



Adipokine levels are associated with insulin resistance in antipsychotics users independently of BMI

Trude S. Jahr Vedal^{a,*}, Nils Eiel Steen^a, Kåre I. Birkeland^b, Ingrid Dieset^a, Elina J. Reponen^a, Jannicke F. Laskemoen^a, Linn Rødevand^a, Ingrid Melle^a, Ole A. Andreassen^a, Espen Molden^c, Erik G. Jönsson^{a,d}

^a NORMENT & K.G. Jebsen Center for Psychosis Research, Institute of Clinical Medicine, University of Oslo and Oslo University Hospital, Oslo, Norway

^b Department of Transplantation Medicine, University of Oslo and Oslo University Hospital, Oslo, Norway

^c Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway

^d Department of Clinical Neuroscience, Center for Psychiatric Research, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Background: The prevalence of obesity, metabolic syndrome and type 2 diabetes mellitus is increased among patients with severe mental disorders, and particularly use of second generation antipsychotic drugs is associated with metabolic side effects. Antipsychotics have been found to alter levels of adipokines which regulate insulin sensitivity, but their role in antipsychotic-associated insulin resistance is not established, and it is unclear whether adipokines affect insulin resistance independently of body mass index (BMI).

Methods: We included 1050 patients with severe mental disorders and 112 healthy controls aged 18–65 years from the Oslo area, Norway. Clinical variables, BMI and use of medication were assessed, fasting blood samples were obtained for calculation of the leptin/adiponectin ratio (L/A ratio) and estimate of insulin resistance using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Case-control analyses were followed by mediation analyses to evaluate the possible direct effect of antipsychotics on HOMA-IR and indirect effect mediated via the L/A ratio. This was performed both with and without adjustment for BMI, in the total sample and in an antipsychotic monotherapy subsample (N = 387).

Results: BMI, L/A ratio and HOMA-IR were significantly higher in patients than controls ($p < 0.001$ – $p = 0.01$). There was a significant direct effect from use of antipsychotics in general on HOMA-IR both without ($b = 0.03$, $p = 0.007$) and with adjustment for BMI ($b = 0.03$, $p = 0.013$), as well as a significant mediating effect via L/A ratio both without ($b = 0.03$, $p < 0.001$) and with adjustment for BMI ($b = 0.01$, $p = 0.041$). Use of olanzapine ($b = 0.03$, $p < 0.001$) or aripiprazole ($b = 0.04$, $p < 0.001$) in monotherapy showed significant effects on HOMA-IR mediated via L/A ratio.

Conclusions: The study suggests that use of antipsychotics may alter adipokine levels, and that increased L/A ratio may play a role in the development of insulin resistance associated with use of antipsychotics also independently of BMI.

1. Introduction

Schizophrenia and bipolar disorders are severe mental disorders with common clinical characteristics like psychotic and affective symptoms in addition to neurocognitive deficits (Grande et al., 2016; Owen et al., 2016). Also, the disorders have some overlapping genetic risk factors and increased risk of obesity, diabetes and cardiovascular disease (Consortium, 2018; Ohaeri and Akanji, 2011). Besides

psychosocial interventions, antipsychotic drugs are the most common treatment for severe mental disorders (Lally and MacCabe, 2015; Singh et al., 2012). However, these drugs have side effects, in particular metabolic, which pose a challenge to both treatment success and general health.

Patients with psychotic disorders have an estimated 15–20 years shorter life span compared to the general population, with premature cardiovascular disease constituting one of the most important causes of

* Corresponding author at: NORMENT KG Jebsen Center for Psychosis Research, Division of Mental Health and Addiction, Building 49, University of Oslo, Oslo University Hospital, 0407 Oslo, Norway.

E-mail address: t.s.j.vedal@medisin.uio.no (T.S.J. Vedal).

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excess mortality (Piotrowski et al., 2017; Ringen et al., 2014). Second generation antipsychotic drugs which are commonly prescribed today are known to induce weight gain and obesity and accelerate the development of metabolic syndrome, which is a risk factor for cardiovascular disease (Abosi et al., 2018; Bak et al., 2014). Type 2 diabetes mellitus is a manifestation of an undesirable metabolic profile and a condition with severe consequences, characterized by elevated blood glucose levels due to insufficient insulin production and insulin resistance (Vijan, 2015). Meta-analyses show that the prevalences of type 2 diabetes mellitus in patients with both schizophrenia and bipolar disorders significantly exceed the prevalence in the general population, and the condition is often underdiagnosed in this patient group (Stubbs et al., 2015; Vancampfort et al., 2015; Ward and Druss, 2015). It is known that diabetes co-occurred with schizophrenia long before the introduction of antipsychotics in the 1950's (Kohen, 2004), and a recent meta-analysis concluded that antipsychotic-naïve patients with non-affective psychosis had significantly reduced glucose tolerance and insulin resistance (Greenhalgh et al., 2017). In addition, the use of antipsychotics has been found to disturb glucose metabolism in healthy volunteers (Burghardt et al., 2018), and the increased risk of type 2 diabetes mellitus has been established in patients with severe mental disorders using antipsychotics (Hirsch et al., 2017). However, various antipsychotic agents have different pharmacological profiles and thereby different propensity to induce metabolic side effects, with use of olanzapine and clozapine posing the highest risk (Rummel-Kluge et al., 2010). Although the association between antipsychotic drugs and development of type 2 diabetes mellitus is observed, the exact mechanisms remain unknown.

