



Meta-analysis of physical activity and effects of social function and quality of life on the physical activity in patients with schizophrenia

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Abstract

Schizophrenia patients have increased mortality and morbidity, mainly due to premature cardiovascular disease resulting from decreased physical activity (PA). However, which PA intensity is impaired in the patients and how factors such as social function and quality of life (QoL) are related to decreased PA is unknown. To assess PA, social function and QoL, the International Physical Activity Questionnaire (IPAQ), Social Functioning Scale (SFS) and Schizophrenia Quality of Life Scale (SQLS), respectively, were used in 109 schizophrenia patients and 69 healthy subjects. A meta-analysis comparing PA intensities (vigorous, moderate and light) assessed by the single PA measurement between schizophrenia patients and healthy subjects after including our case–control sample was performed. Furthermore, the effects of social function and QoL on each level of PA intensity were investigated in patients and controls. The meta-analysis in 212 schizophrenia patients and 132 healthy subjects revealed that patients showed lower total PA, particularly vigorous PA, than controls ($I^2=0$, Hedges' $g=-0.41$, $P=2.80\times 10^{-4}$). The decreased total PA was correlated with impaired total SFS scores ($\beta=0.24$, $P=2.86\times 10^{-3}$), withdrawal ($\beta=0.23$, $P=3.74\times 10^{-3}$) and recreation ($\beta=0.23$, $P=3.49\times 10^{-3}$) without significant heterogeneity between patients and controls. In contrast, the decreased total PA was affected by low independence–performance ($\beta=0.22$, $P=0.034$), employment/occupation ($\beta=0.27$, $P=8.74\times 10^{-3}$), psychosocial ($\beta=-0.24$, $P=0.021$) and motivation/energy ($\beta=-0.26$, $P=0.013$), but only in patients. Similar findings were obtained for vigorous PA but not moderate or light PA. Our findings suggest that the impaired vigorous PA in schizophrenia patients may be mediated by schizophrenia-specific factors of social functioning and QoL. Understanding these factors has important implications for increasing PA participation in schizophrenia patients.

Keywords Schizophrenia · Physical activity · Meta-analysis · Social function · Quality of life

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Introduction

Schizophrenia is a common and complex psychiatric disorder with a lifetime risk of approximately 0.5–1% [1]. The disorder is characterized by a wide spectrum of symptoms, such as delusions, hallucinations, blunted affect and withdrawal, as well as cognitive impairments. Consequently, these symptoms and impairments cause social dysfunction, loss of motivation and poor quality of life (QoL) [2].

Patients with schizophrenia have increased mortality and morbidity compared with the general population [3]. Patients have a shorter lifespan by 10–20 years than the general population, mainly due to premature cardiovascular disease (CVD) [3, 4]. The presence of metabolic syndrome (MetS), which includes abnormal clinical and metabolic

findings, is a predictor of CVD. These abnormal findings include dysglycemia, increased blood pressure, elevated triglyceride levels, low high-density lipoprotein (HDL) cholesterol levels and central adiposity [5]. The prevalence of MetS in patients with schizophrenia is over 30%, which is higher than that in the general population [6]. The reasons for the occurrence of MetS in patients with schizophrenia are complex and include increased genetic risk [7, 8], cardio-metabolic side effects of antipsychotics [9] and an unhealthy lifestyle that includes insufficient physical fitness, poor diet, high rates of cigarette smoking and limited access to general somatic health care [6, 10].

Low physical activity (PA) has been recognized as a prominent behavioral risk factor for CVD and MetS and as an independent risk factor for all-cause mortality [11]. Twin and family studies have indicated moderate to high degrees of heritability of PA behavior and responses to PA interventions [12, 13]. A recent meta-analysis of PA, assessed by a different PA measurement [self-report questionnaire (SRQ; e.g., International Physical Activity Questionnaire, IPAQ) or objective measurement (e.g., accelerometer)], indicated that patients with schizophrenia showed less moderate and vigorous PA but not light PA than controls in limited sample sizes (SRQ, 113 patients with schizophrenia and 63 controls in two studies; objective, 110 patients with schizophrenia and 93 controls in three studies) [14]. However, the meta-analysis indicated considerable heterogeneity in each level of PA intensity because the instruments used to measure PA varied across studies. There are many different ways to analyze PA data, but the IPAQ is a standard, subjective instrument designed primarily for cross-national surveillance of PA in adults (age range of 15–69 years) [15]. To decrease the heterogeneity in each level of PA intensity among studies and increase the sample size, an additional meta-analysis using a single PA measurement, such as the IPAQ, is required.

PA interventions in patients with schizophrenia can improve physical health outcomes, such as cardio-metabolic outcomes and cardiorespiratory fitness, which are better predictors of mortality [16, 17]. Furthermore, it has been indicated that there are beneficial effects of PA on mental health outcomes, such as general psychological well-being [18] and psychiatric and cognitive functioning [19, 20]. Therefore, PA provides important physical and mental health benefits in patients with schizophrenia [21–23]. Because half of all patients with schizophrenia do not meet the established recommendation of 150 min of moderate–vigorous PA per week [14, 24], improving PA levels in patients is a clinical challenge. Negative or depressive symptoms [14, 23], side effects of antipsychotics, unhealthy lifestyle habits, social isolation [23], and lack of social support, finances or facilities [25] have been indicated as potential mediators of PA.

