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Effects of high intensity interval training among overweight individuals with psychotic disorders: A randomized controlled trial

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ABSTRACT

Physical activity has been suggested to reduce the high prevalence of metabolic complications in individuals with psychosis. Although high intensity interval training (HIIT) is efficacious in other populations, it remains poorly studied in psychosis.

Methods: Randomized controlled study comparing the effects of 6 months HIIT supervised program (30-minute treadmill sessions twice a week) to usual-care waiting-list control group. Anthropometric (primary outcome: waist circumference), body composition, blood profile, blood pressure, psychiatric symptoms and global functioning were measured at baseline and 6 months.

Results: Sixty-six individuals with psychosis (62% men; 30.7 ± 7.2 years old; mean BMI: 32.7 ± 5.7 kg/m^2) were randomly assigned to either HIIT (n = 38) or control group (n = 28). Mean attendance rate to HIIT sessions was 64%, although 50% dropped-out the intervention before the end. Few minor adverse events were reported. The intent to treat analysis showed no impact of HIIT on waist circumference (p = 0.25). However, in a post-hoc analysis among the compliant participants (>64% of prescribed sessions), significant improvements in waist circumference (−2.94, SE = 1.41, p = 0.04), negative symptoms (PANSS negative −3.7, SE = 1.39; p = 0.01), social (SOFAS +6.16, SE = 1.76, p = 0.001) and global functioning (GAF +5.38, SE = 2.28, p = 0.02) were observed.

Discussion: HIIT seems to be safe and well accepted in overweight individuals with psychosis. Exercise compliance to HIIT is associated with improvements in waist circumference as well as negative symptoms and functioning. Interventions improving attendance are needed.

1. Introduction

Individuals suffering from severe mental illness (ISMI) (e.g., schizophrenia, schizo-affective disorders) have a decreased life expectancy of 20 to 30 years compared to the general population (Lawrence et al., 2010; Liu et al., 2017). Indeed, compared to healthy matched control subjects, ISMI have an increased risk of developing cardiovascular disease (adjusted odds ratio (AOR): 1.53), coronary heart disease (AOR: 1.51), cerebrovascular disease (AOR: 1.42) and heart failure (AOR: 1.28) (Correll et al., 2017). Furthermore, 32% of ISMI have the metabolic syndrome (defined as a group of risk factors including abdominal obesity (up to 50% in ISMI) (Mitchell et al., 2013; Romain et al., 2017; Vancampfort et al., 2015b), dyslipidemia, elevated blood pressure and glucose intolerance) (Vancampfort et al., 2015b), which increases the risk of cardiovascular diseases (Alberti et al., 2009). Several factors contribute to the higher prevalence of abdominal obesity, such as antipsychotic medication (Bak et al., 2014), genetic predisposition (Osby et al., 2014) and unhealthy lifestyle habits (e.g., low physical activity (Janney et al., 2015), high sedentary behaviour (Vancampfort et al., 2017) and unhealthy eating habits (Dickerson et al., 2005). Therefore, effective interventions for these metabolic complications in ISMI are warranted.

Exercise training was found to show promising results among the different interventions that could improve the metabolic profile of ISMI. Literature reviews and meta-analyses have highlighted the potential role of exercise training in ISMI on cardiovascular disease risk reduction (Chalfoun et al., 2016), cardiorespiratory fitness improvement (Vancampfort et al., 2015a), cognitive functioning (Firth et al., 2017), quality of life (Dauwan et al., 2016; Gorczynski and Faulkner, 2010), social and global functioning (Dauwan et al., 2016; Mittal et al., 2017), depressive symptoms (Rosenbaum et al., 2014) as well as positive and negative symptoms (Bernard and Ninot, 2012; Firth et al., 2015).

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Among the different types of exercise training, high intensity interval training (HIIT) has received great attention in the last decade. HIIT is a type of exercise which consists of alternating repetitive short bouts of high intensity exercise (e.g. sprint running > 85% of maximal oxygen consumption; VO2max) with less active or passive recovery periods (e.g. fast walking < 60% VO2max) (Batacan et al., 2017; Cassidy et al., 2017). Each bout of high intensity exercise can last between 6 s to 4 min, and each recovery period between 10 s to 4 min (Batacan et al., 2017). In previous studies in different "at risk" populations (e.g., obese, type 2 diabetes) or in the general population, HIIT has been reported to be effective, well-tolerated and a more powerful stimulus than traditional continuous moderate intensity exercises (ex. moderate speed jogging at a regular pace) in reducing cardiovascular disease risk by acting on metabolic complications and increasing cardiorespiratory fitness (Batacan et al., 2017; Maurie et al., 2011; Weston et al., 2014). Emerging evidence has suggested that HIIT could significantly increase cardiorespiratory fitness levels in ISMI (Abdel-Baki et al., 2013; Chalfoun et al., 2016; Chapman et al., 2017; Heggelund et al., 2014; Wu et al., 2015). Indeed, a review has suggested that improving cardiorespiratory fitness levels may be a key factor in reducing the risk of mortality in ISMI (Wildgust and Beary, 2010). Regarding improvements in body composition, and metabolic risk factors, results from previous studies using HIIT in ISMI were inconsistent (Abdel-Baki et al., 2013; Heggelund et al., 2014; Wu et al., 2015). However, all these studies were not randomly controlled studies (RCT), were of short duration (<4 months), had a small sample size and only one had a control group. Furthermore, the effect of HIIT on psychotic symptoms and functioning as well as psychosocial factors are not well known. Therefore, the aim of the present study was to investigate the effects of a 6-month HIIT program on body composition (with waist circumference as the primary outcome), metabolic, psychiatric/functional and psychosocial markers in overweight ISMI using a RCT design.