Adipose tissue is an endocrine and metabolically active organ secreting adipokines involved in the regulation of glucose and lipid metabolism and the immune system. One of the most important adipokines is adiponectin, where low plasma levels are associated with obesity, reduced insulin sensitivity and metabolic syndrome (Yamauchi and Kadowaki, 2008). Meta-analyses indicate that patients using second generation antipsychotics, particularly clozapine or olanzapine, have lower adiponectin levels than controls (Bartoli et al., 2015). This may simply reflect an increased amount of adipose tissue in these individuals, but studies have found decreased levels of adiponectin associated with use of antipsychotics also independently of adiposity and body mass index (BMI) (Birkenaes et al., 2009; Sapra et al., 2016). Serum levels of leptin, another prominent adipokine, is found to be higher in patients with schizophrenia compared to controls (Stubbs et al., 2016) and increased with use of antipsychotics, especially related to weight gain (Jin et al., 2008). Both these adipokines may serve as biomarkers for metabolic disturbances and risk of metabolic diseases, but the ratio between the two may provide an even better indicator for risk of insulin resistance, metabolic syndrome and type 2 diabetes mellitus (Lilja et al., 2012; Lopez-Jaramillo et al., 2014). There is a lack of studies investigating the leptin/adiponectin ratio (L/A ratio) in the context of insulin resistance and development of type 2 diabetes mellitus associated with use of antipsychotic drugs, and the significance of the hormone levels beyond weight and BMI remains to be confirmed.

1.1. Aim

We investigated the levels of leptin, adiponectin and insulin resistance in patients with severe mental disorders comparing users of antipsychotics (mainly atypical agents) with non-users and healthy controls. We further examined whether use of antipsychotics was associated with increased insulin resistance and whether this effect was mediated through altered levels of leptin and/or adiponectin expressed by their ratio, both with and without adjustment for BMI. Moreover, we examined these associations in patients using specific antipsychotics in monotherapy compared to unmedicated patients in separate subsample analyses.

2. Material and methods

2.1. Design and participants

The current study is part of the Thematically Organized Psychosis (TOP) study, recruiting patients with severe mental disorders from hospitals in and around Oslo aged between 18 and 65 years and with ability to give informed consent. Exclusion criteria are history of moderate or severe head injury, severe somatic illness including neurological disorders and IQ below 70. In the current study 1050 patients were included. All patients underwent a thorough diagnostic evaluation including personal interview and review of medical records, and the included patients were classified in diagnostic groups according to the Diagnostic and Statistical manual of Mental Disorders, fourth edition (American Psychiatric, 1995) as follows; schizophrenia spectrum disorders (including schizophrenia (N = 378), schizoaffective disorder (N = 84) and schizophreniform disorder (N = 43)), bipolar spectrum disorders (including bipolar disorder type 1 (N = 234), bipolar disorder type 2 (N = 109) and bipolar disorder not otherwise specified (NOS) (N = 21)), psychosis NOS (N = 139) and major depression with psychotic symptoms (N = 42). The inter-investigator diagnostic agreement has been estimated to a satisfying level of 82% with overall $\kappa = 0.77$ (95% CI: 0.60-0.94) (Simonsen et al., 2011).

A healthy control group of N = 112 was recruited through statistical records from the same age group and catchment area as the patients. Further inclusion criteria of the healthy controls include absence of severe mental disorder in the control and among close relatives, and absence of illicit drug use and somatic illness that can interfere with brain function. Of the healthy controls, 12.5% reported use of regular somatic medications. In the present study we included all participants from whom fasting blood samples were available for measurements of glucose and insulin, excluding individuals with known diabetes mellitus (N = 15) and patients with non-detectable serum levels of antipsychotics (N = 33).

2.2. Clinical assessments

For evaluation of the general psychiatric symptom level in the patients the Global Assessment of Functioning symptom scale (GAF-s) (Pedersen et al., 2007) was used. History of medical comorbidities was collected for both patients and controls, and the patients were subjected to a physical examination performed by a physician. All participants underwent assessment of weight and height for calculation of BMI (kg/m²). The majority of the participants had measures of waist circumference (patients N = 788, controls N = 109). The participants were grouped according to their BMI using standard categorization; underweight (BMI < 18.5), normal weight (BMI = 18.5–24.9), overweight (BMI = 25–29.9) or obese (BMI ≥ 30).

2.3. Medication

Information about use of psychotropic drugs among the patients was gathered from medical records and by patient interviews, confirmed by serum concentration measurements. Type of drug(s) and dosage in use were recorded for antipsychotics, antidepressants, antiepileptic drugs and lithium, with data available for 1026 patients. The majority of the patients used psychotropic drugs either alone or in combinations (antipsychotics (N = 750), antidepressants (N = 340), antiepileptic drugs (N = 219) and lithium (N = 84)), while 130 patients did not use any psychotropic drugs.

Of all antipsychotics users, 95% reported use of a second generation drug as their main antipsychotic agent. Total dosage of antipsychotics was calculated according to the World Health Organization's definitions of Defined Daily Doses (DDD) (WHO, 2016) in order to summarize dosages of different agents in individuals using several antipsychotic drugs. Among antipsychotic monotherapy users, the users of the

following most commonly prescribed antipsychotic agents were selected for subsample analyses; olanzapine (N = 126), quetiapine (N = 45), aripiprazole (N = 50) and risperidone (N = 33). Serum concentrations were measured fasting before intake of morning medication. Serum concentration levels were analyzed at the Department of Clinical Pharmacology, St. Olavs hospital, Trondheim, using standard liquid chromatography-mass spectrometry (LC-MS) methods.

