Adipose Tissue Dysregulation at the Onset of Psychosis: Adipokines and Social Determinants of Health

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Abbreviations: CCHS: Canadian Community Health Survey; CVD: Cardio-Vascular Disease; DSM: Diagnostic and Statistical Manual of Mental Disorders; FEP: First-Episode Psychosis; IL-6: Interleukin 6; NF-κB: Nuclear Factor kappa-B; PHQ-9: Patient Health Questionnaire; PSD: Psychosis Spectrum Disorders; TNFα: Tumor Necrosis Factor-alpha; WHeR: Weight-to-Height Ratio; WHODAS: World Health Organization Disability Assessment Schedule (Version 2.0).

ABSTRACT

Recent evidence suggests that patients with psychotic disorders have metabolic disturbances (e.g., insulin resistance, dyslipidemia) at the onset of the disease and before antipsychotic exposure. Such disturbances are strongly associated with adipose tissue dysregulation. Measuring adipokines, the molecular mediators of adipose function, could provide a picture of the state of metabolic regulation at the onset of psychosis. The present study explores adipokine changes in a population of first-episode psychosis (FEP) patients with minimal prior exposure to antipsychotics. The effects of social determinants of health associated with both metabolic and psychotic disorders (childhood trauma, minority status, poverty) were studied as potential determinants of this phenomenon. Data was collected through the Signature project, a biobank of clinical, socio-demographic, and biological markers. Adipokines (leptin, adiponectin, resistin and chemerin) were measured in serum of FEP patients with minimal exposure to antipsychotics (N=48) and controls (N=39). Data were analyzed with univariate (t-tests) and multivariate (linear regression) statistical methods.

Patients, compared to controls, had significantly higher levels of adiponectin and resistin, and significantly lower levels of leptin and chemerin. These results persisted after controlling for sex, waist-to-height ratio, childhood trauma, and ethnic minority status. Adiponectin and chemerin retained their effects after further controlling for tobacco and depression. Resistin increased with childhood trauma scores; chemerin was higher in ethnic minority patients. Adipose tissue dysfunction is present in FEP patients, before exposure to antipsychotics. Social determinants of health contribute to adipose (and metabolic) dysregulation in FEP, but were not the main determinants of this relationship.

Keywords: first-episode psychosis; psychoneuroendocrinology; developmental origins of health and disease; childhood trauma; minority groups.

INTRODUCTION

Psychosis-spectrum disorders (PSD) bear a high degree of metabolic comorbidity (Correll et al., 2017), which contributes to the development of cardiovascular disease, the leading cause of mortality in this population (Hjorthoj et al., 2017). The nature of metabolic morbidity in PSD is complex and multifactorial, and its underlying pathophysiological substrates remain unclear. To address the high rates of cardiometabolic mortality in these patients, it is necessary to understand the nature of metabolic dysregulation in PSD.

Metabolic dysregulation in PSD has been attributed to the side-effects of second-generation antipsychotics (the first line therapeutic options) (Henderson et al., 2015), and the lifestyle changes emerging from negative symptoms (e.g., sedentary behaviors, dietary changes) (Rojo et al., 2015). However, the relationship between schizophrenia and hyperglycemia was already documented more than five decades before the introduction of the first antipsychotic (Kohen, 2004). Furthermore, three meta-analytical reviews of studies with young first-episode psychosis (FEP) patients who were relatively unexposed to antipsychotics, and not chronically affected by cardiovascular risk factors such as tobacco smoking and sedentary behaviors, have demonstrated the presence of subclinical disorders of energy metabolism such as prediabetes (Kucukgoncu et al., 2018) and altered blood lipid levels (Misiak et al., 2017; Pillinger et al., 2017). Altogether, these findings indicate that metabolic dysregulation may already be present at the onset of psychosis, and suggest that some alterations might predate antipsychotic side-effects.

The nature of such intrinsic metabolic anomalies at this early stage could be biological and-or socio-environmental. The most comprehensive genetic study in schizophrenia meta-analyzed genome-wide association studies using polygenic risk scores of cardiometabolic traits (e.g., HDL, leptin, measures of