2. Methods

The present study is reported following the CONSORT guidelines (Moher et al., 2010). The protocol was approved by the Ethics Committee of the research centre of the Centre hospitalier de l'Université de Montréal (CHUM) where the study was performed. All participants provided written informed consent.

2.1. Trial design

RCT with two parallel arms: the exercise intervention group receiving HIIT vs a waiting-list control group.

2.1.1. Setting and location

Participants were recruited over a 5-year period from 2012 to 2017 throughout different clinics (early intervention for psychosis, affective disorders, outpatient's psychosis clinics, and patient aligned care team) at the Department of Psychiatry of the CHUM. The study was advertised using posters in waiting rooms and by several presentations in multidisciplinary team meetings where leaflets were also distributed.

2.2. Participants

2.2.1. Eligibility criteria

To be included, participants had to meet the following criteria: 1) age between 18 and 55 years old, 2) diagnosis of psychotic disorder according to the DSM-IV-TR (e.g., schizophrenia, schizo-affective disorders, bipolar disorders with psychotic features, major depressive disorders with psychotic features) established by the treating psychiatrist, 3) taking antipsychotic medication at a therapeutic dose, 4) overweight or obese (BMI ≥ 25 kg/m^2), 5) waist circumference meeting the criterion for metabolic syndrome (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee et al., 2013) (≥94 cm for men, ≥80 for women), 6) being inactive (<2 sessions of structured physical activity per week, 7) symptoms of psychotic disorders being stable for at least 1 month and 8) no expected changes in medication by the psychiatrist for the next 6 months.

The exclusion criteria were: 1) medical contraindication to exercise, 2) cardiovascular disease, 3) type 1 or type 2 diabetes, 4) orthopedic limitations, 5) eating disorders, 6) uncontrolled thyroid or pituitary disease, 7) pregnant women, or women planning in becoming pregnant within the next year, 8) menopausal or peri-menopausal women, 9) women using depot medroxyprogesterone acetate as a contraception, 10) excessive alcohol consumption (>2 glasses per day), and 11) taking any medication for medical comorbidity, with the exception of psychotropic medication, which can affect the outcomes (e.g., metformin).

The inclusion and exclusion criteria were checked by 3 researchers (AJR, CF, AAB) and were double-checked by another investigator (EL) during a medical evaluation to detect any contra-indication to exercise.

2.3. Intervention

2.3.1. Intervention group

In addition to their usual psychiatric treatment, the intervention group received an exercise training program: a 6-month HIIT performed on a treadmill twice a week on non-consecutive days (as in the pilot study) (Abdel-Baki et al., 2013). They were instructed not to change their other lifestyle habits (e.g., nutrition). Each exercise session lasted for 30 min. The sessions included a 5 min low-intensity warm-up (walking), ten intervals of 2 min each, and a 5-minute cool down (walking). Each interval was composed of a 30 s sprint followed by an active recovery of 90 s. The sprint was performed at 80% of the theoretical maximum heart rate, as measured by a heart rate monitor (Polar Electro, Inc., Woodbury, NY). This intensity was gradually increased to attain 90% of the maximum heart rate. The active recovery was intended to target 50 to 65% of the theoretical maximum heart rate. Regarding the intervention progression, it was adapted according to the participants' ability to reach the required intensity of 80–90% of their maximal heart rate during the sprint phase. If the participant was not in this intensity zone using the same speed as the previous sessions, we then gradually increased the speed of the sprint intervals over time in order to reach the target intensity.

Each exercise session was individually supervised by either an exercise physiologist, an exercise physiologist in training or medical students. Before the students began supervising the exercise training sessions of the participants, they were all trained by a senior exercise physiologist, which supervised the students first training sessions and assured an ongoing supervision of the students to make sure that the standardized exercise training program was properly followed and conducted and that all the standardized training record sheets were properly filled out. The exercise training program was performed in a community centre (*Association Communautaire Centre Sud*), which provided free access to the exercise facilities for this project.

2.3.2. Control group

The control group was a usual care waiting-list group. In this group, participants were asked to continue their follow-ups with their psychiatric care providers and to not change their present lifestyle habits (e.g., exercise, nutrition). After the 6-month RCT period, the same HIIT intervention as the one offered to the intervention group was offered to participants of the control group.

2.3.3. Incentive

At the end of the intervention, all participants from both control and intervention groups, even those who dropped out the study, were offered a 6-month free membership to the same exercise facilities where the intervention was conducted in order encourage them to continue their exercise routine. This reward was provided to thank

participants for their involvement in the project and helping them maintaining the gains by facilitating the continuation of their routine.

2.3.4. Recall procedure and drop-out definition

During the 6-month exercise period, if a participant was absent to an exercise session without notifying the kinesiologist, he or she was contacted to reschedule a new session within the same week. If a participant was absent for 2 weeks (4 sessions) without any news or had explicitly expressed the desire to quit the exercise intervention, the participant was considered as having dropped out of the exercise protocol.

