSEP index was then demonstrated to be associated with all-cause and cause-specific mortality [14].

To estimate patients' SES, postal addresses were obtained and geocoded using Google API via the ggmap R package [15]. Patients with no available personal address were excluded (Supplementary Fig. 1). Each geocoded postal address was matched with a SSEP according to the minimum distance to a reference SSEP building, with a maximum distance of 130.5 meters, as previously described [14].

Statistical analyses

Baseline demographic variables of patients were compared with their SSEP level (below or above the median SSEP) using the χ^2 test of independence for categorical variables and Student's *t*-tests for continuous variables.

Incidence of metabolic syndrome, according to the International Diabetes Federation (IDF) definition [16], as well as the incidence of each individual component of metabolic syndrome was investigated in adult patients (25–65-years old) with low versus high SSEP during the first year of treatment. The Cox proportional hazard model was used, adjusted for confounding variables (age, sex, first available BMI, diagnosis, and treatment categories).

Linear mixed effect models were then used to assess the effect of SSEP on each cardiometabolic parameter during 1–6 months of medications treatment, adjusting for confounding variables (age, sex, baseline BMI, diagnosis, and treatment categories; see Supplementary Appendix). We used the SSEP variable once on a continuous and once on a categorical scale: (a) low SSEP (i.e., SSEP below the first quartile), (b) medium SSEP (i.e., SSEP in the second or third quartile), and (c) high SSEP (i.e., SSEP above the third quartile). Analyses were performed independently in three age groups, young patients (<25 years old), adults 25 to <65 years old, and senior patients ≥65 years old, as the meaning of the SSEP construct varies for different birth cohorts [14]. In adults, subgroup analyses were also run to differentiate the effect on BMI, weight, and WC according to initial BMI and according to treatment categories. All analyses were two-sided with alpha = 0.05. Analyses were performed using the R environment for statistical computing version 3.5.2.

Validation in the UKB sample

We sought to validate our associations in the UKB sample and also aimed to estimate a causal effect through Mendelian randomization (MR). The details of the UKB have been described elsewhere [17]. Briefly, UKB is a prospective cohort study including more than 500,000 individuals (40–69 years) recruited from the United Kingdom during 2006–2010. We selected participants according to quality measures, ethnicity, and relatedness. We then defined a psychiatric population within the UKB based on reported psychotropic medication use to evaluate the association of EA with BMI through a cross-sectional approach. Information regarding the duration of medication treatment as well as of psychiatric diseases were unknown and the UKB sample included presumably a mix of chronic and first-episode patients. EA was used as a proxy for SES, as it is one of the four criteria in the SSEP construct. This trait was also tested for association with BMI, body weight change, and WC change in the Swiss psychiatric cohort to validate its use in the UKB. First, we examined the interaction between EA and the use of weight-inducing medications with BMI. Next, we used a two-sample MR design to estimate the causal effect of EA on BMI in both participants treated with psychotropic medications with high and low propensity to induce weight gain (i.e., category 2 and 3 in Supplementary Table 1 vs. the rest of the defined psychiatric population within the UKB). In other words, we estimated the causal effect in two distinct groups, to determine whether there was a difference in the effect of EA on BMI. MR methodology has been described in detail elsewhere [18]. Briefly, MR is a statistical method applied to large-scale genetic data, which harnesses the fact that genetic variants are inherited randomly and independently from other risk factors of diseases, to estimate the causal effect of an exposure on an outcome of interest. The random distribution of genetic variants at birth minimizes the possibility of confounding or reverse causation as explanations for the link between the exposure and outcome

Table 1. Clinical and demographic parameters of the study sample according to SSEP groups.

	N	Total sample	Low SSEP (29.4 ≤ SSEP < 61.8)	High SSEP (61.8 ≤ SSEP ≤ 86.4)	*p*-value[a]
Age, median (range), y	966	40 (13–96)	37 (13–93)	44 (13–96)	0.06
Men, *n* (%)	966	442 (45.8)	240 (49.8)	202 (41.7)	**0.01**
Smoking, *n* (%)	816	397 (48.7)	211 (51.7)	186 (45.6)	0.09
Main diagnosis, *n* (%)	966				**0.02**
Psychotic disorders (F20-F24;F28-F29)		348 (36)	196 (40.7)	152 (31.4)	
Schizoaffective disorders (F25)		85 (8.8)	47 (9.8)	38 (7.9)	
Bipolar disorders (F30-F31)		163 (16.9)	78 (16.2)	85 (17.6)	
Depressive disorders (F32-F33)		179 (18.5)	76 (15.8)	103 (21.3)	
Organic disorders (F00-F09; F28-F29)		28 (2.9)	12 (2.5)	16 (3.3)	
Other		163 (16.9)	73 (15.2)	90 (18.6)	
Psychotropic treatment group, *n* (%)[b]	966				0.31
Low risk of WG		186 (19.3)	100 (20.8)	86 (17.8)	
Medium risk of WG		582 (60.3)	279 (57.9)	303 (62.6)	
High risk of WG		198 (20.5)	103 (21.4)	95 (19.6)	
Metabolic parameters at first observation[c]					
BMI, median (range), kg/m^2	966	23.2 (13.3–54.1)	23.6 (14.5–54.1)	22.7 (13.3– 53.5)	**0.004**
Overweight (25 ≥ BMI < 30 kg/m^2), *n* (%)		234 (24.2)	125 (25.9)	109 (22.5)	0.05
Obese (BMI ≥ 30 kg/m^2), *n* (%)		122 (12.6)	70 (14.5)	52 (10.7)	
WC, median (range), cm	819	87 (28–162)	88 (45–133)	85 (43–162)	0.09
Central obesity (WC ≥ 94 cm in male or ≥88 cm in female), *n* (%)		339 (41.4)	182 (44.5)	157 (38.3)	0.08
Hypercholesterolemia (≥5 mmol/l), *n* (%)	678	285 (42)	140 (41.2)	145 (42.9)	0.70
LDL hypercholesterolemia (≥3 mmol/l), *n* (%)	639	236 (36.9)	115 (37)	121 (36.9)	1.00
HDL hypocholesterolemia (≤1 mmol/l), *n* (%)	664	82 (12.4)	49 (14.9)	33 (9.9)	0.06
Fasting hypertriglyceridemia (≥2 mmol/l), *n* (%)	664	99 (14.9)	55 (16.6)	44 (13.2)	0.26
Systolic blood pressure, median (range), mmHg	699	120 (72–206)	120 (80–180)	120 (72–206)	0.60
Diastolic blood pressure, median (range), mmHg	699	75 (40–120)	77 (44–117)	74 (40–120)	0.05
Fasting glucose, median (range), mmol/l	492	5 (3–14.9)	5 (3–14.3)	5 (3–14.9)	0.40

Low and high SSEPs indicate SSEPs lower and higher than the median SSEP, respectively.
BMI body mass index, *HDL* high-density lipoprotein cholesterol, *F00-F33* ICD codes, *LDL* low-density lipoprotein cholesterol, *SSEP* Swiss socio-economic position, *WC* waist circumference, *WG* weight gain.
[a]*p*-values were calculated using Student *t*-tests for continuous variables and χ^2 test of independence for categorical variables. Significant *p*-values are indicated in bold.
[b]Amisulpride, aripiprazole, haloperidol, lurasidone, and flupentixol were considered as drugs with a low propensity for WG; quetiapine, risperidone, paliperidone, lithium, mirtazapine, zuclopenthixol, and levomepromazine were classified in the group with medium propensity for WG and valproate, olanzapine and clozapine were considered as having a high propensity for WG.
[c]First observation includes observations at baseline for 86.6% of the sample, at 1 month for 9.5%, and later for 3.8% of the sample.

in the same way that the allocation of a therapy in a randomized controlled trial minimizes this possibility (see Supplementary Appendix).

RESULTS

Population characteristics

From the initial cohort of 1807 patients, 966 were included in the analyses (Supplementary Fig. 1 for patient selection). Clinical and demographic parameters of the cohort are described in Table 1. The median SSEP was 61.8 (range = 29.4–86.4) and was used as a threshold to describe the cohort, stratified as low SSEP (<61.8) and high SSEP (≥61.8). The median age of the cohort was 40 years (range = 13–96 years). The proportion of smokers was higher in the low than in the high SSEP group (52% versus 46%), although the difference did not reach significance. Men represented 45.8% of the cohort and were more likely to have a low SSEP than women (49.8% of men in the low versus 41.7% in the high SSEP group, p = 0.01). In addition, compared to patients with a high SSEP, patients with a low SSEP more likely suffered from psychotic disorders (40.7% versus 31.4%) and were less diagnosed with depression (15.8% versus 21.3%). The three psychotropic medication categories were not associated with SSEP groups. Most of the cohort (60.3%) received medium cardiometabolic risk psychotropic treatment, while a minority received low-risk (19.3%) or high-risk treatment (20.5%). Based on the first available observation, patients with a low SSEP had higher BMIs than those with a high SSEP (median = 23.6 kg/m^2 versus 22.7 kg/m^2; $p = 0.004$), with a trend for a higher prevalence of overweight or obese patients (overweight proportion: 25.9% in the low and 22.5% in the high SSEP group and obese proportion: 14.5% versus 10.7%, $p = 0.05$). The same trend was observed regarding the proportion of central obesity (44.5% versus 38.3%, $p = 0.08$), low HDL-cholesterol (14.9% versus 9.9%, $p = 0.06$), and median diastolic blood pressure (77 mmHg versus 74 mmHg, $p = 0.05$). Finally, 42% of the total sample had total hypercholesterolemia, while median systolic blood pressure and glycaemia were in the range of normal values, with none of these variables being significantly associated with SSEP groupings.

Table 2. Association between SSEP and BMI, weight change, and waist circumference change in the young, adult, and elderly population.

	BMI (kg/m^2)	Weight change (%)	WC change (%)
Young (13 ≤ age<25)	$N = 199$	$N = 199$	$N^a = 145$
SSEP, E (95% CI)	0 (−0.015; 0.015)	0.009 (−0.057; 0.076)	0.035 (−0.254; 0.326)
Low vs medium SSEP, E (95% CI)	−0.39 (−0.84; 0.05)	−1.65 (−3.62; 0.30)	3.15 (−5.96; 12.10)
Low vs high SSEP, E (95% CI)	−0.18 (−0.68; 0.32)	−0.50 (−2.70; 1.66)	−0.88 (−10.72; 8.89)
Adult (25 ≤ age<65)	$N = 526$	$N = 526$	$N^a = 390$
SSEP, E (95% CI)	0.017 (0.004; 0.030)*[b]	0.063 (0.010; 0.116)*	0.141 (0.044; 0.244)**
Low vs medium SSEP, E (95% CI)	0.12 (−0.20; 0.42)	0.39 (−0.86; 1.61)	4.18 (1.87; 6.50)***
Low vs high SSEP, E (95% CI)	0.44 (0.06; 0.84)*	1.60 (0.09; 3.17)*	3.17 (0.25; 6.10)*
Senior (65 ≤ age < 97)	$N = 204$	$N = 204$	$N^a = 117$
SSEP, E (95% CI)	−0.001 (−0.021; 0.018)	0.011 (−0.075; 0.095)	−0.077 (−0.229; 0.083)
Low vs medium SSEP, E (95% CI)	0.31 (−0.21; 0.83)	1.23 (−1.02; 3.51)	1.35 (−2.88; 5.63)
Low vs high SSEP, E (95% CI)	−0.12 (−0.68; 0.45)	−0.36 (−2.79; 2.11)	−2.12 (−6.74; 2.43)

Weight and WC change (in %) were calculated as the difference between the current value and the baseline value divided by the baseline value.
Analyses were performed during a 6-month follow-up period, adjusted by age, sex, first available BMI, diagnosis, risk of psychotropic drug-induced weight gain and were performed using linear mixed models adjusted in a Bayesian framework and using 1,000,000 Markov chain Monte Carlo iterations. SSEP effect was estimated (E (95% CI)) on a continuous and categorical scale (three SSEP categories: first quartile defines low SSEP, second and third quartiles medium SSEP, and fourth quartile high SSEP).
BMI body mass index, *SSEP* Swiss socio-economic position, *WC* waist circumference.
Significant *p*-values are indicated as *$p \le 0.05$; **$p \le 0.01$; ***$p \le 0.001$.
[a]The number of patients included in this analysis was lower than for BMI and weight because of missing WC data.
[b]To understand the magnitude of these results, one can imagine a fictional patient with a baseline BMI of 20, taking a high cardiometabolic risk psychotropic treatment and with a SSEP of 30 (lowest SSEP value in the adult cohort). His/her BMI would increase by 2.2 kg/m^2 (95% CI BMI at 6 months: 21.8–22.6) in 6 months to a value of 22.2 kg/m^2, while the same patient with a SSEP of 86 (highest SSEP value of the adult cohort) would increase his/her BMI by 1.2 kg/m^2 (95% CI BMI at 6 months: 20.1–22.4) in 6 months to a value of 21.2 kg/m^2, translating into a 1 kg/m^2 BMI difference after 6 months of treatment attributable to their SSEP difference.

Longitudinal association of SSEP and cardiometabolic parameters

Although we observed significant weight gain over treatment time, no association between SSEP and cardiometabolic parameters during psychotropic treatment was observed in young patients (<25 years, $n = 199$) and senior patients (≥65 years, $n = 204$). However, significant associations were found in the adult population ($n = 526$) (Table 2). In this age group, SSEP was an important risk factor for the incidence of metabolic worsening during psychotropic treatment: among 366 adult patients without metabolic syndrome at the beginning of the psychotropic treatment, 42 new cases occurred over a one-year follow-up; patients whose SSEP was lower than the median value were three times more likely to develop metabolic syndrome compared to patients with higher SSEP (HR = 3.1, 95% CI: 1.5–6.5, Fig. 1). Results of incidence of individual risk components of metabolic syndrome are described in Supplementary Appendix and presented in Supplementary Fig. 2.

Continuous SSEP were significantly negatively associated with cardiometabolic parameters in adult patients, with an increase of 0.017 kg/m^2 in BMI (95% CI: 0.004–0.030), 0.063% in weight change (95%CI: 0.010–0.116), and 0.141% in WC change (95% CI: 0.044–0.244) per each decrease in SSEP unit (Table 2). Negative associations were also observed when comparing SSEP groups, with higher BMI in patients with low versus high SSEP (0.44 kg/m^2 (95% CI: 0.06–0.84)), weight change (1.60% (95% CI: 0.09–3.17)), and WC change (3.17% (95% CI: 0.25–6.10)). In Supplementary Table 2, adult patients' characteristics are presented stratified into the three SSEP groups that were used in those analyses.

Associations between SSEP and lipid parameters, glucose levels, and blood pressure in the three age groups of the cohort are described in Supplementary Appendix and shown in Supplementary Table 3.

Subgroup analyses conducted in adult patients, stratified by categories of psychotropic treatment showed a stronger association between SSEP and BMI in patients receiving high cardiometabolic risk treatments (Table 3). Indeed, a decrease from a high to low SSEP group was associated with a 0.86 kg/m^2 higher BMI (95% CI: 0.03–1.70) in patients receiving high-risk medications, while no significant association was found in those receiving low-risk medications. The inverse association between SSEP and WC change was relatively strong in patients receiving high as well as low cardiometabolic risk psychotropic medications (0.308% of WC increase per each SSEP unit decrease in patients

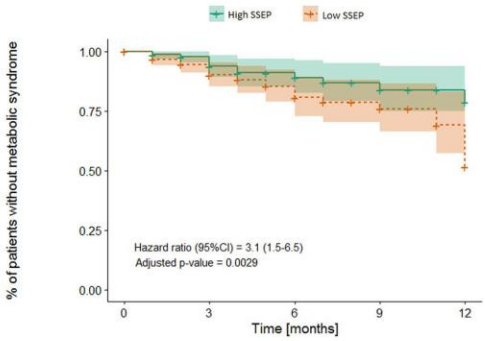

Fig. 1 Incidence of new onset metabolic syndrome according to SSEP over one year of psychotropic treatment in the adult population. Analysis was performed in the adult population (25 ≤ age< 65) and was adjusted by age, sex, first available BMI, diagnosis, risk of psychotropic drug-induced weight gain, using a Cox proportional hazards model ($n = 366$). The number at risk at baseline: 168 High SSEP vs 198 Low SSEP, at 3 months: 98 High SSEP vs 109 Low SSEP, at 6 months: 47 High SSEP vs 54 Low SSEP, at 9 months: 29 High SSEP vs 29 Low SSEP, at 12 months: 16 High SSEP vs 16 Low SSEP. High and Low SSEP groups were defined as SSEP over (≥61.8) vs under (<61.8) median SSEP, respectively.

Table 3. Association between SSEP and BMI, weight change, and waist circumference change stratified by psychotropic medication groups in the adult population.

	BMI (kg/m^2)	Weight change (%)	WC change (%)
High risk drug group[b]	$N = 99$	$N = 99$	$N^a = 69$
SSEP, E (95% CI)	0.026 (−0.002; 0.056)	0.069 (−0.044; 0.178)	0.308 (0.055; 0.568)*
low vs medium SSEP, E (95% CI)	0.09 (−0.60; 0.81)	0.46 (−2.28; 3.21)	5.29 (−0.66; 11.27)
low vs high SSEP, E (95% CI)	0.86 (0.03; 1.70)*	2.40 (0.91; 5.58)	6.27 (−0.99; 13.62)
Medium risk drug group[b]	$N = 307$	$N = 307$	$N^a = 230$
SSEP, E (95% CI)	0.019 (0.001; 0.037)*	0.078 (0.006; 0.151)*	0.059 (−0.042; 0.164)
low vs medium SSEP, E (95% CI)	0.19 (−0.24; 0.61)	0.77 (−1.00; 2.46)	3.24 (0.73; 5.74)*
low vs high SSEP, E (95% CI)	0.46 (−0.07; 0.97)	1.86 (−0.28; 3.98)	2.14 (−0.90; 5.19)
Low-risk drug group[b]	$N = 120$	$N = 120$	$N^a = 91$
SSEP, E (95% CI)	0.003 (−0.028; 0.034)	0.024 (−0.093; 0.139)	0.374 (0.074; 0.675)*
low vs medium SSEP, E (95% CI)	0.03 (−0.63; 0.68)	−0.05 (−2.56; 2.36)	6.21 (0.22; 12.34)*
low vs high SSEP, E (95% CI)	−0.004 (−0.905; 0.920)	0.34 (−3.09; 3.79)	5.53 (−3.34; 14.46)

Weight and WC change (in %) were calculated as the difference between the current value and the baseline value divided by the baseline value.
Analyses were performed in the adult population ($25 \leq$ age < 65) during a 6-month follow-up period and adjusted by age, sex, first available BMI, diagnosis and were performed using linear mixed models adjusted in a Bayesian framework and using 1,000,000 Markov chain Monte Carlo iterations. SSEP effect was estimated (E (95% CI)) on a continuous and categorical scale (three SSEP categories: first quartile defines low SSEP, second and third quartiles medium SSEP, and fourth quartile high SSEP).
BMI body mass index, *SSEP* Swiss socio-economic position, *WC* waist circumference, *WG* weight gain.
Significant *p*-values are indicated as $^*p \leq 0.05$.
[a]The number of patients included in this analysis was lower than for BMI and weight because of missing WC data.
[b]Risk of drug-induced weight gain differs among psychotropic drugs: High-risk drug group includes patients taking valproate, olanzapine, or clozapine; medium-risk drug group includes patients taking quetiapine, risperidone, paliperidone, lithium, mirtazapine, zuclopenthixol, or levomepromazine; low-risk drug group includes patients taking amisulpride, aripiprazole, haloperidol, lurasidone, or flupentixol.

receiving high-risk medications (95% CI: 0.055–0.568) and 0.374% increase in patients receiving low-risk medications (95% CI: 0.074–0.675)). Analyses stratified by initial BMI are described in Supplementary Appendix and in Supplementary Table 4.

