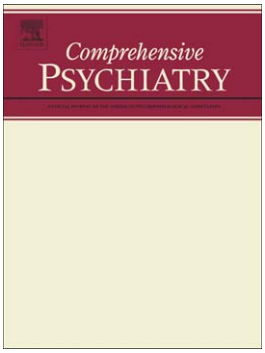

Physical activity ameliorates the association between sedentary behavior and cardiometabolic risk in people with Schizophrenia: A comparison versus controls using accelerometry

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PII: S0010-440X(16)30596-X
DOI: doi: 10.1016/j.comppsych.2017.01.010
Reference: YCOMP 51796

To appear in: *Comprehensive Psychiatry*

Please cite this article as: Stubbs Brendon, Chen Li-Jung, Chung Ming-Shun, Ku Po-Wen, Physical activity ameliorates the association between sedentary behavior and cardiometabolic risk in people with Schizophrenia: A comparison versus controls using accelerometry, *Comprehensive Psychiatry* (2017), doi: 10.1016/j.comppsych.2017.01.010

Physical activity ameliorates the association between sedentary behavior and cardiometabolic risk in people with Schizophrenia: A comparison versus controls using accelerometry

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Statement: This work is not currently under review elsewhere and has not been previously published.

Physical activity ameliorates the association between sedentary behavior and cardiometabolic risk among inpatients with Schizophrenia: A comparison versus controls using accelerometry

Abstract

Objective: A lack of clarity exists regarding the relationship between objectively measured physical activity (PA) and sedentary behavior (SB) and cardiometabolic outcomes in people with schizophrenia. We conducted a large study investigating the independent relationships of PA and SB among inpatients with schizophrenia versus healthy controls (HCs).

Methods: A cross sectional study including 199 inpatients with schizophrenia (mean age 44.0 years, mean illness duration 23.8 years) versus 60 age/ sex/ body mass index matched HCs. Participants wore accelerometers for 7 days to capture SB and daily steps. Cardiometbaolic outcomes included blood pressure, fasting blood glucose (FBG), triglycerides, high-density lipoprotein cholesterol (HDL-C) and waist circumference (WC). Multivariate regression analyses adjusting for multiple confounders were undertaken.

Results: Compared to HCs, patients engaged in more sedentary behavior and less daily steps versus HCs ($p<0.001$). Patients with higher levels of SB (n=89) had increased fasting glucose compared to patients with low levels of SB (105.2 v 96.3 mg/dl, $p<0.05$). In the multivariate analysis, sedentary behavior was associated with higher FBG (β.146, p=.041) but this was ameliorated when daily steps were inserted in to the model (β.141, p=.059). In the final model, higher daily steps were associated with more favorable HDL-C (β=-.226, p=.004), independent of SB and other confounders.

Conclusions: Our data suggest that higher whilst sedentary behaviour is related to worse fasting glucose, this relationship is attenuated when PA is taken into account. Physical activity is also associated with favourable HDL-C. Interventions targeting replacing sedentary behavior with PA may improve metabolic risk.

Key words: physical activity, inactivity, MetS, metabolic syndromes, psychosis

Physical activity ameliorates the association between sedentary behavior and cardiometabolic risk among inpatients with Schizophrenia: A comparison versus controls using accelerometry

1. Introduction

There is now irrefutable evidence that people with schizophrenia have a greatly reduced life expectancy [1]. The greatest contributors to this premature mortality are physical health conditions and in particular cardiometabolic and cardiovascular disease [2]. People with schizophrenia have greatly increased levels of metabolic syndrome [3] whilst approximately 12% have type 2 diabetes [4, 5]. The heightened cardiometabolic risk is evident in the earlier stages of illness, including those who are antipsychotic naïve [4] and is elevated in youth who have recently been exposed to antipsychotic medication [6]. Whilst genetic factors may also contribute to the heightened cardiometabolic risk, there is an increasing realization that lifestyle factors may have a key role in cardiometabolic risk in people with schizophrenia [7].