2.4. Data collection

Data was collected by a researcher (CF, AJR) during research evaluation interviews at baseline and 6 months. Data on exercise sessions (intensity of exercise, presence, etc.) was collected during each exercise session (only for the intervention group) throughout the study by the exercise physiologists. All data were recorded on a specific sheet, which was specifically developed for this study. The control group was instructed not to change their physical activity and not to perform any exercise training program.

2.4.1. Strategies to reduce missing data

To reduce missing data, when a participant explicitly expressed the desire to cease the intervention, he or she was asked if they would still consent to complete the evaluations at 6 months. When a participant did not return our calls, the treating team was contacted to find out when the participant had an appointment with them. During the time of the appointment, one of the researchers (AJR, CF) presented themselves to the appointment in order to ask the participant if he or she would accept to complete the evaluations at 6 months.

2.5. Measures

Socio-demographic data were collected by a questionnaire during the research interview and details about the medication were gathered by chart review.

2.5.1. Primary and secondary outcomes

The primary outcome of the study was waist circumference.

Secondary outcomes were body composition, cardiorespiratory fitness, blood pressure, total cholesterol, High-density Lipoprotein cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C), triglycerides, apolipoprotein B, fasting glucose, and haemoglobin A1c (HbA1c), severity of illness, functioning, quality of life and self-esteem.

2.5.1.1. Measurement of primary outcome (waist circumference). To measure waist circumference, participants were asked to expose their abdominal area and stand in an upright position and place their arms across their chest. Waist circumference was measured at the end of expiration at a level midway between the lowest rib and the iliac crest. The measure was recorded at 0.1 cm precision using a non-stretch tape. To decrease the possibility of bias, waist circumference was systematically measured by the same evaluator. Also, waist circumference was double-checked by another researcher (EL). In case of disagreement, the measure was taken by both researchers together.

2.5.2. Secondary outcomes

2.5.2.1. Blood pressure. Blood pressure (diastolic and systolic blood pressure) was taken manually with a sphygmomanometer in a seated position after 5 min of rest. An appropriate cuff size was selected for each participant based on arm circumference. Conditions were carefully standardized: no talking and cuff on the left arm.

2.5.2.2. Blood sample. Blood samples were collected by a nurse after a 12-hour overnight fast. Fasting plasma glucose was measured by routine biochemistry analysis at the CHUM. Total and HDL-cholesterol were measured by routine enzymatic methods (KonePro; Konelab, Epoo, Finland). LDL-cholesterol was calculated using the Friedwald formula. HbA1c was measured with routine high-performance liquid chromatography (HPLC)-based on ion-exchange procedure.

2.5.2.3. Body composition. Body composition was assessed by bioelectric impedancemetry analysis (BIA; Omron HBF-500CAN, USA). The different outcomes measured were fat mass (%), fat free mass (%), weight (kg), and body mass index (BMI).

2.5.2.4. Cardiorespiratory fitness. Cardiorespiratory fitness was estimated for the intervention group only with an indirect measure of VO_{2max} using the single treadmill walking test (Ebbeling et al., 1991). The treadmill was set at a constant pace for 8 min. During the first 4 min, the level of difficulty of the exercise was constant with the objective to have a heart rate being between 50 and 70% of the participant's age-predicted maximum heart rate. After 4 min, the same walking speed was kept but the treadmill's grade was increased to five degrees for another 4 min. Estimated maximal oxygen consumption (in $ml \cdot kg^{-1} \cdot min^{-1}$) was calculated using the Ebbeling's formula (Ebbeling et al., 1991).

2.5.2.5. Severity of illness, functioning, quality of life and self-esteem. The positive and negative symptoms scale (PANSS) was used to evaluate the symptoms' severity of the psychotic illness (Kay et al., 1987).

The global assessment of functioning scale (GAF) (Hall, 1995) as well as the social and occupation functioning assessment scale (SOFAS) (Morosini et al., 2000) were scored taking into account all available information using information provided by the participant during the research evaluation and completed with chart review.

Quality of life was measured using the short-form Medical Outcome Study General Health Survey (12 items) (McHorney et al., 1992) previously used in ISMI (Su et al., 2014). This scale measured two dimensions (physical and mental health components of quality of life). Scores range from 0 to 100 with higher score representing better health-related quality of life.

Self-esteem was measured using the Rosenberg self-esteem scale. This scale has 10 items, with scores ranging from 0 to 30. Higher scores indicate better self-esteem (Rosenberg, 1965).

2.5.3. Adherence to the exercise protocol

Adherence to the exercise protocol was defined as the number of supervised exercise sessions completed compared with the potential total number of exercise sessions (49 completed sessions = 100% of adherence).

2.6. Randomization and blinding

The 66 participants were randomized in two arms (38 participants in the intervention group and 28 participants in the control group). The randomization was performed by two researchers (AJR, CF) by a drawing. Three different envelopes were used consecutively. Two envelopes contained 22 participants allocations (13 interventions, 9 control) and one of 22 (12 interventions, 10 control).

Participants were unaware of their group allocation until all eligibility criteria were checked and baseline measures completed. Except to generate the random allocation sequence, the PI, Co-PIs were not involved at any moment during the randomization process. Given the protocol, participants could not be blinded to their group of randomization, nor could the assessors, which were also acting as research assistants and sometimes exercise supervisor. The PI, Co-PIs were also blinded to the randomization.

