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A novel biomarker of cardiometabolic pathology in schizophrenia?

Ellen E. Lee[a,b], Dorothy D. Sears[c,d], Jinyuan Liu[b,d], Hua Jin[a], Xin M. Tu[a,b,d], Lisa T. Eyler[a,e], Dilip V. Jeste[a,b,f,g,*]

[a] Department of Psychiatry, University of California San Diego, La Jolla, CA, USA
[b] Sam and Rose Stein Institute for Research on Aging, University of California San Diego, La Jolla, CA, USA
[c] Department of Medicine, University of California San Diego, USA
[d] Department of Family Medicine and Public Health, University of California San Diego, USA
[e] Desert-Pacific Mental Illness Research Education and Clinical Center, Veterans Affairs San Diego Healthcare System, San Diego, CA, USA
[f] Center for Healthy Aging, University of California San Diego, La Jolla, CA, USA
[g] Department of Neurosciences, University of California San Diego, La Jolla, CA, USA

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ABSTRACT

Background: Persons with schizophrenia and schizoaffective disorder (PwS) have high rates of cardiometabolic pathology that contributes to premature mortality. Adiponectin is a metabolic hormone affecting insulin sensitivity and inflammation, and is active in the brain. High-molecular weight (HMW) adiponectin is considered a more sensitive marker of metabolic dysfunction than total adiponectin, but has been poorly studied in schizophrenia.

Methods: This was a cross-sectional study of 100 PwS, age range 26–68 years (46 women), and 93 age- and sex-comparable non-psychiatric comparison (NC) subjects. Assessments included measures of psychopathology, physical health, cognitive function, and circulating biomarkers of metabolic dysfunction (HMW adiponectin, lipids, insulin resistance) and inflammation (high-sensitivity C-reactive protein or hs-CRP, Tumor Necrosis Factor-α, Interleukin-6, and Interleukin-10).

Results: HMW adiponectin levels were lower in PwS compared to NCs. Lower HMW adiponectin levels were associated with higher body mass index (BMI), higher Framingham risk for coronary heart disease, higher number of metabolic syndrome criteria, greater insulin resistance, lower HDL cholesterol, and higher hs-CRP in both groups. Only in PwS, lower HMW adiponectin correlated with younger age. In the best-fit regression models of HMW adiponectin, lower levels were associated with lower HDL cholesterol and minority race/ethnicity in both groups; but with younger age, non-smoking, higher insulin resistance, and a diagnosis of schizoaffective disorder only among PwS, and with male sex, better cognitive functioning, and higher hs-CRP levels in NCs only.

Discussion: HMW adiponectin may be a promising biomarker of cardiometabolic health, especially among PwS. Adiponectin is a potential target for lifestyle and pharmacological interventions. Research on the possible role of HMW adiponectin in modifying cardiometabolic pathology in schizophrenia is needed.

1. Introduction

The mortality gap between persons with schizophrenia and schizoaffective disorder (PwS) and the general population is predominantly due to cardiovascular and metabolic disease-related deaths (Hennekens et al., 2005). Metabolic abnormalities and metabolic syndrome, highly prevalent among PwS, are strong predictors of cardiovascular mortality (Lee, E. et al., 2017).

Adiponectin, a metabolic hormone secreted by adipocytes, regulates insulin sensitivity and obesity, and has been an exciting new focus of research due to its multiple targets of action beyond metabolic processes, including aging, inflammation, cognitive functioning, and mood. Adiponectin has been reported to improve insulin sensitivity and hypertriglyceridemia, increase longevity, inhibit production and release of pro-inflammatory cytokines Tumor necrosis Factor (TNF)-α and Interleukin (IL)-6, promote neuroprotection, and increase longevity (Thundyil et al., 2012) in animal studies. In some (Diniz et al., 2012; Liu et al., 2012), but not all (Carvalho et al., 2014) studies, adiponectin has been purported to have an antidepressant effect in mice and in persons with late-life depression. Adiponectin crosses the blood-brain barrier

* Corresponding author. Sam and Rose Stein Institute for Research on Aging University of California, San Dieg, 9500 Gilman Drive #0664 La Jolla, CA, 92023-0664, USA.
E-mail address: djeste@ucsd.edu (D.V. Jeste).

