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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.

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CONFLICT OF INTEREST

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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%.

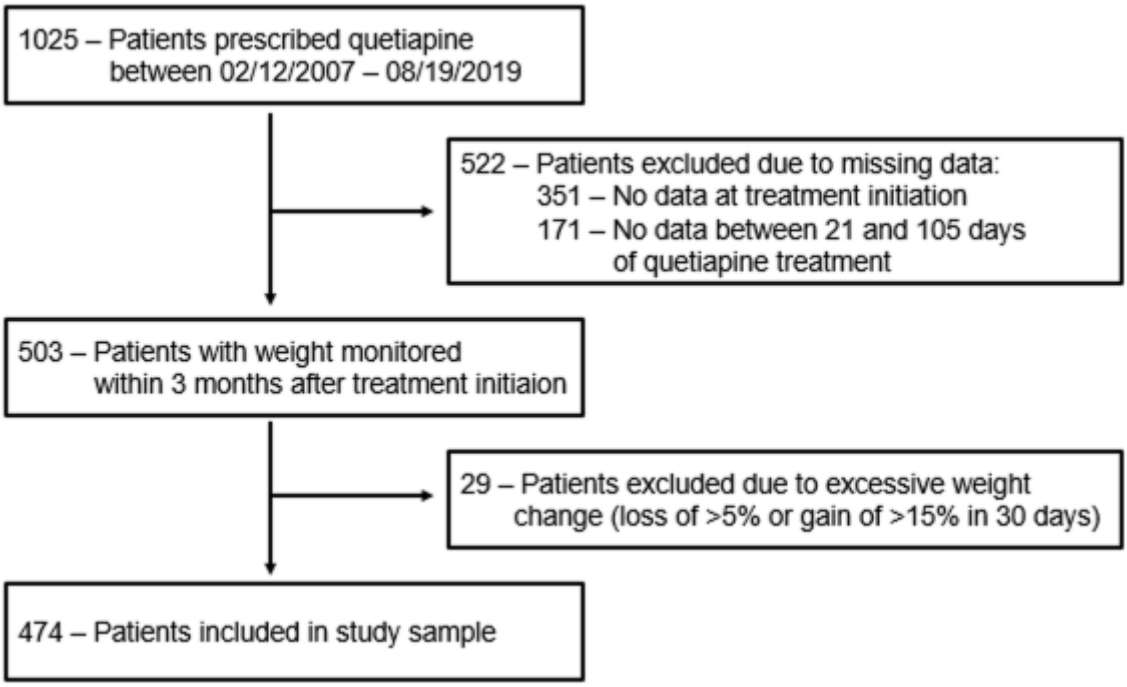

Fig. 1: Inclusion of participants in the study

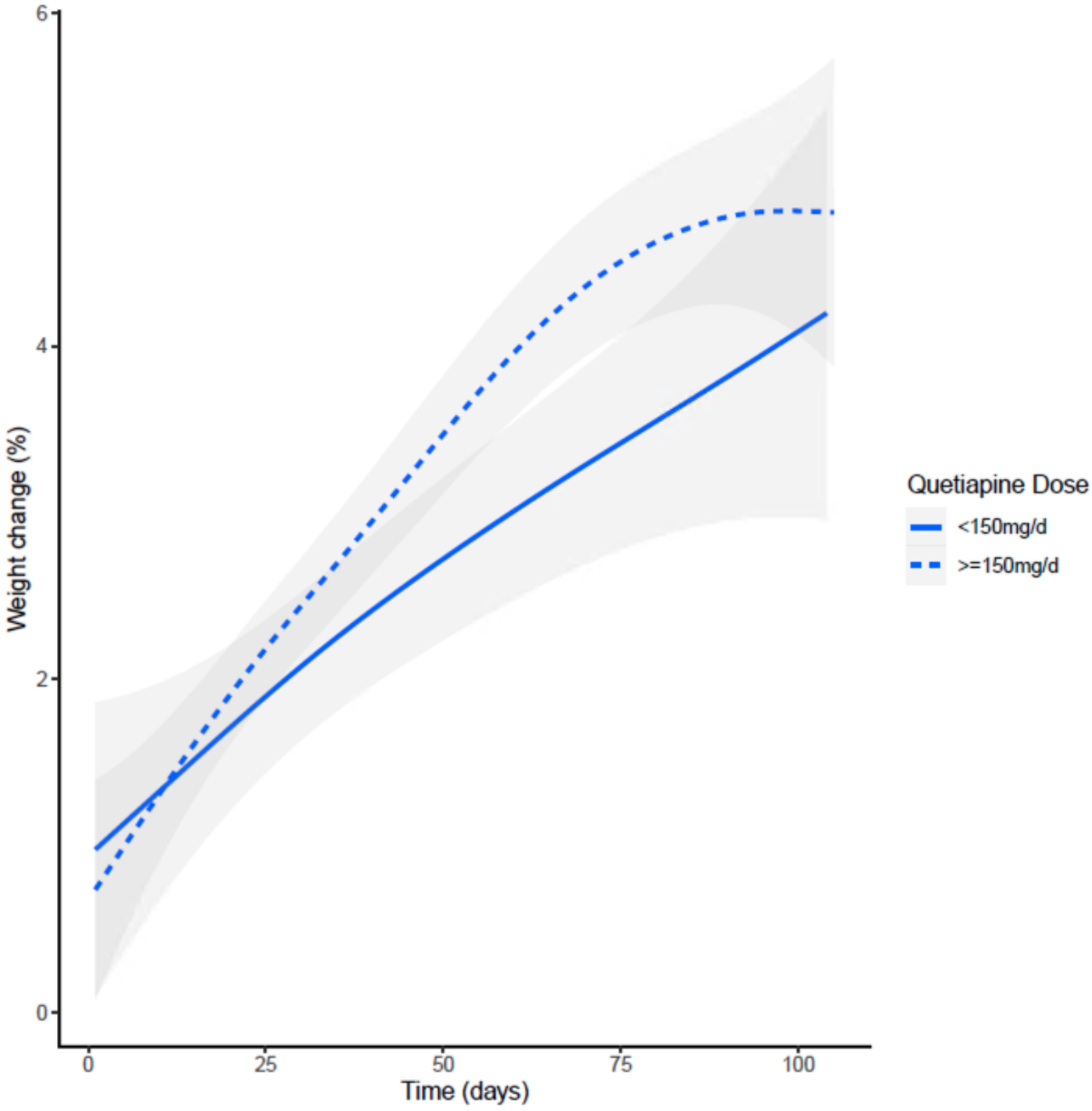

Fig. 2: Weight change over treatment time

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.

Online Supplement

Appendix: Supplementary Results

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

Supplementary Figure 1: Inclusion of patients in the statistical analyses

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

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

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 [32].

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 [32]. 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 [33-35]. 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 [35,36].