3. Statistical methods

3.1. Sample size

Sample size calculation was based on our primary outcome being waist circumference with results from our previous pilot study using HIIT (Abdel-Baki et al., 2013). The assumed between-group difference expected at 6 month was 3.5 cm. This expected difference was assumed to be clinically significant and realistic according to our pilot study. Therefore, considering a power of 80% to detect the expected difference with a standard deviation of 4.5 cm at the α 0.05 level (two-sided), and also considering a conservatory drop-out rate of 40% within the 6-month exercise training, a sample size of 66 participants was considered necessary.

3.2. Data analysis

Descriptive statistics were used to compare participants of randomization groups on their baseline characteristics. Baseline characteristics of participants who completed the 6-month exercise program were compared to those who did not, to identify characteristics associated with exercise drop-out. Similarly, compliant participants (those who completed at least 64% of the sessions) were compared to the non-compliant ones on the same characteristics. This threshold was selected based on our previous pilot study (Abdel-Baki et al., 2013). Categorical data were compared using Chi^2 square analyses and continuous data with one-way ANOVA.

To analyze the efficiency of the proposed exercise intervention on physical characteristics, blood profile, symptoms/functioning and psychosocial outcomes, analyses were performed on an intent to treat basis, comparing baseline data with post intervention measures (6 months) between randomization groups. Secondary analyses were performed to determine the efficacy of HIIT; therefore we selected participants who were considered compliant (e.g., who completed at least 64% of the prescribed exercise sessions; n = 21). The remaining participants of the intervention group (e.g., those who were not considered compliant) were excluded from these secondary analyses. Repeated-measures mixed linear models were used with the restricted maximum of likelihood method of estimation and the unstructured covariance structure was selected. Participants were entered as a random factor. This procedure of parameterization was selected given it adequately fits the data (based on Akaike Information Criterion). This statistical analysis was selected in the present context because it allows available data from all participants to contribute to the results' estimation and therefore provides more accurate estimates. When significant, a post-hoc analysis was performed to locate the effect.

To examine the magnitude of the intervention's effects, the Cohen's *d* was used and by convention, values of 0.2, 0.5, and 0.8 were considered as small, medium, and large effect size, respectively (Cohen, 1992). Given effect size is not directly provided by mixed model analysis, we used another procedure based on mean estimated change and the standard deviation of the control group. This procedure was described in a previous study (Friedmann et al., 2008) and ascertained by a statistician.

To understand the pattern of possible missing data (missing completely at random, missing at random, missing not at random), and the possibility of biased estimates, the Little's MCAR test was performed. If significant, the assumption that data are missing completely at random should be rejected. In our study, the Little's MCAR test found the pattern of missing data to be completely at random (p = 0.26).

4. Results

4.1. Participants

Fig. 1 summarizes recruitment, randomization and the study process (flow chart).

At baseline, the sample was mainly composed of men (n = 40; 60.60%), smokers (n = 36; 55.40%), aged 31.03 ± 7.21 years old, with a mean BMI of 31.96 ± 6.11 kg/m^2. The mean duration since the first hospitalization for psychosis was 6.57 ± 5.83 years. No differences in baseline demographic and clinical characteristics were noted between randomization groups (Table 1).

4.2. Adherence and dropout rates of the exercise training program

Fifty percent of the participants who were randomized to the intervention group dropped-out the exercise program (19 of the 38 participants). Reasons known for drop-out were lack of motivation, exercise too demanding, and exercise program duration. In the control group, 3 of the 28 participants (11%) dropped-out.

For the 38 participants in the intervention group, the mean participation rate to the prescribed exercise intervention was 64.02 ± 38.67% of the sessions (representing 31.87 ± 18.34 sessions of exercise) with a median at 77.55% (interquartile range: 68.88%). Also, 10.50% (n = 4) of the participants who were randomized to the intervention group never attended to any exercise session and 39.5% (n = 15) attended to all of the prescribed exercise sessions. In addition, the participation rate for the participants in the intervention group who did not drop-out was 98.28 ± 2.22% (median = 100%). For those of the intervention group who dropped-out the exercise program before the end, their participation rate was 31.79 ± 22.95% (median = 32.65%).

Following the HIIT protocol, an improvement in estimated VO_{2max} was observed in the whole intervention group only (Pre: 32.67 ± 10.62 vs Post: 45.79 ± 17.45 ml/min/kg; p = 0.005).

4.3. Efficiency of the exercise intervention: intent to treat analysis

4.3.1. Primary outcome: waist circumference

At the end of the 6-month training, compared with the control group, a non-significant reduction of waist circumference (main outcome) was observed (−1.65, 95%CI[−4.54; 1.23], SE = 1.44, p = 0.25; *d* = −0.12) in the intervention group.

4.3.2. Secondary outcomes

Upwards trends were observed for fat free mass improvement (1.11, 95%CI[−0.08; 1.29], SE = 0.58; p = 0.07; d = 0.23) and fat mass reduction (−2.07, 95%CI[−4.53; 0.39], SE = 1.22, p = 0.09; d = −0.24).