adiposity) and found a handful of significant associations (So et al., 2018). However, the direction of the most robust scores (i.e., BMI, HDL, leptin) was paradoxical, implying that patients with schizophrenia would tend to be leaner and have lower cardiometabolic risks, which contradicts epidemiological and clinical data. On the other hand, evidence for the role of social determinants of health as risk factors for psychotic disorders (McKenzie and Shah, 2015), metabolic conditions (Walker et al., 2016), and cardiovascular disease (Rosengren et al., 2004) is substantial. This is particularly true when social adversity occurs early in life. In fact, childhood trauma (Danese and Tan, 2014; Varese et al., 2012), social and material deprivation (Cubbin et al., 2006; Wicks et al., 2005), visible minority status (Falkner and Cossrow, 2014; Kirkbride et al., 2008), and a migrant background (Ishizawa and Jones, 2016; Kirkbride et al., 2012), are strong predictors of metabolic, cardiovascular and psychotic disorders. Since early social adversity is highly prevalent in PSD (Boydell et al., 2004; Cantor-Graae and Selten, 2005; Read et al., 2008), the high rates of metabolic disease in these patients might be facilitated by socio-environmental factors. Indeed, we have previously documented associations between visible minority status as well as physical abuse with glycated hemoglobin (after controlling for BMI) (Veru-Lesmes et al., 2018), and between social deprivation and blood lipids in FEP (Veru-Lesmes et al., 2019).

Considering that metabolic dysregulation may start over 20 years before the diagnosis of diabetes (Dankner et al., 2009), finding clinically detectable changes in FEP patients (age~22) implies the presence of a pathophysiological process with developmental origins, i.e., established perinatally or during childhood. One such process is adipose tissue dysregulation (Samson and Garber, 2014), which promotes insulin resistance (Lee and Lee, 2014), dyslipidemia (Hocking et al., 2013), and inflammation (Landgraf et al., 2015), the key elements of endothelial dysfunction and atherosclerosis. Thus, exploring adipose function might provide clues on the origin of the clinical changes of metabolism observed in FEP patients.

The adipose tissue is a functional endocrine organ (McGown et al., 2014), exerting paracrine and endocrine actions via adipokines (Mechanick et al., 2016). These mediators are central to some pathophysiological processes key to adipose tissue regulation such as adipocyte differentiation and proliferation (e.g., chemerin and resistin) (Alderete et al., 2014), insulin resistance (e.g., resistin, adiponectin) (Rabe et al., 2008) and lipid metabolism (e.g., leptin, adiponectin) (Katsiki et al., 2017). Unsurprisingly, adipokine alterations have been associated with CVD risk (Mattu and Randeva, 2013). The possibility that adipose tissue dysregulation is present at the onset of psychosis, before antipsychotic exposure, has not been tested.

The present study has two main objectives:

To determine if adipose tissue dysregulation, as indicated by changes in adipokine levels, is present in FEP prior to treatment. We hypothesize that FEP patients will have altered levels of the following adipokines: leptin, adiponectin, resistin, and chemerin, when compared to matched controls without diagnosis of a mental disorder.

The second objective is to examine the relationship between adipose tissue dysregulation and social determinants of health within the context of FEP. This exploratory analysis could allow identifying those determinants that might be relevant in this population and further test if such determinants might interact with a diagnosis of PSD to result in adipose tissue dysfunction.

METHODS

Participants and Setting

This project was conducted using data from the Signature project, a data bank of functional dimensions of mental health, i.e., *signatures*, from the biological, psychological and social levels (Lupien

et al., 2017). Participants are first recruited at the emergency department of the Institut Universitaire en Santé Mental de Montréal (IUSMM), a specialized mental health care institution. Participants who grant (written) consent to participate in the project provide blood samples, are interviewed and assessed by a research nurse, and complete a battery of questionnaires assessing mental and physical health issues, as well as psychosocial dimensions. The present project uses data from the initial contact at the psychiatric emergency department of the IUSMM. Data was collected from February 2013 to January 2018 and allowed for a case-control design.

An initial pool was preselected from Signature's main database based on a diagnosis of psychosis-spectrum disorder made by the attending psychiatrists at the emergency department. Confirmation of a first episode of psychosis was established through revision of the clinical files, and cases were only included if they met the following criteria: confirmation of a PSD diagnosis after at least six months of follow-up (made by psychiatrist at IUSSM external consultation), a first episode of psychosis was ascertained (no previous contact with mental health providers for psychotic symptoms, no history of previous antipsychotic/antidepressant treatment), minimal current exposure to antipsychotics or antidepressants (i.e., less than 7 days from day of first prescription to the day of blood sampling), and ages between 18 and 40 years. Exclusion criteria were: substance-induced psychosis, unclear or unconfirmed psychosis-spectrum diagnosis, and diabetes mellitus (clinical file). Controls were recruited by Signature from the same community neighborhoods as the case group. In addition to the exclusion criteria used for patients (above), controls had no history of mental health disorders, which was ascertained with two screening questionnaires: the community assessment of psychotic experiences (CAPE) and the Mood disorder questionnaire (MDQ). The research ethics board of the IUSMM approved the present study.

Outcome Variables

The main outcome variables are serum levels of the following adipokines: leptin, adiponectin, resistin and chemerin. Blood samples were collected by Signature's research nurse at the time of recruitment, and stored (serum) until processing at -80°C. Adipokine levels were measured with commercial ELISA kits, following manufacture's protocols (R&D Systems) by a dedicated laboratory technician from Signature. The mean of two individual ELISA measurements was computed to obtain the final adipokine levels.