The association of EA with BMI, weight change, and WC change was calculated in a small subset of PsyMetab and PsyClin participants ($n = 199$), and the results are presented in Supplementary Table 5.

Epidemiological validation in the UKB

30,334 participants were used for the analysis, including 18,893 controls and 11,441 cases (those taking psychotropic medications with no or low effect on weight and those taking weight increasing psychotropic medications according to Supplementary Table 1: risk 1 and 2 versus 3 and 4). We identified a significant interaction between high-risk medication use and EA on BMI ($p = 0.047$). Subgroup analyses revealed that the association between EA and BMI was stronger in cases (beta: 0.10 SD BMI per 1 SD decrease in age completed education; 95% CI: 0.08–0.12; $p < 5 \times 10^{-16}$) than controls (beta: 0.07 SD BMI per 1 SD decrease in age completed education; 95% CI: 0.05–0.09; $p = 2.6 \times 10^{-14}$). In other words, every year decrease in age completed education was associated with an ~0.17 kg/m^2 increase in BMI in cases.

Estimating the causal effect of education on BMI using MR

The causal effect was estimated in both psychiatric high-risk and low-risk medications users within the UKB. Specifically, there were 18,755 controls and 11,314 cases (slightly different than above, as not all participants passed genetic quality control filters). In both groups, we found a significant effect of EA on BMI, (Supplementary Fig. 3) where the causal effect was stronger in cases (beta: −0.47 SD EA per 1 SD BMI; 95% CI: −0.59 to −0.34; $p = 1.3 \times 10^{-13}$) than in controls (beta: −0.36 SD EA per 1 SD BMI; 95% CI: −0.46 to −0.27; $p = 8.2 \times 10^{-14}$), consistent with the epidemiological analyses. However, the difference between the two estimates was not statistically significant (one-tailed, *t*-test $p = 0.101$).

DISCUSSION

This study revealed that during the first year of observed psychotropic treatment with cardiometabolic risk potential, adults aged 25–65 years with a low SSEP were three times more susceptible to developing metabolic syndrome compared to patients with high SSEP. In addition, these same patients with a low SSEP were particularly susceptible to having a higher BMI, increased body weight and increased WC when prescribed high-risk psychotropic medications. We observed consistent results in the replication analyses in the UKB.

Slightly more women were included in this study, in line with research conducted in Switzerland showing higher utilization of mental health services by women [19]. Notably, women were overrepresented in the high SSEP group. A high SES had previously been associated with better mental health outcomes and interestingly, women with schizophrenia were reported to have a better prognosis than men (with higher remission rates, fewer relapses) [3, 20, 21]. Whether women are relatively biologically protected (e.g., via estrogen), or benefit from a more favorable environment that has a positive impact on mental illness evolution, or whether having a better recovery enables them to attain (or maintain) a higher SES remains to be explored.

The median baseline BMI of the entire cohort was significantly higher in patients with a low SSEP. This result is consistent with data from the general population [6], and could be in part due to the influence of SSEP on weight gain induced by previously prescribed psychotropic medications. Indeed, most patients had already been hospitalized before study recruitment and were not medication-naïve.

No significant association between SSEP and any cardiometabolic parameters during treatment with the studied psychotropic medications was found in young and in elderly patients. However, no information was available on whether young patients were still living with their parents but, according to the Swiss Federal Statistical Office, only 20% of young people aged 18–24 years live alone in Switzerland, suggesting that a significant proportion of

young patients likely still lived with their parents [22]. For such patients, the calculated SSEP actually reflected the SES of their parents and thus might differ from their own SES. Similarly, some elderly patients might also live with their children caring for them, which would also not reflect their own SES. Moreover, elderly patients living in medico-welfare establishments were excluded, as the institutional address would indeed not reflect their personal SES. Therefore, a selection bias was likely present, excluding the oldest and more severely ill patients. Taken together, these limitations might explain the lack of association found in the young and elderly subpopulations. Besides, since compared to the adult group aged 25–65 years, the sample size was <50% for the younger and elderly sample, the impact of socioeconomic factors in these age groups should be further investigated by future larger studies.

Except for systolic blood pressure, no statistically significant association between SSEP and other cardiometabolic parameters was found (glucose, lipid levels, and diastolic blood pressure) in any of the age groups. The positive association linking high SSEP to higher systolic blood pressure is surprising and must be replicated, as the opposite relationship was reported in the general population in a recent meta-analysis [23].

Psychiatric illness is associated with a risk of weight gain, and in this study this risk increases when a psychotropic medication is introduced. Indeed, the greatest association of SSEP with BMI was found in patients receiving high-risk medications, while a weaker association and no association were found in patients taking medium-risk and low-risk medications, respectively. Importantly, we also identified a causal effect of EA on BMI in the UKB psychiatric subpopulation, as shown previously in the whole UKB [24], and found, independently of the duration of treatment, a trend for a stronger effect in participants taking high-risk weight-inducing psychotropic medications compared to those not taking such medications. Socio-economic inequalities negatively impact patients, especially when they are exposed to high-risk medications, making the most disadvantaged patients more vulnerable to medication-induced cardiometabolic adverse effects. The effect of an underlying environmental factor on BMI (in our study, SSEP or EA) seems thus to be exacerbated by the presence of an additional risk factor (in our study, a high-risk medication). This observation also implies that there is a non-negligible proportion of components leading to metabolic side effects that are modifiable. Therefore, targeted interventions could improve outcomes of patients with low levels of education and/or low SES. Among other explanations, mechanistic insight for medication-induced weight gain includes changes in appetite regulation [25, 26]. Interestingly, SES influences diet quality, where people of low SES tend to follow unhealthier diets than do people of high SES. Indeed, a recent Swiss study confirmed dietary differences according to SES indicators, namely education, income, and occupation [27]. It is therefore possible that increased appetite following psychotropic medication initiation has a greater impact on weight gain in patients whose diet is less healthy. It is unknown, however, whether, following prescription of appetite-stimulating medications, strategies to prevent weight gain (e.g., controlled diet or more physical exercise) differ between patients with low compared to higher SES. Educational interventions, which promote healthy eating, should be encouraged, although the evidence to date suggests a limited effect if the price is a deterrent. Strategies involving making healthy food financially accessible, especially for patients with lower SES, may be a worthwhile endeavor [28].

The present study has several limitations and strengths. First, the SSEP score was developed from data recorded in 2000. Unfortunately, replication of the same SSEP construct with more recent data is not possible in Switzerland since the census method has changed. Nonetheless, as socio-economic factors have a long-term effect, having older data is still relevant. Assuming that individuals did not move before the study period, the SSEP reflects the socio-economic environment in which they grew up or spent their life prior to the intervention. Analyses with EA were consistent with findings using the SSEP with a significant association with WC and observed trends for associations with BMI and weight change. Future studies should try to determine which of the four criteria used in the SSEP construct most influences patients' cardiometabolic outcomes (i.e., whether income, education, occupation, or housing conditions affect the patient outcome in different ways). Another limitation of the socio-economic variable used in this study is that the SSEP index is an ecological measure, with the possibility of high-SSEP individuals living in low-SSEP neighborhoods and vice versa. Besides, as the patients' SES was defined based on their personal address, homeless patients, those living in residential facilities, and prisoners, representing a non-negligible part of the psychiatric population, were not included in the study (Supplementary Fig. 1). Moreover, both in the Swiss psychiatric cohort and in the UKB sample, information on illness duration and severity, prior medication, diet behaviors, alcohol consumption, and physical activity were not available, preventing us to adjust the analyses for their potential influence. Despite these limitations, the inception cohort design and longitudinal follow-up after treatment initiation enabled the prospective assessment of SSEP effects on the evolution of cardiometabolic parameters in response to the initiated psychotropic medication in a comprehensive Swiss psychiatric sample treated under real-world conditions. Moreover, the observed inverse association between SSEP and cardiometabolic worsening being strongest in the high weight-gain risk medication group strengthens the validity of our findings. Importantly, the influence of EA on BMI in subjects taking weight gain-inducing psychotropic medications was confirmed in a large population-based cohort.

In summary, in addition to other well-described clinical and environmental risk factors (e.g., young age, first psychotic episode, and low BMI), low SES was associated with an increased risk of worsening of cardiometabolic variables following the prescription of weight gain-inducing psychotropic medications. In all patients, cardiometabolic risk factors, including SES, should be assessed and carefully weighed versus the therapeutic benefits of the prescribed medications.

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ACKNOWLEDGEMENTS

The authors thank the laboratory, nursing, and medical staff who were involved in the metabolic monitoring program and all the participants in PsyMetab, PsyClin, and UKB study. The research has been conducted using the UK Biobank resource (application #16389).

AUTHOR CONTRIBUTIONS

Study concept and design: CE. Acquisition of data: CD, AL, NS, AD, and AG. Analysis and interpretation: CD, MG, RP, CC, JS, and ZK. Drafting of the manuscript: CD, MG, and JS. Critical revision of the manuscript for important intellectual content: All authors. Obtained funding: CE and PC. Administrative, technical, or material support: AS, KP, AvG, and PC.

COMPETING INTERESTS

CE received honoraria for conferences or teaching CME courses from Janssen-Cilag, Lundbeck, Otsuka, Sandoz, Servier, Sunovion, Vifor-Pharma, and Zeller in the past 3 years. AvG received honoraria for a conference or workshop participation from Vifor and Schwabe in the previous 3 years. Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Gedeon Richter, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a stock option holder of LB Pharma. The other authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41398-021-01482-9.

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Supplementary information

Online Supplement:

Appendix: Supplementary Methods, Results and Discussion

Supplementary Table 1: List of psychotropic drugs used in the UKB and their corresponding weight-inducing risk (3 corresponds to highest risk, 2 to medium risk, 1 to low risk, and 0 to no expected risk) and frequency count.

Supplementary Table 2: Clinical and demographic parameters of the adult population (25≤age<65) according to low, medium and high SSEP groups

Supplementary Table 3: Association between SSEP and metabolic parameters in young, adult and elderly population

Supplementary Table 4: Association between SSEP and BMI, weight change and waist circumference change stratified by baseline BMI in the adult population

Supplementary Table 5: Association between educational attainment and BMI, weight change and waist circumference change in the adult population

Supplementary Figure 1: Flowchart of the study population

Supplementary Figure 2: Incidence of new onset metabolic syndrome components dysregulation according to SSEP over one year of psychotropic treatment in the adult population

Supplementary Figure 3: Scatter plot illustrates the MR results estimating the causal effect of educational attainment on BMI in both high risk psychotropic weight-inducing drug-users and non users.

Appendix

METHODS

Linear mixed effect models

Model adjustment was carried out in a Bayesian framework and using a large number (1 million) of Markov chain Monte Carlo iterations [1]. All Bayesian models were adjusted using the MCMCglmm package in R. Reported estimates are mode of posterior probability for each parameter accompanied with the corresponding 95% Credible Interval (CI). We observed satisfactory convergence for all models and results were not sensitive to the number of MCMC iterations.

UKBiobank

Samples were genotyped on either the UK Biobank Array or the UK BiLEVE array. Phasing and imputation were performed using SHAPEIT3 and IMPUTE3, respectively, against a combined haplotype reference panel including UK10K and 1000 Genomes Phase 3. Participants which had withdrawn consent as of February 20, 2020 were removed (n=141). Analyses were filtered based on the following criteria from the "ukb_sqc_v2.txt" bulk data download file containing sample quality control metrics: "in.white.British.ancestry.subset=1", "excess.relatives=0", "putative.sex.chromosome.aneuploidy=0", and a maximum unrelated sample set was determined using kinship metrics from the "ukb1638_rel_sP.txt" file with the "ukb_gen_samples_to_remove" function from the ukbtools Rpackage [2]. Phenotype variables were processed and standardized using to the PHESANT pipeline.

Replication of epidemiological associations in UKB

To replicate the epidemiological association found in the PsyMetab sample, we first derived psychotropic medication use variables according to the medication and health supplements data (Data Field 20003) at study baseline. Specifically, we derived four new binary variables according to reported psychiatric medication use as outlined in Supplementary Table 1 corresponding to their risk for inducing weight gain (high, medium, low and no risk), using the same approach as in PsyMetab, plus an additional category for participants taking psychotropic medications with no reported risk for inducing weight gain. Participants could be defined as "medication user" for multiple categories, as each participant can list as many

medications as necessary. Next, we restricted the sample to only participants who were taking at least one of the listed medications to establish a psychiatric population within the UKB. There was no available information on the duration of treatment and the sample was most probably a mix of chronic and first episode patients. Using this subset, we then sought to evaluate the interaction effect between weight gain-inducing psychotropic medications and education on BMI in a cross-sectional analysis. High-risk medication users were defined as participants taking at least one high- or medium-risk drug, while the remaining participants were considered as low risk users (category 2 and 3 versus 1 and 2 in Supplementary Table 1). Age at completed full-time education (Data Field 845, older age indicated greater education) was used as a proxy for educational attainment (EA), and BMI was evaluated using Data Field 21001. The model was adjusted for age, sex and age squared. When a significant interaction was identified, the effect of age at completed full-time education on BMI was estimated in the two subgroups. BMI and age at completed education were standardized to have a mean of zero and a standard deviation of 1 in each subgroup.

Mendelian randomization

The effect of genetic variants on EA (i.e. the exposure in the MR) was obtained from the Social Sciences Genetic Association Consortium (SSGAC, https://www.thessgac.org/data). Specifically, we used the data for EA reported by Lee et al. for 10K SNPs (file "GWAS_EA.to10K.txt"), which included all lead SNPs ($p < 5 \times 10^{-8}$) for EA, among other inclusion criteria [3]. EA was defined as number of years of schooling completed, measured in over 1.1 million individuals. A set of instrumental variables (IVs) to be used in the MR was selected according to the following procedure. First, the dataset from SSGAC was filtered to only GW-significant SNPs ($p < 5 \times 10^{-8}$) resulting in 2415 SNPs. Second, 373 SNPs were removed because they were both palindromic (i.e. A/T or C/G SNPs) and had MAF < 0.35. SNPs matching these criteria are difficult to harmonize with external datasets, as the strand cannot be easily determined. Third, an additional 9 SNPs were removed because they were not present in the UKB v2 bgen files. Finally, SNPs in both the UKB and passing GW-significance filter were pruned for linkage disequilibrium with a window size of 10000 and r^2 value < 0.001 according to the European samples from the 1000 Genomes Project resulting in 393 SNPs.

The effect of these 393 SNPs on BMI (i.e. the outcome in the MR) were estimated in the UKB in the two subgroups: high-risk psychiatric medication users and the rest of the psychiatric UKB cohort, as defined above. The regression models were adjusted for standard covariates, including age, age squared, sex, and the first 40 principal components, computed in each group separately. BMI was standardized to have a mean of 0 and SD of 1 in each subgroup. The effect of the SNPs on BMI was then harmonized with the EA data. Minor allele frequency (MAF) was calculated in each subgroup (users and non-users). To ensure a sufficient sample size to estimate the effect of the SNP on BMI, SNPs with MAF * n < 5 in a given subgroup were removed from the relevant MR (e.g. for a sample of 100,000, it would be necessary to retain a SNP with MAF < 5e-05). An additional 2 SNPs were removed in both subgroups, resulting in 391 SNPs to be used to estimate the causal effect of EA on BMI. Finally, MR was performed in each group using the inverse-variance weighted (fixed effects) method [4]. Pruning, harmonization and MR analysis were performed using the TwoSampleMR R-package [5].

Replication of results using educational attainment in PsyMetab & PsyClin

Analyses conducted on PsyMetab and PsyClin participants using the SSEP index were replicated in a small subsample (n=199), using only EA as SES indicator. EA was defined according to the Swiss Hospital Medical Statistics [6] as the highest obtained degree, ranging from 1 to 6 (with 1 being no school nor vocational training completed, 2 compulsory schooling, 3 vocational training, 4 high school, 5 university of applied sciences, 6 university).

Linear mixed effect models were then used to assess the associations of EA with BMI, weight, and WC, during 1 to 6 months of treatment with the included psychotropic medications, adjusting for confounding variables (age, sex, baseline BMI, diagnosis and treatment categories) with the exact same methods as described for the analyses of the SSEP effect. We used the EA variable once on a continuous and once on a categorical scale (three EA categories: 1-2; 3-4, 5-6). Analyses were performed in adults 25 to <65 years old.

RESULTS

Longitudinal association of SSEP and cardiometabolic parameters

Incidence of dysregulation of each individual component of metabolic syndrome is presented in Supplementary Figure 2. New onset of hyperglycemia is the only component that showed a statistically significant association with SSEP, with an increased risk in patients with a lower SSEP (HR= 2·8, 95% CI: 1·01-7·5).

Besides, the linear analysis of metabolic parameters evolution showed no association with SSEP, as described in Supplementary Table 3. The only association that reached statistical significance was with systolic blood pressure in the adult cohort, where patients with a low SSEP had a 4·82 mmHg (95%CI: -0·44 to -9·22) lower systolic blood pressure compared to patients with a high SSEP, although the systolic blood pressure change from baseline to 6 months of follow-up was not associated with SSEP.

Associations between SSEP and BMI, weight change and waist circumference change stratified by baseline BMI in the adult population

Subgroup analyses conducted in adult patients, stratified by initial BMI showed that SSEP was negatively associated with BMI and WC change in normal-weight patients (0·015 kg/m2 BMI unit increase per each SSEP unit decrease (95%CI: 0·0003 to 0·03) and 0·142% of WC increase per each SSEP unit decrease (95%CI: 0·015 to 0·27)), while the effect in obese patients did not reach statistical significance (Supplementary Table 4).

The association of EA with BMI, weight change and WC change

Briefly, a lower EA was associated with an increase of 0·180 kg/m2 in BMI (95%CI: -0·026 to 0·382), 0·499% in weight change (95%CI: -0·321 to 1·311), and 1·658% in WC change (95%CI: 0·158 to 3·106) as shown in Supplementary table 5. The association reached statistical significance for WC change (p=0·03) with only a statistical trend observed for BMI (p = 0·08) and no significant association for weight change (p = 0·23).

