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

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Conflict of interest

Dr Eap 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 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.

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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. Objectives: 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 35-74 years) were obtained between 2007 and 2017 from a study with metabolic parameters monitored during psychotropic treatment and between 2003 and 2006 for 6733 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% versus 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% versus 0.1% in women and 0.3% versus 1.8%, p=.01 in men; 10-year risk of CVD deaths >5%: 8.5% versus 8.4%, p=.58, in women and 13.4% versus 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% versus 38.8% per the IDF definition; p=.0004). Conclusion: These findings emphasize the concern that psychiatric patients present an altered metabolic profile and that they do not receive adequate treatment for metabolic disruptiuons. Presence of metabolic disturbances should be routinely assessed, and adequate follow-up is needed to intervene early after illness onset.

Key Words:

Cardiovascular diseases; Metabolic syndrome; Psychiatry; Psychotropic drugs

Introduction

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 (CVD). Furthermore, patients treated with psychotropic drugs including atypical and conventional antipsychotics, mood stabilizers (e.g. valproate and lithium), and antidepressants (e.g. 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 epidemiological 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 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¦PsyCoLaus 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 (i.e. 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 or 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 sub-sample

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 $\chi 2$ 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 ≤ 0.05. Statistical analyses were performed using Stata 14 (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) of women and men respectively 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 of 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 (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 (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 ≤ .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<0.05), 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 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%IC=1.25-1.45, $p<10^{-4}$), 1.9 (95% CI=1.1-3.1, p=.013) and 1.68 (95%IC=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-relatd 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 populationbased 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 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 cardio-vascular 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 helth 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, preventingus 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-seekeing behaviour 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 three 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 treatement. 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 (i.e. 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.

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 highlited 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.

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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)	1216	
Age, median (IQR), y	45 (33-63)	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)	0.65
Bipolar disorders (F30-F31)	85 (13.6)	71 (12.0)	156 (12.8)	0.42
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)	**0.03**
Not available	194 (31.0)	191 (32.4)	385 (31.7)	0.60
Psychotropic medication[d], n (%)				
Low risk	112 (17.9)	131 (22.2)	243 (20.0)	0.06
Medium risk	386 (61.7)	328 (55.6)	714 (58.7)	**0.03**
High risk	128 (20.4)	131 (22.2)	259 (21.3)	0.46
BMI, median (IQR), kg/m^2	24 (21-29)	25 (22-28)	25 (21-28)	0.13
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), mmHg	120 (110-130)	124 (115-136)	120 (110-132)	**$<10^{-4}$**
Diastolic blood pressure, median (IQR), mmHg	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)	0.06
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)	**0.004**
HDL, median (IQR), mmol/l	1.5 (1.2-1.7)	1.2 (1-1.5)	1.3 (1.1-1.6)	**$<10^{-4}$**
D. HDL hypocholesterolemia prevalence, n (%)[e,f]	209 (33.4)	194 (32.9)	403 (33.2)	0.84
Plasma triglyceride, median (IQR), mmol/l	1.1 (0.8-1.6)	1.2 (0.9-1.9)	1.2 (0.9-1.7)	**0.0004**
E. HyperTG prevalence, n (%)[e,f]	162 (26.0)	197 (33.4)	359 (29.6)	**0.004**
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)	0.09
F. Raised fasting glucose prevalence, n (%),[e,f]	156 (25.2)	153 (26.0)	309 (25.6)	0.73
MetS (IDF) prevalence, n (%)	164 (26.3)	138 (23.4)	302 (24.9)	0.24
MetS(ATP) prevalence, n (%)	147 (23.7)	135 (22.9)	282 (23.3)	0.76

[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 more for the rest of the sample.
[b]Statistical significance for differences between men and women was tested using Wilcoxon Mann-Whitney for continuous variables and Pearson chi2 test for categorical variables. P-values in bold are significant (≤0.05).
[c] Diagnoses based on the ICD-10 classification. Organic disorders, anxiety, personality disorder and mental retardation were classified together as « other ».
[d] Psychotropic medication were classified according to the risk of weight gain 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
[e]Thresholds for metabolic abnormalities: A. waist circumference men ≥94 cm, women ≥80 cm and/or BMI > 30kg/m²; B. waist circumference men ≥102cm, women ≥88 cm; C. BP ≥ 130/85 mmHg or treatment for hypertension; D. HDL-C men ≤ 1.03 mM, women ≤ 1.29 mmol/l or lipid-lowering treatment; E. TG ≥ 1.7 mmol/l or lipid-lowering treatment; F. GLC ≥ 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.