2.4. Blood samples

Blood samples were collected in the morning after an over-night fast in all participants between the years 2003 and 2015. Glucose, insulin, leptin and adiponectin were analyzed at the Department of Medical Biochemistry, Oslo University Hospital. Glucose levels were analyzed using standardized platforms from Roche Diagnostics. Insulin, leptin and adiponectin were analyzed at the Hormone Laboratory by radioimmunoassay (RIA) using standard methods. We estimated insulin resistance using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) download computer model HOMA2 by the University of Oxford from 2013 (Wallace et al., 2004). As the calculation is valid only with insulin levels < 400 pmol/L, participants with higher levels were excluded (patients N = 18, controls N = 2). The L/A ratio was calculated for use in statistical analyses.

2.5. Statistical analyses

For analyses of demographic and clinical data, patients were categorized as users or non-users of antipsychotic agents. Statistical group differences were analyzed between healthy controls and all patients, as well as between patients using and not using antipsychotics. Due to biological sex differences in outcome variables, males and females were analyzed separately. We used Mann-Whitney U tests for continuous variables due to skewed distributions and chi-square tests for categorical descriptive variables between groups. Spearman's rho was applied for evaluating the relationship between BMI, HOMA-IR, waist and blood sample values. Mediation analyses based on regression were performed in the whole sample using Hayes's PROCESS tool version 2.16.3 for SPSS. We used model 4 designs defined with HOMA-IR as outcome, use of antipsychotic agents (yes/no) as predictor and L/A ratio as mediator variable; in addition, age, sex, patient/control status, use of lithium, antidepressants and antiepileptic drugs (yes/no) and BMI were included as covariates. This mediation analysis model provides results of three regression series; one series of the effects from the predictor together with the covariates on the mediator variable, and two series of the effects from the predictor and covariates on the outcome variable, both with (assessing the direct effect) and without the mediator variable included as a covariate. Based on these results, the indirect effect of the predictor on the outcome variable via the mediating variable is estimated with p-values from normal theory tests. The analyses were performed for the whole sample with and without BMI, as well as separately for males and females, with and without BMI included. Antipsychotic total DDD was also included for evaluation of contribution from antipsychotic dose. See Fig. 1 for visualization of the overall mediation analysis.

We used Kruskal-Wallis tests for comparison of BMI, L/A ratio and HOMA-IR in unmedicated patients and monotherapy users of olanzapine, quetiapine, aripiprazole and risperidone in a subsample of the patients (N = 387). For the variables with significant group differences, additional Mann-Whitney U tests were performed comparing each monotherapy group to the unmedicated patients. Analyses for assessing the potential mediating effect of L/A ratio on HOMA-IR were performed by similar design in the subsample as for the whole sample, using each of the antipsychotic agents as predictors and including sex, age, BMI and use of the other antipsychotic agents as covariates. All the mediation analyses were evaluated regarding the underlying assumptions for regression analyses, and HOMA-IR and L/A ratio variables were log-

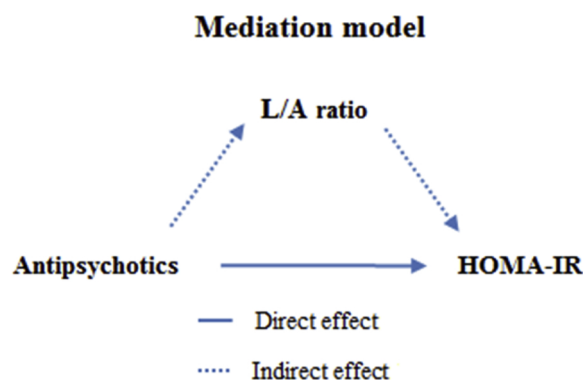


Fig. 1. Description of the mediation analysis design.

Abbreviations: L/A ratio = Leptin/adiponectin ratio; HOMA-IR = Homeostatic Assessment Model for Insulin Resistance.

transformed in order to enhance the residual distributions. We used Spearman's rho for evaluating the relationship between serum concentration of each antipsychotic agent and L/A ratio as well as HOMA-IR in the monotherapy subsample.

Statistical analyses were performed using IBM SPSS Statistics software package version 25.0 for Windows. All analyses were two-tailed with a significance level set to $p < 0.05$.

2.6. Ethical considerations

Written informed consent was obtained from all participants and the study was carried out in accordance with the Declaration of Helsinki. The study was approved by the Regional Ethics Committee and the Norwegian Data Inspectorate.

3. Results

3.1. Descriptives

Descriptive data of the sample are shown in Table 1. Overall, patients had significantly higher BMI and waist circumference than controls. Insulin resistance was significantly more pronounced in patients than in controls, and while adiponectin levels were lower and L/A ratio higher in female patients vs female controls, these were not significantly different in males. There were significantly more patients with schizophrenia spectrum disorders and fewer with bipolar spectrum receiving treatment with antipsychotics compared to the number not receiving antipsychotics. BMI and waist were higher in female patients on antipsychotics compared to those without antipsychotics, while there was no significant difference in males. HOMA-IR, leptin levels and the L/A ratio were significantly higher among patients using antipsychotics compared to patients not using these drugs.

3.2. Correlations between the metabolic factors

To estimate the associations between BMI, waist circumference and hormone levels for insulin resistance, a series of correlation analyses were performed in healthy controls and patients using and not using antipsychotics, separately (Table 2). There were strong and highly significant correlations between both BMI and HOMA-IR and the other variables, except between HOMA-IR and leptin in the healthy controls. For patients using antipsychotics, BMI ($\rho = 0.463$) and L/A ratio ($\rho = 0.465$) displayed the highest correlations to HOMA-IR, higher than waist circumference and the separate hormone levels. The distribution of each individual's combined levels of HOMA-IR and L/A ratio is visualized by scatterplots of the patients and controls in Fig. 2.

Table 1
Demographic and descriptive data of patients and healthy controls.