Predictor Variables

The main predictor variable, as indicated by the case-control design of the study, is the presence of a diagnosis of FEP. The social determinants of health used to predict metabolic function are: childhood trauma, visible minority background, and socioeconomic status (Cozier et al., 2014; Danese and Tan, 2014; Senese et al., 2009; Wang and Beydoun, 2007). Childhood trauma was assessed with the Childhood Experiences of Violence Questionnaire (CEVQ), a seven-question validated instrument exploring a history of physical (victim and/or witness), and sexual abuse in childhood (Walsh et al., 2004). Total CEVQ scores were used as the main trauma variable. Visible minority background was self-reported, and obtained from Signature's demographic questionnaire. Participants were asked to select which ethnic group or groups they belong to. The variable was then dichotomized; participants who identify themselves as belonging to an ethnic group other than "white" were classified as coming from a visible minority background. Income was also self-reported (raw estimation), and acquired from Signature's demographic questionnaire.

Two clinical variables with potential confounding effects were included: depression and current tobacco smoking. The total score from the depression scale from the Patient Health Questionnaire (PHQ-

9) was used to assess the level of depressive symptoms. The PHQ-9 consists of nine DSM IV-based items, and has been validated and frequently used as a screening, measuring, and diagnostic tool for depressive symptoms (Kroenke et al., 2001). The questionnaire from the Canadian Community Health Survey (Statistics Canada) was used to appraise tobacco smoking. Current tobacco consumption was dichotomized classifying participants as smokers (daily or intermittent), versus non-smokers.

In addition, the effect of the participant's sex was tested given the sexually dimorphic character of physiologic responses at the endocrine level (Geer and Shen, 2009), and marked differences in exposure to childhood trauma (Stoltenborgh et al., 2011). Similarly, the effect of age was considered as the risk for metabolic disease increases with it. Finally, the participant's waist-to-height ratio (WHeR) was included to control for body fat mass. Adipose tissue mass is strongly correlated with leptin (Kelesidis et al., 2010) and adiponectin (Lara-Castro et al., 2006; Seven et al., 2015) levels. As such, controlling for WHeR allows comparing the individual's adipokine secretion state regardless of body fat mass. Furthermore, since ethnicity-derived cut-offs for abdominal obesity are country-specific (Wang et al., 2010), controlling for this factor in an ethnically mixed population preferentially controls for biological differences, allowing for a better appraisal of environmental influences.

Statistical Analyses

Demographical comparisons between participants with a FEP and controls were conducted with Student's t or chi-square tests. Leptin levels exhibited an exponential distribution, which is a typical phenomenon observed when measuring this molecule (Blum et al., 1997). Thus, this variable was treated with a logarithmic transformation. Other adipokines followed a normal distribution.

The first objective, to determine the effect of a FEP diagnosis on adipokine levels, was tested using Student's t-tests (2-sided, equal variances). The second objective, to test the association of psychosis-associated factors on metabolic function, including social determinants of health, was conducted first by exploring the univariate relationships between these predictors and adipokine levels. Those predictors with significant effects were further tested together in a multiple regression model. This was conducted using a hierarchical procedure that allowed assessing the distinct contribution of different groups of variables to the total adipokine variance. The first block contains inherent individual characteristics including FEP diagnosis, sex, and WHeR. The second block tests for the effect of social determinants of health, i.e., visible minority status, and childhood trauma. The final block examines the association with behavioral confounders, namely tobacco smoking and depression. The differences between the final models and univariate results were used to guide post-hoc analyses. All analyses were conducted with the R language and environment for statistical computing (version 3.2.3) (Venables and Smith, 2015).

RESULTS

Sample Characteristics

A comparison of characteristics for patients and controls (Table 1) shows that the patient group had a significantly higher proportion of male participants and a greater proportion of individuals from visible minority backgrounds but the latter difference did not reach statistical significance. Finally, controls had borderline significant higher WHeRs. Patients had an average of 2.3 (SD ±1.6) days of exposure to medication, and most of the sample had two or less days of exposure (Supplementary figure 1).