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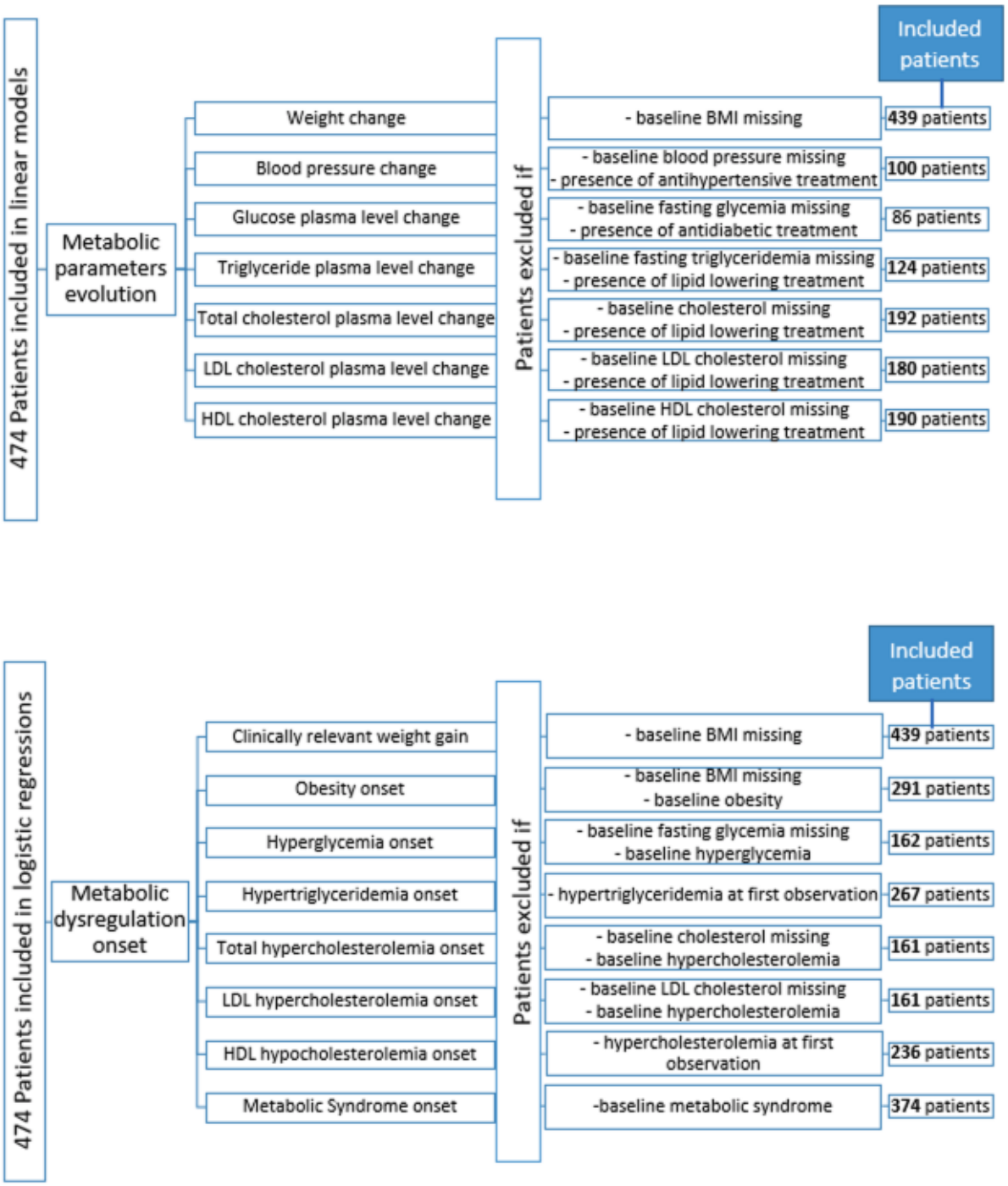
Supplementary Table 1: List of psychotropic medications ranked according to their propensity to induce weight gain and treatments for cardiometabolic diseases

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		

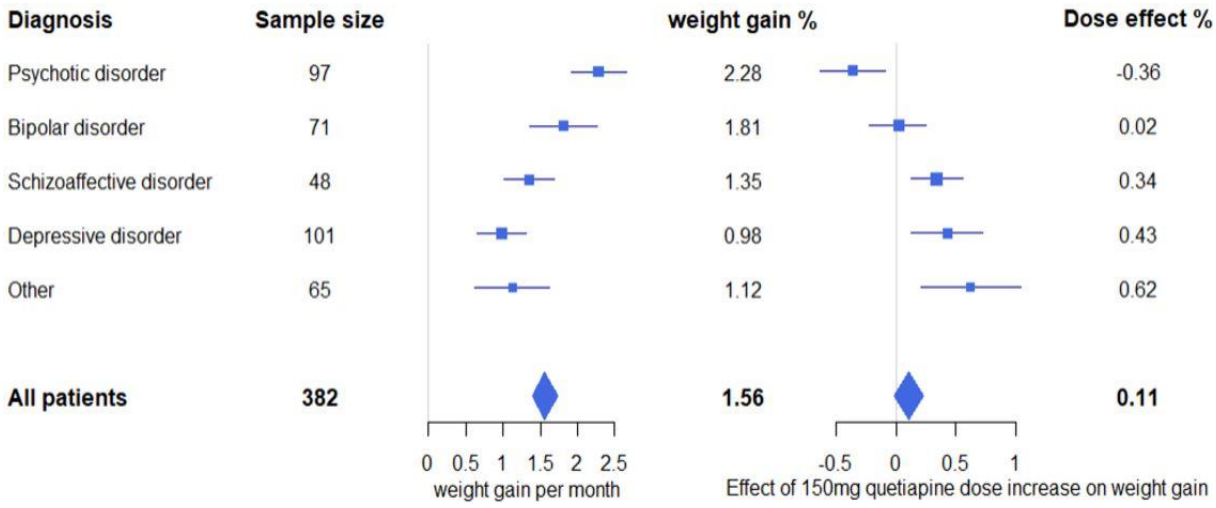
Pharmaceutical products containing a combination of drugs were not listed for simplicity reasons

[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 [37]. 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.