Males	HC	NO	AP ^a	HC vs P	NO vs AP
N	68	137	397		
Age	31 (15)	32 (19)	28 (14)	p = 0.233	p = 0.006
Ethnicity, Caucasian %	98.5	83.9	79.1	p < 0.001	p = 0.269
Diagnostic group %					p < 0.001
Schizophrenia spectrum		27.0	62.7		
Bipolar spectrum		46.0	19.6		
Other psychosis		19.0	15.1		
Major depression		8.0	2.5		
GAF-S		52 (22)	40 (18)		p < 0.001
BMI	24.4 (4.4)	26.0 (5.8)	26.2 (6.2)	p = 0.010	p = 0.254
BMI category %				p = 0.035	p = 0.640
Underweight	0	0.8	1.1		
Normal weight	53.7	39.2	38.4		
Overweight	37.3	42.3	37.9		
Obese	9.0	17.7	22.6		
Waist cm	91 (16)	93 (17)	94 (19)	p = 0.030	p = 0.201
Leptin pmol/L	304 (359)	370 (372)	428 (535)	p = 0.011	p = 0.025
Adiponectin mg/L	7.8 (4.1)	9.1 (5.8)	8.8 (6.5)	p = 0.090	p = 0.428
L/A ratio	39 (64)	36 (64)	48 (88)	p = 0.234	p = 0.026
Glucose mmol/L	5.2 (0.3)	5.0 (0.6)	5.0 (0.7)	p = 0.011	p = 0.943
Insulin pmol/L	68 (22)	71 (45)	88 (60)	p < 0.001	p < 0.001
HOMA-IR	1.3 (0.4)	1.3 (0.9)	1.6 (1.1)	p < 0.001	p < 0.001

Females	HC	NO	AP ^b	HC vs P	NO vs AP
N	44	163	353		
Age	30 (12)	30 (18)	30 (16)	p = 0.669	p = 0.908
Ethnicity, Caucasian %	100	86.5	86.7	p = 0.019	p = 1.00
Diagnostic group %					p < 0.001
Schizophrenia spectrum		16.6	54.4		
Bipolar spectrum		69.9	30.9		
Psychosis NOS		9.2	10.8		
Major depression		4.3	4.0		
GAF-S		55 (20)	45 (20)		p < 0.001
BMI	22.6 (4.0)	23.8 (5.2)	24.8 (6.6)	p = 0.017	p = 0.008
BMI category %				p = 0.325	p = 0.040
Underweight	4.8	5.7	2.1		
Normal weight	59.5	53.8	49.1		
Overweight	28.6	27.8	28.6		
Obese	7.1	12.7	20.2		
Waist, cm	79 (13)	82 (18)	86 (19)	p = 0.001	p = 0.002
Leptin pmol/L	810 (797)	873 (804)	1181 (1361)	p = 0.060	p < 0.001
Adiponectin mg/L	16.9 (9.8)	13.5 (9.2)	13.1 (8.7)	p = 0.002	p = 0.153
L/A ratio	48 (66)	61 (93)	96 (151)	p = 0.004	p = 0.001
Glucose mmol/L	4.9 (0.5)	4.9 (0.6)	4.9 (0.6)	p = 0.829	p = 0.673
Insulin pmol/L	56 (24)	68 (38)	74 (53)	p < 0.001	p = 0.006
HOMA-IR	1.0 (0.5)	1.3 (0.7)	1.4 (1.0)	p < 0.001	p = 0.007

The patients are dichotomized according to the use of antipsychotics or not. Numbers are presented as median values (IQR) or percentages. Statistical tests were performed using Mann-Whitney U tests and chi-square tests, comparing all controls and patients in addition to a separate comparison of patients using antipsychotics or not.

Abbreviations: AP = Patients using antipsychotics; BMI = Body mass index; GAF-s = Global assessment of functioning symptom score; HOMA-IR = Homeostatic model assessment of insulin resistance; HC = Healthy controls; L/A ratio = Leptin/Adiponectin ratio; N = Number; NO = Patients not using antipsychotics; NOS = Not otherwise specified; P = Patients.

^a Among males, 4.5% reported use of a first generation drug as their main antipsychotic agent.

^b Among females, 5.9% reported use of a first generation drug as their main antipsychotic agent.

Table 2
Relationship between different variables associated with overweight and body-mass index (BMI) and homeostatic model assessment of insulin resistance (HOMA-IR).

Group	BMI			HOMA-IR		
	HC	NO	AP	HC	NO	AP
BMI				0.250	0.311	0.463
Waist	0.798	0.878	0.853	0.377	0.291	0.412
Leptin	0.325	0.481	0.536	0.103 ns.	0.327	0.332
Adiponectin	-0.447	-0.361	-0.409	-0.247	-0.237	-0.337
L/A ratio	0.631	0.608	0.659	0.266	0.431	0.465

Separate analyses in healthy controls (HC), patients using (AP) and patients not using (NO) antipsychotics with Spearman's correlation coefficients. p < 0.01 for all correlations besides for leptin and HOMA-IR in the HC group.

Abbreviations: AP = Patients using antipsychotics; BMI = Body mass index; HC = Healthy controls; HOMA-IR = Homeostatic model assessment of insulin resistance, L/A ratio = Leptin/Adiponectin ratio; NO = Patients not using antipsychotics; NS = Non-significant.