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and acts directly on adiponectin receptors in the cortex, hypothalamus, and pituitary gland (Thundyil et al., 2012). Higher adiponectin levels have been associated with better executive function and global cognitive functioning (Wennberg et al., 2016), and lower risk of myocardial infarction, coronary artery disease, coronary heart disease, and other cardiovascular events (Sattar et al., 2006). Longitudinal studies have shown adiponectin levels to be predictive of changes in levels of high-density lipoprotein (HDL) cholesterol and high-sensitivity C-reactive protein (hs-CRP) (Niu et al., 2013), carotid atherosclerosis (Hui et al., 2014), future metabolic dysfunction (Kim et al., 2013), and functional decline (Newman et al., 2016). Adiponectin is present in several multimeric forms with varied biological effects (Scherer et al., 1995). While most published clinical studies have examined total adiponectin levels, high-molecular weight (HMW) multimeric form of adiponectin is considered a more sensitive measure of metabolic function/dysfunction than total adiponectin levels (Hirose et al., 2010; Pajvani et al., 2003; Waki et al., 2003).

Among PwS, lower adiponectin levels have been reported in some (Jin et al., 2008; Stubbs et al., 2016) but not all, of the published studies (Beumer et al., 2012; Song et al., 2013). A recent meta-analysis found lower total adiponectin levels to be associated with treatment with second generation antipsychotics, and in particular with clozapine and olanzapine, but not risperidone (Bartoli et al., 2015b). We found only two reports of HMW adiponectin levels in PwS. Richards et al. (2006) evaluated 18 Australian adults with schizophrenia (9 on olanzapine and 9 on conventional antipsychotics) and 16 NC subjects matched for age, sex, and body mass index (BMI) (mean age 39 years), and reported lower HMW adiponectin levels in PwS compared to the NCs (Richards et al., 2006). Chen et al. (2011) assessed 109 normal-weight Taiwanese PwS (mean age 44 years) on clozapine or haloperidol, and reported that HMW adiponectin levels were correlated with HDL cholesterol levels and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values (Chen et al., 2011). Neither of these studies examined the relationships of HMW adiponectin with other relevant clinical variables (mental health, cognitive functioning, physical health, and inflammation.)

To our knowledge, the present study is the first in the US to examine HMW adiponectin levels and their clinical and biomarker correlates in a large (n = about 100 per group) well-characterized sample of PwS and NCs, age 26–68 years. We hypothesized that (1) HMW adiponectin levels would be worse (i.e., lower) in PwS compared to the NCs, and (2) lower HMW adiponectin levels would be associated with older age, male sex, impaired cognitive function, worse physical health (including higher BMI and increased Framingham risk for coronary heart disease), and elevated inflammatory markers. Finally, we sought to obtain significant sociodemographic and clinical coefficients in best-fit models of HMW adiponectin levels.

2. Methods

2.1. Study participants

Participants included persons with schizophrenia or schizoaffective disorder and age- and sex-comparable NCs, age 26–65 years, enrolled in an ongoing study of aging in schizophrenia. The present study sample with HMW adiponectin levels partially overlaps with the study samples in which inflammatory markers were previously reported (Hong et al., 2017; Lee et al., 2016; Lee, E.E. et al., 2017). The psychiatric diagnosis was based on Structured Clinical Interview for the DSM-IV-TR (SCID) (First et al. 2002). We excluded people with alcohol or other non-tobacco substance abuse or dependence within 3 prior months, and a major neurological or medical disorder affecting the ability to complete study procedures. PwS were recruited from psychiatric clinic settings at UC San Diego as well as community advertisements throughout the greater San Diego area. NCs were recruited through a variety of methods, including from an ongoing study of successful aging in the community population, recruitment flyers in the community, ResearchMatch.org, and word-of-mouth. Subjects were sampled using consecutive recruitment. Refusal rates were approximately 20%. The study protocol was approved by the UC San Diego Human Research Protections Program, and all participants provided a written informed consent.