Table 2. Clinical variables and prevalence of metabolic syndrome in the 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)	3544 (52.6)		283 (44.6)	3189 (47.4)		634	6733
Age, median (IQR), y	49 (43-61)	52 (44-62)	**0.02**	49 (41-58)	51 (43-61)	**0.002**	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)	1812 (26.9)
BMI, median (IQR), kg/m2	25 (22-29)	24 (22-28)	**0.004**	26 (23-29)	26 (24-29)	0.48	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)	**0.0006**	94 (85-105)	89 (79-98)
A. Central obesity prevalence (IDF) , n(%)[b]	265 (75.7)	1974 (55.7)	**<10^{-4}**	166 (59.1)	1734 (54.4)	0.84	431 (68.3)	3708 (55.1)
B. Central obesity prevalence (ATP) , n(%)[b]	199 (56.9)	1152 (32.5)	**<10^{-4}**	112 (39.9)	823 (25.8)	**0.0006**	311 (49.3)	1975 (29.3)
Systolic blood pressure, median (IQR), mmHg	120 (110-130)	122 (112-135)	0.17	125 (116-138)	130 (120-142)	**<10^{-4}**	123 (112-135)	126 (116-139)
Diastolic blood pressure, median (IQR), mmHg	80 (70-88)	77 (70-84)	**0.03**	80 (75-90)	81 (74-88)	0.75	80 (71-89)	79 (72-86)
C. Hypertension prevalence, n(%)[b]	97 (27.6)	1069 (30.2)	0.79	106 (37.5)	1354 (42.5)	**0.03**	203 (32.0)	2423 (36.0)
Treated for hypertension, n (%)[c]	44 (45.4)	660 (61.7)	0.07	42 (39.6)	689 (50.9)	0.61	86 (42.4)	1349 (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. HDL 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 triglyceride, 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)	0.81	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)	1096 (34.4)	**0.02**	226 (35.7)	1672 (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)	**0.047**	5.3 (4.9-5.9)	5.5 (5.2-6)	0.30	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)	**0.0005**	104 (36.9)	1596 (50.1)	**<10^{-4}**	213 (33.8)	2527 (37.5)
Diabetes prevalence,[d] n(%)	31 (8.8)	142 (4.0)	**0.002**	31 (11.0)	294 (9.2)	0.36	62 (9.8)	436 (6.5)
Treated for diabetes, n(%)[c]	17 (54.8)	92 (64.8)	0.46	17 (54.8)	183 (62.2)	0.64	34 (54.8)	275 (63.1)
MetS (IDF) prevalence, n(%)	110 (31.6)	636 (18.0)	**<10^{-4}**	98 (34.8)	1025 (32.1)	0.97	207 (33.0)	1661 (24.7)
Treated[e], n(%) [c]	46 (42.6)	370 (58.5)	0.21	39 (39.4)	472 (46.1)	0.96	85 (41.1)	842 (50.9)
MetS(ATP) prevalence, n(%)	97 (27.9)	530 (15.0)	**<10^{-4}**	93 (33.0)	829 (26.0)	**0.04**	190 (30.2)	1359 (20.2)
Treated[e], n(%) [c]	44 (45.8)	323 (61.6)	0.07	36 (40.9)	413 (49.9)	0.99	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/m2; 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.