3.3. Mediation analyses

3.3.1. Whole sample

We examined in a mediation model whether there was a direct effect from use of antipsychotics on insulin resistance and whether this effect was mediated through the L/A ratio adjusted for covariates, as shown in Fig. 3. The overall model with BMI explained 30.3% of the variance in HOMA-IR and 56.1% of the variance in the L/A ratio. Use of antipsychotics was significantly contributing to the L/A ratio both without (unstandardized coefficient b = 0.12, p < 0.001) and with adjustment for BMI (b = 0.05, p = 0.036), and the L/A ratio significantly contributed to HOMA-IR both without (b = 0.23, p < 0.001) and with BMI (b = 0.17, p < 0.001). In the model without BMI as covariate there was both a significant direct (b = 0.03, p = 0.007) and indirect effect mediated via L/A ratio level (b = 0.03, p < 0.001) of antipsychotics on HOMA-IR. When BMI was added to the model the effect sizes were reduced, but both directions remained significant (b = 0.03, p = 0.013; b = 0.01, p = 0.041, respectively). Tables presenting the results from the mediation analyses with L/A ratio and HOMA-IR adjusted for L/A ratio can be found in the Supplementary material.

When examining the individual contributions to the model from the other covariates, BMI was positively associated with both L/A ratio and HOMA-IR (p < 0.001). With BMI included, use of antidepressants (b = 0.05, p = 0.037) and antiepileptic drugs (b = -0.12, p < 0.001) also significantly contributed to the L/A ratio level. Of the psychotropic drug groups in this model, however, only use of antipsychotics had a significant direct effect on HOMA-IR when L/A ratio was adjusted for, while use of antidepressants also contributed to HOMA-IR in the series where L/A ratio was excluded (b = 0.03, p = 0.039). In addition, the analysis was run with total antipsychotics DDD in patients; with BMI included, DDD neither contributed to the L/A ratio (p = 0.397) nor HOMA-IR (p = 0.158).

In the total sample analysis with BMI included female sex was positively contributing to the L/A ratio (b = 0.35, p < 0.001), while negatively contributing to HOMA-IR (b = -0.08; p < 0.001) when L/A ratio was adjusted for. Due to the large sex differences in hormone levels, mediation analyses were also performed in males and females separately. These results adjusted for BMI are presented in Fig. 4. We found that use of antipsychotics had a significant direct effect on

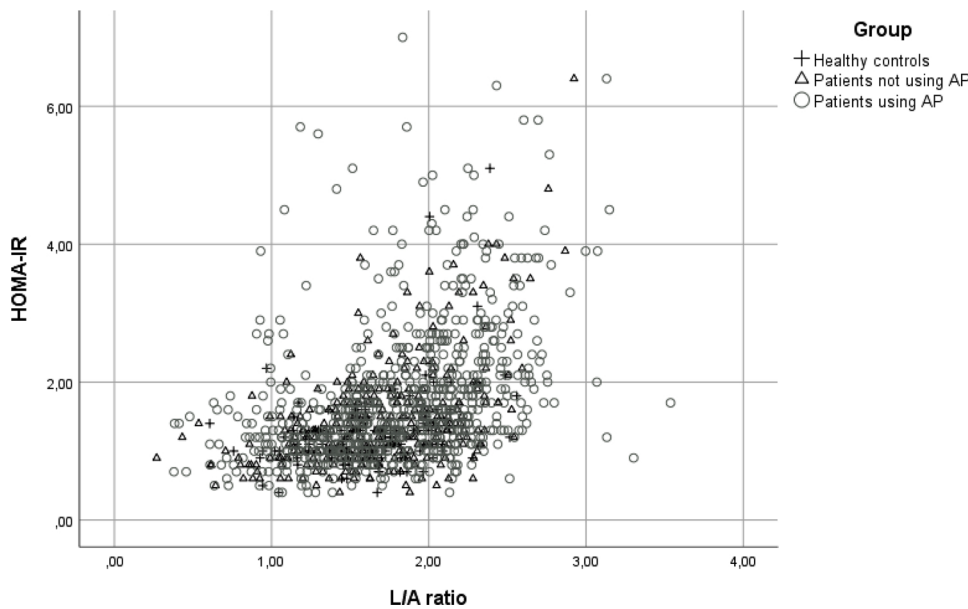


Fig. 2. Scatterplot of the association between insulin resistance (HOMA-IR) and leptin/adiponectin ratio levels in patients and healthy controls. Statistical analyses of correlations are presented in Table 2. The L/A ratios are presented as logarithmic values. **Abbreviations:** AP = Antipsychotics; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; L/A ratio = Leptin/adiponectin ratio.

HOMA-IR in males both without ($b = 0.05, p = 0.010$) and with ($b = 0.05, p = 0.015$) BMI included, while the indirect effect via the L/A ratio was significant in the model without BMI ($b = 0.03, p = 0.011$) but not with BMI included ($b = 0.01, p = 0.119$). In females, there were no significant direct effects neither without ($p = 0.224$) nor with BMI included ($p = 0.271$), while there was a significant indirect effect without BMI ($b = 0.03, p = 0.005$), and significant indirect effect at a trend-level with BMI included ($p = 0.01, p = 0.096$).