Patients with schizophrenia may experience functional deficits, including high levels of internalized stigma,

unstable levels of self-esteem, inability to maintain social relationships and social dysfunction in their daily lives, and they consequently tend to have a poor QoL [26, 27]. QoL refers to the well-being of individuals and societies, i.e., the negative and positive features of life. QoL is a subjective experience and is multi-dimensional in nature [26]. Poor QoL in patients with schizophrenia is associated with many factors, such as social function and MetS [28]. Intrapersonal and interpersonal factors, such as motivation, interpersonal communication and social isolation, have been associated with PA in the general population [29]. Previous studies have assessed the relationships between PA and QoL in patients with schizophrenia [30, 31]. An impaired physical health-related QoL (HRQoL), but not mental HRQoL, contributes to a lack of PA during leisure time in patients with schizophrenia [31]. However, the schizophrenia-specific effects of detailed social function and QoL factors on various levels of PA intensity are unknown. Understanding these factors in patients with schizophrenia has important implications for the successful delivery of interventions to increase PA participation.

It is not yet clear which PA intensity (vigorous, moderate and light), assessed using a single IPAQ measurement, is impaired in patients with schizophrenia compared with healthy subjects. To our knowledge, it also remains unclear whether the impaired PA is associated with lower social function and QoL in either patients with schizophrenia or healthy subjects. We hypothesized that patients with schizophrenia would exhibit decreases in specific levels of PA intensity compared with healthy subjects, as well as that the decreased PA would be specifically related to impaired social function and QoL only in patients with schizophrenia, not in healthy subjects. Here, we performed a meta-analysis of PA intensities (vigorous, moderate and light) assessed by the IPAQ between patients with schizophrenia and healthy subjects after including our Japanese case–control sample. Furthermore, the effects of social function and QoL, assessed using questionnaires focused on schizophrenia, on each level of PA intensity were investigated in patients with schizophrenia and healthy subjects.

Methods

Subjects in the case–control study

The subjects in our case–control study consisted of 109 patients with schizophrenia [24 inpatients/85 outpatients, 52 males/57 females, mean age \pm standard deviation (SD): 44.6 ± 11.4 years] and 69 healthy subjects (42 males/27 females, 35.7 ± 10.9 years). All subjects were of Japanese descent and all were biologically unrelated to at least the second degree. Patients were recruited from both the

outpatient and inpatient populations at Kanazawa Medical University Hospital and related psychiatric hospitals. Each patient with schizophrenia had been diagnosed by at least two trained psychiatrists on the basis of unstructured clinical interviews, medical records and clinical conferences [32–35]. Diagnoses were made according to the criteria in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). Healthy subjects were recruited through local advertisements and from hospital staff at Kanazawa Medical University. Healthy subjects were evaluated using unstructured psychiatric interviews to exclude individuals with current or past contact with psychiatric services or who had received psychiatric medication. Subjects were excluded from the analysis (1) if their age was under 18 or over 65 years and (2) if they had neurological or medical conditions that could affect the central nervous system, including atypical headaches, head trauma with loss of consciousness, chronic lung disease, kidney disease, chronic hepatic disease, active cancer, cerebrovascular disease, epilepsy, seizures, substance-related disorders or mental retardation. In contrast, subjects were included in the analysis regardless of whether they had MetS, CVD or diabetes mellitus (DM). Demographic information is shown in Supplementary Table 1. Among the patients, 105 received antipsychotics (16 typical, 67 atypical, and 22 a combination of typical and atypical), whereas four patients received no antipsychotics at the time of investigation. The gender ratio, height and weight did not differ significantly between the patients and controls ($P > 0.05$), whereas the mean age, body mass index (BMI), years of education and estimated premorbid intelligence quotient (IQ) were significantly different between the patients and controls ($P < 0.05$). Current clinical symptoms and side effects of the antipsychotics in patients with schizophrenia were evaluated using the Positive and Negative Syndrome Scale (PANSS) [36] and the Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) [37], respectively. Written informed consent was obtained from all subjects after the procedures were fully explained. This study was performed according to the World Medical Association's Declaration of Helsinki and was approved by the Research Ethical Committee of Kanazawa Medical University.

Measurement of PA

To assess PA, the Japanese version of the Short-Form IPAQ, a self-report questionnaire, was administered [38]. The structured format required participants to recall the time they spent at each level of PA intensity [(1) vigorous, (2) moderate and (3) light] over the preceding 7 days [15]. Following the IPAQ protocol (<http://www.ipaq.ki.se>), a metabolic equivalent (MET)-min per week for each level of PA was calculated by a MET energy expenditure estimate and

the reported min per week. The MET levels were obtained according to Ainsworth's study [39]. The following values were used for the analysis of IPAQ data: vigorous PA = 8.0 METs, moderate PA = 4.0 METs and light PA = 3.3 METs. The weighted MET-min per week values were calculated as MET intensity \times duration (in min) \times frequency (days/week). Total PA (MET-min/week) was calculated as the sum of the three levels of PA. A previous study indicated that the IPAQ can be considered a reliable surveillance tool with which to assess PA levels in patients with schizophrenia [24].

Meta-analysis of PA assessed by the IPAQ in patients with schizophrenia and controls

The meta-analysis of PA assessed by the IPAQ was performed according to the PRISMA guideline [40]. We searched for studies in the PubMed and PsycINFO databases using the search terms "International Physical Activity Questionnaire", "IPAQ" or "physical activity" and "schizophrenia" to perform the meta-analysis. Our search data encompassed all publications up to May 2017. Additionally, references cited in the publications that we obtained were searched to identify additional, potentially relevant studies that may not be listed in PubMed and PsycINFO.