In the general population, there is an established evidence base that physical activity offers a protective effect against the development of an adverse metabolic profile [8, 9]. Of concern, a recent meta-analysis established that people with schizophrenia engaged in low levels of physical activity and approximately half do not meet the recommended weekly guidelines [10]. To date, a small number of studies [11, 12] have suggested that lower levels of activity are associated with a worse metabolic profile. Whilst helpful, almost all of these studies have relied on small sample sizes (n<75) and relied upon self-report physical activity measures which are known to have questionable accuracy and psychometric properties [13].

There is also a growing evidence base in the general population that sedentary behavior, independent from physical activity, is associated with an increased risk of diabetes, cardiovascular disease and mortality[14]. Sedentary behavior is defined as any waking activity characterized by an energy expenditure ≤ 1.5 metabolic equivalents including tasks such as sitting or reclining posture [15]. A recent meta-analysis demonstrated that people with schizophrenia spend approximately 12.5 hours a day being sedentary which is among the highest in any population in the world [16]. Two studies have suggested that self-report sitting behavior is associated with adverse metabolic profile [17, 18]. Whilst helpful in furthering our understanding the potential deleterious relationship of sedentary behavior on people with schizophrenia, the reliance upon self-report sedentary behavior introduces a bias, and the question of whether physical activity and sedentary behavior have independent influences on metabolic profiles remains unanswered.

Given the aforementioned, the current study had the following aims: 1) Compare

objectively measured sedentary behavior and physical activity among inpatients with schizophrenia versus controls. 2) Investigate the potential independent relationships between sedentary behavior and physical activity with cardiometabolic outcomes among inpatients with schizophrenia.

2. Methods

The current study adopted a cross sectional design and took place in Taiwan [19].

2.1 Participants

Participants who were residing across six long stay psychiatric wards at Jianan Mental Hospital, were invited to take part in the current study. Specific inclusion criteria were 1) Diagnosis of schizophrenia (according to DSM IV [20] made by an independent psychiatrist), 2) Individuals who were stable and on the same antipsychotic medicine regime for at least three months. Exclusion criteria included patients who were unable to communicate, immobile, or had any major neurological disorder (e.g. stroke).

A healthy control group was recruited from the staff of two hospitals and universities. The control group was matched with patients according to age, sex and body mass index (BMI). Specific inclusion criteria were a) No present or past history of any mental illness, b) not taking any psychotropic medication. A total of 60 participants were selected to ensure comparable gender balance, age and BMI ranges to the schizophrenia group.

The study was approved by the Institutional Review Board of Jianan Mental Hospital. All participants provided informed written consent.

2.2 Measures

2.2.1 Outcome variable: Cardiometabolic risk factors

The parameters of cardiometabolic risk factors collected included waist circumference (WC), systolic/diastolic blood pressure (SBP/DBP), serum triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and fasting glucose (FBG). WC, SBP, and DBP were measured by the hospital nurses. Data on TG, HDL-C, and FBG were obtained through venous blood samples, which were taken in the morning before breakfast and examined in the hospital.

2.2.2 Independent variable: Sedentary behavior and steps per day

Sedentary behaviour and steps per day were captured using the ActiGraph (wActiSleep, Pensacola, FL, USA), a tri-axial accelerometer. The ActiGraph has been validated previously among people with schizophrenia [21-24]. Accelerometers are

the optimal free living measure in people with schizophrenia, since self-report measures such as the IPAQ [25] lack accuracy [13]. Research assistants provided the standardized instructions for wearing the accelerometers. Specifically, participants were told to wear the accelerometer on the wrist of the non-dominant hand for 7 consecutive days and to remove it during bathing or water activities. The accelerometers were initialized, downloaded and analyzed with ActiLife software version 6 (ActiGraph LLC). Sedentary behaviour was defined according to the cut-off point outlined by Freedson [26] as activities $\leqq$100 counts per minute (cpm), representing a threshold corresponding with sitting, reclining, or lying down. The steps per day were also calculated by the software and were used to present physical activity among participants. Sedentary time and steps were categorized into two levels: 'Low and High' in a binary split about the mean in order to demonstrate differences in key variables between these groups among inpatients with schizophrenia.