DISCUSSION

Longitudinal association of SSEP and cardiometabolic parameters

The association between hyperglycemia incidence and SSEP narrowly reached statistical significance. This result is interesting and would reveal an increased susceptibility to hyperglycemia in patients with a low as compared to patients with a higher SSEP. Nevertheless, this finding was based on a small sample of participants (n=201 participants at baseline) and needs replication in a future larger study.

The absence of a statistically significant association for glucose levels and diastolic blood pressure could either be due to a too-short follow-up period (i.e, 6 months), or due to insufficient statistical power, as more data were missing for these parameters than for BMI, weight and WC. While the absence of a statistically significant association could also represent reality and highlight a specific influence of SSEP on BMI, weight and WC, these same variables are strongly associated with metabolic parameters and blood pressure, so that only other, unmeasured variables would be able to explain the dissociation between weight-based and metabolic associations with SSEP. Future studies should investigate this question in more detail.

Associations between SSEP and BMI, weight change and waist circumference change stratified by baseline BMI in the adult population

A low initial BMI has been consistently shown to be associated with greater psychotropic drug-induced weight gain [7, 8], and in the present study, the observed association between SSEP and BMI was significant in normal-weight patients. In overweight and obese patients, the absence of associations between SSEP and BMI and weight gain could be due to insufficient statistical power (n=148 and n=78 overweight and obese patients, respectively, versus n=302 normal-weight patients). Alternatively, the presence of a ceiling effect would also have limited our ability to detect such associations if the psychotropic medication-related weight gain had occurred before study entry.

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Supplementary Table 1: List of psychotropic medications used in the UKB and their corresponding weight-inducing risk (3 corresponds to highest risk, 2 to medium risk, 1 to low risk, and 0 to no expected risk) and frequency count.

Medication	Count	Risk	UKB coding
Valproate	1130	3	1140872216, 1141172838, 1140872198, 1140872214, 1140872200
Olanzapine	416	3	1140928916, 1141167976
Clozapine	37	3	1141200458, 1140867420, 1140882320, 1141201792
Amitriptyline	7367	2	1140867658, 1140867934, 1140867948, 1140867938, 1140879616
Mirtazapine	1069	2	1141152732, 1141152736
Lithium	609	2	1140867490, 1140867520, 1140917270, 1140867504, 1140867518, 1140867494, 1140910976, 1140867498
Clomipramine	261	2	1140879620
Quetiapine	259	2	1141152848, 1141152860
Nortriptyline	222	2	1140867818, 1140867940, 1140867942
Risperidone	199	2	1140867444, 1141177762
Imipramine	194	2	1140879630
Chlorpromazine	139	2	1140879658, 1140910358, 1140863416
Trimipramine	71	2	1140867756, 1140867758
Doxepine	31	2	1140867640
Zuclopenthixol	26	2	1140882100, 1140867342
Levomepromazine	5	2	1140909802, 1140867122
Chlorprothixene	0	2	1140856052
Flupenthixol	80	1	1140867150, 1140867152, 1140867952
Amisulprid	68	1	1141153490, 1141184742
Haloperidol	60	1	1140867168, 1140867184, 1140867092, 1140867180
Aripiprazole	48	1	1141202024, 1141195974
Sulpiride	45	1	1140867304, 1140882376, 1140867306
Promazine	25	1	1140879746
Sertindole	0	1	1140927956, 1140927970
Citalopram	6583	0	1140921600, 1141151946
Fluoxetine[1]	4897	0	1140879540, 1140867876, 1141174756
Paroxetine	1764	0	1140882236, 1140867888
Venlafaxine	1710	0	1140916282, 1140916288
Sertraline	1636	0	1140867878, 1140867884
Diazepam	1078	0	1140863152, 1141157496, 1140863244, 1140863250, 1140863238
Escitalopram	1022	0	1141190158, 1141180212
Temazepam	759	0	1140863202, 1140863210
St. John's Wort	663	0	1201
Trazodone	527	0	1140879634, 1140882244
Duloxetine	376	0	1141200564, 1141200570, 1141201834
Nitrazepam	225	0	1140863182, 1140863194, 1140863196
Lorazepam	125	0	1140863302, 1140863364
Clobazam	74	0	1140863268, 1140863272
Oxazepam	50	0	1140863442
Reboxetine	47	0	1141151978, 1141151982
Lormetazepam	40	0	1140863176
Fluvoxamine	27	0	1140879544, 1140867860
Moclobemide	21	0	1140867920, 1140867922
Bupropion[1]	20	0	1141176854, 1141176858, 1141180638

Flurazepam	6	0	1140863110, 1140863112
Alprazolam	5	0	1140863308, 1140863310, 1140863238
Bromazepam	1	0	1140863318, 1140863320
Clorazepate	1	0	1140863274, 1140863276, 1140910374
Ketazolam	0	0	1140855860
Prazepam	0	0	1140855944, 1140855946

[1]As these drugs are known to decrease weight in some cases, a sensitivity analysis was conducted removing individuals who were taking these drugs and the interaction remained significant (n = 25,419, p = 0·020).

Supplementary Table 2: Clinical and demographic parameters of the adult population (25≤age<65) according to low, medium and high SSEP groups

	N	Total sample	low SSEP[1] (29.9 ≤ SSEP < 54.5)	medium SSEP[1] (54.5 ≤ SSEP < 68.6)	high SSEP[1] (68.6 ≤ SSEP ≤ 86.4)	p-value[2]
Age, median (range), y	526	40 (25 - 64)	36 (25 - 64)	41 (25 - 64)	45 (25 - 63)	**0.006**[b]
Men, n(%)	526	253 (48.1)	66 (47.5)	143 (51.1)	44 (41.1)	0.21
Smoking, n(%)	457	262 (57.3)	73 (59.8)	138 (58)	51 (52.6)	0.53
Main diagnosis, n(%)	526					0.59
Psychotic disorders (F20-F24;F28-F29)		212 (40.3)	62 (44.6)	110 (39.3)	40 (37.4)	
Schizoaffective disorders (F25)		68 (12.9)	20 (14.4)	37 (13.2)	11 (10.3)	
Bipolar disorders (F30-F31)		117 (22.2)	22 (15.8)	66 (23.6)	29 (27.1)	
Depressive disorders (F32-F33)		81 (15.4)	20 (14.4)	43 (15.4)	18 (16.8)	
Other		48 (9.1)	15 (10.8)	24 (8.6)	9 (8.4)	
Psychotropic medication group, n(%)[3]	526					0.10
Low risk of WG		120 (22.8)	30 (21.6)	71 (25.4)	19 (17.8)	
Medium risk of WG		307 (58.4)	75 (54)	167 (59.6)	65 (60.8)	
High risk of WG		99 (18.8)	34 (24.5)	42 (15)	23 (21.5)	
Metabolic parameters at first observation[4]						
BMI, median (range), kg/m^2	526	24.0 (13.6 - 53.5)	24.0 (14.7 - 43.3)	24.0 (13.6 - 43.7)	23.7 (16.6 - 53.5)	0.64
Overweight (25≥BMI<30 kg/m^2), n(%)		148 (28.1)	38 (27.3)	84 (30)	26 (24.3)	0.30
Obese (BMI≥30 kg/m^2), n(%)		76 (14.5)	26 (18.7)	38 (13.6)	12 (11.2)	
WC, median (range), cm	462	88 (45 - 136)	87 (45 - 128)	90 (62 - 136)	87 (62 - 121)	0.21
Central obesity (WC≥94 cm in male or ≥88 cm in female), n(%)		205 (44.4)	52 (43)	115 (46.6)	38 (40.4)	0.56
Hypercholesterolemia (≥5mmol/l), n(%)	355	175 (49.3)	45 (46.4)	90 (48.7)	40 (54.8)	0.54
LDL hypercholesterolemia (≥3mmol/l), n(%)	334	148 (44.3)	40 (43)	77 (45.3)	31 (43.7)	0.93
HDL hypocholesterolemia (≤1mmol/l), n(%)	350	47 (13.4)	15 (15.5)	25 (13.9)	7 (9.6)	0.52
Fasting hypertriglyceridemia (≥2mmol/l), n(%)	351	67 (19.1)	18 (18.8)	41 (22.5)	8 (11)	0.10
Systolic blood pressure, median (range), mmHg	412	120 (72 - 180)	120 (86 - 180)	120 (80 - 174)	116.5 (72 - 165)	0.91
Diastolic blood pressure, median (range), mmHg	412	79 (46 - 120)	80 (55 - 106)	79 (47 - 120)	76 (46 - 101)	0.39
Fasting glucose, median (range), mmol/l	271	5 (3 - 14.9)	5.1 (3 - 14.3)	4.9 (3.61 - 14.9)	4.94 (4.2 - 8)	0.17

Metabolic parameters at last observation [4]						
BMI, median (range), kg/m^2	526	24.7 (16.2 - 45.9)	24.6 (17.4 - 43.6)	24.7 (16.8 - 45.9)	24.9 (16.2 - 39.2)	0.46
Overweight (25≥BMI<30 kg/m^2), n(%)		159 (30.2)	43 (30.9)	84 (30)	32 (29.9)	1.00
Obese (BMI≥30 kg/m^2), n(%)		91 (17.3)	24 (17.3)	48 (17.1)	19 (17.8)	
WC, median (range), cm	470	91 (60 - 143)	90 (60 - 142)	91 (62 - 143)	89.5 (64 - 140)	0.77
Central obesity (WC≥94 cm in male or ≥88 cm in female), n(%)		243 (51.7)	60 (50.4)	138 (54.6)	45 (45.9)	0.33
Hypercholesterolemia (≥5mmol/l), n(%)	297	154 (51.9)	37 (48.1)	84 (56)	33 (47.1)	0.35
LDL hypercholesterolemia (≥3mmol/l), n(%)	275	125 (45.5)	32 (43.8)	68 (49.6)	25 (38.5)	0.31
HDL hypocholesterolemia (≤1mmol/l), n(%)	294	39 (13.3)	10 (13)	20 (13.5)	9 (13)	1.00
Fasting hypertriglyceridemia (≥2mmol/l), n(%)	292	74 (25.3)	12 (15.6)	44 (30.1)	18 (26.1)	0.06
Systolic blood pressure, median (range), mmHg	227	120 (82 - 180)	116 (82 - 180)	120 (85 - 180)	120 (90 - 150)	0.58
Diastolic blood pressure, median (range), mmHg	227	77 (46 - 120)	76 (50 - 106)	77.5 (46 - 120)	78 (60 - 100)	0.40
Fasting glucose, median (range), mmol/l	207	5.1 (3.1 - 9.3)	5 (4.1 - 7)	5.2 (3.6 - 9.3)	5.2 (3.1 - 8.3)	0.06

Abbreviations: BMI: body mass index, LDL: low-density lipoprotein cholesterol, HDL: high-density lipoprotein cholesterol, SSEP: Swiss socio-economic position, WC: waist circumference, WG: weight gain

[1]Total sample is divided into 3 groups according to the SSEP: first quartile defines low SSEP, second and third quartiles medium SSEP and fourth quartile high SSEP.

[2]p-values were calculated using ANOVA for continuous variables and χ^2 test of independence for categorical variables. Significant p-values are indicated in bold and letters indicate which groups show significant difference calculated using Bonferroni corrected Student's t-test: [a] indicates difference between low and medium SSEP, [b] between low and high SSEP and [c] between medium and high SSEP.

[3]Amisulpride, aripiprazole, haloperidol, lurasidone and flupentixol were considered as drugs with a low propensity for WG; quetiapine, risperidone, paliperidone, lithium, mirtazapine, zuclopenthixol and levomepromazine were classified in the group with moderate propensity for WG and valproate, olanzapine and clozapine were considered as having a high propensity for WG.

[4]First observation includes observations at baseline for 90% of the sample and at 1 month for 10% of the sample. Last observation includes observations up to 6 months after treatment initiation.

Supplementary Table 3: Association between SSEP and metabolic parameters in the young, adult and elderly population

Part A: Lipids (i.e. Total cholesterol, LDL-cholesterol, HDL-cholesterol and Triglycerides)

	Total cholesterol (mmol/l)	**LDL-cholesterol (mmol/l)**	**HDL-cholesterol (mmol/l)**	**Triglycerides (mmol/l)**
Young (13≤age<25)	N[1] = 149	N[1] = 146	N[1] = 148	N[1] = 148
SSEP, E (95%CI)	0.001(-0.012 ; 0.014)	0(-0.011 ; 0.012)	-0.001(-0.006 ; 0.004)	0.004(-0.006 ; 0.013)
low vs medium SSEP, E (95%CI)	0.06(-0.33 ; 0.45)	0.04(-0.31 ; 0.38)	-0.02(-0.17 ; 0.13)	0.09(-0.20 ; 0.38)
low vs high SSEP, E (95%CI)	0.19(-0.25 ; 0.61)	0.11(-0.27 ; 0.49)	-0.02(-0.18 ; 0.16)	0.24(-0.07 ; 0.56)
	Total cholesterol change (%)	**LDL change (%)**	**HDL change (%)**	**Triglycerides change (%)**
	N[1] = 124	N[1] = 111	N[1] = 117	N[1] = 117
SSEP, E (95%CI)	0.053(-0.294 ; 0.399)	0.305(-0.298 ; 0.898)	0.196(-0.159 ; 0.568)	-0.254(-1.326 ; 0.814)
low vs medium SSEP, E (95%CI)	0.30(-11.07 ; 11.31)	0.04(-19.08 ; 19.53)	3.79(-7.94 ; 15.43)	10.02(-25.80 ; 44.81)
low vs high SSEP, E (95%CI)	4.26(-7.62 ; 16.32)	11.21(-9.36 ; 31.60)	4.03(-8.36 ; 16.51)	12.44(-25.35 ; 49.27)
	Total cholesterol (mmol/l)	**LDL-cholesterol (mmol/l)**	**HDL-cholesterol (mmol/l)**	**Triglycerides (mmol/l)**
Adult (25≤age<65)	N[1] = 400	N[1] = 386	N[1] = 401	N[1] = 400
SSEP, E (95%CI)	-0.001(-0.011 ; 0.01)	0.002(-0.007 ; 0.012)	-0.003(-0.007 ; 0.001)	0.001(-0.012 ; 0.015)
low vs medium SSEP, E (95%CI)	-0.08(-0.33 ; 0.19)	-0.019(-0.24 ; 0.20)	-0.03(-0.11 ; 0.05)	-0.12(-0.44 ; 0.19)
low vs high SSEP, E (95%CI)	-0.09(-0.41 ; 0.23)	0.02(-0.26 ; 0.30)	-0.07(-0.18 ; 0.03)	-0.02(-0.41 ; 0.38)
	Total cholesterol change (%)	**LDL change (%)**	**HDL change (%)**	**Triglycerides change (%)**
	N[1] = 300	N[1] = 276	N[1] = 297	N[1] = 297
SSEP, E (95%CI)	-0.023(-0.247 ; 0.201)	0.016(-0.370 ; 0.412)	-0.063(-0.305 ; 0.172)	0.198(-0.637 ; 1.028)
low vs medium SSEP, E (95%CI)	0.75(-4.69 ; 6.08)	-0.87(-10.16 ; 8.62)	1.02(-4.64 ; 6.77)	3.89(-16.27 ; 23.85)
low vs high SSEP, E (95%CI)	1.87(-4.84 ; 8.57)	3.09(-8.59 ; 14.76)	1.70(-5.24 ; 8.92)	4.40(-19.84 ; 29.41)

	Total cholesterol (mmol/l)	LDL-cholesterol (mmol/l)	HDL-cholesterol (mmol(l)	Triglycerides (mmol/l)
Senior (65≤age<97)	N[1] = 139	N[1] = 134	N[1] = 138	N[1] = 136
SSEP, E (95%CI)	-0.012(-0.031 ; 0.007)	-0.013(-0.029 ; 0.003)	0(-0.007 ; 0.006)	-0.003(-0.011 ; 0.005)
low vs medium SSEP, E (95%CI)	0.01(-0.52 ; 0.53)	-0.05(-0.51 ; 0.40)	-0.03(-0.21 ; 0.15)	-0.05(-0.29 ; 0.20)
low vs high SSEP, E (95%CI)	-0.38(-0.91 ; 0.16)	-0.44(-0.90 ; 0.03)	-0.01(-0.19 ; 0.17)	-0.15(-0.40 ; 0.09)
	Total cholesterol change (%)	**LDL change (%)**	**HDL change (%)**	**Triglycerides change (%)**
	N[1] = 166	N[1] = 152	N[1] = 160	N[1] = 161
SSEP, E (95%CI)	-0.167(-0.479 ; 0.142)	-0.465(-1.018 ; 0.103)	0.140(-0.247 ; 0.537)	-0.241(-0.897 ; 0.419)
low vs medium SSEP, E (95%CI)	-1.26(-9.84 ; 7.61)	-2.48(-18.43 ; 13.36)	-2.76(-13.60 ; 7.75)	-4.34(-23.31 ; 14.32)
low vs high SSEP, E (95%CI)	-0.42(-9.10 ; 8.45)	-9.79(-26.09 ; 6.14)	7.63(-3.12 ; 18.48)	-6.66(-25.33 ; 12.38)

Part B: Systolic and Diastolic Blood Pressure and Glucose

	Systolic blood pressure (mmHg)	**Diastolic blood pressure (mmHg)**	**Glucose (mmol/l)**
Young (13≤age<25)	N[1] = 126	N[1] = 126	N[1] = 101
SSEP, E (95%CI)	-0.002(-0.180 ; 0.173)	-0.051(-0.214 ; 0.113)	0.001(-0.008 ; 0.009)
low vs medium SSEP, E (95%CI)	3.18(-1.87 ; 8.24)	-0.06(-4.81 ; 4.63)	0.15(-0.12 ; 0.41)
low vs high SSEP, E (95%CI)	1.05(-4.69 ; 6.88)	-0.13(-5.52 ; 5.24)	0.11(-0.18 ; 0.40)
	Systolic blood pressure change (%)	**Diastolic blood pressure change (%)**	**Glucose change (%)**
	N[1] = 113	N[1] = 113	N[1] = 72
SSEP, E (95%CI)	0.045(-0.190 ; 0.284)	-0.001(-0.349 ; 0.350)	0.092(-0.145 ; 0.327)
low vs medium SSEP, E (95%CI)	3.89(-2.98 ; 10.81)	-5.34(-15.46 ; 4.70)	5(-2.42 ; 12.44)
low vs high SSEP, E (95%CI)	3.19(-4.77 ; 10.94)	-0.01(-11.47 ; 11.57)	4.27(-3.67 ; 11.89)
	Systolic blood pressure (mmHg)	**Diastolic blood pressure (mmHg)**	**Glucose (mmol/l)**
Adult (25≤age<65)	N[1] = 293	N[1] = 293	N[1] = 291
SSEP, E (95%CI)	-0.153(-0.305 ; -0.004)*	-0.015(-0.138 ; 0.107)	0.004(-0.006 ; 0.014)
low vs medium SSEP, E (95%CI)	-3.39(-7.04 ; 0.15)	-1.35(-4.35; 1.53)	-0.03(-0.27 ; 0.21)
low vs high SSEP, E (95%CI)	-4.82(-9.22 ; -0.44)*	0.14(-3.45 ; 3.73)	0.11(-0.19 ; 0.40)
	Systolic blood pressure change (%)	**Diastolic blood pressure change (%)**	**Glucose change (%)**
	N[1] = 224	N[1] = 224	N[1] = 169
SSEP, E (95%CI)	-0.051(-0.240 ; 0.147)	-0.050(-0.272 ; 0.171)	0.025(-0.240 ; 0.280)
low vs medium SSEP, E (95%CI)	-3.21(-7.99 ; 1.42)	-3.25(-8.49 ; 2.29)	-3.99(-10.42 ; 2.47)
low vs high SSEP, E (95%CI)	-2.36(-8.02 ; 3.28)	-2.48(-8.95 ; 4.02)	3.32(-4.29 ; 10.76)

	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Glucose (mmol/l)
Senior (65≤age<97)	N[1] = 47	N[1] = 47	N[1] = 62
SSEP, E (95%CI)	-0.320(-0.882 ; 0.231)	-0.012(-0.418 ; 0.382)	-0.014(-0.037 ; 0.008)
low vs medium SSEP, E (95%CI)	-5.39(-22.15 ; 11.12)	-7.57(-18.62 ; 3.76)	0.04(-0.58 ; 0.66)
low vs high SSEP, E (95%CI)	-4.58(-20.33 ; 11.16)	3.33(-7.36 ; 13.85)	-0.18(-0.74 ; 0.39)
	Systolic blood pressure change (%)	**Diastolic blood pressure change (%)**	**Glucose change (%)**
	N[1] = 32	N[1] = 32	N[1] = 29
SSEP, E (95%CI)	-0.290(-1.210 ; 0.616)	-0.425(-1.417 ; 0.558)	-0.455(-1.026 ; 0.112)
low vs medium SSEP, E (95%CI)	5.77(-26.52 ; 37.11)	3.72(-31.03 ; 39.30)	-1.40(-20.58 ; 18.01)
low vs high SSEP, E (95%CI)	-10.64(-40.96 ; 18.91)	-8.68(-40.94 ; 25.11)	-4.69(-19.91 ; 10.41)

Abbreviations: HDL: high-density lipoprotein; LDL: low-density lipoprotein; SSEP: Swiss socio-economic position

Metabolic parameter changes (in %) were calculated as the difference between the current value and the baseline value divided by the baseline value.