Next, studies, including the current case-control study in a Japanese population, were included in the meta-analysis if they met the following criteria: (1) published in a peer-reviewed journal in English, (2) compared patients with schizophrenia with healthy subjects using the IPAQ, and (3) contained information on the means and SDs for each level of PA for both patients and controls. The available information on age, gender, duration of illness, in- or outpatient status, BMI and diagnostic criteria was also collected. Two raters (KO and YK) independently verified the validity of the data in all included articles.

Measurement of social functioning

To measure social functioning, the Japanese version of the Social Functioning Scale (SFS), a self-report questionnaire, was administered [41]. This scale assesses social functioning in several areas and is intended for use in patients with schizophrenia [32, 42]. The SFS has seven subscales: (1) withdrawal (time spent alone, initiation of conversation, and social avoidance), with a score range of 0–15; (2) interpersonal communication (number of friends/having a romantic partner and quality of communication), with a score range of 0–12; (3) independence–performance (performance of skills necessary for independent living), with a score range of 0–39; (4) independence–competence (ability to perform skills necessary for independent living), with a score range of 0–39; (5) recreation (engagement in a range of common hobbies, interests, and pastimes), with a score range of 0–45;

(6) prosocial activities (engagement in a range of common social activities, e.g., sports), with a score range of 0–66; and (7) employment/occupation (engagement in productive employment or a structured program with daily activities), with a score range of 0–10. The total score is the sum of the seven domain scores and ranges from 0 to 226. A higher score indicates a higher level of social functioning.

Measurement of QoL

To measure QoL, the Japanese version of the Schizophrenia Quality of Life Scale (SQLS), which addresses the perceptions and concerns of patients with schizophrenia, was administered [43]. The SQLS is a 30-item self-report questionnaire with responses scored from 0 to 4 that evaluates QoL on three subscales: (1) psychosocial, (2) motivation and energy and (3) symptoms and side effects [44]. The score for each subscale can be converted from 0 to 100 in such a way that a higher score indicates greater impairment in QoL.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 24.0 software (IBM Japan, Tokyo, Japan). Because we recruited part of a community-based sample, most demographic variables, including age and years of education, were not fitted to a normal distribution based on the Kolmogorov–Smirnov test ($P > 0.05$) as described in most clinical studies. Therefore, the continuous variables, such as age and years of education, were analyzed using the non-parametric Mann–Whitney U test. The differences in categorical variables, such as gender, were analyzed using Pearson's χ^2 test. The differences in PA, social functioning and QoL between patients and controls were analyzed via multiple linear regression with each level of PA, social functioning and QoL as dependent variables and diagnosis as an independent variable. In addition, to examine the influence of social function or QoL on PA, we performed multiple linear regression analyses with each level of PA as the dependent variable and social function or QoL as the independent variable separately in patients and controls. Age and gender were included as covariates to control for confounding factors. The correlations between each level of PA and clinical variables were assessed using non-parametric Spearman's correlation coefficients.

The meta-analyses were performed using the Comprehensive Meta-Analysis (CMA) Version 2.0 software package [45]. Cochran's Q test was performed to assess possible heterogeneity (I^2) between individual studies or between patients and controls. The effect sizes (Hedges' g or β) and 95% confidence intervals (CIs) were estimated using a random-effects model if there was evidence of heterogeneity ($P < 0.05$). Otherwise, a fixed-effects model was used

($P > 0.05$). Effect sizes (Hedges' g) indexing the standardized differences in each level of PA between patients and controls were calculated on the basis of reported statistics (the mean of the schizophrenia samples minus the mean of the healthy subjects, divided by the pooled SD). To control for differences in sample size between studies for which mean effect sizes were computed, studies were weighted according to the estimates of inverse variance. Publication bias was assessed using Egger's regression asymmetry test with a funnel plot of the effect size against standard error (SE) in each study. A leave-one-out sensitivity analysis was performed by iteratively removing one study at a time to confirm that our findings were not driven by any single study. The β and SEs in patients and controls were obtained from the multiple regression analyses to examine the influences of social function or QoL on PA. A meta-analysis of the β and SEs was performed to calculate overall effect sizes and 95% CIs for all subjects. The significance level was set at a two-tailed $P < 0.05$ for all statistical tests. The significance level was adjusted using Bonferroni correction for independent tests.

Results

Differences in PA between patients with schizophrenia and healthy subjects in a Japanese population

We first investigated differences in total PA (MET-min/week) between patients with schizophrenia and healthy subjects in a Japanese population. The patients showed nominally lower PA than controls ($\beta = -0.16$, $P = 0.038$). Next, we investigated differences in vigorous, moderate and light PA (min/week) between patients and controls. Of the three intensities, vigorous PA was nominally lower in the patients than in the healthy subjects ($\beta = -0.16$, $P = 0.029$), while moderate and light PA were not significantly different between patients and controls ($P > 0.05$). However, after adjusting for age and gender, there were no significant differences in total PA or any intensities of PA between the groups, although the patients had marginally lower total ($\beta = -0.14$, $P = 0.079$), vigorous ($\beta = -0.11$, $P = 0.15$) and light ($\beta = -0.12$, $P = 0.14$) PA than the controls (Table 1). Then, we examined the differences in total PA and each PA level between inpatients and outpatients. The inpatients showed nominally lower total PA ($\beta = -0.20$, $P = 0.039$) and light PA ($\beta = -0.19$, $P = 0.050$) than outpatients (Supplementary Table 2).