2.2.3 Covariates

Details of participants sociodemographic information was collected including data on age ($\leqq$40 or >40), sex, smoking habits, alcohol consumption, and education. Participants smoking and alcohol status were subsequently categorized based on self-report as 'Yes (current/former smoker or drinker)' and 'No' (never).

Positive and negative syndrome scale (PANSS). All patients completed the PANSS[27], a tool specifically developed to assess the severity of symptoms and measure general psychopathology among patients with schizophrenia [27]. The PANSS is a 30-item rating scale, including three subscales: Positive Symptoms (7 items), Negative Symptoms (7 items), and General Psychopathology (16 items). For each item, there are seven rating points with increasing levels of psychopathology severity from 1 (asymptomatic) to 7 (extremely symptomatic). The PANSS score is the sum of ratings across items, with ranging between 7-49 for the Positive and Negative Scales and 16-112 for the General Psychopathology Scale. Higher scores demonstrate more severe symptoms.

Medications. Information of antipsychotics medications and sleeping pills use was collected through the hospital records. The use of antipsychotics medications was converted into a daily equivalent dosage of chlorpromazine [28] and the daily equipotent dosage of Lorazepam were also calculated for each patient based on the defined daily dose (DDD) of WHO Collaborating Centre for Drug Statistics Methodology [29] (http://www.whocc.no/ddd/definition_and_general_considera/).

2.3. Statistical analyses

The percentages or differences between patients with schizophrenia and the

control group were examined using independent t-tests and Chi-square tests. Differences of sedentary time, steps, metabolic parameters, and clinical state profiles between levels of sedentary behaviors and steps in patients with schizophrenia were examined by independent t-tests. Two-step forced entry multivariate regression analyses were computed to examine the associations of sedentary levels on each metabolic parameter. The dependent variable was sedentary levels and variables entered into the model were demographic variables (age, sex, education), smoking, alcohol consumption, medications, and PANSS, followed by steps. All analyses were performed with IBM SPSS statistics 22 and a *p*-value less than 0.05 was considered as statistically significant in this study.

3. Results

Overall, from 200 participants who were approached, 199 inpatients took part in the current study. On average, inpatients were 44.0 years old, with a mean illness duration of 23.8 years and almost two thirds were male (full details summarized in table 1). The healthy control group was of similar age, sex and BMI, however patients were more likely to smoke, have a lower number of years in education, whilst no difference was observed in alcohol intake (table 1).

Table 1 here

3.1 Differences in sedentary behavior, daily steps and cardiometabolic risk in patients versus controls

Full details are presented in figure 1. Briefly, patients engaged in significantly more sedentary behavior (581.1 v 336.4 minutes per day, $p<0.001$) and less daily steps (6628 v 10976, $p<0.001$). Moreover, patients had a higher waist circumference, triglyceride and fasting blood glucose but lower HDL-C (figure 1). No difference in systolic or diastolic blood pressure was observed.

Figure 1 here

3.2 Differences in cardiometabolic profile between patients with low and high sedentary behavior and daily steps

Table 2 provides a summary of the univariate analyses comparing key variables between patients with high and low sedentary behavior and daily steps. Compared to patients with lower levels of sedentary behavior (n=110), patients with higher levels of sedentary behavior (n=89) had increased fasting glucose (105.2 v 96.3 mg/dl, $p<0.05$) and a longer hospital stay (11.5 v 16.1 months, $p<0.05$). Patients with higher levels of daily steps (n=106) had an increased HDL-C (mg/dl) and longer hospital duration versus patients with less daily steps (n=93) (table 2).

Table 2 here

3.3 Exploring the independent relationships between sedentary behavior and daily steps with cardiometabolic profile in patients

Table 3 reports the multivariate associations between sedentary behavior and each cardiometabolic outcome. Only higher levels of sedentary behavior were associated with increased fasting blood glucose after the adjustment of multiple other risk factors (β=.146, p=0.42). After adjusting for daily steps in the final model (table 4), the relationship between sedentary behavior and fasting glucose moved beyond the threshold of significance (p=0.59). In the final adjusted model, lower daily steps was significantly associated with lower HDL-C independent of sedentary behavior and multiple other confounders (β-.226, p=.004).