Analyses were performed during a 6-month follow-up period and adjusted by age, sex, first available BMI, diagnosis, risk of psychotropic drug-induced weight gain and were performed using linear mixed models adjusted in a Bayesian framework and using 1,000,000 Markov chain Monte Carlo iterations. SSEP effect was estimated (E (95%CI)) on a continuous and categorical scale (three SSEP categories: first quartile defines low SSEP, second and third quartiles medium SSEP and fourth quartile high SSEP). Significant p-values are indicated as *p≤0.05; **p≤0.01; ***p≤0.001.

[1]The number of patients included in the analyses differs because of missing data.

Supplementary Table 4: Association between SSEP and BMI, weight change and waist circumference change stratified by baseline BMI in the adult population

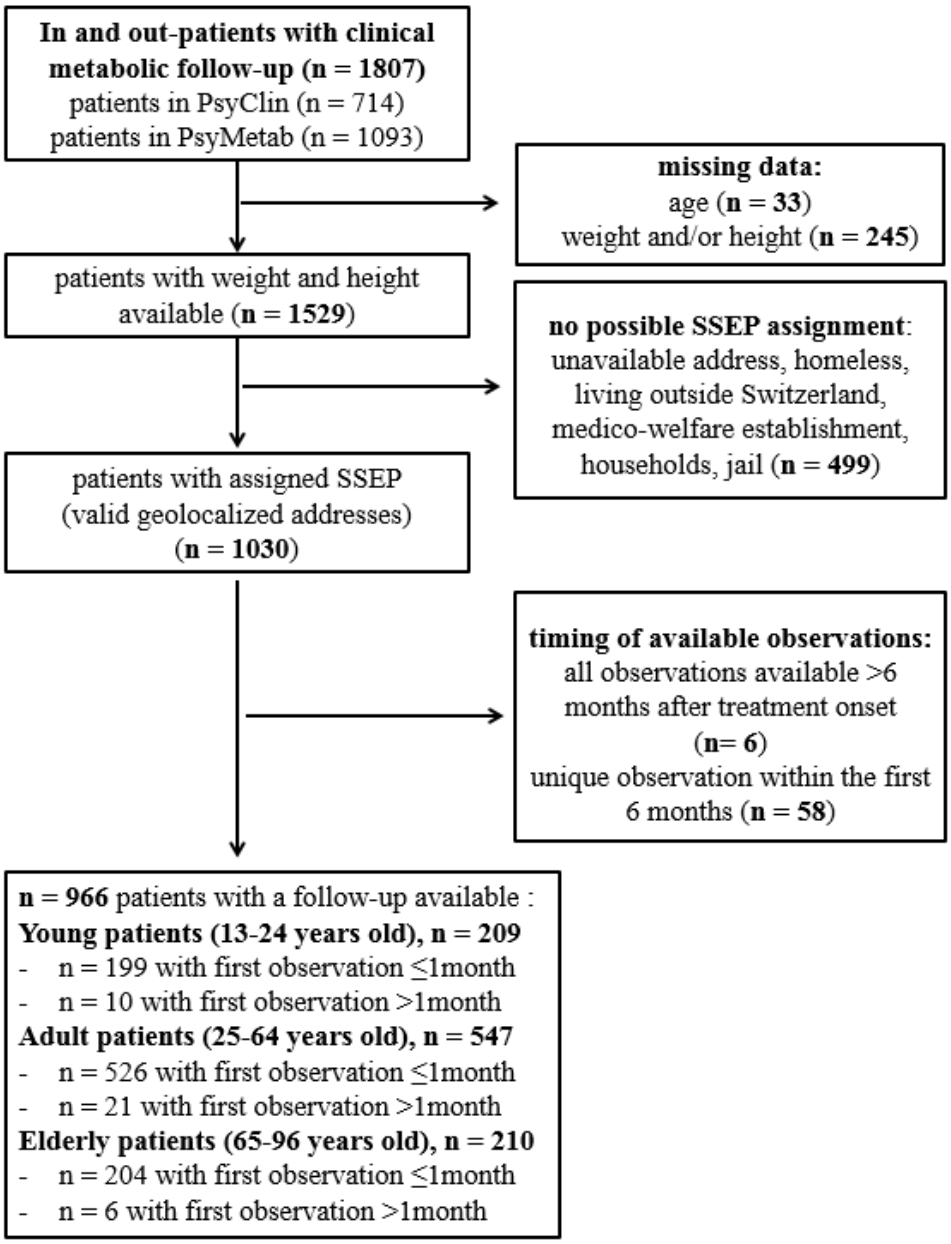
	BMI (kg/m^2)	**Weight change (%)**	**WC change (%)**
Obese (BMI>30 kg/m^2)	N = 76	N = 76	N[1] = 54
SSEP, E (95%CI)	0.048(-0.011 ; 0.108)	0.144(-0.020 ; 0.312)	0.015(-0.177 ; 0.210)
low vs medium SSEP, E (95%CI)	-0.65(-1.92 ; 0.55)	-1.49(-4.98 ; 2.02)	0.12(-3.72 ; 4.17)
low vs high SSEP, E (95%CI)	1.34(-0.20 ; 2.89)	3.71(-0.73 ; 8.05)	-0.76(-6.08 ; 4.77)
Overweight (25≤ BMI kg/m^2 <30)	N = 148	N = 148	N[1] = 107
SSEP, E (95%CI)	0.006(-0.018 ; 0.030)	0.020(-0.069 ; 0.108)	0.183(-0.043 ; 0.419)
low vs medium SSEP, E (95%CI)	0.29(-0.24 ; 0.83)	1.07(-0.91 ; 3.05)	5.28(0.40 ; 10.10)*
low vs high SSEP, E (95%CI)	0.20(-0.51 ; 0.91)	0.70(-1.98 ; 3.33)	1.50(-5.47 ; 8.66)
Normal weight (BMI<25 kg/m^2)	N = 302	N = 302	N[1] = 229
SSEP, E (95%CI)	0.015(0.0003 ; 0.030)*	0.064(-0.007 ; 0.135)	0.142(0.015 ; 0.270)*
low vs medium SSEP, E (95%CI)	0.16(-0.20 ; 0.54)	0.50(-1.18 ; 2.27)	4.57(1.32 ; 7.76)**
low vs high SSEP, E (95%CI)	0.38(-0.07 ; 0.82)	1.57(-0.55 ; 3.61)	4.14(0.42 ; 7.94)*

Abbreviations: BMI: body mass index, SSEP: Swiss socio-economic position, WC: waist circumference, WG: weight gain
Weight and WC change (in %) were calculated as the difference between the current value and the baseline value divided by the baseline value.
Analyses were performed in the adult population (25≤age<65) during a 6-month follow-up period and adjusted by age, sex, first available BMI, diagnosis, risk of psychotropic drug-induced weight gain and were performed using linear mixed models adjusted in a Bayesian framework and using 1,000,000 Markov chain Monte Carlo iterations. SSEP effect was estimated (E (95%CI)) on a continuous and categorical scale (three SSEP categories: first quartile defines low SSEP, second and third quartiles medium SSEP and fourth quartile high SSEP). Significant p-values are indicated as *p≤0.05; **p≤0.01; ***p≤0.001.
[1]The number of patients included in this analysis was lower than for BMI and weight because of missing WC data.

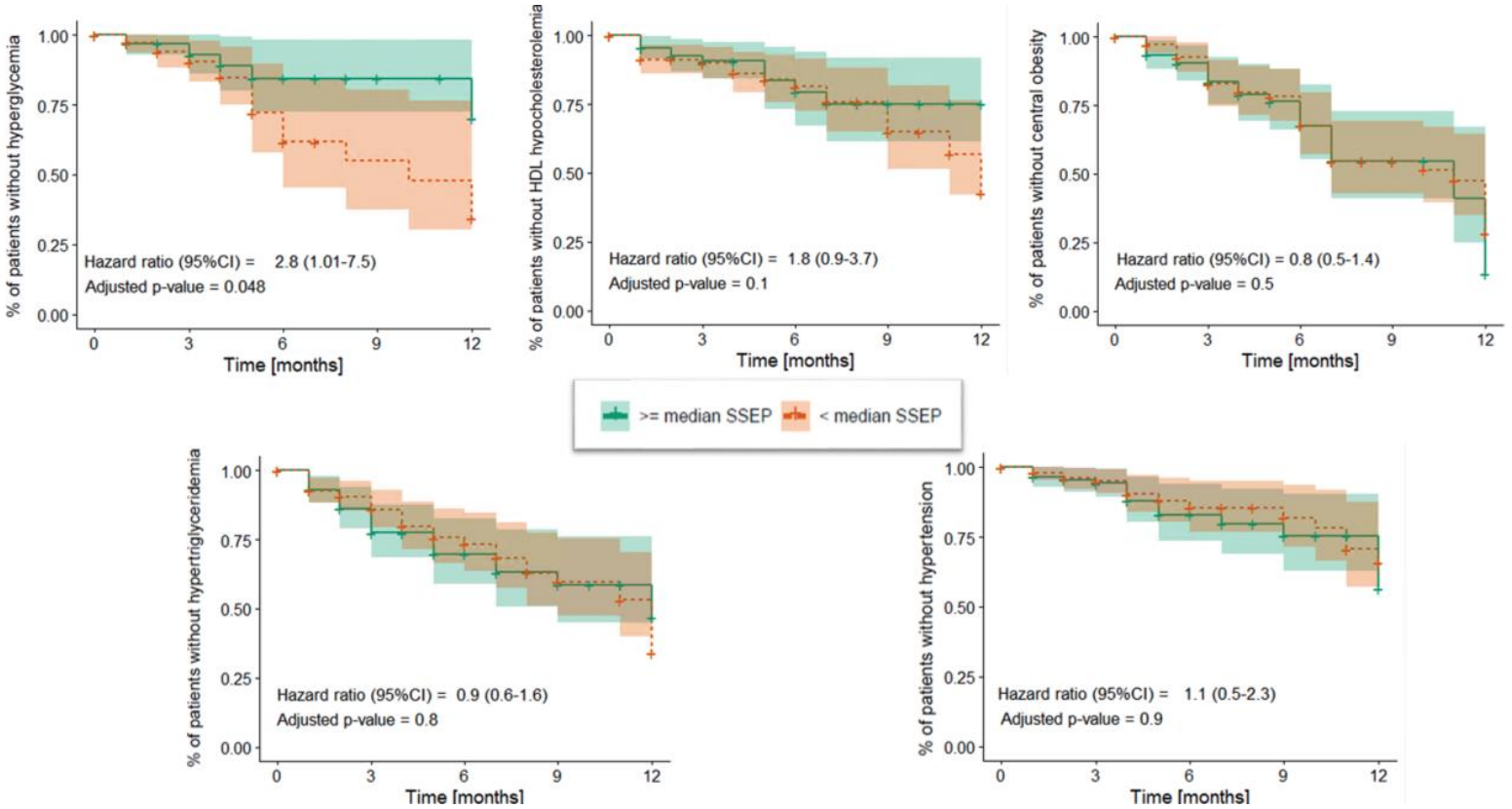
Supplementary Table 5: Association between educational attainment and BMI, weight change and waist circumference change in the adult population

	BMI (kg/m^2)	**Weight change (%)**	**WC change (%)**
Adult (25≤age<65)	N = 119	N = 119	N[1] = 96
EA, E (95%CI)	0.180(-0.026 ; 0.382)	0.499(-0.321 ; 1.311)	1.658(0.158 ; 3.106)*
low vs medium EA, E (95%CI)	-0.10(-0.74 ; 0.57)	-0.39(-3.04 ; 2.17)	-0.10(-4.90 ; 4.80)
low vs high EA, E (95%CI)	0.47(-0.32 ; 1.26)	1.09(-2.13 ; 4.21)	5.82(0.03 ; 11.79)

Abbreviations: BMI: body mass index, EA: educational attainment, SSEP: Swiss socio-economic position, WC: waist circumference
Weight and WC change (in %) were calculated as the difference between the current value and the baseline value divided by the baseline value. Analyses were performed during a 6-month follow-up period, adjusted by age, sex, first available BMI, diagnosis, risk of psychotropic drug-induced weight gain and were performed using linear mixed models adjusted in a Bayesian framework and using 1,000,000 Markov chain Monte Carlo iterations. Educational attainment effect was estimated (E (95%CI)) on a continuous and categorical scale (three EDU categories: 1-2 defines low EDU, 3-4 medium EDU and 5-6 high EDU). Significant p-values are indicated as *p≤0.05.
[1]The number of patients included in this analysis was lower than for BMI and weight because of missing WC data.

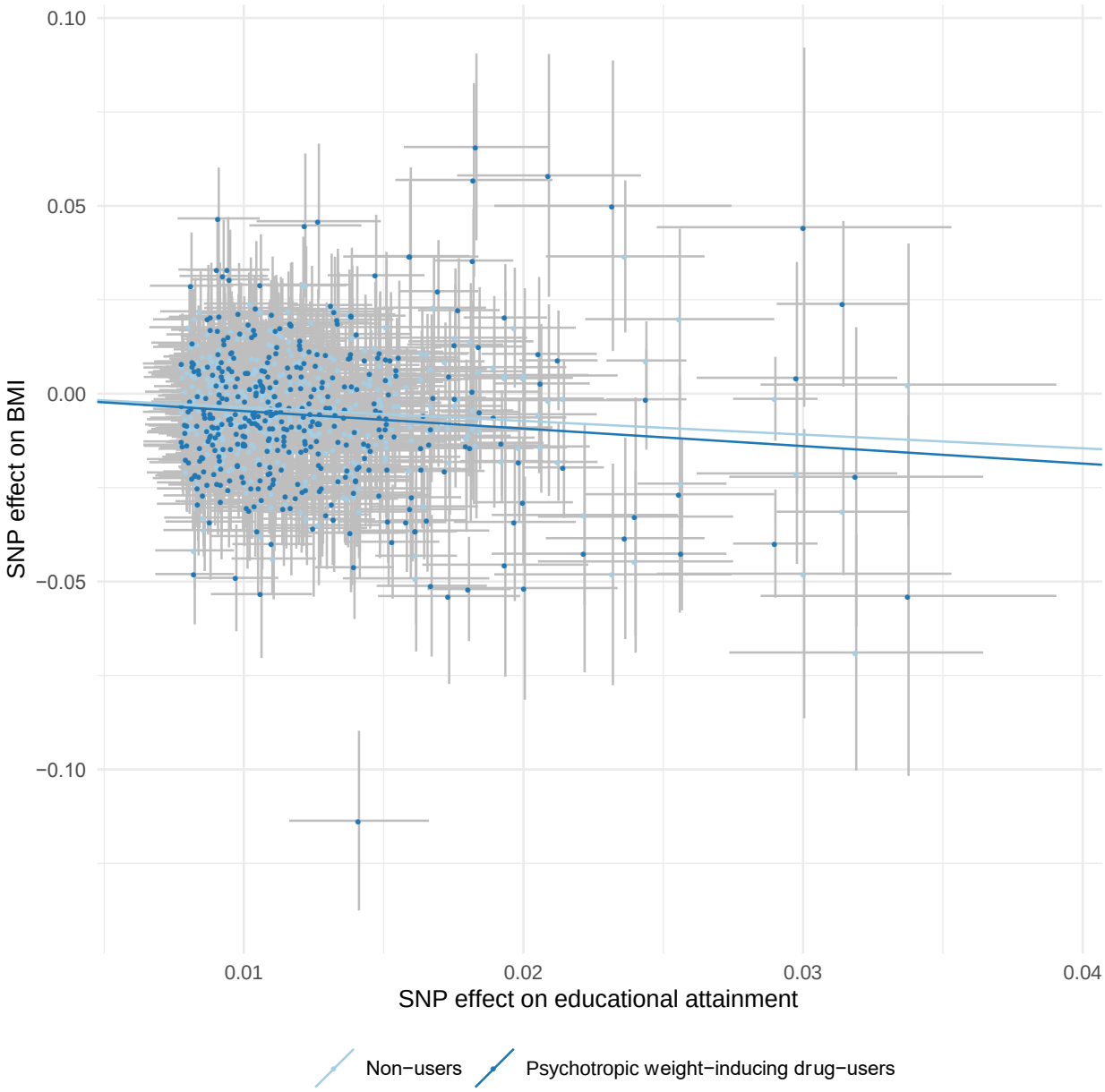


Supplementary Figure 1: Flowchart of the study population



Supplementary Figure 2: Incidence of new onset metabolic syndrome components dysregulation according to SSEP over one year of psychotropic treatment in the adult population

Analysis was performed in the adult population (25≤age<65) and was adjusted by age, sex, first available BMI, diagnosis, risk of psychotropic drug-induced weight gain, using a Cox proportional hazards model. Number at risk for each analysis: **Hyperglycemia**: at baseline: 95 High SSEP vs 106 Low SSEP, at 3 months: 44 High SSEP vs 50 Low SSEP, at 6 months: 14 High SSEP vs 13 Low SSEP, at 9 months: 9 High SSEP vs 8 Low SSEP, at 12 months: 6 High SSEP vs 7 Low SSEP; **HDL hypocholesterolemia**: at baseline: 100 High SSEP vs 121 Low SSEP, at 3 months: 52 High SSEP vs 70 Low SSEP, at 6 months: 20 High SSEP vs 34 Low SSEP, at 9 months: 12 High SSEP vs 21 Low SSEP, at 12 months: 9 High SSEP vs 12 Low SSEP; **Central obesity**: at baseline: 94 High SSEP vs 113 Low SSEP, at 3 months: 53 High SSEP vs 67 Low SSEP, at 6 months: 26 High SSEP vs 44 Low SSEP, at 9 months: 12 High SSEP vs 19 Low SSEP, at 12 months: 6 High SSEP vs 10 Low SSEP; **Hypertriglyceridemia**: at baseline: 108 High SSEP vs 131 Low SSEP, at 3 months: 60 High SSEP vs 77 Low SSEP, at 6 months: 23 High SSEP vs 34 Low SSEP, at 9 months: 14 High SSEP vs 20 Low SSEP, at 12 months: 10 High SSEP vs 14 Low SSEP; **Hypertension**: at baseline: 101 High SSEP vs 129 Low SSEP, at 3 months: 46 High SSEP vs 59 Low SSEP, at 6 months: 16 High SSEP vs 22 Low SSEP, at 9 months: 13 High SSEP vs 17 Low SSEP, at 12 months: 9 High SSEP vs 14 Low SSEP. High and Low SSEP groups were defined as SSEP over (≥61.8) vs under (<61.8) median SSEP, respectively.