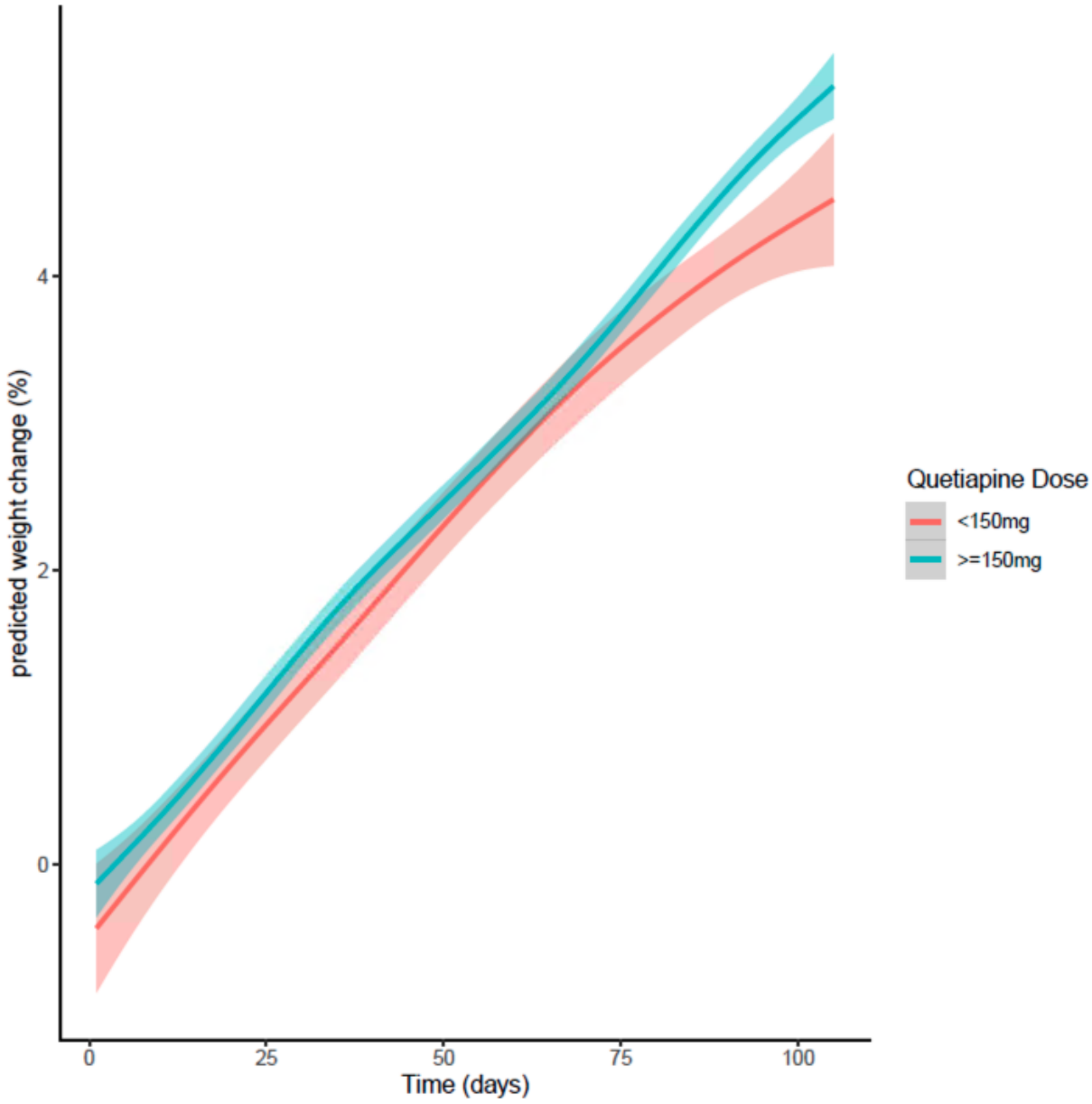


Supplementary Figure 1: Inclusion of patients in the statistical analyses



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.