Adipokines (Cases vs. Controls)

All tested Adipokine levels were significantly different between FEP patients and controls (Figure 1) in unadjusted analyses. Compared to controls, patients had significantly lower levels of leptin (patients =7.56±.0.3, controls =8.94±0.17 pg/ml; t= 3.84, df= 83, p<0.01) and chemerin (patients =47.06±.2.21, controls =75.32±3.8 ng/ml; t= 6.72, df= 85, p<0.01), and higher levels of adiponectin (patients =9.02±.0.56, controls =6.42±0.57 µg/ml; t= -3.23, df= 85, p<0.01) and resistin (patients =8.18±.0.43, controls =6.67±0.40 ng/ml; t= -2.54, df= 85, p=0.01). A post-hoc sensitivity analysis was conducted to evaluate the strength of the association between FEP diagnosis and adipokine levels by days of medication exposure, and examine the possibility that such changes depended on the metabolic side effects of medication. Two sets of t-tests were conducted including only patients that were either drug-naive (N=7), or had a maximum of three days of medication exposure (N=37), and compared both groups with the controls. Both analyses mirrored the results obtained with the complete sample, the number of medication exposure days did not alter the direction of the effects, only resulting in a decrease in power of the coefficients (Supplementary tables 1a-b).

Univariate Analyses

Univariate analyses depict the individual relationship between predictors and adipokines for the whole sample (patients and controls), which consisted of correlations (Pearson) for continuous variables and Student's t-tests for categorical variables (tables 2 and 3). Total trauma had a significant positive correlation with resistin, and a negative correlation with chemerin. Among the trauma scale components, physical violence was associated with higher levels of resistin and lower levels of chemerin, and at the same time showed a non-significant trend in association with lower levels of leptin. Depression scores significantly predicted higher resistin, and lower chemerin levels. Leptin increased in association with self-reported income. Females had significantly lower levels of leptin and chemerin, and borderline (p=0.06) lower levels of adiponectin. Chemerin was found to be significantly higher in participants

belonging to the visible minority group. Tobacco smoking had a dampening effect that was statistically significant on leptin, but less robust on adiponectin (p=0.06).

Multivariate Models

In the first two steps of the hierarchical model, after controlling for sex, WHeR, childhood trauma and visible minority background, all differences in adipokine levels seen in the univariate models between cases and controls remained significant (Tables 4a-d). In the last step, after adding smoking and depression, differences by diagnosis were still significant for adiponectin and chemerin. *Leptin* and *adiponectin* levels were significantly higher in women, and increased in proportion to WHeR. Taken together, FEP diagnosis, sex and WHeR explained 69% of the variability of *leptin*, and 28% in the case of *adiponectin*. *Resistin* levels had a borderline significant association (p=0.05) with higher (Std Beta=0.23) childhood trauma scores after taking into account all other variables. Replacing total scores of trauma with those of physical violence resulted in a similar picture, but this was not the case when testing for the influence of sexual violence, indicating that the former was the main driver of the effects of trauma in this sample (Supplementary table 2). After controlling for sex and WHeR, FEP diagnosis significantly explained 9% of variance of *resistin*, with an additional 5% being explained by childhood trauma. When accounting for the effect of all selected predictors, *chemerin* increased in proportion with WHeR, was significantly lower in association with ethnic minority, and was higher in smokers. The complete model explained 57% of the variance of this adipokine.

DISCUSSION

The present study documented the presence of adipose tissue dysregulation at the onset of psychosis –and before significant antipsychotic exposure–, indicated by significant differences in serum levels of

leptin, adiponectin, resistin, and chemerin between FEP patients and controls. These associations were robust, as illustrated by a sensitivity analysis, which also ruled out the possibility that such changes depended on the metabolic effects of antipsychotic medications. Furthermore, these changes remained true after taking into account the influence of personal, psychosocial, and behavioral factors, and showed that adiponectin and chemerin had the strongest associations with FEP. Social determinants of health played a role in adipose dysregulation in this cohort. Childhood trauma scores predicted higher levels of resistin, and belonging to an ethnic minority was associated with lower levels of chemerin. These influences were independent of FEP patient status. In addition, smokers had significantly lower levels of chemerin, females tended to have higher adipokine levels, and except for resistin, strong associations were observed between adipokine levels and adipose mass as indicated by WHeR. The young age of the participants (~25yr patients, ~27yr controls), and the negligible exposure to antipsychotic medication in the patient group are compelling arguments suggesting that adipose tissue dysregulation develops before treatment is initiated for a FEP. This would imply an innate or early-acquired susceptibility, i.e., a metabolic diathesis. While psychosocial factors promote metabolic disease and act throughout development, and hence were tested as potential influences, our data does not support an etiological role of these in the origins of metabolic dysregulation at the onset of psychosis.

To date, most studies measuring adipokines in FEP have examined their change after exposure to antipsychotic pharmacotherapy, but only a few have tested these parameters without this influence. A meta-analysis of FEP studies concluded that there was no difference in adiponectin levels between patients and controls (Bartoli et al., 2015). However, included studies greatly differed in the average age of their cohorts, and indeed some reported significant but contradicting findings (Shiloah et al., 2007; van Nimwegen et al., 2008). Still, a study with drug-naive patients in a similar age range as our sample concurred with our finding of increased adiponectin (Song et al., 2013). Another study found increased leptin and no differences in resistin levels, but some patients had received up to three months of

antipsychotic treatment (Bocchio-Chiavetto et al., 2018). It would seem, therefore, that the amount of exposure to antipsychotic medication was an important determinant of the results of such studies, suggesting that the negligible period of antipsychotic exposure in our patient sample may provide a more accurate picture of adipokine function at FEP.