3.3.2. Monotherapy subsample

Table 3 shows the differences between unmedicated patients and patients using various antipsychotic drugs in the monotherapy subsample. We found a significant difference in both L/A ratio ($p = 0.012$) and HOMA-IR ($p = 0.047$) between the groups. The additional Mann-Whitney U tests revealed significantly higher levels of L/A ratio and HOMA-IR in the olanzapine group ($p = 0.033, p = 0.006$) and the aripiprazole group ($p = 0.007, p = 0.019$) compared the unmedicated patients, while the comparisons of the quetiapine and risperidone groups to the unmedicated were non-significant. The significant contributions from olanzapine and aripiprazole were confirmed in subsample mediation analyses adjusted for covariates (Fig. 5). Both aripiprazole ($b = 0.24, p < 0.001$) and olanzapine ($b = 0.17, p < 0.001$) demonstrated significant contributions to the L/A ratio and also significant indirect effects via L/A ratio on HOMA-IR ($p < 0.001$). However, only for olanzapine a direct effect on HOMA-IR was indicated (trend level significance: $b = 0.04, p = 0.073$). Further, the subsample

correlation analyses between the serum concentrations of each drug with L/A ratio and HOMA-IR demonstrated significant correlations between the L/A ratio and serum concentrations of olanzapine ($\rho = 0.281, p = 0.002$) and quetiapine ($\rho = 0.419, p = 0.005$), while HOMA-IR was only significantly correlated with serum concentration of quetiapine ($\rho = 0.382, p = 0.011$). Serum concentration of aripiprazole was neither associated with L/A ratio ($p = 0.676$) nor HOMA-IR ($p = 0.145$). Scatterplots of the associations between serum concentrations and L/A ratio and HOMA-IR within the respective monotherapy groups are presented in the Supplementary material.

4. Discussion

In this large, well-characterized sample of patients with severe mental disorders and healthy controls we found that use of antipsychotic drugs was significantly associated with higher level of insulin resistance, with a significant mediating effect through increased leptin/adiponectin ratio. These associations remained significant after adjusting for BMI, indicating a potential diabetogenic effect of antipsychotic drugs beyond the effect on BMI. Among specific antipsychotic agents used in monotherapy, use of olanzapine and aripiprazole were significantly associated with HOMA-IR via L/A ratio level, while serum concentration analyses of these drugs only revealed a significant positive correlation between serum concentration of olanzapine and L/A ratio. This suggests individual differences in the propensity as well as mechanisms to induce insulin resistance among different antipsychotic

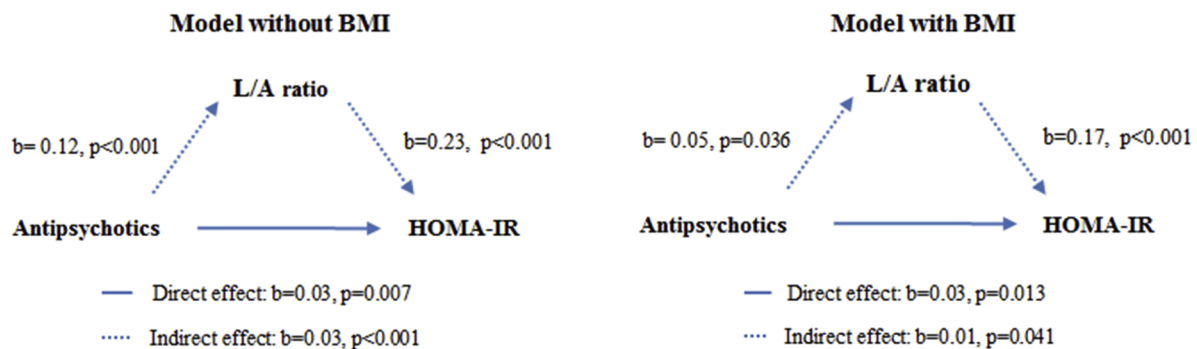


Fig. 3. Statistical model of the association between use of antipsychotics and insulin resistance and the mediation through leptin/adiponectin ratio, with and without BMI included as covariate.

Abbreviations: BMI = Body mass index; L/A ratio = Leptin/Adiponectin ratio; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance.

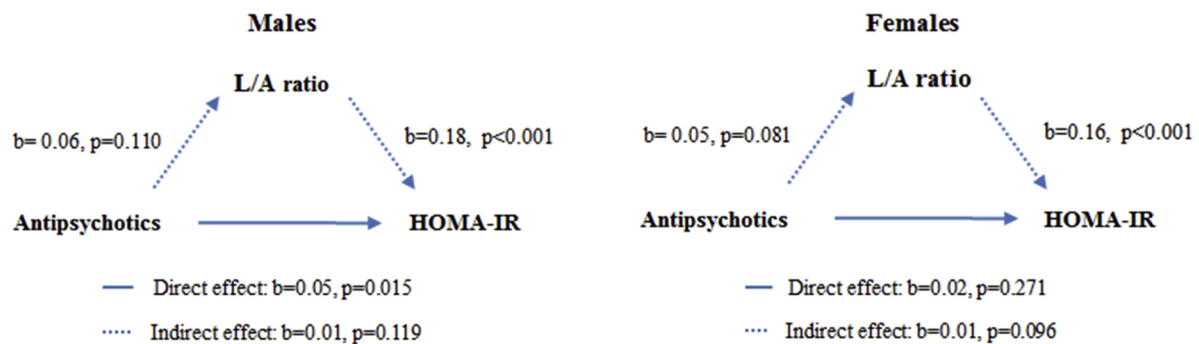


Fig. 4. Statistical model of the association between use of antipsychotics and insulin resistance and the mediation through leptin/adiponectin ratio in males and females separately, adjusted for BMI.

Abbreviations: BMI = Body mass index; L/A ratio = Leptin/Adiponectin ratio; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance.

agents.