We also investigated correlations between each PA level and clinical variables, such as PANSS and DIEPSS scores and chlorpromazine equivalents of total antipsychotics in patients. No correlations were identified between each

Table 1 Differences in PA, social functioning and QoL between schizophrenia patients and healthy subjects

	Schizophrenia	Control	<i>P</i> values (β)
Physical activity	(<i>n</i> = 109)	(<i>n</i> = 69)	
Total PA (MET-min/week)	1012.9 ± 2079.3	1677.5 ± 2040.1	0.079 (−0.14)
Vigorous PA (min/week)	16.6 ± 67.2	47.2 ± 118.1	0.15 (−0.11)
Moderate PA (min/week)	44.4 ± 244.4	47.0 ± 107.1	0.95 (< −0.01)
Light PA (min/week)	272.2 ± 632.2	404.7 ± 535.1	0.14 (−0.12)
Social functioning	(<i>n</i> = 95)	(<i>n</i> = 66)	
Total score of the SFS	105.7 ± 30.6	147.2 ± 18.2	<u>1.04 × 10^{−18} (−0.66)</u>
Withdrawal	9.9 ± 2.5	11.6 ± 2.2	<u>2.17 × 10^{−7} (−0.42)</u>
Interpersonal communication	6.3 ± 2.8	10.4 ± 1.6	<u>2.86 × 10^{−21} (−0.70)</u>
Independence–performance	23.8 ± 7.9	32.0 ± 4.4	<u>2.57 × 10^{−14} (−0.59)</u>
Independence–competence	28.7 ± 8.9	36.7 ± 3.2	<u>1.14 × 10^{−10} (−0.51)</u>
Recreation	20.5 ± 8.2	23.5 ± 7.4	<u>2.34 × 10^{−3} (−0.25)</u>
Prosocial activities	10.9 ± 9.5	23.1 ± 8.0	<u>3.63 × 10^{−13} (−0.56)</u>
Employment/occupation	5.6 ± 3.8	9.8 ± 1.2	<u>1.32 × 10^{−13} (−0.56)</u>
Quality of life	(<i>n</i> = 94)	(<i>n</i> = 65)	
PS (psychosocial)	47.5 ± 18.9	24.9 ± 14.2	<u>2.59 × 10^{−14} (0.59)</u>
ME (motivation/energy)	48.6 ± 18.2	32.2 ± 13.4	<u>2.26 × 10^{−10} (0.50)</u>
SE (symptoms/side effects)	28.1 ± 15.5	11.5 ± 10.7	<u>2.54 × 10^{−10} (0.49)</u>

Means ± SD are shown. *P* values (*P* < 0.05) are shown in boldface and are underlined

PA physical activity, MET metabolic equivalent, SFS social functioning scale

PA level and clinical variables (*P* > 0.05, Supplementary Table 3), except for positive correlations between vigorous PA and height ($\rho = 0.27$, $P = 5.14 \times 10^{-3}$) and between light PA and duration of illness ($\rho = 0.19$, $P = 0.045$).

Meta-analysis of the PA differences assessed by the IPAQ between patients and controls

We found 296 relevant articles in PubMed and PsycINFO using the search terms described in the “Methods” section. According to the inclusion and exclusion criteria (Supplementary Fig. 1), a total of three studies including the present study were finally included in the meta-analysis, with a total of 212 patients with schizophrenia and 132 healthy subjects [10, 46]. As the subjects used in Vancampfort’s studies [10, 47–49] overlapped, we selected one study [10] to include. All patients were diagnosed with schizophrenia according

to DSM-4 or -5 criteria, although the patients included in Ostermann’s study (2013) were restricted to only paranoid schizophrenia. The characteristics of the samples included in the meta-analysis [10, 46] are shown in Table 2.

Because there was marginal heterogeneity in total PA among the studies ($I^2 = 67.4$, $P = 0.047$, Fig. 1 and Supplementary Table 4), a random-effects model was used for total PA. According to Begg’s funnel plot test for asymmetry, no evidence of publication bias was observed ($p = 0.88$). The meta-analysis revealed a significant difference in total PA between patients with schizophrenia and healthy subjects (Fig. 1, Hedges’ $g = -0.53$, $P = 0.012$). Next, we performed meta-analyses of each level of PA in patients and controls. There was no significant heterogeneity in vigorous PA or light PA among the studies ($I^2 = 0$, $P > 0.37$), while there was significant heterogeneity in moderate PA among the studies ($I^2 = 83.5$, $P = 2.32 \times 10^{-3}$) (Fig. 1 and Supplementary

Table 2 Demographic information included in the meta-analysis of PA assessed by the IPAQ between schizophrenia patients and healthy subjects

References	Country	Schizophrenia patients (<i>n</i> = 212)						Control group (<i>n</i> = 132)				Diagnostic criteria
		<i>n</i>	Age	%M	DOI	In/out	BMI	<i>n</i>	Age	%M	BMI	
Vancampfort et al. [10]	Belgium (Kortenberg)	80	36.8 ± 10.0	68.8	13	In/out	26.3	40	37.1 ± 10.3	68.0	25.7	DSM-IV
Ostermann et al. [46]	Germany (Jena)	23	28.4 ± 5.3	69.6	4.1	In	24.0	23	28.2 ± 4.1	73.9	23.6	DSM-IV
Ohi et al. (present study)	Japan (Kanazawa)	109	44.6 ± 11.4	47.7	18	In/out	24.4	69	35.7 ± 10.9	60.9	22.9	DSM-5