An interpretation of the potential implications arising from the changes in adipokine levels documented by the present study follows. Leptin acts as a negative feedback signal controlling energy balance by promoting appetite reduction when adipose mass increases (Park and Ahima, 2015). Thus, the lower levels observed in FEP patients might indicate a deficient secretion, resulting in an impaired adipose-hypothalamic feedback, which in turn would not prevent adipose tissue mass to increase in association with energy intake. Adiponectin enhances insulin action, glucose uptake, and oxidation of fatty acids (Wang and Scherer, 2016), resulting in lower insulin resistance. The documented increase could represent a compensatory mechanism driven by the impairment in leptin function. Resistin contributes to insulin resistance in specific situations (Codoner-Franch et al., 2014), hinders adipocyte differentiation (negative feedback control of adipogenesis) (Kim et al., 2001), and promotes inflammation and vascular disease (Wei and Wong, 2011). The observed increase could potentially explain the higher risk for the development of cardiometabolic disease observed in FEP. Chemerin acts in the adipose tissue as an essential promoter of adipocyte differentiation, while in mature adipocytes it has roles in adipogenesis and lipolysis through an autocrine fashion. Moreover, it modulates the expression of core metabolic genes such as leptin and adiponectin (Goralski et al., 2007). Chemerin affects glucose metabolism by promoting insulin resistance in muscle cells (Sell et al., 2009). Its decreased levels are thus paradoxical, but could potentially be responsible for the dysregulation observed in the production of leptin and adiponectin. Finally, given the close roles of adipokines in inflammation (Hutcheson, 2015), the documented adipokine changes could contribute, or be part of, the pro-inflammatory imbalance described in early psychosis (Garcia-Bueno et al., 2014).

Altogether, the findings of the present study allow us to postulate that: 1) sub-clinical metabolic anomalies are present at the onset of psychotic disorders (and perhaps earlier) before exposure to antipsychotic medication; 2) the adipose tissue plays a central role in this phenomenon; 3) phenomena such as insulin resistance, adipose tissue development, lipid metabolism, and inflammation could be affected, possibly explaining the increased susceptibility for disorders of energy metabolism in PSD; 4) the crosstalk between the immune and the adipose tissue may be altered in FEP; and 5) some of the examined psychosis-associated clinical and psychosocial factors independently contribute to adipose dysregulation.

Strengths of the present study include strict inclusion criteria for selection of a sample of FEP with minimal exposure to antipsychotics. This decision was validated by the sensitivity analysis, which indicated that the brief window of medication exposure (0-6 days) had no influence on adipokine levels. In addition, the collection of clinical and psychosocial data, blood sampling, and processing of biological specimens were conducted by a team of trained professionals from the Signature bank. Using the waist-to-height ratio, which better estimates the proportion of visceral fat compared to BMI (Ashwell et al., 2012), was a more accurate way to control for adiposity than BMI. Lastly, to our knowledge, this is the first study exploring the association between early life adversity and metabolic function in FEP, and the first to measure chemerin levels in FEP.

The main limitation of the present study was the relatively small number of participants, which required limiting the number of variables in the final models. Ideally, all theoretical predictors of metabolic dysfunction should be included in the regression models. However, this would have unfavorably reduced the number of participants per regression group. Nonetheless, the selection of the final predictors to construct the main multivariate model was based on the univariate results, which

allowed keeping an adequate variable-to-observation ratio, and the construction of parsimonious models. While in the final model including seven predictors, the coefficients of FEP diagnosis for leptin and resisitin were not significant, the fact that these were in the previous steps indicates that this was likely due to a loss of power. In spite of these limitations, the number of participants was considerable taking into account the depth and consistency of biological, clinical and psychosocial phenotyping. Moreover, the effect sizes of the adipokine effects were substantial even after controlling for other predictors. The proportion of male vs female participants was significantly uneven between patients and controls. Nevertheless the documented effects remained significant after this variable was controlled for in the multivariate models. Finally, it would have been optimal to have a continuous measure of tobacco smoking (e.g. number of cigarettes smoked per day), particularly to test a dose-response relationship. Similarly, only a proxy variable was available to estimate the influence of physical activity, and information on dietary behaviors and habits was not available.