Table 3. Quantification of the 10-year cardiovascular risk 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)	0.54	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 (r ≥5%), n(%)	30 (8.5)	296 (8.4)	0.58	38 (13.4)	528 (16.6)	0.42	68 (10.7)	824 (12.3)
intermediate risk (2.5≥ r < 5%), n(%)	26 (7.4)	240 (6.8)	0.50	27 (9.5)	476 (15.0)	0.18	53 (8.4)	716 (10.7)
low risk (1.5≥ r <2.4%), n(%)	21 (6.0)	269 (7.6)	0.50	34 (12.0)	316 (10.0)	0.02	55 (8.7)	585 (8.7)
very low risk (r <1.5%), n(%)	274 (78.1)	2723 (77.2)	0.24	184 (65.0)	1856 (58.4)	0.83	458 (72.2)	4579 (68.3)
FRS, median (IQR), %	0.40 (0.18-0.81)	0.41 (0.17-0.93)	0.57	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 (r >20%), n(%)	0	2 (0.1)	-	1 (0.3)	58 (1.8)	**0.01**	1 (0.1)	60 (0.9)
intermediate risk (10< r ≤20%), n(%)	0	5 (0.1)	-	7 (2.5)	192 (6.0)	**0.0002**	7 (1.1)	197 (2.9)
low risk (6< r ≤10%), n(%)	3 (0.9)	14 (0.4)	0.66	19 (6.7)	376 (11.8)	**0.0006**	22 (3.5)	390 (5.8)
very low risk (r ≤6%), n(%)	348 (99.1)	3521 (99.4)	0.95	256 (90.5)	2559 (80.4)	**$<10^{-4}$**	604 (95.3)	6080 (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.

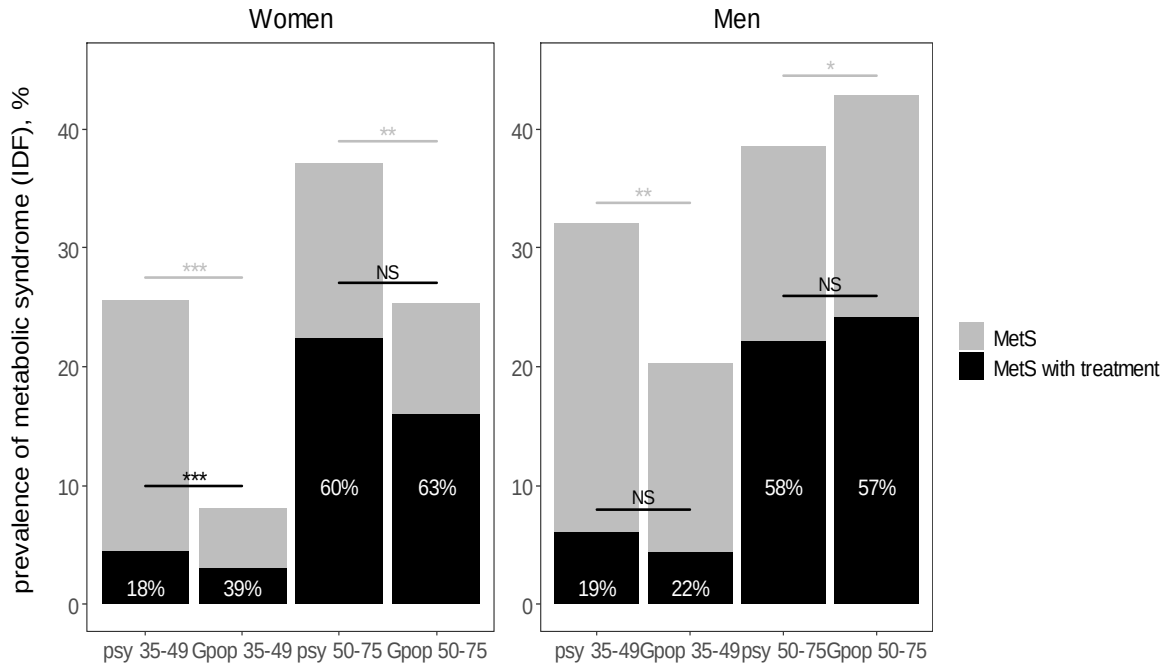

Figure 1. Age and sex-stratified prevalence of metabolic syndrome (IDF) and cardiovascular disease medication intervention in the psychiatric sample 2 and comparison with the population-based sample[a,b,c]

[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.