At the end of the training, an improvement was found for global functioning (5.83, 95%CI[1.52; 10.14], SE = 2.14, p = 0.009; d = 0.59) and the post-hoc test indicated significant improvement in the intervention group (4.26, 95%CI[1.25; 7.28], SE = 1.50, p = 0.006) and no change in the control group (1.56, 95%CI[−1.52; 4.65], SE = 1.53, p = 0.31). Similarly, a significant effect was found on social functioning (7.44, 95%CI[4.07; 10.82], SE = 1.68, p < 0.0001; d = 0.76) and post-hoc test indicated significant improvement of social functioning in the intervention group (4.13, 95%CI[1.76; 6.49], SE = 1.18; p = 0.001) and a deterioration in the control group (−3.32, 95%CI[−5.72; −0.92], SE = 1.19; p = 0.008).

Regarding the psychiatric symptoms, a significant reduction of negative symptoms was noted following the exercise intervention (−3.89, 95%CI[−6.50; −1.29], SE = 1.29, p = 0.004; d = −0.48). Post-hoc test indicated a significant decrease of negative symptoms in the intervention group (−2.69, 95%CI[−4.47; −0.92], SE = 0.88, p = 0.004) and no change in the control group (1.19, 95%CI[−0.71; 3.10], SE = 0.95, p = 0.21).

No other effects of HIIT were found on other physical characteristics, blood profile parameters, positive symptoms and general psychopathology, quality of life or self-esteem (Table 2).

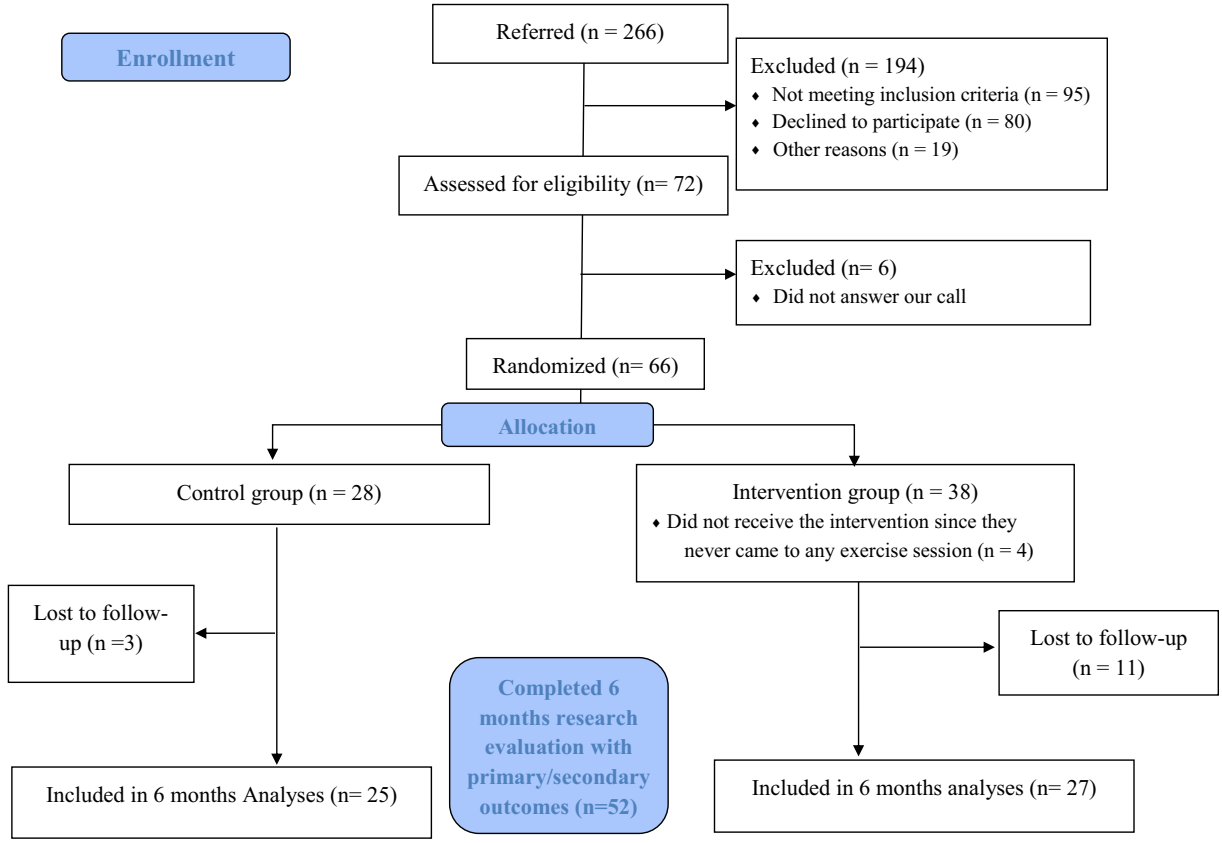

Fig. 1. Flowchart of the study.

4.4. Efficacy of HIIT: effects of the intervention in compliant participants only (>64% of sessions)

Twenty-one out of the 38 participants (55.2%) in the intervention group completed >64% of the prescribed exercise sessions. Compared to participants who did not achieve 64% (n = 17), compliant participants had a better global (50.59 ± 8.45 vs 59.38 ± 12.80, p = 0.02) and social (49.71 ± 6.95 vs 61.71 ± 11.86, p = 0.001) functioning. Table 3 shows comparison of baseline characteristics between compliant and non-compliant participants. Post–hoc analyses were performed for the compliant participants only to determine HIIT efficacy.