Supplementary Figure 3: **Scatter plot illustrates the MR results estimating the causal effect of educational attainment on BMI in both high risk psychotropic weight-inducing drug-users and non users.**
Each point represents a SNP, where the x-axis illustrates the effect of the SNP on EA as calculated in SSGAC and the y-axis illustrated the effect on BMI in the UKB. The regression line represents the overall causal effect in each subgroup. We observed a stronger effect in high risk drug-users as compared with non-high risk drug users, as seen by the difference between the two slopes of the lines.

Project 3: Effect of quetiapine, from low to high dose, on weight and metabolic traits: results from a prospective cohort study

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Accepted in Pharmacopsychiatry (01.06.2021); DOI: 10.1055/a-1525-2820

Effect of quetiapine, from low to high dose, on weight and metabolic traits: results from a prospective cohort study

Running title: Dose dependency of quetiapine metabolic side effects

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ABSTRACT

Introduction: The atypical antipsychotic quetiapine is known to induce weight gain and other metabolic complications. The underlying mechanisms are multifactorial and poorly understood with almost no information on the effect of dosage. Concerns were thus raised with the rise in low-dose quetiapine off-label prescription (i.e. <150 mg/day).

Methods: In this study, we evaluated the influence of quetiapine dose for 474 patients included in PsyMetab and PsyClin studies on weight and metabolic parameter evolution. Weight, blood pressure, lipid and glucose profiles were evaluated during a follow-up period of 3 months after treatment initiation.

Results: Significant dose-dependent metabolic alterations were observed. Daily dose was found to influence weight gain, and increase the risk of undergoing clinically relevant weight gain (≥7% from baseline), while it was also associated with a change in plasma levels of cholesterol (total cholesterol, LDL cholesterol and HDL cholesterol) as well as with increased odds of developing hypertriglyceridemia, total and LDL hypercholesterolemia. No impact of a dose increase on blood pressure and plasma glucose level was observed.

Discussion: The dose-dependent effect highlighted for weight gain and lipid alterations emphasizes the importance of prescribing the minimal effective dose. However, as the effect size of a dose increase on metabolic worsening is low, the potential harm of low-dose quetiapine should not be dismissed. Prescriptions must be carefully evaluated and regularly questioned in light of side effect onset.

KeyWords: Antipsychotic drugs, Off-Label prescription, Safety profile, Cardio-metabolic health, Dose-dependent side effect

INTRODUCTION

People suffering from severe mental illness are at increased risk of developing metabolic syndrome and cardiovascular diseases when compared to the general population [1]. These physical conditions contribute to the shortened life expectancy observed in this vulnerable population [1, 2]. Besides the underlying illness-related factors and unhealthy lifestyle responsible for this concerning situation, several psychotropic drugs, including antipsychotics, can also lead to the development of metabolic disturbances [1]. Weight gain following antipsychotic treatments, known as antipsychotic-induced weight gain (AIWG) is indeed widely described in the literature [3-6].

Despite more than two decades of research in this area, the mechanisms involved in AIWG are still only partially understood [7]. They are multifactorial and likely result from a complex association of various neurobiological and metabolic pathways [7, 8]. Psychotropic treatments differ in their propensity to induce metabolic disturbances, with olanzapine and clozapine carrying the greatest risk for weight gain [4]. Regardless of the type of medication, there are considerable inter-individual variations in onset of metabolic side effects, and only a few clinical risk factors such as young age or a low body weight when first exposed to an antipsychotic treatment have been described [5]. Identification of these factors is critical to making the right choice when prescribing an antipsychotic, in order to minimize the occurrence of metabolic dysregulation. Strategies to manage AIWG in clinical practice comprise lifestyle interventions, switching antipsychotics and treatment with other medications to reverse weight gain [9, 10].

Dose-lowering strategies have also been discussed but to date there is a lack of evidence concerning the relationship between antipsychotic dose and weight gain [4, 9, 11]. In addition, it is essential to better characterize the dose-effect of AIWG outside the recommended dose range as well, since it is a common practice to either prescribe higher doses for patients who are not responding to treatment, or lower doses to manage off-label conditions, such as anxiety, insomnia or obsessive-compulsive disorders [12, 13]. This issue is of particular

concern for quetiapine, for which off-label use in low doses is important, despite the absence of demonstrated efficacy and safety [14-17].

A literature review on AIWG dose-effect [11] included 6 studies addressing the dose effect of quetiapine weight gain with prescribed daily doses ranging from 75 mg to 750 mg per day for a follow-up of 6 to 52 weeks. Only one of them reported a difference in the odds of gaining clinically relevant weight (CRW, ≥7% of baseline body weight) after 6 weeks between patients receiving doses <250mg versus <750mg per day. The 5 remaining studies conclude that there is no clear weight gain-dose relationship. It is noteworthy that these studies did not evaluate the effect of dose on other metabolic outcomes. Subsequently, summarized results from studies on the number needed to harm (NNH) to induce CRW reported inconclusive results as to a dose effect [18]. Finally and more recently, some studies have specifically addressed the effect of low doses of quetiapine (<200mg/d), highlighting substantial metabolic changes [19, 20], while others comparing low to higher doses (cut-off set at 75 mg/d) or high to very high doses (cut-off set at 800 mg/d) found significant weight gain differences between groups [21, 22].

These conflicting results prevent a clear conclusion from being drawn concerning the dose effect of quetiapine-induced weight gain. In addition, the dose-dependency of other metabolic outcomes is scarcely described and warrants better characterization. In the present study, we aimed to tackle this important clinical question by evaluating whether quetiapine dose modulates weight gain as well as other metabolic outcomes.

METHODS

Study design

We collected data from in- and out-patients who started treatment with quetiapine, as part of a cohort study (PsyMetab) described elsewhere [23]. Briefly, metabolic parameters were monitored following internal guidelines after the introduction of a psychotropic medication with a risk of weight gain in the Department of Psychiatry of the Lausanne University Hospital, in the Department of Psychiatry of the Geneva University Hospital and in a private mental health care center (Les Toises) [24]. Informed consent was obtained for the inclusion of patients in the PsyMetab study, which allows the use of clinical data (for the present study, data from 06/14/2007 to 08/06/2019). In addition, the Ethics Committee of the Canton of Vaud (CER-VD) granted access to clinical data of followed-up patients in the Department of Psychiatry of the Lausanne University Hospital until the end of 2015 due to the non-interventional post hoc analysis design (PsyClin; for the present study, data from 10/13/2007 to 12/03/2015).

Patients from PsyMetab-PsyClin were included in the current analyses if they were started on quetiapine treatment with a first evaluation within 21 days following initiation and a minimum of two weight measurements recorded within the first 3 months of treatment (Fig. 1). Patients were either drug-naïve or had received previous antipsychotic treatments.

Variables and measurements

Metabolic parameters including body weight, blood pressure and plasma levels of glucose, triglycerides and cholesterol (total cholesterol, LDL cholesterol and HDL cholesterol) were extracted from patients' medical records as well as information on diagnosis, age, height, sex and smoking status. Metabolic syndrome was defined according to the International Diabetes Federation (IDF) as the presence of central obesity plus any two of the following factors in metabolic dysregulation: hyperglycemia, elevated blood pressure, hypertriglyceridemia and low HDL cholesterol level [25]. Diagnostic groups were established according to ICD-10 classification. We obtained data on quetiapine total daily dose, concurrent use of a psychotropic drug with risk of weight gain (most antipsychotics, mood stabilizers and some

antidepressants) and medications indicated for the treatment of metabolic disturbances (lipid-lowering, antidiabetic and antihypertensive treatments) either prescribed (outpatients) or administered (inpatients); see Supplementary Table 1 for the complete list of medications. Quetiapine dose was defined as low or high when it was below or above 150 mg per day for more than 50% of the follow-up period. The cut-off of 150 mg per day was chosen as it is the lowest prescribed dose for official indications [26], lower doses indicating an off-label use.

Statistical analyses

Baseline demographic variables and metabolic parameters of patients were described and compared according to low or higher quetiapine dose using the $\chi 2$ test of independence for categorical variables and Student's t-tests for continuous variables.

We modeled the effect of quetiapine dose on weight change over the first three months of treatment using a linear mixed effects model, adjusting for confounding variables [age, sex, baseline body mass index (BMI), previous and co-prescription of psychotropic treatment, diagnosis and setting of care (in-/outpatient status)]. We then tested the effect of interactions between age and baseline BMI with quetiapine dose on weight gain. Analyses were conducted on a follow-up period of three months, as previous studies have reported that most weight gain occurs within the first months of treatment and that early metabolic changes are good predictors for further deterioration [4, 5, 22, 27, 28]. In addition, analysis of extended periods of treatments (i.e., over 3 months) appears less reliable due to a lower number of available biological measurements (because of the internal guideline requiring check-ups at 0, 1, 2, 3 months, and then only at 6 and 12 months), because of a reduced number of patients with long term follow-up, and because of possible reduced adherence to treatment during long term periods. As a sensitivity analysis, we used a subgroup of patients for which we had data up to one year of treatment and performed a piecewise linear regression model with weight evolution over one year, with a knot at three months. Quetiapine dose effect was assessed using the variable on a continuous and categorical scale (low/higher dose). The same analysis was carried out to characterize the dose association with the other metabolic parameters (adjusting

for age, sex and baseline metabolic trait). To further characterize the clinical relevance of metabolic changes, we used mixed effects logistic regression models, adjusting for confounding variables (same as above), to evaluate the risk of developing metabolic dysregulation (i.e., the development of a CRW, of obesity, of hyperglycemia, of hypertension and of dyslipidemia). Inclusion of patients in the various analyses is displayed in Supplementary Fig. 1.

All analyses were two-sided with alpha=0.05. Data preparation was conducted using Stata 16 (StataCorp; College Station, Texas) and analyses were performed using the R environment for statistical computing version 4.0.2.

RESULTS

A total of 474 patients were included in the study. A description of the sample's characteristics is presented in Table 1. The median quetiapine dose was 300 mg per day (interquartile range (IQR) = 100-563), with approximately one-third of the cohort receiving doses lower than 150 mg per day. The median age was 42.5 years old (IQR = 25-60) with patients being prescribed low doses of quetiapine being 11.5 years older than those receiving higher doses ($p<10^{-4}$). Men represented 46.2% of the sample with no significant difference between dose groups. Median follow-up duration was 59 days, with a minimum of 21 days and a maximum of 105 days, and took place at a hospital for 57.6% of patients being prescribed low doses and reached 85.5% of patients being prescribed higher doses ($p<10^{-4}$). Main diagnoses were psychotic disorders (22.4%) and depression disorders (22.4%) followed by bipolar disorder (15.6%), with a very different prevalence based on quetiapine dose prescription ($p<10^{-4}$). One-third of patients being prescribed higher doses of quetiapine had a concomitant prescription of another psychotropic medication with a risk of weight gain, while it concerned 17.9% of patients prescribed low doses (p=0.001).

Regarding metabolic parameters at the time of quetiapine first prescription, the median BMI was 23.6 (IQR = 20.7-27.0) with a prevalence of overweight and obese subjects of 48.0 and 34.5%, respectively. Hypertension and hypertriglyceridemia were present in 43.6 and 40.0%, respectively, of low quetiapine dose users, and 27.2 and 25.1% of higher dose users (p=0.004 for hypertension, p=0.01 for hypertriglyceridemia), while the prevalences for the other traits in metabolic dysregulation were similar between the two dose groups and reached 19.1% for hyperglycemia, 46.9% for total hypercholesterolemia, 45.2% for LDL hypercholesterolemia and 44.7% for HDL hypocholesterolemia. These metabolic alterations resulted in a prevalence of metabolic syndrome of 17.7% in low-dose users and 10.2% in higher-dose users (p=0.03).

Mean weight gain over treatment time is displayed in Fig. 2, separating patients taking less than 150 mg/d and those taking 150 mg or more. The median weight gain at the last study visit was 2.7% (IQR = 0-6.3) and was significantly higher in the group being prescribed higher

quetiapine doses (median weight gain in % (IQR): 1.5 (0-4.2) in low-dose versus 3.2 (0-6.8) in the higher-dose group, p=0.002). Throughout treatment, 13.9% of patients receiving low doses underwent CRW, while this proportion reached 30.3% of patients who received higher doses ($p<10^{-4}$).

After correcting with baseline BMI, age, sex and setting of care, weight gain over treatment time was significantly increased when patients were prescribed higher doses of quetiapine. Interestingly, baseline BMI was negatively associated with weight gain (p<0.001) and a trend was observed toward a negative association between age and weight gain (p=0.059). Baseline BMI, unlike age, interacted positively with quetiapine dose effect on weight change (p=0.02). The setting of care had a notable impact on weight, with hospitalized patients gaining 1.49% more weight than outpatients (95% CI = 0.64-2.33). We found no difference in weight change between men and women. Diagnosis, previous and co-prescription of a psychotropic drug known to induce weight gain were not added as covariates, as none had a significant impact on the outcome nor on the estimates of the other co-variables, while their inclusion did not improve the model (see Supplementary Appendix). In our model, each increase of 150 mg of quetiapine daily dose was associated with an increase of 0.12% (95% CI = 0.01-0.24) of weight gain during the first three months of treatment (Table 2). However, when quetiapine dose was used as a categorical variable (below or above 150 mg/d), the estimated effect was not statistically significant, as shown in Supplementary Figure 3. The piecewise linear regression model confirmed that weight gain was more pronounced early after treatment initiation, with an increase in baseline weight of 1.02% (95% CI = 0.73-1.30) per month during the first three months, while the increase from three months to one year was estimated to be 0.28% (95% CI = 0.20-0.36) per month.

Table 2 summarizes the effect of quetiapine daily dose increase on the evolution of all monitored metabolic parameters. Briefly, when corrected with baseline parameter value, age and sex, a statistically significant impact was revealed for changes in cholesterol levels: total cholesterol change was 2.02% higher (95% CI =0.91-3.12), LDL cholesterol 3.27% higher

(95% CI = 1.51-5.04) and HDL cholesterol 1.34% lower (95% CI = 0.16-2.51) for each 150 mg increase of quetiapine daily dose, while no significant association was observed with blood pressure, glucose and triglyceride levels. When estimating the impact of a dose lower or higher than 150 mg per day, the effect remained significant on total and LDL cholesterol change: 6.39% (95% CI = 0.84-11.95) for increased total cholesterol change and 10.96% (95% CI = 1.96-19.96) for increased LDL cholesterol change.

The occurrence of new metabolic dysregulation was important following treatment introduction, and obesity reached a proportion of 42.7% of the sample at the end of the follow-up period. As shown in Table 3, the odds of experiencing CRW were greater with a higher dose of quetiapine [OR (95% CI) =1.16 (1.04-1.31) for each 150 mg/d increase], but for the development of obesity, the association was not significant. Regarding the other metabolic traits, hyperglycemia and HDL hypocholesterolemia onset were not associated with quetiapine dose, whereas the odds of hypertriglyceridemia, total and LDL hypercholesterolemia onset were increased with higher doses of quetiapine [OR (95% CI) = 1.49 (1.11-2.00), 1.56 (1.22-1.99) and 1.58 (1.24-2.00), respectively]. The OR of hypertension occurrence depending on quetiapine dose could not be calculated due to too few cases of new-onset hypertension. Doses equal or higher than 150 mg per day were significantly associated with the occurrence of CRW and LDL hypercholesterolemia [OR (95% CI) = 2.26 (1.26-4.03) and 3.92 (1.01-15.16), respectively], but not with the other metabolic disturbances. When investigating the impact of the dose on metabolic syndrome development, no significant interaction was revealed.

DISCUSSION

In this retrospective analysis of 474 patients followed up for a period of 3 months after quetiapine initiation, we observed an association between quetiapine dose increase, weight gain and other metabolic alterations. More specifically, an increase of quetiapine daily dose was significantly associated with higher weight gain and increased odds of experiencing a CRW, while it was also associated with a rise in levels of cholesterol as well as increased odds of developing hypertriglyceridemia, total and LDL hypercholesterolemia. We could not, however, highlight any impact on blood pressure and glucose level during this short period of time. Eventually, the likelihood of developing metabolic syndrome was not increased with higher quetiapine doses.

Despite the association between quetiapine dose and weight increase, the clinical relevance of the effect is low. Thus, for a patient with an initial weight of 70 kg, an increase in quetiapine daily dose of 150 mg would result in a 84g-greater weight gain (95% CI = 7-168g). This effect was statistically significant in our cohort as we benefitted from a good statistical power, which might explain why other studies with smaller sample sizes could not reveal such a small effect [11]. Indeed, when modeling quetiapine dose as a categorical variable (lower or higher than 150 mg/d), our statistical power was reduced and the effect on weight gain was no longer significant.