Obesity is characterized as the highest risk factor for developing type 2 diabetes mellitus, rendering antipsychotic weight gain an assumed important contributing factor to the increased diabetes risk associated with use of antipsychotics. Weight gain is nonetheless easily observable and measurable by the clinician, while insulin resistance and ultimately type 2 diabetes mellitus may remain undetected for a long time; a particular challenge for this patient group due to inferior follow-up of medical comorbidities (Ward and Druss, 2015). Other studies have also found metabolic alterations from use of antipsychotic drugs independently of BMI and weight gain (Birkenaes et al., 2009; Kim et al., 2010), and there seem to be a range of mechanisms involved in the disturbance of the glucose metabolism. Adipose tissue and the secreted levels of leptin and adiponectin are highly relevant for the development of insulin resistance as these adipokines are directly involved in the regulation of insulin sensitivity (Yadav et al., 2013; Yamauchi and Kadowaki, 2008). Antipsychotics have been found to affect these adipokines in an unfavorable direction, and alterations of these hormone levels are suggested as possible antipsychotic drug actions associated with the development of type 2 diabetes mellitus together with the affinity of several neurotransmitter receptors including histamine H1-receptors, serotonergic 5-HT_{2c} receptors and adrenergic receptors (Starrenburg and Bogers, 2009). Antipsychotics have been found to directly affect human adipocyte gene expression and adipokine levels in vitro, although the mechanisms altering the hormone levels are not fully known (Sarvari et al., 2014). However, potential mechanisms causing antipsychotic-associated diabetes mellitus besides obesity seem to involve intracellular disturbance of insulin signaling pathways as well as direct and indirect β -cell damage, mechanisms which may also be independent of weight gain (Chen et al., 2017). In the present study we found a significant association between use of antipsychotics and L/A ratio as well as an indirect effect on insulin resistance via the L/A ratio. However, there was also a direct effect from antipsychotics on insulin resistance when the L/A ratio was adjusted for, indicating contribution from other mechanism(s) to increased insulin resistance as well. Moreover, both this direct and the indirect effect remained significant when BMI was adjusted for,

suggesting a diabetogenic influence from antipsychotics beyond that of BMI.

Our results are in accordance with the substantial metabolic side effects reported for olanzapine, as described in the literature (Rummel-Kluge et al., 2010). Olanzapine-induced weight gain is an evident side effect contributing to the risk of diabetes, with a suggested possible diabetogenic mechanism mediated via the muscarinic M3 receptor (Himmerich et al., 2015). We found a significant effect also from serum concentration of olanzapine on L/A ratio. Aripiprazole, on the other hand, is generally appreciated as causing less weight gain and metabolic side effects than other second generation antipsychotics drugs. This was recently confirmed in a review of real-world data, which also concluded with a lower risk of type 2 diabetes mellitus (Citrome et al., 2014). In the present study we found a stronger effect on L/A ratio and indirectly on HOMA-IR via this ratio from aripiprazole than from olanzapine. A possible explanation of these unexpected aripiprazole findings may be carryover side effects from previous use of other antipsychotic drugs with unfavorable metabolic profiles, as all the monotherapy groups had short median treatment duration of their antipsychotic drug. However, glucose metabolism disturbance has been observed with antipsychotic drugs already during the initial months of treatment (van Winkel et al., 2008), and aripiprazole add-on treatment to olanzapine as well as drug switch from olanzapine to aripiprazole has been found beneficial regarding glucose metabolism after a short period of time (Arnoldy et al., 2014; Wang et al., 2013). Moreover, there have been reported cases of ketoacidosis after use of aripiprazole (Church et al., 2005; Makhzoumi et al., 2008), findings of induced insulin resistance with aripiprazole (Teff et al., 2013) and induced expression of leptin and adiponectin in adipocytes from aripiprazole (Sarvari et al., 2014), which can support our results of a possible diabetogenic effect of this antipsychotic agent. As olanzapine and aripiprazole have different neurotransmitter receptor profiles, it is likely that these drugs differ in the mechanisms for suggested impact on glucose metabolism. However, there is sparse literature on adipokine level alterations and insulin resistance associated with aripiprazole, and the suggested associations reported here should be confirmed in independent follow-up samples.

When we examined the influence from total antipsychotic DDD we

Table 3

Comparisons of metabolic parameters in patients using antipsychotic agents in monotherapy using Kruskal-Wallis test.

	Unmedicated	Olanzapine	Quetiapine	Aripiprazole	Risperidone	Sig.
N	130	129	45	50	33	
DoT		3.0 (9.0)	2.3 (11.0)	2.0 (3.3)	2.8 (3.2)	$p = 0.011$
BMI	24.1 (6.4)	24.2 (6.6)	25.0 (5.8)	25.3 (4.9)	24.5 (2.7)	$p = 0.887$
L/A ratio	42 (80)	58 (97)	55 (116)	79 (159)	37 (59)	$p = 0.012$
HOMA-IR	1.3 (0.8)	1.4 (0.9)	1.4 (0.9)	1.5 (1.0)	1.6 (1.1)	$p = 0.047$

Abbreviations: BMI = Body mass index; DoT = Duration of treatment in months; N = Numbers; HOMA-IR = Homeostatic model assessment for insulin resistance; L/A ratio = Leptin/Adiponectin ratio; Sig = Statistical significance.

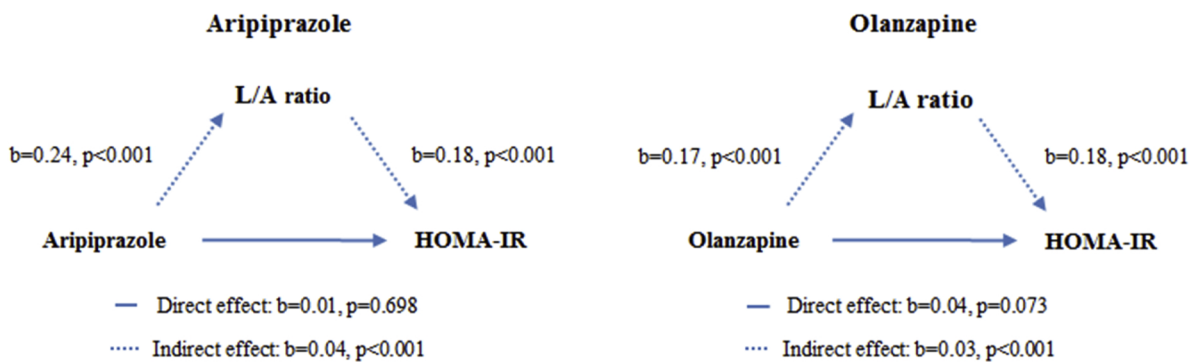


Fig. 5. Statistical model of the association between use of aripiprazole or olanzapine and insulin resistance and the mediation through leptin/adiponectin ratio, adjusted for BMI.