2.2. Sociodemographic and clinical characteristics

Trained study staff administered standardized assessments for: antipsychotic type and dose (WHO Collaborating Centre for Drug Statistics Methodology, 2019), psychopathology [Patient Health Questionnaire-9 (PHQ-9) for depression (Kroenke et al., 2001), Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS, respectively) (Andreasen, 1983, 1984)], mental well-being and physical well-being [Medical Outcomes Survey - Short Form 36 (SF-36)] (Ware and Sherbourne, 1992), and medical co-morbidity (Cumulative Illness Rating Scale) (Linn et al., 1968). Study staff also assessed the participants for current and past smoking history.

2.3. Cognitive measures

Standardized cognitive assessments included the Delis-Kaplan Executive Function System for executive functioning (Delis et al., 2001) and the Telephone Interview for Cognitive Status or TICS (modified) for global cognitive impairment (van den Berg et al., 2012).

2.4. Metabolic health

BMI was calculated, national guidelines were used to define the criteria for metabolic syndrome (Grundy et al., 2005) and Framingham risk for Coronary heart disease (D'Agostino et al., 2008).

2.5. Metabolic biomarker assays

HMW adiponectin was assayed using the Quantikine® Human HMW Adiponectin/Acrp30 Immunoassay (R&D Systems, Minneapolis, MN), an enzyme-linked immunosorbent assay (ELISA) at the UC San Diego Clinical and Translational Research Institute (CTRI) lab from serum samples.

Fasting glucose, insulin, and lipid levels were measured as reported previously (Lee et al., 2016). Insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) scores computed as follows: (Matthews et al., 1985):

HOMA-IR Formula = [Fasting plasma insulin (mIU/L) * Fasting plasma glucose (mmol/L)]/ 22.5.

2.6. Inflammatory biomarker assays

Plasma hs-CRP, TNF-α, IL-6, and IL-10 levels were measured as reported previously (Lee, E.E. et al., 2017).

2.7. Statistical analyses

Due to the very small number of published studies of HMW adiponectin levels in PwS compared to controls, there was no *a priori* estimation of sample size. Continuous variables were assessed for violation of distribution assumptions (skew and kurtosis) and were log-transformed as necessary. Independent sample t-tests, Chi-square tests, or Independent Samples Kruskal-Wallis tests were used to assess differences between groups. Spearman's correlations were performed to assess the relationships of HMW adiponectin with sociodemographic and clinical variables. We used locally weighted scatterplot smoothing (LOWESS) curve fitting, a nonparametric method to fit the relationship

between the metabolic markers and Framingham risk scores which we then fit with cubic functions (Tibshirani, 1996).

We performed multiple regression analyses, aided by least absolute shrinkage and selection operator (LASSO) variable selection, to identify the best multivariable model for HMW adiponectin. In the multiple regression analysis, regression coefficients were made commensurate by standardizing each variable. Independent variables were ranked by the order in which they entered the LASSO regression. LASSO overcomes various limitations of classic variable selection procedures such as multicollinearity to provide reliable selection of independent variables (Chen et al., 2016). Independent variables selected by LASSO were entered into the linear model for further trimming, using backward elimination, as univariate analysis may also miss significant predictors, and such models may be biased (Wang et al., 2017). All analyses were carried out in R.

We present effect sizes and p-values for all of these statistical tests, and interpret greater than medium effect sizes (i.e., Cohen's $d \geq 0.45$ or rho ≥ 0.30) as meaningful. Significance was defined as $\alpha < 0.05$ (two-tailed) for all analyses and False Discovery Rate (FDR) was used to account for multiple comparisons in the best-fit regression models and comparison of correlations to ensure overall Type 1 error at $\alpha = 0.05$.