Table 3 and 4 here

In a sensitivity analysis, inpatients were categorized into three groups according to antipsychotic medication: first generation (n=47), second generation (n=115) and First+Second generation combined (n=37). We performed ANOVA tests and found no significant difference between drug types and Waist, SBP, DBP, TG, or FBG. The only significant difference was found between drug types and HDL-C (p=.019) (First generation: HDL-C = 42.83(mean), Second: 49.08, First+Second: 45.54; First>Second, p=.024). Finally, we conducted the regression models for HDL-C and FBG (because steps and sedentary time were only significantly related to these two variables) replacing the Chlopromazine doses with the dummy variable (drug types). Similar results were found for the association of step/sedentary with HDL-C or FBG as to the original model using chlorpromazine equivalents (results available from corresponding author on request).

4. Discussion

To our knowledge, the current study is the first to explore the independent relationships between objectively measured sedentary behavior and daily steps and cardiometabolic risk factors among inpatients with schizophrenia and controls. The study has produced several novel findings. First, our data suggest that among inpatients, higher levels of sedentary behavior are associated with elevated fasting blood glucose compared to those who are less sedentary. Moreover, compared to those who engage in higher amounts of daily steps, those taking less daily steps, have worse HDL-C levels (the good cholesterol). Multivariate analyses suggest that once daily steps are taken into account, the relationship between sedentary behavior and worse fasting glucose is ameliorated. In addition, lower daily steps is independent from

multiple confounders (including sedentary behavior), associated with lower HDL-C.

Previous research, in the general population has established that a one hour increase in sedentary behavior is associated with a 22% and 39% increased risk of diabetes and metabolic syndrome respectively [14, 30]. The literature suggesting the deleterious impact of sedentary behavior among people with schizophrenia is relatively sparse, although clearly there are concerns given the recently reported high levels [16]. Previous Stubbs et al [17] demonstrated among 250 people with established psychosis of similar age to the current study that higher levels of sedentary behavior were independently associated with increased C reactive protein [17]. In another study Vancampfort et al [18] found that patients (total n=76) who reported sitting more than 10.4 hours per day had a higher BMI, waist circumference and fasting glucose concentrations and experienced more negative and cognitive symptoms than those sitting less than 5.8 hours per day. Our study extends the literature, since it is the first study using objective sedentary behavior to explore the potential independent relationship with cardiometabolic outcomes. In particular, our data suggests that higher levels of sedentary behavior are associated with higher fasting blood glucose.

Interestingly, the relationship between sedentary behavior and fasting blood glucose was attenuated once objectively measured daily steps were adjusted for in the model. Moreover, it appears that higher daily steps are independently associated with more favorable HDL-C levels. These are relationships that have not previously been reported in the literature using accelerometers and help to shed some light on the respective metabolic risk associated with activity and sedentary behavior. In the general population, there is a robust relationship between the number of steps and cardiometabolic risk [31, 32]. Consequently, recommendations exist that people strive to achieve 10,000 steps per day, or at least 7,500 in some special populations [31]. Within our study, whilst the control group met the recommended guidelines, those with schizophrenia engaged in just over 6,000 steps. Our data suggest that increasing daily steps might be an important strategy to mitigate metabolic risk in people with established psychosis. Moreover, walking is known to be a favored strategy for physical activity among people with schizophrenia and confers good health benefits [33, 34]. Therefore, the combined message of ‘sitting less and walking more’ might offer health benefits for people with psychosis [35]. Clearly, future longitudinal and interventional work are required to test these hypotheses and see if increasing activity levels and reducing sedentary behavior improves cardiometabolic profile and other health outcomes.

Some limitations should be noted. First, our data are cross sectional and directionality of the variables cannot be clarified. Second, the participants were all

inpatients with established psychosis and the results may not be generalizable. Future research should consider these relationships in outpatients. Moreover, future research should consider younger populations during earlier onset of illness and before metabolic risk increases. For instance, targeting people experiencing first episode psychosis to reduced sedentary behaviors and increase activity levels may be a particularly key time to prevent the onset of metabolic disease. Nonetheless, the current study is the largest to consider objective sedentary behavior and daily steps and metabolic outcomes among inpatients with schizophrenia.