Abbreviations: BMI = Body mass index; L/A ratio = Leptin/Adiponectin ratio; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance.

found no significant associations with L/A ratio or HOMA-IR with BMI included. One reason for this may be the different side effect profiles of various antipsychotic agents neutralizing each other when summarized in a total dose calculation. Metabolic side effects have been found dose-dependent by others (Simon et al., 2009), and the serum concentration of olanzapine was highly significantly associated with L/A ratio also in our study. Interestingly, we also found a significant correlation between serum concentration level of quetiapine and both L/A ratio and HOMA-IR, while use per se was neither associated with L/A ratio nor HOMA-IR. There are reported cases of quetiapine associated with hyperglycemia, ketoacidosis and diabetes mellitus (Koller et al., 2004; Vuk et al., 2017), and a large epidemiological study found a dose-dependent risk of diabetes with use of olanzapine across both intermediate and high doses, while the dose-dependent risk for quetiapine was only evident in the highest dose range (Ulcickas Yood et al., 2011). Our finding may be explained by a subgroup of quetiapine users on very high doses accounting for the association with serum concentration, as can be suspected when viewing the scatterplots describing these associations (Supplementary).

The patients in our total sample also used other psychotropic drugs like antidepressants, lithium and antiepileptic drugs, which may have some effect on weight gain and/or type 2 diabetes mellitus (Abosi et al., 2018). In the present study we also found use of antidepressants associated with increased L/A ratio, and the significant impact on insulin resistance seemed to be dependent on this ratio, explaining a possible diabetogenic component also from this psychotropic drug group. A recent review concludes that antidepressants users have an increased risk of new-onset diabetes (Salvi et al., 2017), while there is a lack of available research investigating the role of adiponectin with these drugs (Himmerich et al., 2015). Interestingly, use of antiepileptic drugs was negatively associated with L/A ratio, suggesting that the increased diabetes risk from antiepileptic drugs may be mediated via a different mechanism. However, a review article has described an association between use of valproic acid and lower adiponectin levels as well as weight gain and development of insulin resistance, contradicting our results (Belcastro et al., 2013). Antipsychotics seems to be the most extensively studied psychotropic drug group regarding this topic, but attention should be paid to the potentially increased risk of metabolic side effects of different psychotropic drugs, both individually and when used in polypharmacy, as polypharmacy is common in clinical practice (Ballon and Stroup, 2013).

Our findings indicate that there may be significant sex differences in the associations between antipsychotic drug use and observed metabolic disturbances. We found a positive association between female sex and L/A ratio in the total sample which can be explained by the higher levels of these hormones observed in females, both in our study and described in the literature (Lilja et al., 2012). On the contrary, there was a negative direct association between female sex and HOMA-IR in

the whole sample as compared to male sex, and the mediation analyses performed in females and males separately emphasized both significant direct and indirect effects among males while only significant indirect effects among females. Antipsychotic-associated weight gain and metabolic disturbance has been found more prevalent in females than males (Papanastasiou, 2013), and metabolic distinctions between males and females may be related to sex differences in adipose tissue distribution, sex hormone levels and/or sex-specific pharmacokinetics and dynamics (Haack et al., 2009). Our findings suggest that L/A ratio-associated insulin resistance is evident in both sexes while males also demonstrate diabetogenic effects beyond this with use of antipsychotics, which calls for further research on the possible sex-specific mechanisms involved.

The median age and BMI in our participants were rather low with respect to risk of developing type 2 diabetes mellitus; still we found significant associations between antipsychotics and insulin resistance in our sample. This emphasizes the importance of taking the risk of premature diabetes and cardiovascular disease in this patient group seriously at an early stage. Clinicians should be aware of possible diabetogenic effects of aripiprazole and use of quetiapine in high doses, keeping in mind that unfavorable metabolic alteration may occur independently of observable weight gain.

4.1. Limitations

The cross-sectional design of this study renders our conclusions on causality of the associations described suggestive. Further, the influence from smoking and other factors relevant for metabolic changes were not addressed, and we cannot rule out confounders related to bias in selecting individual drugs for specific types of patients, as this is a naturalistic sample. Another limitation is that the majority of participants were ethnical Caucasians, restricting the generalizability of the present study. However, good clinical practice should try to limit the metabolic side effects, which would make it more difficult to find the associations reported here. A strength of the study was the available measures of antipsychotic drug serum concentrations, allowing assurance of actual intake and thereby presumed effect of the prescribed drugs.

5. Conclusions

The present results suggest that antipsychotic-associated alterations in adipokine levels may be a mechanism contributing to insulin resistance in people with severe mental disorders receiving antipsychotic drug treatment, and that this diabetogenic effect may have impact beyond BMI. These findings provide novel insight into possible mechanisms related to the increased cardiovascular morbidity and mortality in severe mental disorders, and may have implications for how to reduce this co-morbidity in a clinical setting.

Declaration of interests

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.psyneuen.2019.01.001>.

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