3. Results

The study sample included 100 PwS and age- and sex-comparable NCs, age 26–65 years, Fifty-eight percent of PwS met criteria for metabolic syndrome, compared to 20% of the NC group ($X^2 = 28.4$, $df = 1$, $p < 0.001$). PwS had higher levels of peripheral inflammatory cytokines, worse levels of lipids, hemoglobin A1c, and HOMA-IR, and, consistent with our hypothesis, lower levels of HMW adiponectin than NCs (Table 1). Ninety-two of the 100 PwS reported taking antipsychotic medications. Of these 92 patients, 82% were on atypical antipsychotics only, 5% on typical antipsychotics only, and 13% on both atypical and typical antipsychotic medications. Eleven PwS were receiving olanzapine monotherapy, eight were on clozapine monotherapy, and ten were receiving risperidone monotherapy. There were very few PwS on other antipsychotic monotherapies. The HMW adiponectin levels were not significantly different among these olanzapine, clozapine, and risperidone subgroups (mean [SD]: 3.6 [2.6] versus 3.0 [3.2] versus 3.5 [2.1], respectively, Independent samples Kruskal-Wallis Test, $df = 2$, $p = 0.68$).

Within the PwS group, 48% percent ($N = 48$) of the participants were diagnosed with schizoaffective disorder, while 52 participants were diagnosed with schizophrenia. Compared to the schizophrenia subgroup, the participants with schizoaffective disorder were significantly different in the following ways: younger (mean age [SD] 45.2 [9.9] versus 49.7 [10.3] years, $t(98) = -2.23$, $p = 0.03$), more depressed (mean PHQ-9 score [SD] 10.5 [7.4] versus 5.8 [5.1], $t(93) = 3.6$, $p < 0.001$), and with worse mental well-being on SF-36 scale (mean [SD] 37.4 [11.5] versus 46.0 [10.2], $t(97) = -4.0$, $p < 0.001$). The two subgroups did not differ by sex, race/ethnicity, smoking, daily antipsychotic dose, positive and negative symptom severity, BMI, physical comorbidities or physical well-being on SF-36 scale. The schizoaffective group had significantly lower HMW adiponectin levels (mean [SD] 3.34 [0.39] versus 3.52 [0.31], $t(98) = -2.48$, $p = 0.02$), but similar levels of lipids, insulin resistance, and hemoglobin A1c compared with the schizophrenia group. Subgroup diagnosis (schizoaffective disorder versus schizophrenia) was included in the best-fit regression for the best-fit regression model.

Several correlations between HMW adiponectin and other variables were significant in both PwS and NCs (e.g., Hispanic and Other Race/Ethnicity, higher BMI, higher HOMA-IR, and higher hs-CRP associated with lower HMW adiponectin) (Supplemental Table 1). HMW adiponectin and Framingham risk for coronary heart disease had an inverse U-shaped relationship in both PwS and NCs. Adiponectin levels were not correlated with severity of depression and overall cognitive functioning. Adiponectin was consistently correlated with several measures of physical health, e.g., BMI, waist circumference, number of metabolic syndrome criteria, HOMA-IR, HDL cholesterol, and hs-CRP levels in both groups. However, there were a few notable differences in the correlations. In only the NC group, lower HMW adiponectin was associated with male sex. In contrast, only in the PwS, HMW adiponectin was correlated with age, although there were no significant interactions of age by diagnostic group (Wald statistic 3.40, $p = 0.33$). The HMW adiponectin-duration of illness correlation was not significant when controlling for age ($r = -0.04$, $p = 0.74$). In PwS, HMW adiponectin was also associated with current cigarette smoking, waist-to-hip ratio, triglycerides levels, and IL-6 levels. HMW adiponectin levels were not significantly associated with daily antipsychotic dose.