Conclusion

In conclusion, we have reported that patients presenting with a first episode of psychosis show substantial changes in adipokine production even prior to exposure to antipsychotic medication. Such changes signal the presence of adipose tissue dysregulation in PSD, and suggest the possibility of abnormal adipocyte differentiation and deviant recruitment of immune cells to the adipose organ. The manifestation of such changes pre-treatment indicates the presence of a diathesis, i.e., a constitutional susceptibility for the development of metabolic disease in psychosis. This is congruent with the high levels of comorbidity observed in these patients, and is likely worsened by side effects of antipsychotic medications. Furthermore, the findings of the present study are consistent with recent advances in the understanding of physical health in psychosis, i.e., that psychosis is a multi-systemic disorder in which the immune system has a central role (Pillinger et al., 2018). This study also substantiates the role of

social determinants on mental and metabolic health, and further studies should continue to explore their potential role in explaining the high rates of comorbidity described in the literature.

The reported findings could redirect the search for genetic variants and epigenetic changes, and underscore the importance of gene-environment interactions. Further confirmation with larger samples is needed, as identifying those individuals with higher metabolic liability would importantly aid in guiding treatment. From a clinical perspective, unraveling the particularities of metabolic dysfunction in psychotic disorders could lead to a more informed design of antipsychotic medications, as well as the development of hypolipidemic or antidiabetic agents tailored to this population. Such knowledge could also improve the delineation of preventive strategies impacting the main causes of morbidity and mortality in psychotic disorders. Finally, adipokines have the potential to be used as ancillary laboratory markers profiling the immuno-metabolic state of patients with PSD, making them ideal tools to gauge the state of metabolic control in FEP.

Table 1. Demographic Comparison Between FEP Cases and Controls

Demographic	FEP (N=48)		Controls (N=39)		Test Statistic		
	Mean	SD	Mean	SD	*t*	df	*p* (2-tail)
Age	25.73	6.30	27.54	7.97	1.18	85	0.24
Income	17294.35	18529.17	21660.53	22900.83	0.95	79	0.35
BMI	24.13	5.54	25.25	3.97	1.06	85	0.29
WHeR	0.48	0.11	0.52	0.06	1.95	85	0.05
	N	%	N	%	x^2	df	*p* (2-tail)
Sex (male)	41	85.4%	23	59.0%	7.74	1	0.01
Minority (yes)	19	40.4%	8	21.1%	3.64	1	0.06

BMI: Body mass index; df: degrees of freedom; FEP: First-episode of psychosis; N: group size, p: statistical significance (>0.05); SD: Standard deviation; t: Student's t statistic, WHeR: Waist-to-height ratio; x2: chi-square statistic

Table 2. Correlation matrix, adipokines and continuous variables

	Leptin (log)	Adipo-nectin	Resis-tin	Cheme-rin	Age	Income	Total Trauma	Physical Violence	Physical Abuse	Sexual Violence	Number Trauma	Depres-sion	WHeR
Leptin(log)	1	-0.173	-0.047	0.498**	0.110	0.236*	-0.092	-0.199†	-0.142	0.209†	-0.036	-0.062	0.464**
Adiponectin		1	0.021	-0.303**	-0.177	-0.154	0.068	-0.036	-0.060	0.180†	0.034	0.081	-0.239*
Resistin			1	-0.071	-0.097	0.010	0.249*	0.248*	0.168	0.028	0.191†	0.225*	-0.081
Chemerin				1	0.205†	0.161	-0.200†	-0.239*	-0.225*	0.010	-0.187†	-0.298**	0.437**
Age					1	0.435**	-0.058	-0.022	0.025	-0.088	0.013	-0.123	0.328**
Income						1	0.143	0.157	0.176	0.016	0.261*	-0.039	0.363**
Total Trauma							1	0.889**	0.869**	0.446**	0.817**	0.051	0.043
Physical Violence								1	0.970**	-0.005	0.735**	0.081	-0.008
Physical Abuse									1	0.025	0.637**	0.109	0.026
Sexual Violence										1	0.377**	0.032	0.143
Number Traumas											1	0.034	0.175
Depression												1	-0.067

WHeR: Waist-to-height ratio

Table 3. Adipokines by grouping variables: sex, minority status and smoking status

	Leptin (log)	Adiponectin	Resistin	Chemerin
Male (mean±SD)	9.72 ±0.96	9179.6 ±4316.76	7.68 ±3.30	68018.5 ±24696.2
Female (mean±SD)	7.63 ±1.69	7375.96 ±3716.73	7.44 ±2.72	56749.8 ±23216.2
t	-5.61	-1.91	-0.35	-1.96
df	83	85	85	85
p	<0.01	0.06	0.73	0.05
Non-minority (mean±SD)	8.28 ±1.77	7675.3 ±3779.35	7.32 ±2.02	66481.2 ±24091.4
Minority (mean±SD)	7.96 ±1.88	7880.6 ±4254.63	7.79 ±4.22	46919.3 ±17271.7
t	-0.74	0.22	0.70	-3.79
df	81	83	83	83
p	0.46	0.82	0.48	<0.01
Smoker (mean±SD)	7.61 ±1.94	8867.54 ±4488.87	7.92 ±3.1	54733.8 ±20855.4
Non-smoker (mean±SD)	8.54 ±1.6	7232.66 ±3463.4	7.25 ±2.71	62781.4 ±25431.4
t	2.39	-1.91	-1.07	1.53
df	83	85	85	85
p	0.02	0.06	0.29	0.13

df: degrees of freedom; p: statistical significance (>0.05); SD: Standard deviation; t: Student's t statistic