Means ± SD are shown

%M %male, DOI duration of illness (years), In/out inpatient/outpatient, BMI body mass index

Fig. 1 Forest plots demonstrating the effect size estimates of the differences in each physical activity (PA) category between schizophrenia patients and healthy subjects. The results are presented using effect sizes with 95% CIs in the forest plots for each study. The diamond in the bottom portion represents the pooled effect size with the 95% CI. A positive effect size means that patients have higher PA than controls, while a negative effect size means that patients have lower PA than controls

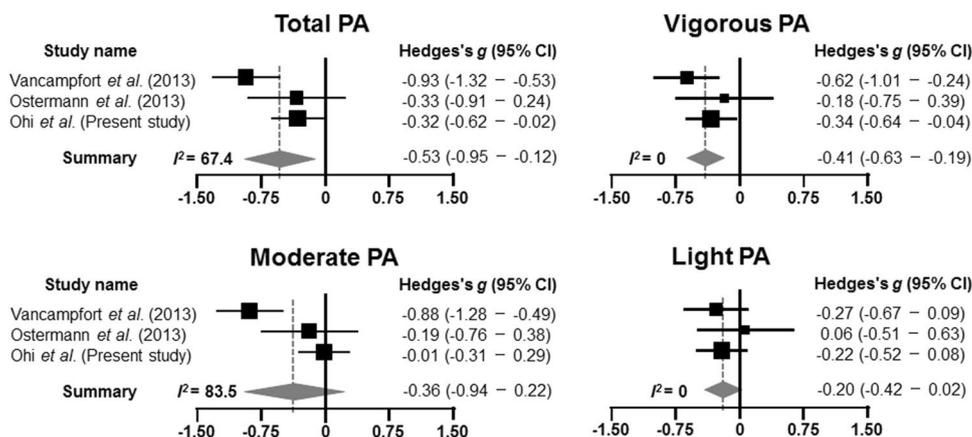


Table 4). Our meta-analyses revealed a significant difference in vigorous PA between patients and controls (Fig. 1, $g = -0.41$, $P = 2.80 \times 10^{-4}$). In contrast, the meta-analyses did not show significant differences in moderate PA ($g = -0.36$, $P = 0.22$) or light PA ($g = -0.20$, $P = 0.068$) between patients and controls. The results for vigorous PA remained significant even after Bonferroni correction ($\alpha = 0.05/3$ intensities, $P_{\text{corrected}} = 8.40 \times 10^{-4}$). Patients with schizophrenia showed lower PA, particularly vigorous PA, than healthy subjects. To assess whether any individual study had undue influence on the outcome, we further performed a leave-one-out sensitivity analysis (Supplementary Table 4). The overall effect sizes and P values were recalculated when each study was removed. The results remained significant for total PA ($g = -0.32$ to -0.73) and vigorous PA ($g = -0.30$ to -0.48) even after removing each study. The significance for light PA was marginal when Ostermann's study (2013) was omitted ($g = -0.25$, $P = 0.040$). In contrast, moderate PA was not significant even after removing each study ($P > 0.05$).

Differences in social functioning and QoL between patients and controls

The differences in social functioning and QoL between patients and controls were investigated. Consistent with our previous study [32], patients with schizophrenia showed significantly lower social functioning than healthy subjects (Table 1, total SFS score, $\beta = -0.66$, $P = 1.04 \times 10^{-18}$; withdrawal, $\beta = -0.42$, $P = 2.17 \times 10^{-7}$; interpersonal communication, $\beta = -0.70$, $P = 2.86 \times 10^{-21}$; independence–performance, $\beta = -0.59$, $P = 2.57 \times 10^{-14}$; independence–competence, $\beta = -0.51$, $P = 1.14 \times 10^{-10}$; recreation, $\beta = -0.25$, $P = 2.34 \times 10^{-3}$; prosocial activities, $\beta = -0.56$, $P = 3.63 \times 10^{-13}$ and employment/occupation, $\beta = -0.56$, $P = 1.32 \times 10^{-13}$). In addition, patients showed significantly lower QoL than controls (Table 1, psychosocial, $\beta = 0.59$, $P = 2.59 \times 10^{-14}$; motivation/energy, $\beta = 0.50$,

$P = 2.26 \times 10^{-10}$ and symptoms/side effects, $\beta = 0.49$, $P = 2.54 \times 10^{-10}$). These findings remained significant even after Bonferroni correction ($\alpha = 0.05/10$ subscales, all $P_{\text{corrected}} < 0.05$). Next, we examined the differences in social functioning and QoL between inpatients and outpatients. The inpatients showed significantly lower social functioning than outpatients (Supplementary Table 2, total SFS score, $\beta = -0.41$, $P = 3.16 \times 10^{-5}$; withdrawal, $\beta = -0.33$, $P = 8.40 \times 10^{-4}$; independence–performance, $\beta = -0.45$, $P = 2.50 \times 10^{-6}$; independence–competence, $\beta = -0.41$, $P = 3.58 \times 10^{-5}$; recreation, $\beta = -0.28$, $P = 5.71 \times 10^{-3}$; and employment/occupation, $\beta = -0.37$, $P = 2.19 \times 10^{-4}$). In contrast, there were no significant differences in interpersonal communication, prosocial activities or any QoL between inpatients and outpatients ($P > 0.05$).