4.4.1. Primary outcome

At the end of the 6-month training, compared to the control group, a significant reduction of waist circumference was observed (−2.94, 95% CI[−5.78; −0.09], SE = 1.41, p = 0.04; d = −0.20). Post-hoc test indicated a significant decrease of −3.17 cm (95%CI[−5.30; −1.05], SE = 1.05; p = 0.004) in the intervention group and no change in the control group (p = 0.80).

4.4.2. Secondary outcomes

Regarding the blood profile, an upwards trend was observed for HDL-C in the intervention group (0.11, 95%CI[−0.02; 0.25], SE = 0.06, p = 0.09, d = 0.38).

Compared with the control group, a significant effect was found on global functioning (5.38, 95%CI[0.78; 9.98], SE = 2.28, p = 0.02, d = 0.54) with improved functioning in the intervention group (3.84, 95% CI[0.39; 7.29], SE = 1.71; p = 0.03) and no change in the control group (p = 0.31). Similarly, a significant effect was observed in social functioning (6.16, 95%CI[2.60; 9.72], SE = 1.76, p = 0.001, d = 0.63) with an improvement in the intervention group (2.83, 95%CI[0.17; 5.49], SE = 1.31; p = 0.03) while a deterioration was observed in the control group (−3.33, 95%CI[−5.69; −0.97], SE = 1.17; p = 0.007). Also, a significant decrease in negative symptoms was found following the intervention (−3.70, 95%CI[−6.51; −0.88], SE = 1.39, p = 0.01, d = −0.46) with a significant decrease in the intervention group (−2.49, 95%CI[−4.57; −0.42], SE = 1.03; p = 0.01) and no change in the control group (p = 0.21) (Table 4).

No other significant results were observed regarding the other studied physical or blood profile characteristics, psychotic symptoms, quality of life or self-esteem (Table 4).

4.5. Adverse events

In the intervention group, adverse events were recorded in seven participants, which included back pain (n = 2), knee pain (n = 2), muscle pain (n = 1), cramps (n = 1). One participant had a minor injury (ankle sprain).

5. Discussion

Considering the available scientific evidence, physical activity should be considered as an important component in the management of metabolic complications associated with obesity in ISMI. Although HIIT has been thoroughly studied in many populations showing promising effects, few studies were available on the impact of HIIT in ISMI. The present RCT shows that a supervised 6-month HIIT program is safe and well accepted. Although no effects were found on waist circumference (the primary outcome) in the intent to treat analysis, a secondary post-hoc analysis showed a significant reduction in waist circumference (−3,17 cm) in those compliant to the program (>64% of the sessions). It improves both global and social functioning, negative symptoms and showed potential effects on body composition markers such as fat mass reduction and fat free mass augmentation. However, as reported in previous literature reviews and meta-analyses (Vancampfort et al.,

Table 1
Baseline characteristics of the ISMI population at baseline. Comparison between the 2 randomization groups (intervention vs control).

	Total sample	Control	Intervention	p value
Sociodemographics				
Gender, n (%)				0.47
Females	25 (37.9)	12 (42.9)	13 (34.2)	
Males	41 (62.1)	16 (57.1)	25 (65.8)	
Age (years)	30.73 ± 7.23	32.12 ± 7.10	29.70 ± 7.24	0.18
Smokers, n (%)	36 (55.4)	17 (63)	19 (50)	0.27
BMI (kg/m^2)	32.65 ± 5.68	33.58 ± 6.28	31.97 ± 5.17	0.26
Waist circumference (cm)	107.33 ± 13.19	110.89 ± 14.37	104.71 ± 11.75	0.06
Fat mass (%)	36.64 ± 8.44	37.32 ± 8.55	36.18 ± 8.47	0.62
Marital status, n (%)				0.17
Single	48 (72.7)	21 (75.0)	27 (71.1)	
Married/cohabitation	16 (24.2)	5 (17.9)	11 (28.9)	
Widowed/divorced	2 (3.0)	2 (7.1)	0 (0)	
Educational level (completed), n (%)				0.86
Primary school	5 (7.6)	2 (7.1)	3 (7.9)	
Secondary school	26 (39.4)	12 (42.9)	14 (36.8)	
Diploma of professional studies	5 (7.6)	3 (10.7)	2 (5.3)	
College diploma	15 (22.7)	6 (21.4)	9 (23.7)	
University diploma	15 (22.7)	5 (17.9)	10 (26.3)	
Working status, n (%)				0.29
Unemployed	38 (57.6)	14 (50)	24 (63.2)	
1–20 h/week	15 (22.7)	9 (32.1)	6 (15.8)	
>20 h/week	13 (19.7)	5 (17.9)	8 (21.1)	
Race/ethnicities, n (%)				0.49
Caucasian	43 (65.2)	16 (57.1)	27 (71.1)	
Black	8 (12.1)	4 (14.3)	4 (10.5)	
Others	15 (22.7)	8 (28.6)	7 (18.4)	
Psychiatric diagnosis, n (%)				0.85
Schizophrenia	18 (27.3)	7 (25)	11 (28.9)	
Schizo-affective disorders	20 (30.3)	8 (28.6)	12 (31.6)	
Bipolar disorders	20 (30.3)	10 (35.7)	10 (26.3)	
NOS psychosis	7 (10.6)	3 (10.7)	4 (10.5)	
MDD	1 (1.5)	0 (0)	1 (2.6)	
Early psychosis	30 (45.5)	10 (35.7)	20 (52.6)	0.17
Time since first hospitalization (years), (M ± SD)	6.57 ± 5.83	6.96 ± 6.76	6.29 ± 5.11	0.65
Medication, n (%)				
Quetiapine	24 (36.4)	11 (39.3)	13 (34.2)	0.67
Risperidone	21 (31.8)	10 (35.7)	11 (28.9)	0.56
Paliperidone	15 (22.7)	7 (25.0)	8 (21.1)	0.83
Clozapine	15 (22.7)	5 (17.9)	10 (26.3)	0.42
Olanzapine	18 (27.3)	9 (32.1)	9 (23.7)	0.45
Antidepressants	21 (31.8)	5 (17.9)	16 (42.1)	0.07
Lithium	27 (40.9)	9 (32.1)	18 (47.4)	0.21
At least two antipsychotics	34 (51.5)	18 (64.3)	16 (42.1)	0.12
Antipsychotics + mood stabilizer/antidepressant	45 (68.2)	15 (53.6)	30 (78.9)	0.055
Severity of symptoms/social functioning (M ± SD)				
Global assessment of functioning (GAF)	56.85 ± 11.06	58.75 ± 9.87	55.45 ± 11.79	0.23
Social and occupational functioning Assessment scale (SOFAS)	58.27 ± 11.01	60.89 ± 9.82	56.34 ± 11.56	0.09
PANSS - positive symptoms	11.86 ± 4.5	11.67 ± 4.15	12.0 ± 4.79	0.77
PANSS - negative symptoms	15.45 ± 7.11	15.07 ± 8.12	15.73 ± 6.37	0.72
PANSS - general psychopathology	29.80 ± 8.21	29.15 ± 7.87	30.27 ± 8.53	0.59