Table 4a. Hierarchical Multiple Linear Regression Model: Leptin (log-transformed)

Leptin (n-log)	Step 1		Step 2		Step 3	
N= 81	**Demographic**		**SDH**		**Confounders**	
Coefficient Statistics	**β**	***p***	**β**	***p***	**β**	***p***
FEP	0.14	0.04	0.16	0.03	0.15	0.10
Sex	-0.48	<0.01	-0.47	<0.01	-0.47	<0.01
WHeR	0.59	<0.01	0.60	<0.01	0.60	<0.01
Minority			0.06	0.41	0.05	0.44
CEVQ.total			0.02	0.73	0.02	0.77
Smoker (yes/no)					0.03	0.66
Depression					0.02	0.86
Step Statistics	**ΔR2**	**Δ*p***	**ΔR2**	**Δ*p***	**ΔR2**	**Δ*p***
	0.69	<0.01	<0.01	0.66	<0.01	0.90
Model Statistics	**R2**	***p***	**R2**	***p***	**R2**	***p***
	0.69	<0.01	0.69	<0.01	0.69	<0.01

Abbreviations at the end of the table

Table 4b. Hierarchical Multiple Linear Regression Model: Adiponectin

Adiponectin	Step 1		Step 2		Step 3	
N= 83	**Demographic**		**SDH**		**Confounders**	
Coefficient Statistics	**β**	***p***	**β**	***p***	**β**	***p***
FEP	-0.41	<0.01	-0.43	<0.01	-0.54	<0.01
Sex	-0.29	0.01	-0.31	<0.01	-0.35	<0.01
WHeR	-0.25	0.01	-0.29	0.01	-0.26	0.01
Minority			-0.16	0.12	-0.13	0.20
CEVQ.total			0.02	0.86	0.01	0.96
Smoker (yes/no)					-0.04	0.73
Depression					-0.20	0.10
Step Statistics	**ΔR2**	**Δ*p***	**ΔR2**	**Δ*p***	**ΔR2**	**Δ*p***
	0.28	<0.01	0.02	0.30	0.03	0.25
Model Statistics	**R2**	***p***	**R2**	***p***	**R2**	***p***
	0.28	<0.01	0.30	<0.01	0.32	<0.01

Abbreviations at the end of the table

Table 4c. Hierarchical Multiple Linear Regression Model: Resistin

Resistin	Step 1		Step 2		Step 3	
N= 83	**Demographic**		**SDH**		**Confounders**	
Coefficient Statistics	**β**	***p***	**β**	***p***	**β**	***p***
FEP	-0.32	0.01	-0.26	0.03	-0.20	0.19
Sex	-0.11	0.31	-0.13	0.26	-0.11	0.35
WHeR	0.04	0.70	0.04	0.69	0.03	0.77
Minority			0.03	0.77	0.02	0.87
CEVQ.total			0.22	0.05	0.23	0.05
Smoker (yes/no)					-0.02	0.86
Depression					0.09	0.51
Step Statistics	**ΔR2**	**Δ*p***	**ΔR2**	**Δ*p***	**ΔR2**	**Δ*p***
	0.09	0.05	0.05	0.14	0.01	0.78
Model Statistics	**R2**	***p***	**R2**	***p***	**R2**	***p***
	0.09	0.05	0.14	0.04	0.14	0.10