Effects of social functioning and QoL on PA in patients and controls

We first investigated the effects of social functioning and QoL on total PA separately in patients and controls and then performed meta-analyses of the effects in all subjects. Of the total SFS score and the seven subscales, high total PA was significantly affected by a high total SFS score ($\beta = 0.24$, $P = 2.86 \times 10^{-3}$), low tendency to withdrawal ($\beta = 0.23$, $P = 3.74 \times 10^{-3}$) and high recreation ($\beta = 0.23$, $P = 3.49 \times 10^{-3}$) without significant heterogeneity between patients and controls ($P > 0.05$) (Fig. 2a). In contrast, high total PA was marginally affected by high independence–performance ($\beta = 0.22$, $P = 0.034$) and high employment/occupation ($\beta = 0.27$, $P = 8.74 \times 10^{-3}$), but only in the patients ($I^2 = 25.8\text{--}75.5$, $P = 0.25\text{--}0.045$). Of the QoL subscales, low total PA was marginally affected by greater impairments of psychosocial ability ($\beta = -0.24$, $P = 0.021$) and motivation/energy ($\beta = -0.26$, $P = 0.013$), but only in the patients ($I^2 = 72.2\text{--}87.5$, $P = 4.67 \times 10^{-3}\text{--}0.056$) (Fig. 2b).

In the patient group, 13 patients with schizophrenia (11.9%) were involved in vigorous PA (> 0 min/week for

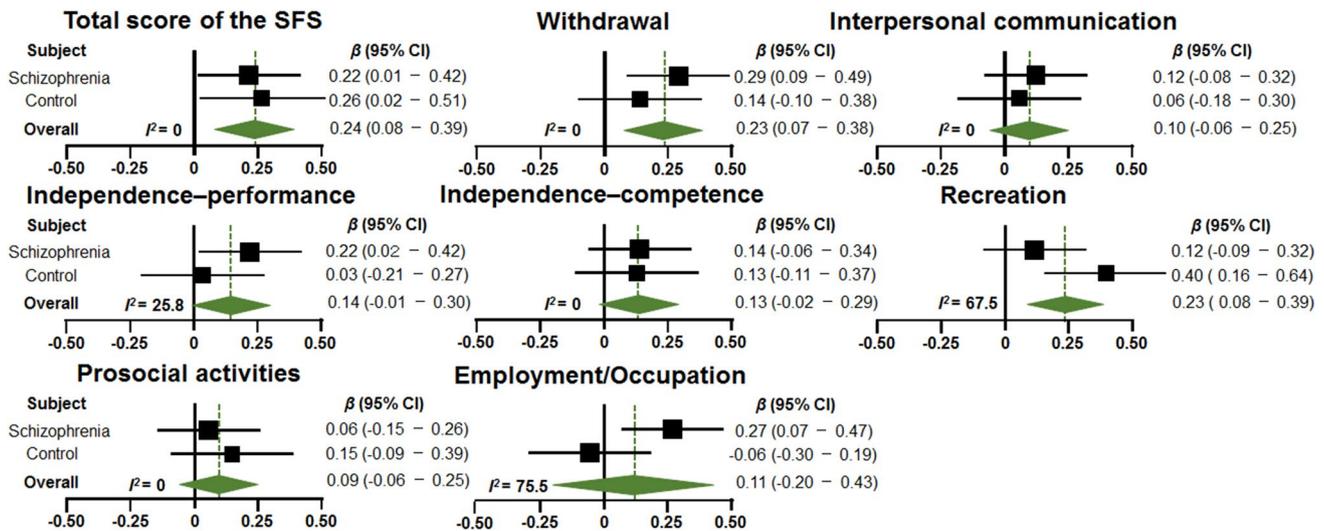
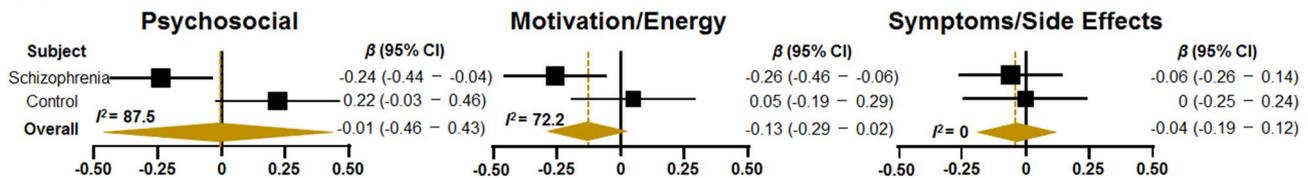
(a) Social Function**(b) Quality of Life**

Fig. 2 Effects of social functioning (a) and QoL (b) on total PA in schizophrenia patients and healthy subjects. A positive effect size indicates correlations of better social functioning or worse QoL with

total PA level, while a negative effect size indicates correlations of worse social functioning or better QoL with total PA level