2016), persistence and even initiation of the prescribed exercise programs remains an important issue as 50% of the participants dropped out of the exercise program in the present study including 10% who did not even start despite reminders.

The present study corroborates results from previous non-randomized controlled studies showing that HIIT interventions can substantially reduce waist circumference (Abdel-Baki et al., 2013; Bredin et al., 2013) but has no impact on BMI, or the lipid profile in ISMI (Abdel-Baki et al., 2013; Heggelund et al., 2014) and in people with obesity (Batacan et al., 2017). Indeed previous reviews and meta-analyses on ISMI, showed that the impacts of exercise alone on anthropometric measures were null to small, and unclear on the cardiometabolic profile (Batacan et al., 2017; Firth et al., 2015; Rosenbaum et al., 2014). Finally, it should be noted that all of our participants were taking antipsychotic medication, which is known to impair the metabolic profile (De Hert et al., 2011). Whether this medication prevents the positive effects of exercise on ISMI's metabolic profile needs to be raised.

HIIT improved both global and social functioning and, reduced negative symptoms as reported in previous meta-analyses and reviews (Firth et al., 2015; Rosenbaum et al., 2014) showing that physical activity, independently of its intensity, improves negative symptoms and feelings of depression among ISMI. Interestingly, in a qualitative study, ISMI described physical activity, and more particularly HIIT, as an effective strategy to manage their symptoms or to be distracted from them (Hargreaves et al., 2017). However, even though improvement in psychiatric symptoms can be explained by distraction and other psychological effects (e.g., increased self-esteem), other mechanisms such as physiological mechanisms (e.g., effects of exercise on the HPA axis), or inflammatory mechanisms (e.g., cytokines) can be evocated (Mikkelsen et al., 2017). Nevertheless, physical activity should be considered as an effective strategy to integrate in rehabilitation programs to improve not only waist circumference but also functioning and negative symptoms in ISMI.

However, no effects were observed on self-esteem as well as in both the physical and mental components of quality of life similarly to previous research showing null to small effects on those variables in ISMI (Firth et al., 2015; Heggelund et al., 2014; Scheewe et al., 2013). It should be noted that the effects of exercise, and more particularly

Table 2
Effects of HIIT in ISMI vs ISMI on waiting list control group-Intent to treat analyses. Data are estimated marginal means (standard errors). Significant findings are in bold.