We highlighted a positive interaction effect of baseline BMI with quetiapine dose on weight change, meaning that when baseline BMI is higher, the effect of an increase of quetiapine dose has a greater impact on weight. This could be interpreted as follows: an individual with a low BMI is sensitive to quetiapine-induced weight gain and a small dose will be sufficient to increase weight, while another patient with a higher initial BMI is slightly protected against weight gain such that small doses will have very limited effect and he will undergo a weight increase with higher doses.

To our knowledge, the only other studies that reported greater weight gain with higher quetiapine doses compared groups receiving doses below or above 75 mg [22] or 800 mg per

day [21]. In the first case, the differences in weight gain between the two dosage groups after 6 weeks of treatment were 1.6 kg and 1.1 kg for women and men, respectively. This effect is much larger than the one we observed. The reported results might depend on the dose cut-off that was chosen and the duration of treatment, although we did not obtain a significant association either when we applied a 75 mg/d cut-off and restricted our follow-up to a maximum of 6 weeks (data not shown). However, most importantly, the authors of this study only conducted their analysis on dosage subgroups separately and did not give any description of these two subgroups' characteristics nor did they perform multivariate analysis. Due to the observational cohort study design, the two populations might largely differ, as the dose prescription was not attributed at random but was supposedly based on clinical factors and/or practice. The higher dose group might have been therefore more vulnerable to weight gain because of baseline risk factors that were not accounted for in the analysis, inflating the dose effect of quetiapine. Indeed, in our cohort, patients receiving low doses were older, had overall worse baseline metabolic conditions and were hospitalized less. The univariate comparison of their weight gain thus led to a significant difference ($p=0.002$). In the second study, the authors evaluated weight gain in patients having had a one-month treatment with 800 mg/d of quetiapine who further continued the treatment with either 800 mg/d or higher dosages. The higher-dose group gained weight after augmentation whereas the other group remained stable. This difference did not remain significant when they considered BMI change. Direct comparison with our data was not possible as we did not have a large enough number of patients with a >800mg/d quetiapine dosage, which is off-label.

From our data, we can thus conclude that prescribing an off-label quetiapine dose lower than 150 mg per day induces weight gain very similar to that of a higher dosage. This is in line with previous reports of important weight gain following treatments with low doses of quetiapine [19, 20]. Nevertheless, a slight increase in weight gain with dose augmentation was observed across the whole dose range of quetiapine. This effect is also noticeable on the risk of

experiencing an important weight gain. Prescription of the lowest effective dose is thus highly recommended to minimize weight gain.

Concerning the other metabolic traits, the risk of a rapid worsening of lipid parameters and of dyslipidemia onset with psychotropic treatments (including quetiapine) and the importance of lipid monitoring was already expressed in a previous work conducted with patients from the same Swiss cohort [28]. LDL hypercholesterolemia was shown to be significantly associated with the expected risk categorization of psychotropic drugs, with quetiapine conferring an intermediate risk, while the other lipid phenotypes were not differently affected by the various medications. Interestingly, LDL cholesterol was also the lipid parameter that showed the greatest association with quetiapine dose. Patients with doses of quetiapine equal or higher than 150 mg per day were indeed nearly 4 times more likely to develop LDL cholesterol dyslipidemia within a short period of time (i.e., 3 months). As for glucose level and blood pressure, the lack of association with quetiapine dose can result from underpowered analyses: as these parameters were less monitored, only a subset of all patients could be analyzed, and with few measurements over time. In clinical practice, blood pressure is less often monitored than other metabolic parameters after treatment initiation and the effect of antipsychotics on hypertension risk is not well-established [7]. The absence of a dose effect can also possibly reflect a relatively low impact of quetiapine on blood pressure change. The effect of quetiapine on glucose profile has, however, been more consistently described, although alterations might only appear after a longer period of treatment [29]. Altogether, our data do not allow us to conclude the dose effect of quetiapine on these two metabolic parameters within the three-month period following quetiapine initiation; extended periods of treatment should be examined in future studies.

Several limitations of the present work need to be expressed. First, quetiapine doses are only a rough approximation of actual bodily exposure to the drug, as daily doses and plasma concentrations are poorly correlated [30, 31]. To better establish the biological relevance of dosage influence on weight gain, these analyses should be replicated using quetiapine plasma

concentrations. This also raises the question of the characterization of the dose during treatment. As opposed to randomized clinical trials in which fixed doses can be studied, our followed-up patients received flexible doses over time according to clinical needs. This makes the dose-response estimation less precise and only valid for large dose increments. Besides, adherence to treatment was not ascertained and poor compliance could thus interfere with our results. However, among hospitalized patients, administered dose rather than prescribed dose was extracted from the medical files, increasing our confidence in the accuracy of this variable. Eventually, information on concomitant diseases (apart from metabolic diseases) and lifestyle factors such as diet or physical activity were not available, preventing us from controlling for the possible effect of these parameters on weight. However, limiting our investigation to the early weight gain, directly following treatment initiation, enabled us to minimize the impact of the other environmental factors (that most likely remained unchanged during this period). Effect of diagnosis, previous and co-prescription of another psychotropic drug did not seem to alter the effect of a dose increase on weight gain, although we did not have enough data to clearly establish their impact. Further studies should evaluate the influence of these parameters, also better characterizing specific psychiatric symptoms and severity of disease as they could be confounding the dose effect observed on weight gain and metabolic changes. Despite these limitations, results from our cohort study provide valuable evidence from real world practice. The dose effects highlighted for weight gain and lipid alterations emphasize the importance of prescribing the minimal effective dose, but without dismissing the potential harm of quetiapine doses below 150 mg per day. Metabolic monitoring should be implemented in all clinical settings and for every patient, no matter the prescribed dose. Given that the dose effect is small, low-dose off-label prescriptions should be carefully considered and limited, favoring alternative approaches. The indication of treatment must be carefully evaluated and regularly questioned in light of side effect onset.

ACKNOWLEDGMENTS

The authors thank the laboratory, nursing and medical staff who were involved in the metabolic monitoring program and all the participants in PsyMetab and PsyClin.

FUNDING

This work was supported in part by the Swiss National Research Foundation (CE and PC: 320030-120686, 324730-144064, 320030-173211; CE; PC, KJP: 320030-200602). The funding sources had no role in the writing of the manuscript or in the decision to submit it for publication.

CONFLICT OF INTEREST

CBE received honoraria for conferences or teaching CME courses from Janssen-Cilag, Lundbeck, Otsuka, Sandoz, Servier, Sunovion, Vifor-Pharma, and Zeller in the past 3 years. The other authors report no potential conflicts of interest in relation to the subject of this study.

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Table 1: Clinical and demographic parameters of the study sample according to quetiapine dose

	Total sample	**Low dose group <150mg/d**	**Higher dose group ≥150mg/d**	**p-value[1]**
Number of patients	474	144	330	
Age, median (IQR), years	42.5 (25-60)	49.5 (33-74.5)	38 (24-55)	**$<10^{-4}$**
Men, n(%)	219 (46.2)	62 (43.1)	157 (47.6)	0.36
Follow-up duration, median (IQR), days	59 (34-88)	56 (35-82)	60 (33-90)	0.29
Quetiapine dose, median (IQR), mg/d	300 (100-563)	50 (25-100)	400 (267-600)	
Smoking, n/total (%)	213/472 (45.1)	56/144 (38.9)	154/328 (48.0)	0.08
Hospital stay, n (%)	365 (77.0)	83 (57.6)	282 (85.5)	**$<10^{-4}$**
Main diagnosis, n (%)				**$<10^{-4}$**
psychotic disorders (F20-F24;F28-F29)	106 (22.4)	15 (10.4)	91 (27.6)	
schizoaffective disorders (F25)	53 (11.2)	7 (4.9)	46 (13.9)	
bipolar disorders (F30-F31)	74 (15.6)	12 (8.3)	62 (18.8)	
depressive disorders (F32-F33)	106 (22.4)	45 (31.3)	61 (18.5)	
other	71 (15.0)	36 (25.0)	35 (10.6)	
not available	64 (13.5)	29 (20.1)	35 (10.6)	
Baseline metabolic parameters[2]				
Weight, median (IQR), kg	M: 73 (64-81) F: 62 (53-71)	M: 74 (64-84) F: 62 (53-69)	M: 72 (64-81) F: 62 (53-72)	M:0.41 F :0.18
BMI, n ; median (IQR), kg/m^2	n=441; 23.6 (20.7-27.0)	n=136; 23.7 (21.1-27.2)	n=305; 23.4 (20.5-26.7)	0.55
Overweight/Obesity, n/total (%)	216/450 (48.0)	72/141 (51.1)	144/309 (46.6)	0.38
Obesity, n/total (%)	159/461 (34.5)	54/141 (38.3)	105/320 (32.8)	0.25
Hypertension, n/total (%)	99/303 (32.7)	44/101 (43.6)	55/202 (27.2)	**0.004**
Raised fasting plasma glucose, n/total (%)	52/273 (19.1)	21/84 (25.0)	31/189 (16.4)	0.10
Fasting hypertriglyceridemia, n/total (%)	83/280 (29.6)	34/85 (40.0)	49/195 (25.1)	**0.01**
HDL hypocholesterolemia, n/total (%)	135/302 (44.7)	46/95 (48.4)	89/207 (43.0)	0.38
Total hypercholesterolemia, n/total (%)	142/303 (46.9)	49/92 (53.3)	93/211 (44.1)	0.14
LDL hypercholesterolemia, n/total (%)	133/204 (45.2)	48/92 (52.2)	85/202 (42.1)	0.11
Metabolic syndrome IDF, n/total (%)	52/419 (12.4)	22/124 (17.7)	30/295 (10.2)	**0.03**
Previously treated by psychotropic medication, n/total (%)[3]	156/330 (47.3)	30/107 (28.0)	126/223 (56.5)	**$<10^{-4}$**
Co-medication, n/total(%)[3]				
psychotropic medication with risk for weight gain	131/456 (28.7)	24/134 (17.9)	107/322 (33.2)	**0.001**
antidiabetic drug	18/397 (4.5)	7/117 (6.0)	11/280 (3.9)	0.37
antihypertensive drug	57/397 (14.4)	24/117 (20.5)	33/280 (11.8)	**0.02**
lipid lowering drug	30/397 (7.6)	14/117 (12.0)	16/280 (5.7)	**0.03**

Abbreviations: BMI: body mass index, F: Female, HDL: high-density lipoprotein, F00-F33: ICD codes, IDF: International Diabetes Federation, IQR: interquartile range, LDL: low-density lipoprotein, M: Male.
[1]p-values were calculated using Student t-tests for continuous variables and χ^2 test of independence for categorical variables. Significant p-values are indicated in bold.
[2]Baseline observation includes observations within 21 days following quetiapine initiation. Overweight/Obesity defined as BMI ≥ 25 or obesity; Obesity defined as central obesity according to IDF definition; Total hypercholesterolemia defined as Cholesterol ≥ 5mmol/l or presence of lipid-lowering treatment; LDL hypercholesterolemia defined as LDL ≥ 3mmol/l or presence of lipid-lowering treatment; and other metabolic disturbances defined according to IDF definition.
[3]See Supplementary data for the list of considered drugs.

Table 2: Association of metabolic parameters change with quetiapine daily dosage

Metabolic parameter change[1] %	N[2]	Effect of 150 mg increase of quetiapine daily dose[3], E (95% CI)	Effect of low vs. higher quetiapine dose, E (95% CI)
Weight	439	0.12 (0.01 to 0.24)*	0.29 (-0.46 to 1.05)
Systolic blood pressure	100	-0.38 (-1.46 to 0.70)	-0.47 (-4.88 to 3.94)
Diastolic blood pressure	100	-0.41 (-1.65 to 0.83)	0.57 (-4.42 to 5.56)
Glucose	86	-0.23 (-2.40 to 1.94)	-6.57 (-15.30 to 2.16)
Triglycerides	124	4.94 (-0.26 to 10.15)	7.84 (-15.69 to 31.36)
Total Cholesterol	192	2.02 (0.91 to 3.12)**	6.39 (0.84-11.95)*
LDL Cholesterol	180	3.27 (1.51 to 5.04)***	10.96 (1.96-19.96)*
HDL Cholesterol	190	-1.34 (-2.51 to -0.16)*	-4.30 (-10.17 to 1.56)

Abbreviations: HDL: high-density lipoprotein, LDL: low-density lipoprotein
Analyses were performed during a 3-month follow-up period, adjusted by age, sex, baseline parameter value (and setting of care for weight change) and were performed using linear mixed models. Quetiapine dose effect was estimated (E (95% CI)) on a continuous and categorical scale (low dose <150mg/d ≥ higher dose). Significant p-values are indicated as *p≤0.05; **p≤0.01; ***p≤0.001.
[1]Metabolic parameter changes (in %) were calculated as the difference between the current values and the baseline values divided by the baseline values.
[2]The number of patients included in analyses varies according to availability of data as stated in Supplementary Figure 1.
[3]To understand the magnitude of these results, one can imagine a fictional patient taking a quetiapine daily dose of 200 mg and gaining 2% of his/her baseline weight after 3 months of treatment. If the same patient took a quetiapine dose of 350 mg per day, he/she would have gained 2.12% of his/her baseline weight.

Table 3: Association of metabolic disturbance onset with quetiapine daily dosage

Metabolic disturbance onset	N[1]	Effect of 150mg increase of quetiapine daily dose[2], OR (95% CI)	Effect of low vs. higher quetiapine dose, OR (95% CI)
CRW	439	1.16 (1.04-1.31)*	2.26 (1.26-4.03)**
Obesity	291	0.97 (0.85-1.10)	0.93 (0.53-1.64)
Hyperglycemia	162	0.99 (0.65-1.51)	1.12 (0.19-6.47)
Hypertriglyceridemia	267	1.49 (1.11-2.00)**	1.02 (0.21-4.91)
Total hypercholesterolemia	161	1.56 (1.22-1.99)***	2.39 (0.66-8.66)
LDL hypercholesterolemia	161	1.58 (1.24-2.00)***	3.92 (1.01-15.16)*
HDL hypocholesterolemia	236	1.01 (0.79-1.30)	0.42 (0.11-1.58)
Metabolic Syndrome	374	1.06 (0.87-1.28)	1.44 (0.58-3.58)

Abbreviations: CRW: clinically relevant weight gain, HDL: high-density lipoprotein, LDL: low-density lipoprotein

Analyses were performed during a 3-month follow-up period, adjusted by age, sex, baseline parameter value (and setting of care for weight change) and were performed using mixed effects logistic regression models. Models for hypertriglyceridemia and HDL hypercholesterolemia were not adjusted by baseline values due to availability of data. Quetiapine dose was estimated (E (95% CI)) on a continuous and categorical scale (low dose <150mg/d ≥ higher dose). Significant p-values are indicated as *p≤0.05; **p≤0.01; ***p≤0.001.

[1]The number of patients included in analyses varies according to availability of data as stated in Supplementary Figure 1.

[2]To understand the magnitude of these results, one can imagine a fictional patient taking a quetiapine daily dose of 200 mg. If the same patient took a quetiapine dose of 350 mg per day, his/her odds of undergoing a CRW would increase by 16%.

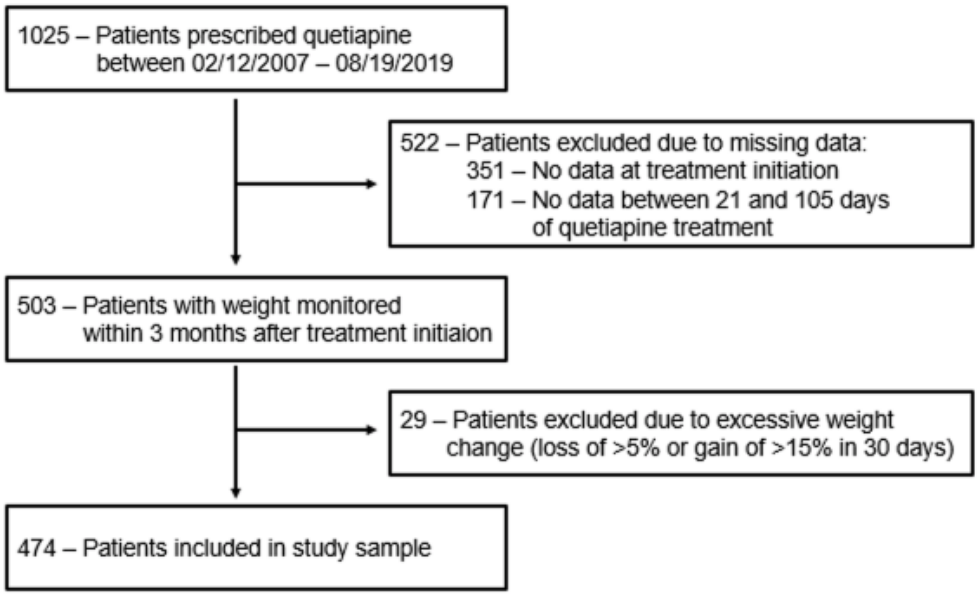

Fig. 1: Inclusion of participants in the study

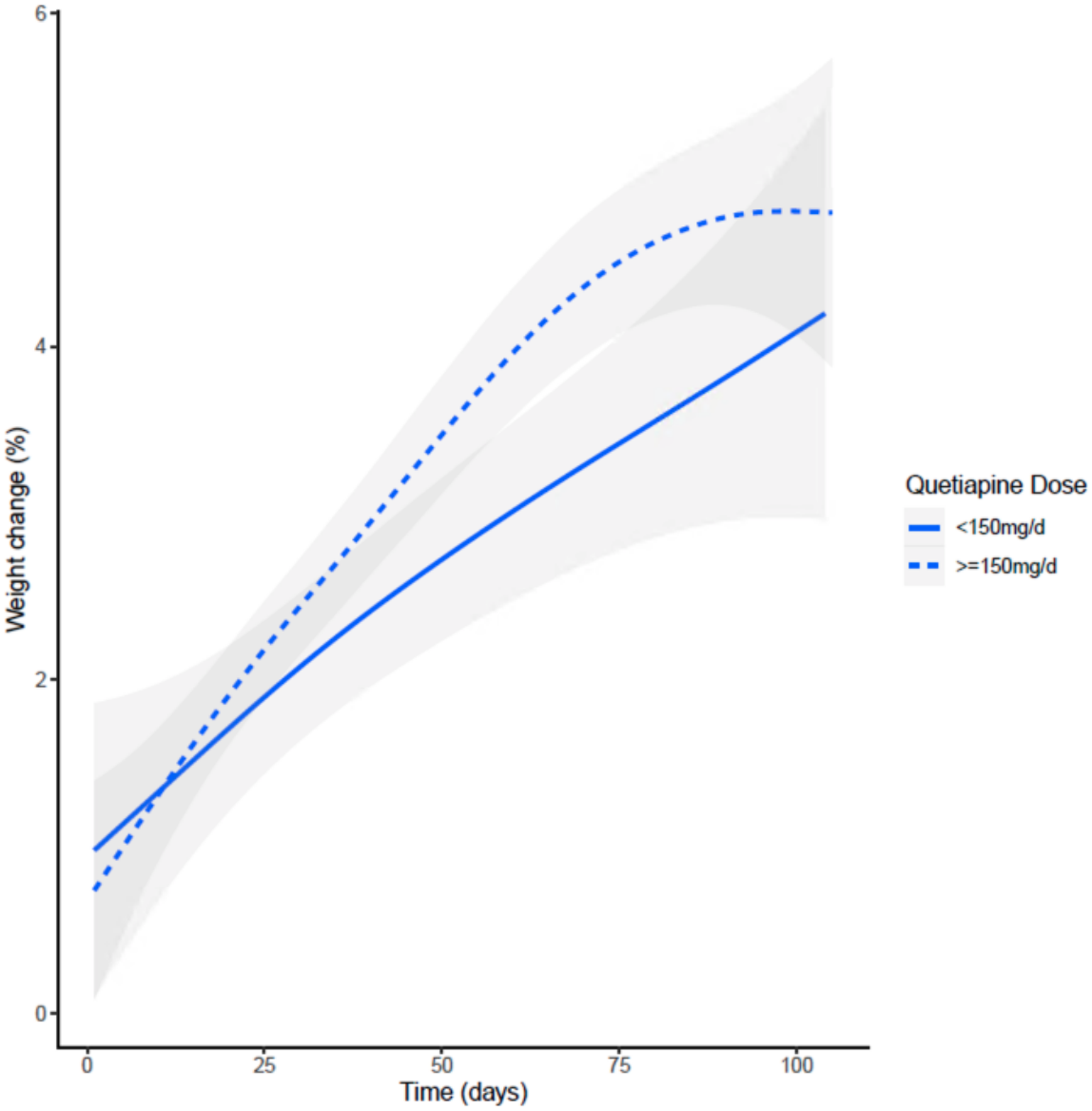

Fig. 2: Weight change over treatment time

Mean weight gain (with its 95% CI) observed following quetiapine treatment initiation is displayed, separating patients taking less than 150 mg per day or 150 mg or more per day.