vigorous activity). In contrast, 15 healthy subjects (21.7%) spent marginally more time performing vigorous PA than the patients ($\chi^2 = 3.1$, $P = 0.080$). Therefore, we divided these participants into two groups: individuals involved in vigorous PA (over 0 min) and those without vigorous PA (0 min). Next, we investigated the effects of social functioning and QoL on vigorous PA in patients and controls. Regarding social functioning, high vigorous PA was marginally affected by high total SFS score ($\beta = 0.19$, $P = 0.014$), low tendency to withdrawal ($\beta = 0.21$, $P = 7.46 \times 10^{-3}$) and high recreation ($\beta = 0.18$, $P = 0.027$), without significant heterogeneity between the patients and controls ($P > 0.05$) (Fig. 3a). In contrast, high vigorous PA was affected by high independence-performance ($\beta = 0.33$, $P = 1.21 \times 10^{-3}$) and high employment/occupation ($\beta = 0.23$, $P = 0.024$), but only in patients ($I^2 = 81.5$ – 83.4 , $P = 0.020$ – 0.014). Regarding the QoL subscales, low vigorous PA was marginally affected by greater impairments of psychosocial ability ($\beta = -0.27$, $P = 9.11 \times 10^{-3}$) and motivation/energy ($\beta = -0.22$, $P = 0.036$), but only in patients ($I^2 = 54.4$ – 80.3 , $P = 0.14$ – 0.024) (Fig. 3b). The findings between total and vigorous PA, but not moderate or light PA, were similar (Supplementary Figs. 2 and 3). The effect sizes for each

level of PA in patients and controls are summarized in Supplementary Table 5.

Discussion

A meta-analysis that included 212 patients with schizophrenia and 132 healthy subjects revealed that total PA assessed by a single measurement with the IPAQ was decreased in patients with schizophrenia compared with healthy subjects. Of the three PA intensities, vigorous PA was more impaired in patients than in controls without heterogeneity among the three studies. It was unclear what types of social function and QoL influenced PA participation in patients with schizophrenia and healthy subjects. Therefore, this study is the first to investigate the influence of social function and QoL on the decreased PA in patients with schizophrenia and healthy subjects. We found that impaired PA was affected by a high tendency toward withdrawal and low recreation without heterogeneity between patients and controls. In contrast, the impaired PA was affected by independence-performance, employment/occupation, psychosocial and motivation/energy subscales in patients with schizophrenia only. These

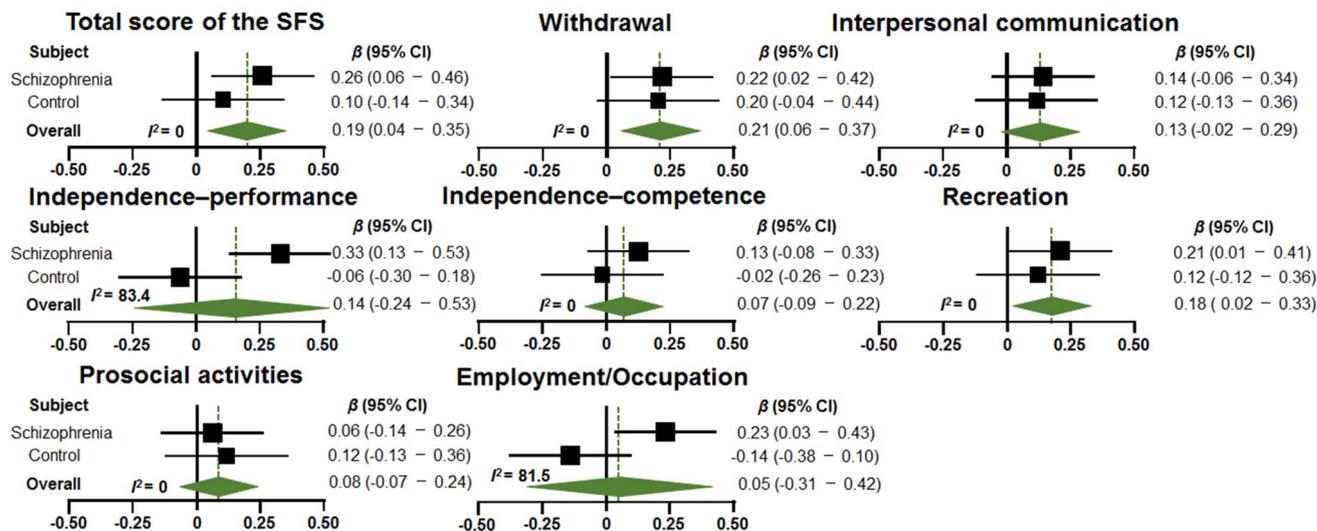
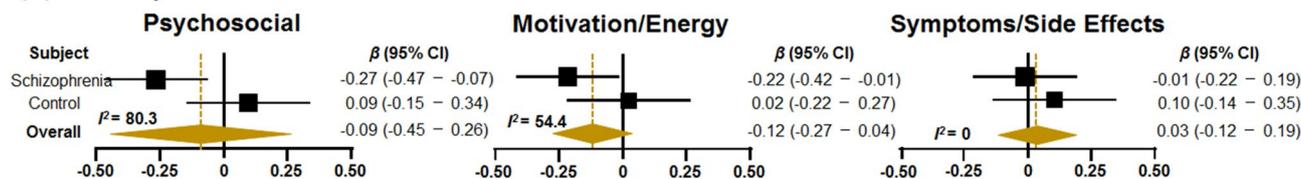
(a) Social Function**(b) Quality of Life**

Fig. 3 Effects of social functioning (a) and QoL (b) on vigorous PA in schizophrenia patients and healthy subjects. A positive effect size indicates correlations of better social functioning or worse QoL with

vigorous PA level, while a negative effect size indicates correlations of worse social functioning or better QoL with a vigorous PA level

findings were observed for vigorous PA but not moderate or light PA.