With the best-fit regression models achieved with all the variables as potential correlates of lower HMW adiponectin in both diagnostic groups, minority race/ethnicity and lower HDL cholesterol were significant factors in the models (Table 2). Additionally, the model in PwS included younger age, non-smoking, higher HOMA-IR levels (increased insulin resistance), and a diagnosis of schizoaffective disorder as significant factors, while the model in NCs had male sex, higher overall cognitive functioning, and higher hs-CRP levels as significant factors.

4. Discussion

Consistent with our hypothesis, HMW adiponectin levels were lower in PwS compared to NCs. Lower HMW adiponectin levels were associated with higher BMI, worse Framingham risk for coronary heart disease, greater number of metabolic syndrome criteria, greater insulin resistance, lower level of HDL cholesterol, and higher levels of hs-CRP in both PwS and NCs. More than half of the PwS met criteria for metabolic syndrome. In the NC group only, lower HMW adiponectin was associated with male sex. In PwS only, HMW adiponectin was correlated with younger age. In the best-fit multiple regression models of HMW adiponectin, lower adiponection levels were associated with lower levels of HDL cholesterol and minority race/ethnicity in both groups, but with younger age, current non-smoking, higher insulin resistance and diagnosis of schizoaffective disorder only among PwS, and with male sex, higher overall cognitive functioning, and higher hs-CRP levels in NCs only.

The finding that (HMW) adiponectin levels were worse in PwS appears to be consistent with reported results on total adiponectin in adults with chronic schizophrenia stable on antipsychotics (Sugai et al., 2012), though, in the current study, the levels were not significantly correlated with the antipsychotic dose. The current study did not account for type of antipsychotic as a large majority received atypical antipsychotics alone. One study reported no difference in adiponectin levels in PwS compared to NCs though these studies included participants who were non-obese, recently started on antipsychotics, antipsychotic-naïve, or first-episode patients (Balotsev et al., 2019). Key factors, including antipsychotic type, obesity, and duration of antipsychotic use may also contribute to the adiponectin levels observed in the present study.

Other studies in persons without schizophrenia have also reported higher HMW adiponectin levels with aging (Kizer et al., 2010, 2011; LeCaire and Palta, 2015; Sanders et al., 2014), proposing that higher levels in older adults may not be reflective of better health as they might be in younger persons. For example, lower adiponectin levels in young and healthy middle-aged adults (age 40–70 years) were associated with higher incidence of cardiovascular diseases and events (Sattar et al., 2006). Paradoxically, in older community-dwelling persons (age 65 + years), higher adiponectin levels were associated with greater cardiovascular and stroke risk and mortality (Kizer et al., 2012). Of note, our sample was limited to 26–68 years of age and the relationship with age was only observed in the PwS. Furthermore, the best-fit model in PwS found that younger age was linked with lower HMW adiponectin levels, which might reflect a survivor effect such that

Table 1
Demographic and clinical measures in schizophrenia and non-psychiatric comparison groups.