In conclusion, our study confirms that inpatients with established schizophrenia are highly sedentary and engage in considerably less daily steps than the recommended amount. Our study also suggests that whilst higher levels of sedentary behavior are associated with higher fasting glucose, this relationship may be attenuated by factoring in daily steps. Moreover, higher daily steps are independently associated with a more favorable HDL-C level. Future interventional work is required to consider if interventions focusing on 'sitting less and walking more' can improve metabolic outcomes in people with schizophrenia.

Funding

LJC's work was in part supported by the National Taiwan University of Sport and the Taiwan Ministry of Science and Technology (103-2410-H-028-001-MY2).

BS receives funding from the National Institute for Health Research Collaboration for Leadership in Applied Health Research & Care Funding scheme. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Declaration of interest

The authors declare that there is no conflict of interest.

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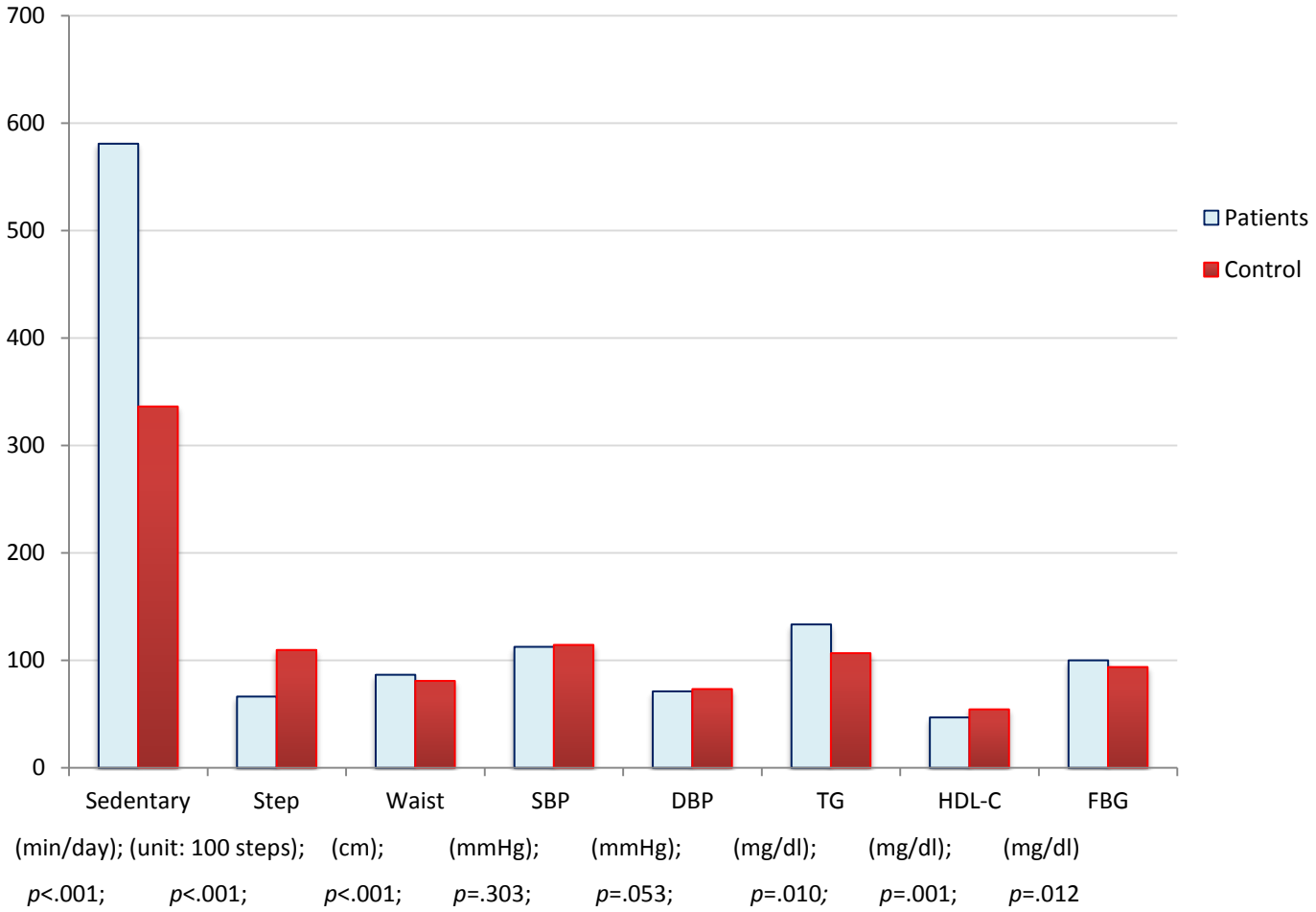