Although we could not detect differences in any PA in our Japanese case–control sample, our meta-analysis did detect differences in total and vigorous PA but not moderate or light PA between patients with schizophrenia and healthy subjects. Compared with previous studies in other countries (Belgium and Germany) [10, 46], vigorous and moderate PA in the Japanese population were relatively low in both patients and controls [e.g., vigorous PA in healthy subjects: the present study, 47.2 min/week; Ostermann et al. (2013), 84.6 min/week; Vancampfort et al. (2013), 88.9 min/week]. Approximately, 50% of patients with schizophrenia have met the established recommendations of 150 min of moderate-vigorous PA per week [14, 24], whereas only 9.2% of patients and 23.2% of controls met the recommendation in our Japanese population. However, leave-one-out sensitivity analysis for the meta-analysis of PA indicated that the findings for total PA ($g = -0.32$ to -0.73) and vigorous PA ($g = -0.30$ to -0.48) were not driven by any single study. The reason why we could not detect differences in total or vigorous PA may depend on individual variability in the level of PA in our subjects because the SDs of the PA were

relatively large in this study compared with previous studies [10, 46].

A recent meta-analysis using a subjective PA measurement, the IPAQ (113 patients with schizophrenia and 63 healthy subjects in two studies), showed that patients had less vigorous and moderate PA than controls, with heterogeneity between studies [14]. In this study, we added our Japanese sample to the meta-analysis, and the sample size included in our meta-analysis (212 patients with schizophrenia and 132 healthy subjects) was double that in the previous study [14]. There remained no heterogeneity in light PA among studies ($I^2 = 0$). The heterogeneity (I^2) in vigorous PA among studies was decreased from 36.1 to 0. In contrast, there was still high heterogeneity in moderate PA among studies ($I^2 = 83.5$). The effect sizes of vigorous (approximately Hedges' $g = -0.40$) and light (approximately Hedges' $g = -0.20$) PA among studies were similar, while the effect sizes of moderate PA varied between studies. Stubbs et al. (2016) reported that vigorous PA was overestimated in patients with schizophrenia, while moderate and light PA were underestimated in the patients when PA levels measured by subjective PA measurement were compared with those measured by objective PA measurement.

Therefore, the difference in vigorous PA between patients and controls may be much larger. We suggest that increasing vigorous PA would prevent schizophrenia patients from developing MetS and CVD.

Previous studies reported correlations between PA and several clinical variables [10, 14]. Depressive symptoms and older age were correlated with less vigorous PA in patients with schizophrenia [14]. Low physical fitness was associated with illness duration, smoking, presence of MetS and more severe negative, depressive and cognitive symptoms [10]. The clinical symptoms and antipsychotics used for alleviating symptoms may produce MetS and decreased PA. Although we did not examine all of these correlations in this study, there were positive correlations between vigorous PA and height and between light PA and duration of illness in our patients. Compared with a previous study [10], the correlation between PA and illness duration was in the opposite direction. In contrast, there were no correlations between PA and dosage of antipsychotics, current psychiatric symptoms or side effects of antipsychotics. These findings may be due to clinical heterogeneity in patients with schizophrenia.

We revealed that the decreased PA, particularly vigorous PA, was affected by low social function and QoL in patients with schizophrenia and healthy controls. Regarding social functioning, the high tendency toward withdrawal and decreased recreation were related to decreased PA in both patients and controls. In contrast, low independence–performance and low employment/occupation were related to decreased PA only in patients. Regarding QoL, greater impairments of psychosocial and motivation/energy were related to decreased PA only in patients. The effect sizes of social function and QoL on PA were small to moderate. PA behavior and the responses to PA interventions [12, 13], as well as the risk for schizophrenia [50], had moderate to high degrees of heritability. Of the social function and QoL factors, withdrawal and motivation/energy may be more strongly associated with genetic factors than with environmental factors, while recreation and employment/occupation may be more associated with environmental factors than with genetic factors, although the heritability of these factors is unknown. As common genetic factors may contribute to the neural mechanisms of schizophrenia and PA behavior, further research is required to investigate whether PA and these factors are intermediate phenotypes of schizophrenia.

There are several limitations to this study. The evaluations of PA and Social function, using IPAQ and SFS, have been originally targeted for outpatients with schizophrenia [24, 42] although the subsequent studies have investigated these factors in inpatients as well as outpatients [14, 32]. We showed that inpatients had marginally lower PA and significantly lower social function, but not QoL, than outpatients in our Japanese population. On the other hand, a previous meta-analysis has shown that inpatients had higher vigorous

PA than outpatients [14]. We could not divide patients into inpatients and outpatients in our meta-analysis because of a few studies. Further meta-analysis using a larger sample size is needed to separate inpatients and outpatients. Each inclusion and exclusion criterion for the studies included in our meta-analysis was distinct. We did not exclude individuals with MetS and CVD, whereas Vancampfort et al. (2013) excluded these subjects. Given that the prevalences of MetS and CVD are higher in patients with schizophrenia than in healthy subjects, our patient group included more individuals with MetS and CVD compared with the control group. Our participants consisted of a community-based sample of patients with schizophrenia and healthy subjects. Therefore, demographic variables, such as age and gender, may not have been matched between groups, although these variables were treated as covariates. These factors may affect our findings.

In conclusion, the meta-analysis revealed that patients with schizophrenia had decreased PA compared with healthy subjects. Of the three intensities (vigorous, moderate and light), the difference in PA between groups was derived from vigorous PA in particular. The decreased vigorous PA was affected by common social functioning and QoL factors between patients with schizophrenia and healthy controls as well as specific factors in patients with schizophrenia. Understanding these factors has important implications for increasing PA participation in patients with schizophrenia. We suggest that specifically increasing vigorous PA should be a priority for PA interventions to improve the health of patients with schizophrenia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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