	Non-psychiatric Comparison Subjects			Schizophrenia/Schizoaffective			t or X^2	df	p	Cohen's d
	N	Mean	SD	N	Mean	SD				
Sociodemographic										
Age (years)	93	47.6	11.9	100	47.5	10.3	0.05	191	0.96	0.01
Female sex – N (%)		52 (56)			46 (46)		1.90	1	0.17	
Race/Ethnicity							4.06	2	0.13	
Caucasian (%)		55.9			42.0					
Hispanic (%)		28.0			40.0					
Other (%)		16.1			18.0					
Education (years)	93	14.5	2.1	100	12.4	2.3	6.60	191	< 0.001	1.35
Current smoker (%)		7.5			55		49.8	1	< 0.001	
Past smoker only (%)		23			26		0.31	1	0.58	
Psychopathology and Treatment										
Duration of Illness (years)				98	24.6	11.3				
Antipsychotics daily dose[a]				100	1.88	1.62				
Depression (PHQ-9)	87	2.07	3.10	95	8.06	6.71	−7.84	135	< 0.001	−1.62
Positive Symptoms (SAPS)				100	6.87	4.09				
Negative Symptoms (SANS)				100	7.87	4.18				
Mental Wellbeing (SF-36)	87	54.4	6.0	99	41.8	11.6	9.04	184	< 0.001	1.91
Cognitive functioning										
Executive functioning (D-KEFS)	93	0.36	0.60	100	−0.53	0.76	8.98	191	< 0.001	1.84
Global cognitive functioning (TICS)	91	37.2	4.2	97	30.8	6.2	8.20	186	< 0.001	1.70
Metabolic Syndrome Criteria										
Number of Metabolic Syndrome Criteria[b]	93	1.58	1.39	100	2.80	1.36	−6.18	191	< 0.001	−1.26
BMI (kg/m^2)	92	27.3	5.92	99	32.3	7.38	−5.21	189	< 0.001	−1.07
Waist-to-Hip Ratio	90	0.91	0.07	97	0.98	0.08	−5.80	185	< 0.001	−1.20
Framingham Relative Risk for CHD[c]	88	1.15	0.65	92	1.39	0.72	−2.40	178	0.02	−0.51
General Physical Health										
Physical comorbidities (CIRS)	92	3.10	3.59	100	6.05	4.28	−5.15	190	< 0.001	−1.06
Physical well-being (SF-36)	87	51.8	8.9	99	42.9	10.2	6.35	184	< 0.001	1.33
Markers of Metabolic Pathology										
HMW Adiponectin (μg/mL)	93	6.18	5.3	100	3.7	3.27	3.87	191	< 0.001	0.78
Total Cholesterol (mg/dL)	89	186.2	33.7	98	175.7	40.2	1.92	185	0.06	0.40
HDL Cholesterol (mg/dL)	89	55.9	14.6	98	47.2	13.5	4.25	185	< 0.001	0.88
LDL Cholesterol (mg/dL)	89	109.6	30.8	92	96.9	33.8	2.65	179	0.009	0.56
Triglycerides (mg/dL)	89	111.7	98.8	98	164.4	115.1	−3.34	185	0.001	−0.69
Hemoglobin A1c (%)	80	5.61	0.47	91	6.10	1.37	−3.21	113	0.002	−0.68
Insulin Resistance (HOMA-IR)	84	1.86	1.21	91	4.15	5.14	−5.35	173	< 0.001	−1.15
Inflammatory Biomarkers										
hs-CRP (mg/dL)	92	1.92	2.92	100	4.89	5.68	−6.09	190	< 0.001	−1.25
IL-6 (pg/mL)	80	0.76	0.88	91	1.25	1.37	−4.07	169	< 0.001	−0.89
TNF-α (pg/mL)	80	2.44	0.72	91	3.07	1.20	−4.14	169	< 0.001	−0.90
IL-10 (pg/mL)	78	0.37	0.36	89	0.48	0.47	−2.21	165	0.03	−0.49

CHD = Coronary heart disease.
CIRS = Cumulative Illness Rating Scale (32)D-KEFS = Delis-Kaplan Executive Function System (33).
HDL = high-density lipoprotein.
Hemoglobin A1c = glycosylated hemoglobin.
HMW = high-molecular weight.
HOMA-IR = Homeostatic Model Assessment of Insulin Resistance (36).
Hs-CRP = high-sensitivity C-reactive protein.
IL = Interleukin.
LDL = low-density lipoprotein.
PHQ-9 = Patient Health Questionnaire-9; measure of depression (28).
SANS = Scale for the Assessment of Negative Symptoms (29).
SAPS = Scale for the Assessment of Positive Symptoms (30).
SF-36 = Medical Outcomes Survey - Short Form 36; measure of mental and physical functioning (31).
TICS-M = Telephone Interview for Cognitive Status – Modified (34).
TNF = Tumor Necrosis Factor.

[a] Antipsychotic medication daily dosages were converted to WHO average daily doses based on published standards (27).