Figure 1: Sedentary time, steps, and metabolic parameters between patients with schizophrenia and controls

Table 1: Characteristic of patients with schizophrenia and controls

Variables % or Mean(SD)	n	Patients	n	Controls	*p*
Age (years)	199	44.0(9.9)	60	41.1(9.6)	.052
BMI (kg/m^2)	199	24.3(4.3)	60	23.9(3.7)	.520
Education (years)	199	11.4(2.2)	60	14.9(3.5)	<.001
Sex (%)					
Female	77	38.7	26	43.3	.520
Male	122	61.3	34	56.7	
Smoke (%)					.001
Never	114	57.3	49	81.7	
Yes	85	42.7	11	18.3	
Alcohol (%)					.771
Never	166	83.4	51	85.0	
Yes	33	16.6	9	15.0	

Table 2: Key variables in patients with schizophrenia by levels of sedentary and steps

Variables / Mean(SD)	Sedentary time (cut-off: 581.1 min/day)			Steps (cut-off: 6628.1 steps)		
	Low (n=110)	High (n=89)	*p*	Low (n=93)	High (n=106)	*p*
Sedentary (min/day)	493.3(73.2)	689.6(91.8)	**<.001**	623.6(142.8)	543.8(99.1)	**<.001**
Steps (unit: 1 step)	7614.9(3578.0)	5408.5(2618.3)	**<.001**	3648.8(1809.7)	9242.0(1920.3)	**<.001**
Waist (cm)	87.6(11.6)	85.8(10.6)	.253	86.4(12.2)	87.1(10.2)	.703
SBP (mmHg)	112.9(12.6)	112.2(13.9)	.725	111.1(14.1)	113.9(12.2)	.132
DBP (mmHg)	71.0(9.2)	71.5(8.3)	.690	70.6(9.2)	71.7(8.4)	.391
TG (mg/dl)	135.7(75.2)	131.0(67.5)	.643	133.6(66.6)	133.7(76.3)	.991
HDL-C (mg/dl)	46.7(13.5)	47.3(13.2)	.768	44.6(11.7)	49.0(14.3)	**.018**
FBG (mg/dl)	96.3(19.1)	105.2(37.1)	**.042**	102.4(33.6)	98.3(23.9)	.334
PANSS	61.4(20.1)	64.9(20.0)	.209	65.7(20.6)	60.6(19.2)	.071
Chlorpromazine equivalent doses	859.4(856.0)	833.1(688.6)	.815	912.0(864.4)	791.2(715.4)	.279
Lorazepam equivalent doses	1.1(1.4)	1.1(1.1)	.886	1.0(1.1)	1.2(1.4)	.402
Time since illness onset (year)	23.2(7.1)	24.5(5.8)	.193	24.2(6.0)	23.4(7.0)	.429
Duration of hospitalization (month)	16.1(19.5)	11.5(13.1)	**.047**	10.3(6.7)	17.3(22.0)	**.002**

Key: Waist: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, TG: triglycerides, HDL-C: high-density lipoprotein, FBG: fasting blood glucose, PANSS: Positive and negative syndrome scale

Table 3: Multivariable linear regressions of metabolic parameters in patients with schizophrenia (without adjusting steps)