Abbreviations at the end of the table

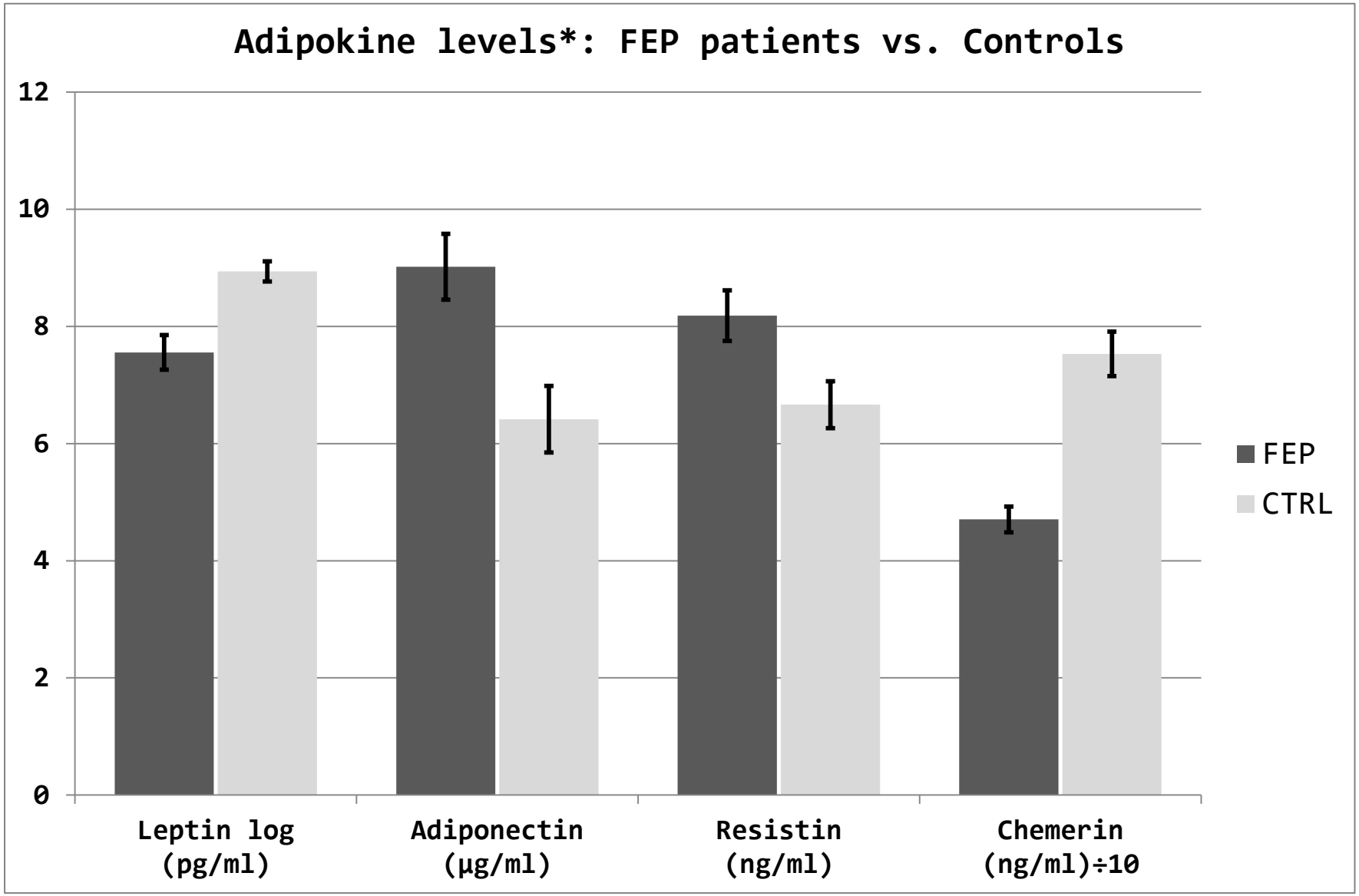
Table 4c. Hierarchical Multiple Linear Regression Model: Chemerin

Chemerin	Step 1		Step 2		Step 3	
N= 83	**Demographic**		**SDH**		**Confounders**	
Coefficient Statistics	**β**	***p***	**β**	***p***	**β**	***p***
FEP	0.48	<0.01	0.42	<0.01	0.50	<0.01
Sex	-0.10	0.25	-0.12	0.14	-0.13	0.13
WHeR	0.39	<0.01	0.35	<0.01	0.37	<0.01
Minority			-0.21	0.01	-0.22	0.01
CEVQ.total			-0.06	0.46	-0.04	0.58
Smoker (yes/no)					-0.18	0.04
Depression					<0.01	0.98
Step Statistics	**ΔR2**	**Δ*p***	**ΔR2**	**Δ*p***	**ΔR2**	**Δ*p***
	0.50	<0.01	0.04	0.03	0.03	0.12
Model Statistics	**R2**	***p***	**R2**	***p***	**R2**	***p***
	0.50	<0.01	0.54	<0.01	0.57	<0.01

Abbreviations at the end of the table

Table 4 abbreviations:
CEVQ.total: Childhood Experiences of Violence Questionnaire total score; FEP: First-episode psychosis diagnosis; SDH: Social determinant of health;
Guide: FEP: 1=fep, 2=ctrl; Sex: 1=male, 2=female; Minority 1=white, 2=minority; Smoker:1=yes, 2=no.

Figure 1. Adipokines by FEP diagnosis



Adipokine levels by FEP diagnosis: patients (FEP) versus controls (CTRL). Columns: means, error bars: standard error of the mean.
*Please note that the measurement units of each adipokine are different and were adjusted to fit in the graph.

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