[b] Criteria for metabolic syndrome were the following: elevated waist circumference (≥ 102 cm for men, ≥ 88 cm for women), elevated triglycerides (≥ 150 mg/dL or on medications for elevated triglycerides), elevated HDL cholesterol levels (< 40 mg/dL for men, < 50 mg/dL for women), or elevated blood pressure readings (systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg or on medications for hypertension) (35).

[c] For 10-year risk for coronary heart disease (36).

sicker individuals with schizophrenia do not survive to middle age.

Consistent with the literature, we found lower (HMW) adiponectin levels to be linked with increased cardiovascular disease risk (Christou and Kiortsis, 2013), minority race/ethnicity (Azrad et al., 2013), higher BMI (Bai et al., 2009), and increased pro-inflammatory cytokine levels (Song et al., 2013) in PwS and the NC group. These findings may support the theory that inflammatory changes observed in first-episode psychoses are linked mechanistically with metabolic dysregulation through shared genetic mutations and the traverse of cytokines through the blood-brain barrier (Lin and Shuldiner, 2010). Other underlying biological mechanisms of both schizophrenia psychopathology and metabolic dysregulation include dysregulated adipokine release from

Table 2
Best-fit regression models of high-molecular weight (HMW) adiponectin in the two groups.

Factor	HMW Adiponectin								
	Schizophrenia/Schizoaffective				Non-psychiatric Comparison group				
	B	SE	FDR p	R^2	Factor	B	SE	FDR p	R^2
Age	0.005	0.003	0.04	0.04	**Gender (male)**	−0.19	0.07	0.01	0.05
Race (Hispanic)	−0.03	0.06	0.03	0.08	**Race (Hispanic)**	−0.13	0.07	0.001	0.11
Race (Other)	−0.20	0.07		0.07	**Race (Other)**	−0.33	0.09		
Current smoker (no)	0.13	0.06	0.03	0.06	**Overall cognitive functioning**[a]	−0.02	0.008	0.01	0.06
HOMA	−0.19	0.09	0.04	0.20	**HDL cholesterol**	0.006	0.003	0.03	0.04
HDL cholesterol	0.01	0.002	< 0.001	0.05	**hs-CRP**	−0.18	0.07	0.02	0.05
Schizoaffective diagnosis	−0.15	0.06	0.02	0.05					

BMI = body mass index.
FDR = False discovery rate-corrected.
HDL = high density lipoprotein.
HMW = high-molecular weight.
HOMA = insulin resistance.
Hs-CRP = high-sensitivity C-reactive protein.
[a] As assessed with the Telephone Interview for Cognitive Status – Modified (34).

adipose tissue, oxytocin system dysfunction (Quintana et al., 2017), hypothalamic-pituitary-adrenal (HPA) axis dysfunction, autonomic dysfunction (Chung et al., 2013), and circadian clock disruption (Barandas et al., 2015).

We did not observe significant correlations between HMW adiponectin and cognitive performance in PwS. Surprisingly, the best-fit model identified worse overall cognitive functioning to be associated with higher adiponectin levels in the NC group. While a few studies in older community-based samples have reported higher adiponectin levels to be associated with worse cognitive functioning (Sharma et al., 2016; Wennberg et al., 2016), the current investigation had a few key differences: inclusion of only young to middle-aged adults and, within the NC group, a narrow range of cognitive scores as those with clinically significant cognitive impairment were excluded.

We also found that current smoking was associated with higher HMW adiponectin levels in PwS, which diverges from findings in the general population where most studies have shown adiponectin levels are lower in current smokers in a dose-response relationship, even after adjusting for age, diet, alcohol consumption and exercise (Kotani et al., 2012). The review by Kotani and colleagues propose that nicotine-related inhibition of adiponectin gene expression and smoking-provoked oxidative stress, inflammation and vascular damage may contribute to the differences in adiponectin levels. Two cross-sectional studies found no significant difference between smokers and non-smokers with: worse adiponectin levels in ex-smokers compared to current smokers (Abbasi et al., 2006) and inclusion of ex-smokers who had quit within the last 6 months in their non-smoking group (Jang et al., 2007). These findings suggested that smoking may have longer lasting effects on adiponectin levels. Smoking is much more common in PwS compared to the general population and can lower BMI, which may have opposing effects on cardiometabolic health.