Variables	Waist (R^2= 13.4)		SBP (R^2= 5.8)		DBP (R^2= 1.1)		TG (R^2= 5.5)		HDL-C (R^2= 8.0)		FBG (R^2= 15.6)	
	Beta	p	Beta	p	Beta	p	Beta	p	Beta	p	Beta	p
Age (>40) [a]	-.131	.070	.001	.984	-.042	.581	.047	.533	.182	**.015**	.147	**.039**
Sex (Male) [a]	.284	**.001**	.243	**.008**	.046	.622	.206	**.024**	-.122	.173	-.287	**.001**
Education	-.015	.840	.010	.896	.015	.847	.017	.820	-.032	.664	-.074	.300
Smoke (Yes) [a]	.161	.060	-.069	.442	.011	.905	-.038	.671	-.123	.165	-.052	.536
Alcohol (Yes) [a]	-.012	.875	.061	.439	.002	.980	.022	.782	-.026	.738	-.031	.677
PANSS	.174	**.030**	-.118	.159	.008	.929	-.162	.053	-.020	.809	.014	.862
Chlorpromazine equivalent doses	-.054	.455	-.112	.141	-.059	.451	.021	.779	-.004	.957	-.031	.672
Lorazepam equivalent doses	.018	.804	.028	.711	.050	.520	-.076	.315	.061	.417	-.005	.947
Time since illness onset (year)	-.015	.832	-.043	.567	.039	.611	.055	.464	-.072	.332	-.108	.130
Duration of hospitalization (month)	.074	.308	-.022	.769	.043	.579	.047	.538	-.033	.660	.097	.176
Steps (Low) [a]												
Sedentary time (High) [a]	-.004	.959	-.019	.801	.036	.642	-.022	.773	-.016	.826	.146	**.041**

Key: [a]: dummy variable, Waist: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, TG: triglycerides, HDL-C: high-density lipoprotein, FBG: fasting blood glucose, PANSS: Positive and negative syndrome scale

Table 4: Multivariable linear regressions of metabolic parameters in patients with schizophrenia (adjusting steps)

Variables	Waist (R^2= 13.8)		SBP (R^2= 6.3)		DBP (R^2= 1.4)		TG (R^2= 5.7)		HDL-C (R^2= 12.1)		FBG (R^2= 15.6)	
	Beta	p	Beta	p	Beta	p	Beta	p	Beta	p	Beta	p
Age (>40) [a]	-.133	.064	.004	.954	-.040	.604	.045	.551	.190	**.009**	.147	**.040**
Sex (Male) [a]	.296	**.001**	.229	**.013**	.034	.718	.215	**.020**	-.163	.068	-.284	**.001**
Education	-.012	.866	.007	.922	.013	.870	.019	.803	-.040	.585	-.073	.305
Smoke (Yes) [a]	.160	.062	-.067	.451	.012	.895	-.039	.664	-.119	.170	-.053	.535
Alcohol (Yes) [a]	-.011	.888	.059	.450	.001	.992	.023	.773	-.030	.692	-.031	.681
PANSS	.187	**.022**	-.104	.218	.019	.823	-.172	**.044**	.020	.804	.011	.895
Chlorpromazine equivalent doses	-.064	.385	-.102	.184	-.050	.528	.014	.851	.027	.720	-.033	.651
Lorazepam equivalent doses	.028	.705	.018	.816	.041	.603	-.069	.368	.030	.688	-.002	.975
Time since illness onset (year)	-.019	.795	-.039	.601	.042	.583	.053	.486	-.061	.403	-.109	.128
Duration of hospitalization (month)	.089	.233	-.038	.625	.029	.714	.057	.460	-.080	.286	.101	.171
Steps (Low) [a]	.071	.352	-.075	.344	-.067	.412	.051	.519	-.226	**.004**	.018	.810
Sedentary time (High) [a]	-.024	.754	.002	.978	.054	.498	-.036	.646	.047	.535	.141	.059

Key: [a]: dummy variable, Waist: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, TG: triglycerides, HDL-C: high-density lipoprotein, FBG: fasting blood glucose, PANSS: Positive and negative syndrome scale

Highlights

- Sedentary behavior is related to worse fasting glucose, while this relationship is attenuated when physical activity is taken into account among inpatients with schizophrenia.
- Physical activity is associated with favourable high-density lipoprotein cholesterol among inpatients with schizophrenia.
- Interventions targeting replacing sedentary behavior with physical activity may improve metabolic risk among inpatients with schizophrenia.