Supplementary information

Online Supplement:

Appendix

RESULTS

Information on diagnosis, previous and concurrent use of another psychotropic treatment were incomplete. The inclusion of these covariates thus led to a reduction of statistical power. After analyzing their effect on weight gain in separate models, it was decided not to include them in the principal models.

Impact of diagnosis on weight gain

Weight gain induced by psychotropic drugs might differ according to psychiatric disorders, while some studies also tend to show that weight gain occurs irrespective of diagnosis [1].

To evaluate the effect of diagnosis on weight, it was included in the model as a covariate, along with age, sex, baseline BMI and setting of care. In this model, the effect of diagnosis on weight gain was not statistically significant, while the effect sizes of the other covariates remained very similar as compared to the model that did not include diagnosis. However, the effect of quetiapine daily dose was not statistically significant in this model (effect of a 150mg increase on weight gain: 0.11% [95% CI: -0.02-0.23], p=0.087). This loss of statistical significance was most probably due to decreased power. Indeed, diagnosis was missing for 64 patients and the model including this covariate was thus performed with a smaller sample size. To confirm this hypothesis, a model on the subpopulation with known diagnosis, but without adding diagnosis as a covariate was performed and gave very similar results (effect of a 150mg increase on weight gain: 0.10% [95% CI: -0.02-0.22], p=0.089). For these reasons and as the quality of the model (based on Akaike information criterion (AIC)) was not improved with diagnosis as a covariate, diagnosis was not retained in the final model.

To further investigate the effect of diagnosis, the weight gain was modelled in each subgroup of psychiatric disorder, as an exploratory analysis. Supplementary Figure 2 displays the results of weight gain per month, and the effect of a 150mg quetiapine daily dose increase when corrected by age, sex, baseline BMI and setting of care. These results tend to show differing effects according to diagnosis following treatment initiation. Nonetheless, they need to be interpreted with caution as a number of baseline characteristics largely differed between subgroups. The differences observed might thus be dependent on factors other than the diagnosis alone. The sample size in each subgroup is also limited, preventing to generalize results to all patients diagnosed with the same disorders. Future studies should more precisely assess the effect of the dose in diagnosis subgroups.

Impact of previous psychotropic treatment on weight gain

The first episode of psychosis and being prescribed a psychotropic treatment for the first time is a risk factor for important weight gain and metabolic side effects [1]. It is less clear whether the dose effect would differ depending on this parameter. Data on previous treatment was unfortunately missing or of poor confidence for the majority of the included patients and the evaluation of quetiapine dose effect on first-episode versus chronic patients could only be conducted on a subsample of the whole cohort.

Data regarding previous treatment was available for 156 patients, where 7, 82 and 67 patients had already been prescribed one or more low-risk, moderate-risk and high-risk psychotropic treatment, respectively. For the remaining participants, no information was given on previous treatment and it was difficult to differentiate between missing data and true drug-naïve patients. Nonetheless, 174 patients with no information on previous treatment but otherwise very few missing data could be considered drug naïve patients.

In the subgroup of patients who had previously received a psychotropic treatment, a slightly smaller weight gain than the one reported in the complete sample was found when correcting for age, sex, baseline BMI and setting of care (1.47% [95% CI: 1.22-1.73] weight gain per month, versus 1.55% [95% CI: 1.39-1.72] in all patients). Besides, a dose increase of quetiapine had no effect on weight gain in the subgroup of patients who had previously received a psychotropic treatment (effect of a 150mg increase on weight gain: -0.03% [95% CI: -0.20-0.14], p=0.7).

In a second step, weight gain was modelled correcting for age, sex, baseline BMI and setting of care in all patients with information on previous treatment, adding “previous treatment” as a co-variable (0-1). In this model, the effect of quetiapine dose increase was similar to the one highlighted in the complete sample, but did not reach statistical significance (effect of a 150mg increase on weight gain: 0.12% [95% CI: -0.01-0.26], p=0.067), probably due to a lower statistical power (n=312). As expected, the effect of a previous treatment reduced weight gain, although the effect was not statistically significant either (effect of previous treatment on weight gain: -0.76% [95% CI: -1.54-0.02], p=0.058).

The results tend to confirm an effect of previous treatment on weight gain, as expected. Besides, the dose effect of quetiapine seems less pronounced in patients who already received a psychotropic treatment. As the sample size in this subsample was much smaller, and the 95% confidence interval is relatively wide and includes the effect observed in the total sample, it is however not possible to conclude

for a different effect in this subpopulation. The dose effect should be further evaluated in future studies addressing this question specifically in well characterized drug-naïve patients versus chronic patients.

Impact of co-prescription of psychotropic treatment on weight gain

The effect of antipsychotic augmentation on body weight is not clearly established and might depend on the associated compounds [2-4]. This effect is also difficult to delineate from the effect of the severity of the disease, as more severely ill patients tend to be more often treated with polypharmacy [4, 5].

The effect of the co-prescription of another psychotropic treatment on weight gain was assessed adding a covariable (0-1) in the linear model adjusted for age, sex, baseline BMI and setting of care. We observed a statistically non significant effect of polypharmacy: 0.43% [95% CI:-0.30-1.16], p=0.25). Besides, the estimates of all other covariates, including quetiapine dose, remained almost identical (estimates values and significance). The model included 16 fewer participants than the model not accounting for co-medication because of missing data. As for the analysis with diagnosis, the quality of the model (based on Akaike information criterion (AIC)) was not improved with psychotropic co-medication as a covariate. Favoring simplicity in model construction, co-medication was not retained in the final model.

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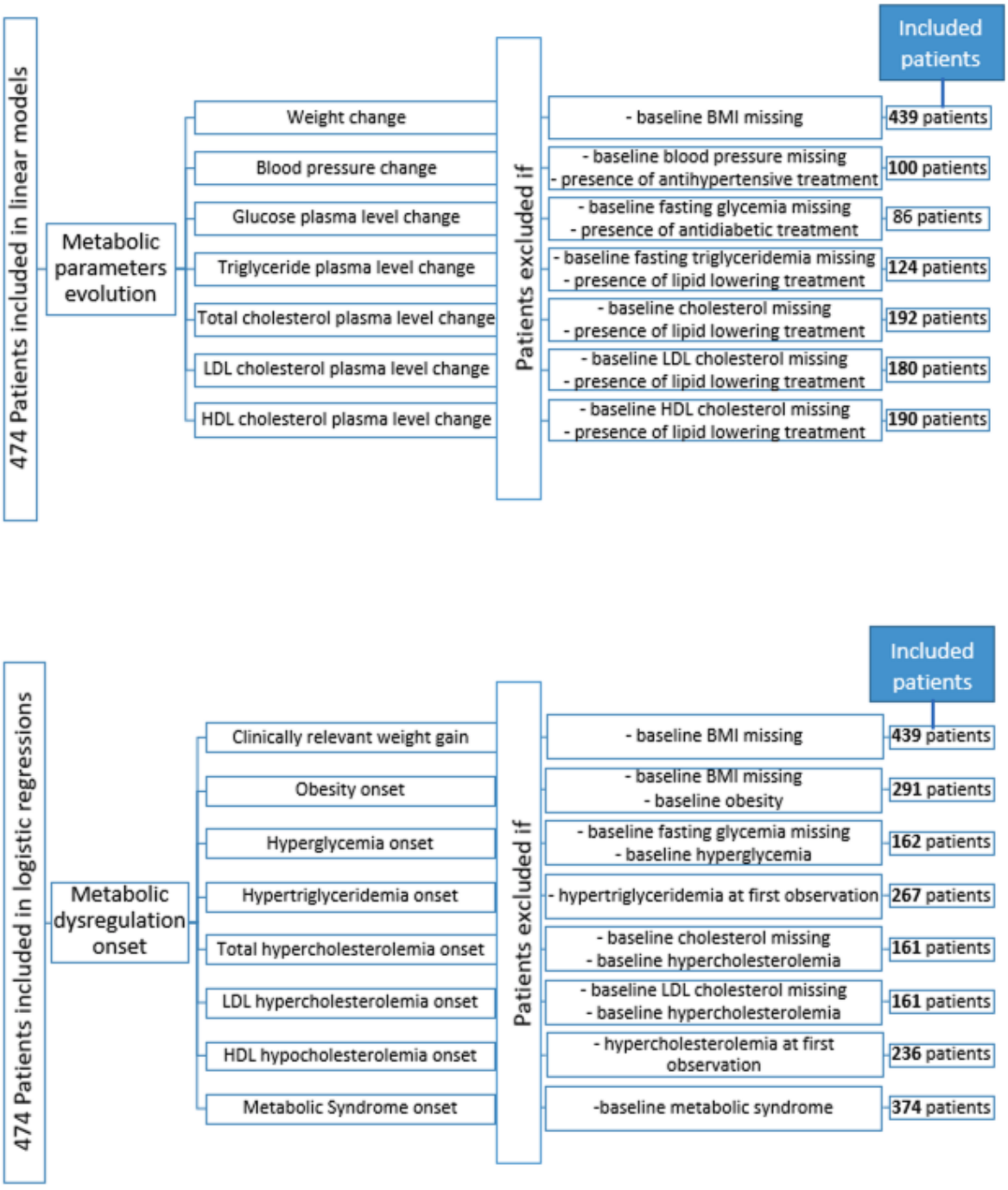
Supplementary Table 1: List of psychotropic medications ranked according to their propensity to induce weight gain and treatments for cardiometabolic diseases

Psychotropic drug[1]			**Antihypertensive drug**		**Antidiabetic treatment**	
Medication	**ATC coding**	**Risk**[2]	**Medication**	**ATC coding**	**Medication**	**ATC coding**
Amisulpride	N05AL05	1	Spironolactone	C03DA01	Metformin	A10BA02
Aripiprazole	N05AX12	1	Aliskirene	C09XA02	Human Insulin	A10AC01
Chlorprothixene	N05AF03	1	Amlodipine	C08CA01	Aspart Insulin	A10AB05
Haloperidol	N05AD01	1	Irbesartan	C09CA04	Gliclazide	A10BB09
Lurasidone	N05AE05	1	Candesartan	C09CA06	Glargine Insulin	A10AE04
Pipamperone	N05AD05	1	Metoprolol	C07AB02	Lispro Insulin	A10AD04
Amitriptyline	N06AA09	2	Captopril	C09AA01	Sitagliptin	A10BH01
Clomipramine	N06AA04	2	Amilorid	C03DB01	Degludec Insulin	A10AE06
Imipramine	N06AA02	2	Bisoprolol	C07AB07	Rosiglitazone	A10BG02
Levomepromazine	N05AA02	2	Enalapril	C09AA02		
Lithium	N05AN01	2	Losartan	C09CA01	**Lipid-lowering treatment**	
Mirtazapine	N06AX11	2	Perindopril	C09AA04	**Medication**	**ATC coding**
Paliperidone	N05AX13	2	Carvedilol	C07AG02	Atorvastatin	C10AA05
Risperidone	N05AX08	2	Diltiazem	C08DB01	Ezetimib	C10AX09
Zuclopenthixol	N05AF05	2	Valsartan	C09CA03	Simvastin	C10AA01
Clozapine	N05AH02	3	Félodipine	C08CA02	Rosuvastatin	C10AA07
Olanzapine	N05AH03	3	Hydrochlorothiazide	C03AA03	Pravastatin	C10AA03
Valproic acid	N03AG01	3	Telmisartan	C09CA07	Fenofibrate	C10AB05
			Furosemide	C03CA01		
			Lisinopril	C09AA03		
			Nebivolol	C07AB12		
			Nifédipine	C08CA05		
			Atenolol	C07AB03		
			Propranolol	C07AA05		
			Sotalol	C07AA07		
			Torasemide	C03CA04		
			Labetalol	C07AG01		
			Olmesartan	C09CA08		
			Lercanidipine	C08CA13		

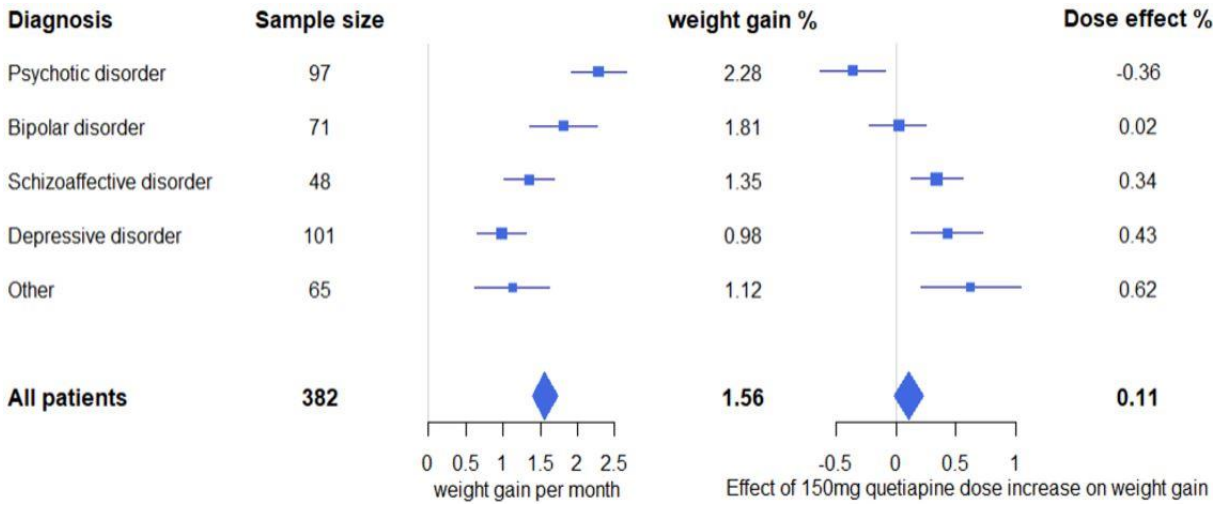
Pharmaceutical products containing a combination of drugs were not listed for simplicity reasons

[1]medication in bold are those prescribed both as co-medication and as previous treatment.

[2] the risk for weight gain was categorized on three levels, as already described [23]. Among the 131 patients prescribed a psychotropic co-medication carrying a risk of weight gain, 5.3% were receiving low-risk treatments (r=1), while 56.5% were receiving moderate risk (r=2) and 38.2% high risk (r=3). Among the 156 patients who had previously received a psychotropic treatment carrying a risk of weight gain, 4.5% had received low-risk treatments (r=1), while 52.6% had received moderate risk (r=2) and 42.9% high risk (r=3). There was no statistically significant difference in the distribution of drugs according to the potency to induce weight gain between patients receiving low doses of quetiapine and patients receiving high doses.

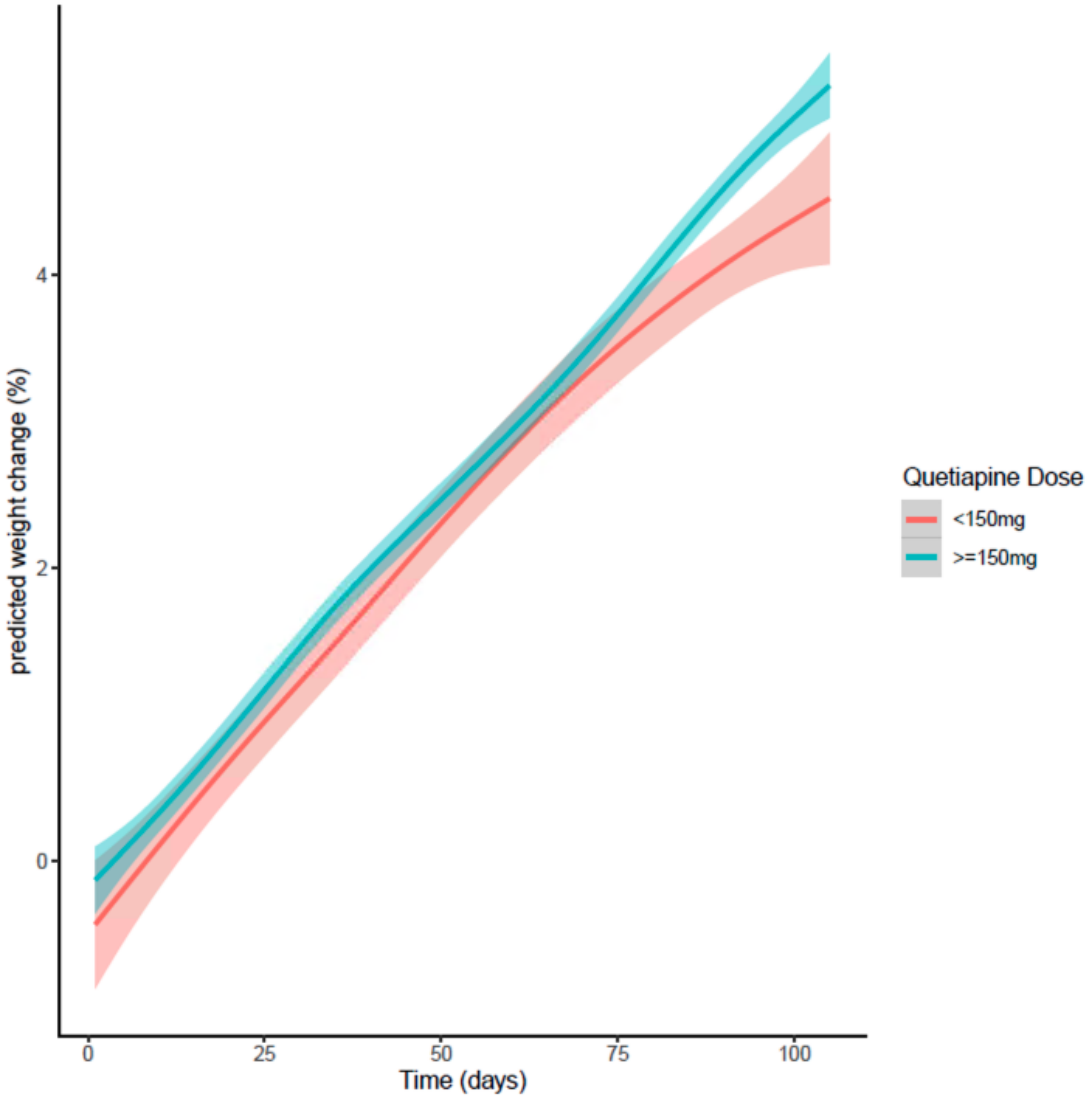


Supplementary Figure 1: Inclusion of patients in the statistical analyses



Supplementary Figure 2: weight gain and dose effect stratified by diagnosis

Weight gain per month and quetiapine dose effect on weight predicted by the linear model, adjusted for baseline BMI, age, sex and setting of care, stratified according to diagnosis.