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 criterion 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	

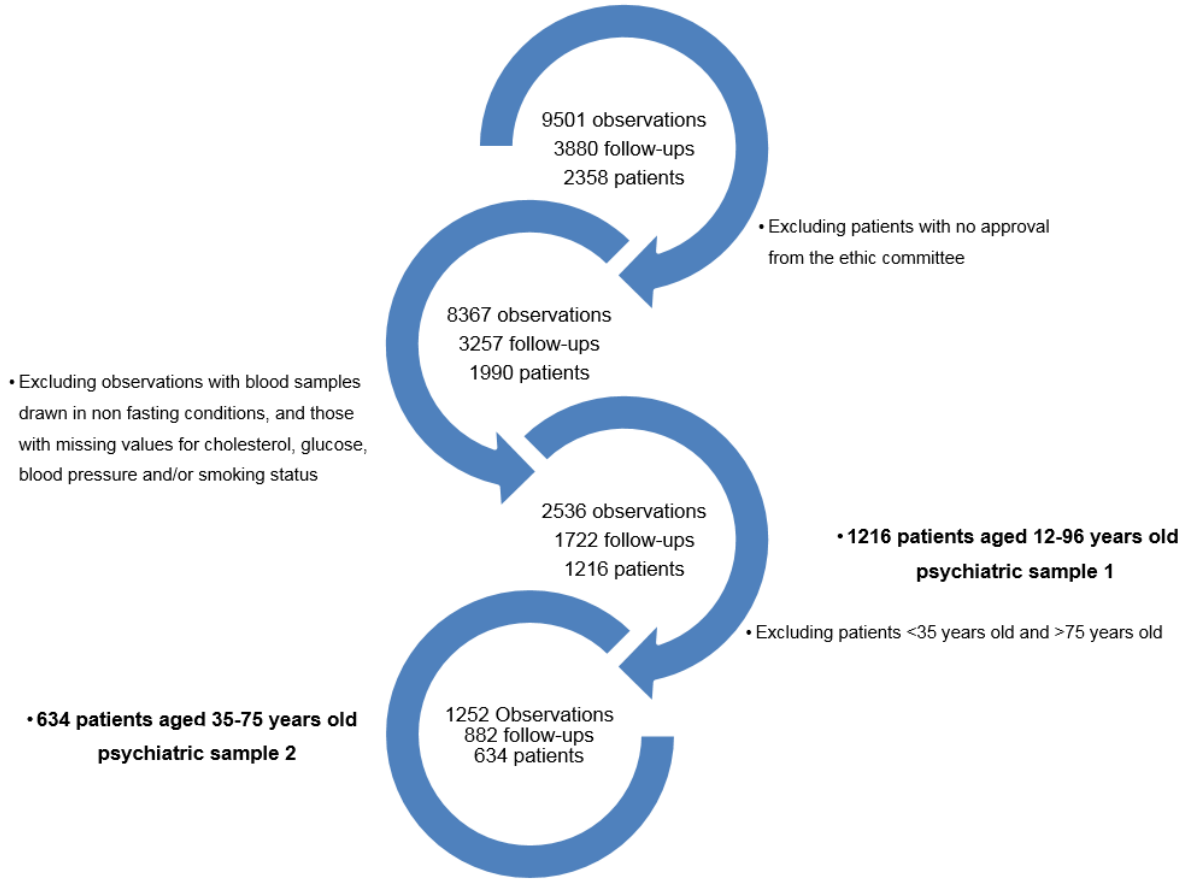
Supplementary Table 4. Prevalence of metabolic syndrome and CVD medication intervention stratified into two age groups in the psychiatric sample 2 and comparison with the population-based sample

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