The high rate of metabolic syndrome among the PwS (58%) was striking, in the context of a large meta-analysis study that reported an overall rate of 32.5% (Mitchell et al., 2013). The higher rate in the current study may reflect the longer mean duration of illness (24.6 years), current treatment with antipsychotics (92%), sizeable proportion with Hispanic ethnicity (40%), and rising rates of metabolic syndrome in the United States during the last two decades (Moore et al., 2017). These sample characteristics may affect generalizability of the findings to other populations.

Diagnosis of schizoaffective disorder remained a significant predictor in the best-fit model for adiponectin levels in PwS, even though the schizophrenia and schizoaffective groups did not differ by antipsychotic dose and age/sex. A meta-analysis of 30 studies (Bartoli et al., 2015a) reported that persons with schizoaffective disorder were more likely to have metabolic syndrome compared with persons with schizophrenia. Other work has shown that schizoaffective disorder is a variant of schizophrenia, rather than a mood disorder (Evans et al., 1999). Our previous work in oxidative stress and inflammatory biomarkers did not find differences between the schizophrenia and schizoaffective disorder subgroups (Lee et al., 2016; Lee, E.E. et al., 2017). Further longitudinal studies with larger sample sizes are needed to explore the possibility of different biological mechanisms underlying schizophrenia versus schizoaffective disorder.

Limitations of the present study include the cross-sectional design, which rules out making causal inferences. The study did not include a group of people with other serious mental illnesses, so specificity of our results to schizophrenia remains uncertain. The study sample was limited to community-dwelling stable outpatients with schizophrenia and the findings may not be generalizable to first episode psychosis or treatment-resistant subjects. There was no *a priori* sample size estimation due to the very small number of published studies of HMW adiponectin in PwS. The total adiponectin levels were not assessed in this study, as that would require a different assay. This limits the ability to compare with HMW adiponectin levels within this study. Also, it was not possible to assess and control for type of antipsychotic (due to a small number of participants on typical antipsychotics), lifetime antipsychotic exposure, quality of healthcare, physical activity, and diet, all of which may contribute to differences in adiponectin levels.

Further studies are warranted to examine HMW adiponectin levels longitudinally to assess their predictive associations. The biological consequences of HMW adiponectin in persons with schizophrenia remain unclear, though it may be a potential biomarker of cardiometabolic risk. Cardiometabolic disease drives the mortality gap for this serious mental illness and is an important focus of intervention and treatment. Adiponectin has been a target of some lifestyle and medical/surgical interventions in the general population. Exercise and dietary changes, yoga, smoking cessation, and bariatric surgery (Lim et al., 2014) have been reported to increase adiponectin levels in persons with metabolic syndrome or pre-diabetes. Pharmacological studies have also demonstrated that medications (e.g., thiazolidinediones (PPAR-γ agonists), statins, angiotensin II receptor blockers, calcium channel blockers, beta-blockers, and certain dietary supplements) increase adiponectin levels (Lim et al., 2014). Despite the extensive research in the general population, interventions to modify adiponectin have been rarely studied in PwS (Kuo et al., 2013).

HMW adiponectin may be a novel and useful biomarker of cardiometabolic health in PwS. Longitudinal examination of the changing role of HMW adiponectin with aging, especially in schizophrenia, may further our understanding of metabolic hormones and cardiometabolic dysregulation in PwS as well as in the general population. The potential to modify adiponectin in a patient population that is at very high risk for cardiometabolic problems should also be considered for future intervention development.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.06.011.

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Conflicts of interest

The authors declare no financial or other relationship relevant to the subject of this article.

Potential conflicts of interest

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