Supplementary Figure 3: Linear model of weight gain over treatment time

Weight gain predicted by the linear model, adjusted for baseline BMI, age, sex and setting of care slightly increases with higher doses of quetiapine: For each 30 days of treatment, body weight gain is 1.55% (95% CI: 1.39-1.72) more important and for each 150 mg quetiapine daily dose increase, it is 0.12% (95%CI: 0.01-0.24) further increased.

Co-authorship publications – Abstracts

Published articles

Association Between Plasma Caffeine and Other Methylxanthines and Metabolic Parameters in a Psychiatric Population Treated With Psychotropic Drugs Inducing Metabolic Disturbances

Delacrétaz A, Vandenberghe F, Glatard A, Levier A, **Dubath C**, Ansermot N, Crettol S, Gholam-Rezaee M, Guessous I, Bochud M, von Gunten Armin, Conus P, Eap CB.

Published in Frontiers in Psychiatry (2018); DOI: 10.3389/fpsyt.2018.00573

Importance: Multiple studies conducted in the general population identified an association between self-reported coffee consumption and plasma lipid levels. To date, no study assessed whether and which plasma methylxanthines (caffeine and/or its metabolites, i.e., paraxanthine, theophylline, and theobromine) are associated with plasma lipids. In psychiatric patients, an important coffee consumption is often reported and many psychotropic drugs can induce a rapid and substantial increase of plasma lipid levels.

Objective: To determine whether plasmamethylxanthines are associatedwithmetabolic parameters in psychiatric patients receiving treatments known to induce metabolic disturbances.

Design, Setting, and Participants: Data were obtained from a prospective study including 630 patients with metabolic parameters [i.e., body mass index (BMI), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), and fasting triglycerides (TG)] monitored routinely during psychotropic treatment.
Exposures: Plasma methylxanthines levels.

Main Outcomes and Measures: Metabolic variables including BMI and plasma lipid levels.

Results: Multivariate analyses indicated that BMI, TC, HDL-C, and non-HDL-C increased significantly with increasing total methylxanthines ($p_{corrected} \leq 0.05$). In addition, compared to patients with plasma caffeine concentration in the lowest quartile, those with caffeine concentration in the highest quartile were twice more prone to suffer from non-HDL hypercholesterolemia ($p_{corrected} = 0.05$), five times more likely to suffer from hypertriglyceridemia ($p_{corrected} = 0.01$) and four times more susceptible to be overweight ($p_{corrected} = 0.01$).

Conclusions and Relevance: This study showed that plasma caffeine and other methylxanthines are associated with worsening of metabolic parameters in patients receiving psychotropic treatments known to induce metabolic disturbances. It emphasizes that important caffeine consumption could be considered as an additional environmental risk factor for metabolic worsening in patients receiving such treatments.

Amisulpride: Real-World Evidence of Dose Adaptation and Effect on Prolactin Concentrations and Body Weight Gain by Pharmacokinetic/Pharmacodynamic Analyses

Glatard A, Guidi M, Delacrétaz A, **Dubath C**, Grosu C, Laaboub N, von Gunten A, Conus P, Csajka C, Eap CB

Published in Clinical Pharmacokinetics (2019); DOI: 10.1007/s40262-019-00821-w

Background: Amisulpride is an antipsychotic used in a wide range of doses. One of the major adverse events of amisulpride is hyperprolactinemia, and the drug might also induce body weight gain.

Objective: The aims of this work were to characterize the pharmacokinetics of amisulpride in order to suggest optimal dosage regimens to achieve the reference range of trough concentrations at steady-state ($C_{min,ss}$) and to describe the relationship between drug pharmacokinetics and prolactin and body weight data.

Methods: The influence of clinical and genetic characteristics on amisulpride pharmacokinetics was quantified using a population approach. The final model was used to simulate $C_{min,ss}$ under several dosage regimens, and was combined with a direct E_{max} model to describe the prolactin data. The effect of model-based average amisulpride concentrations over 24 h (C_{av}) on weight was estimated using a linear model.

Results: A one-compartment model with first-order absorption and elimination best fitted the 513 concentrations provided by 242 patients. Amisulpride clearance significantly decreased with age and increased with lean body weight (LBW). Cmin,ss was higher than the reference range in 65% of the patients aged 60 years receiving 400 mg twice daily, and in 82% of the patients aged > 75 years with a LBW of 30 kg receiving 200 mg twice daily. The pharmacokinetic/ pharmacodynamic model included 101 prolactin measurements from 68 patients. The E_{max} parameter was 53% lower in males compared with females. Model-predicted prolactin levels were above the normal values for $C_{min,ss}$ within the reference range. Weight gain did not depend on C_{av}.

Conclusions: Amisulpride treatment might be optimized when considering age and body weight. Hyperprolactinemia and weight gain do not depend on amisulpride concentrations. Modification of the amisulpride dosage regimen is not appropriate to reduce prolactin concentrations and alternative treatment should be considered.

Psychotropic drug-induced genetic-epigenetic modulation of CRTC1 gene is associated with early weight gain in a prospective study of psychiatric patients

Delacrétaz A, Glatard A, **Dubath C**, Gholam-Rezaee M, Sanchez-Mut JV, Gräff J, von Gunten A, Conus P, Eap CB.

Published in Clinical epigenetics (2019); DOI: 10.1186/s13148-019-0792-0

Background: Metabolic side effects induced by psychotropic drugs represent a major health issue in psychiatry. CREB-regulated transcription coactivator 1 (CRTC1) gene plays a major role in the regulation of energy homeostasis and epigenetic mechanisms may explain its association with obesity features previously described in psychiatric patients. This prospective study included 78 patients receiving psychotropic drugs that induce metabolic disturbances, with weight and other metabolic parameters monitored regularly. Methylation levels in 76 CRTC1 probes were assessed before and after 1 month of psychotropic treatment in blood samples.

Results: Significant methylation changes were observed in three CRTC1 CpG sites (i.e., cg07015183, cg12034943, and cg 17006757) in patients with early and important weight gain (i.e., equal or higher than 5% after 1 month; FDR p value = 0.02). Multivariable models showed that methylation decrease in cg12034943 was more important in patients with early weight gain (≥ 5%) than in those who did not gain weight (p = 0.01). Further analyses combining genetic and methylation data showed that cg12034943 was significantly associated with early weight gain in patients carrying the G allele of rs4808844A>G (p = 0.03), a SNP associated with this methylation site (p =0.03).

Conclusions: These findings give new insights on psychotropic-induced weight gain and underline the need of future larger prospective epigenetic studies to better understand the complex pathways involved in psychotropic-induced metabolic side effects.

Lipid Disturbances in Adolescents Treated With Second-Generation Antipsychotics: Clinical Determinants of Plasma Lipid Worsening and New-Onset Hypercholesterolemia

Delacrétaz A, Vandenberghe F, Glatard A, **Dubath C**, Levier A, Gholam-Rezaee M, Holzer L, Ambresin AE, Conus P, Eap CB

Published in the Journal of Clinical Psychiatry (2019); DOI: doi.org/10.4088/JCP.18m12414

Objective: Lipid disturbances following treatment with second-generation antipsychotics (SGAs) represent a major health concern. A previous study determined that early changes of plasma lipid levels ≥ 5% during the first month of treatment with SGAs predicts further lipid worsening and development of dyslipidemia. This current study aimed to determine the proportion of adolescents with early lipid changes ≥ 5% and who develop dyslipidemia during SGA treatment.

Methods: Data were obtained from a 1-year longitudinal study ongoing since 2007 including 53 adolescent psychiatric (ICD-10) patients (median age 16.5 years; interquartile range [IQR], 14.8–17.5 years) whose metabolic parameters were monitored prospectively during treatment. Plasma lipid levels (total, low-density lipoprotein, high-density lipoprotein [HDL-C], and non–high-density lipoprotein cholesterol and fasting triglycerides) were measured at baseline and after 1, 3, and/or 12 months of SGA treatment.

Results: Half (n = 26; 49%) the adolescents had an early increase of total cholesterol levels by 5% or more during the first month of treatment, and one-third (n = 8/24; 33%) developed new-onset hypercholesterolemia during the first year of treatment. Hypercholesterolemia developed more frequently in female patients (P = .01) and in patients with an early increase of total cholesterol ≥ 5% (P = .02). Finally, patients whose HDL-C levels decreased by ≥ 5% during the first month of treatment had a larger HDL-C worsening after 3 months of treatment as compared with patients with early decrease of HDL-C by < 5% (P = .02).

Conclusions: This study underlines the importance of prospectively monitoring metabolic parameters in adolescents after the introduction of SGAs.

Psychological trauma occurring during adolescence is associated with an increased risk of greater waist circumference in Early Psychosis patients treated with psychotropic medication

Alameda L, Levier A, Gholam-Rezaee M, Golay P, Vandenberghe F, Delacretaz A, Baumann P, Glatard A, **Dubath C**, Herane-Vives A, Rodriguez V, Solida A, Do KQ, Eap CB, Conus P

Published in PLOS ONE (2020); DOI: 10.1371/journal.pone.0242569

Background: It has been suggested that exposure to Childhood Trauma [CT] may play a role in the risk of obesity in Early Psychosis [EP] patients; however, whether this is independently of age at exposure to CT and the medication profile has yet to be investigated.

Methods: 113 EP-patients aged 18–35 were recruited from the Treatment and Early Intervention in Psychosis Program [TIPP-Lausanne]. Body Mass Index [BMI], Weight Gain [WG] and Waist Circumference [WC] were measured prospectively at baseline and after 1, 2, 3, 6 and 12 months of weight gain inducing psychotropic treatment. Patients were classified as Early-Trauma and Late-Trauma if the exposure had occurred before age 12 or between ages 12 and 16 respectively. Generalized Linear Mixed-Models were adjusted for age, sex, socioeconomic status, baseline BMI, medication and for diagnosis of depression.

Results: Late-Trauma patients, when compared to Non-Trauma patients showed greater WCs during the follow-up [$p = 0.013$]. No differences were found in any of the other follow-up measures.

Conclusions: Exposition to CT during adolescence in EP-patients treated with psychotropic medication is associated with greater WC during the early phase of the disease. Further investigation exploring mechanisms underlying the interactions between peripubertal stress, corticoids responsiveness and a subsequent increase of abdominal adiposity is warranted.

Valproate is associated with early decrease of high-density lipoprotein cholesterol levels in the psychiatric population

Delacretaz A, Glatard A, **Dubath C**, Gholam M, Gamma F, von Gunten A, Conus P, Eap CB

Published in Basic and Clinical Pharmacology and Toxicology (2021); DOI: 10.1111/bcpt.13580

Few studies have evaluated the influence of valproate on the deterioration of the lipid profile in psychiatric patients. This observational study aimed to compare the evolution of metabolic parameters in a sample of adult patients starting valproate (n = 39) with a control group (n = 39) of patients starting aripiprazole, a drug associated with a low risk of metabolic deterioration. Data were obtained from a prospective study including psychiatric patients with metabolic parameters monitored during the first year of treatment. During the first month of treatment with valproate (median: 31 days [IQR: 25-36]), mean body mass index increased significantly (from 24.8 kg/m(2) at baseline to 25.2 kg/m(2) after one month; P = .03) and mean HDL-C levels decreased significantly (from 1.39 mmol/L to 1.27 mmol/L; P = .02). In comparison, these metabolic variables remained stable during the first month of treatment with aripiprazole. The proportion of patients with early (ie during the first month of treatment) HDL-C decrease of >/= 5% was significantly higher under valproate (54%) than aripiprazole (15%) treatment (P < .001). These findings remind the importance of a prospective metabolic monitoring in patients who initiate valproate treatment. Further research should be conducted on larger samples and should focus on finding effective interventions to prevent such metabolic adverse effects.

Metabolomic alteration induced by psychotropic drugs: short-term metabolite profile as a predictor of weight gain evolution

Lenski M, Sidibé J, Gholam M, Hennart B, **Dubath C**, Augsburger M, von Gunten A, Conus P, Allorge D, Thomas A, Eap CB

Published in Clinical and Translational Science (2021); DOI: 10.1111/cts.13122

Psychotropic drugs can induce strong metabolic adverse effects, potentially increasing morbidity and/or mortality of patients. Metabolomic profiling, by studying the levels of numerous metabolic intermediates and products in the blood, allows a more detailed examination of metabolism dysfunctions. We aimed to identify blood metabolomic markers associated with weight gain in psychiatric patients. Sixty-two patients starting a treatment known to induce weight gain were recruited. Two hundred six selected metabolites implicated in various pathways were analyzed in plasma, at baseline and after one month of treatment. Additionally, 15 metabolites of the kynurenine pathway were quantified. This latter analysis was repeated in a confirmatory cohort of 24 patients. Among the 206 metabolites, a plasma metabolomic fingerprint after one month of treatment embedded 19 compounds from different chemical classes (amino acids, acylcarnitines, carboxylic acids, catecholamines, nucleosides, pyridine and tetrapyrrole) potentially involved in metabolic disruption and inflammation processes. The predictive potential of such early metabolite changes on 3 months of weight evolution was then explored using a linear mixed-effects model. Of these 19 metabolites, short-term modifications of kynurenine, hexanoylcarnitine, and biliverdin, as well as kynurenine/tryptophan ratio at one month, were associated with 3 months weight evolution. Alterations of the kynurenine pathway were confirmed by quantification, in both exploratory and confirmatory cohorts. Our metabolomic study suggests a specific metabolic dysregulation after one month of treatment with psychotropic drugs known to induce weight gain. The identified metabolomic signature could contribute in the future to the prediction of weight gain in patients treated with psychotropic drugs.

Submitted articles

Risperidone's daily dose effects on weight and other metabolic parameters: a prospective cohort study

Piras M, **Dubath C**, Gholam M, Laaboub N, Grosu C, Gamma F, Solida A, Plessen KJ, von Gunten A, Conus P, Eap CB

Submitted in the Journal of Clinical Psychiatry, currently under review (submitted on the 27th of May 2021)

Background. Atypical antipsychotics can induce metabolic side effects, but whether they are dose-dependent remains unclear.

Objective. To assess the effect of risperidone and/or paliperidone dosing on weight gain, blood lipids, glucose and blood pressure alterations.

Methods. Data for 438 patients taking risperidone and/or its metabolite (paliperidone) for up to one year were obtained from a longitudinal study monitoring metabolic parameters.

Results. For each mg increase in dose, we observed a weight increase of 0.16% (p=0.002), 0.29%, 0.21% and 0.25% (p<0.001) at one, three, six and twelve months of treatment, respectively. Moreover, dose increases of 1mg raised the risk of a ≥5% weight gain after one month (OR 1.18; p=0.012), a strong predictor of important weight gain in the long term. Splitting the cohort into age categories, the dose had an effect on weight change after three months of treatment (up to 1.63%, p=0.008) among adolescents (≤17 years-old), at three (0.13%, p=0.013) and twelve (0.13%, p=0.036) months among adults (>17 and <65 years-old), and at each time-points (up to 1.55%, p<0.001) among older patients (≥65 years-old). In the whole cohort, for each additional mg we observed a 0.05 mmol/l increase in total cholesterol after one year of therapy (p=0.018).

Conclusion. Although of small amplitude, these results show an effect of risperidone's daily dose on weight gain and blood cholesterol levels. Particular attention should be given to the decision of increasing the drug dose, and minimum effective dosages should be preferred.

Associations between high plasma methylxanthines levels, sleep disorders and polygenic risk scores of caffeine consumption or sleep duration in a Swiss psychiatric cohort

Laaboub N, Gholam M, Sibailly G, Sjaarda J, Delacrétaz A, **Dubath C**, Grosu C, Piras M, Ansermot N, Crettol S, Vandenberghe F, Grandjean C, Gamma F, Bochud M, von Gunten A, Plessen KJ, Conus P, Eap CB

Submitted in the Journal of Clinical Psychiatry, on the 3rd of August 2021

Objective: We first sought to examine the relationship between plasma levels of methylxanthines (caffeine and its metabolites) and sleep disorders, and secondarily between polygenic risk scores (PRS) of caffeine consumption or sleep duration with methylxanthine plasma levels and/or sleep disorders in a psychiatric cohort.

Methods: Plasma levels of methylxanthines were quantified by ultra-high performance liquid chromatography / tandem mass spectrometry. In inpatients, sleep disorder diagnosis was defined using ICD-10 “F51.0”, sedative drug intake before bedtime, or hospital discharge letters, while a subgroup of sedative drugs was used for outpatients. The PRS of coffee consumption and sleep duration were constructed using publicly available GWAS results from the UKBiobank.

Results: 1747 observations (1060 patients) were included (50.3% of observations with sleep disorders). Multivariate analyses adjusted for age, sex, body mass index, setting of care and psychiatric diagnoses showed that patients in the highest decile of plasma levels of methylxanthines had more than double the risk for sleep disorders compared to the lowest decile (OR=2.13, p=0.004). PRS of caffeine consumption was associated with plasma levels of caffeine, paraxanthine, theophylline and with their sum (β=0.1; 0.11; 0.09; and 0.1, pcorrected=0.01; 0.02; 0.02; and 0.01, respectively) but not with sleep disorders. A trend was found between the PRS of sleep duration and paraxanthine levels (β=0.13, pcorrected=0.09).

Discussion: Very high caffeine consumption is associated with sleep disorders in psychiatric in- and outpatients. Future prospective studies should aim to determine the benefit of reducing caffeine consumption in high caffeine-consuming patients suffering from sleep disorders.