	Control (N = 28)		N	Intervention (N = 38)		N	Cohen's d	P time * group
	PRE	POST		PRE	POST			
Physical characteristics								
Weight (kg)	100.61 (3.78)	100.13 (3.49)	28	93.76 (3.25)	93.38 (3.04)	38	0.01	0.95
BMI (kg/m^2)	33.58 (1.05)	33.19 (1.04)	28	31.97 (0.901)	32.05 (0.91)	38	0.07	0.46
Waist circumference (cm)	110.89 (2.40)	110.64 (2.27)	28	104.71 (2.06)	102.79 (2.0)	38	−0.12	0.25
Fat mass (%)	36.96 (1.70)	38.29 (1.71)	23	36.41 (1.39)	35.67 (1.46)	34	−0.24	**0.09**
Fat free mass (%)	29.13 (1.02)	28.41 (1.03)	23	29.77 (0.83)	30.16 (0.86)	34	0.23	**0.07**
Heart rate (bpm)	84.93 (2.62)	80.85 (2.26)	28	85.32 (2.24)	77.81 (2.14)	38	−0.23	0.35
Systolic blood pressure (mm Hg)	112.14 (2.78)	108.19 (2.35)	28	113.63 (2.38)	110.18 (2.19)	38	0.03	0.88
Diastolic blood pressure (mm Hg)	72.18 (1.91)	65.64 (1.56)	28	69.55 (1.64)	68.32 (1.47)	38	0.52	**0.048**
Blood profile								
Total cholesterol (mmol/L)	5.04 (0.18)	4.86 (0.18)	28	4.68 (0.15)	4.58 (0.18)	37	0.08	0.69
HDL cholesterol (mmol/L)	1.27 (0.06)	1.18 (0.06)	28	1.18 (0.05)	1.2 (0.05)	37	0.28	0.09
LDL cholesterol (mmol/L)	2.88 (0.16)	2.93 (0.16)	27	2.75 (0.14)	2.67 (0.16)	36	−0.34	0.52
Triglycerides (mmol/L)	1.89 (0.21)	1.81 (0.21)	28	1.71 (0.18)	1.57 (0.20)	37	−0.06	0.82
HbA1C	0.055 (0.001)	0.053 (0.001)	27	0.053 (0.001)	0.052 (0.001)	36	0.20	0.09
ApoB (g/L)	0.94 (0.05)	0.92 (0.04)	28	0.86 (0.04)	0.89 (0.04)	36	0.18	0.42
Fasting glucose (mmol/L)	5.26 (0.10)	5.28 (0.10)	28	5.08 (0.08)	5.11 (0.09)	38	0.01	0.98
Severity of symptoms/social functioning								
Global assessment of functioning (GAF)	58.75 (2.05)	57.18 (2.01)	28	55.45 (1.76)	59.71 (1.87)	38	0.59	**0.009**
Social and occupational functioning (SOFAS)	60.89 (2.02)	57.57 (1.99)	28	56.34 (1.73)	60.47 (1.81)	38	0.76	**<0.0001**
PANSS - positive symptoms	11.56 (0.85)	11.24 (0.81)	27	12.0 (0.73)	10.85 (0.78)	37	−0.2	0.46
PANSS - negative symptoms	15.03 (1.34)	16.23 (1.06)	27	15.73 (1.15)	13.03 (0.99)	37	−0.48	**0.004**
PANSS - general psychopathology	29.05 (1.56)	26.81 (1.42)	27	30.27 (1.33)	24.87 (1.39)	37	−0.40	0.16
Psychosocial outcomes								
Quality of life - physical component	59.03 (3.74)	69.59 (4.61)	23	57.79 (3.13)	63.25 (4.07)	33	−0.26	0.33
Quality of life - mental component	68.52 (2.78)	71.63 (3.36)	23	62.29 (2.33)	66.93 (2.98)	33	0.13	0.71
Self-esteem	25.53 (0.45)	25.23 (0.52)	21	24.58 (0.36)	24.05 (0.46)	34	−0.09	0.75

HIIT, on ISMI's psychosocial markers are not well characterized. Indeed, even though a recent meta-analysis among participants with schizophrenia showed a beneficial effect of physical activity on the physical component of quality of life but not on the mental component, the overall effect size was small (Dauwan et al., 2016). Therefore, the evidence about physical activity efficacy on these markers remains weak.

In terms of feasibility, it is important to note that the global attendance rate (for all the participants randomized to the intervention group) was acceptable with a median of attendance at 77% over the 6 months of this intervention. This is close to the median of 82% (mean 68%) from our previous 3 month pilot study and is also in accordance with a previous review (Firth et al., 2015). This percentage is very similar to what was found in previous HIIT studies with shorter durations (Abdel-Baki et al., 2013; Chapman et al., 2017) and highlights that HIIT may be a feasible strategy for training among ISMI. Also, this high percentage of attendance is noteworthy because it showed that ISMI could engage in a long-term exercise training program as long as supervision is offered. Future studies may want to investigate if ISMI could maintain a long-term exercise intervention without supervision. It should be noted that for some participants many recalls by the treating team, or the exercise supervisor were necessary to insure such a compliance level and, in our study, higher compliance with the intervention was associated with increased effects of HIIT. Furthermore, effect on waist circumference was only detected among the compliant participants. Nevertheless, despite a good attendance, we found that 50% of participants from the intervention group (those with lower social functioning at baseline) dropped out the exercise intervention. This drop-out rate is higher compared to previous meta-analyses, which showed a drop-out rate of 32% (range 0–90%) in exercise interventions among ISMI (Firth et al., 2015; Vancampfort et al., 2016). It is also higher than the 36% drop-out rate from our previous pilot study, which had an identical intervention but lasted for 3 months (Abdel-Baki et al., 2013). However, previous research evaluating different types of behavioural treatment (including exercise, counseling, psychotherapy) showed that drop-out rates could be as high as 80% in people with obesity (Baillot et al., 2015; Messier et al., 2010; Moroshko et al., 2011). Moreover, Vancampfort et al. (2016) identified other factors that could lower drop-out rates in physical activity interventions in ISMI, such as exercise intensity, supervision, qualified professionals (e.g., exercise physiologists), and motivational components. Indeed, the intensity of HIIT could be difficult for some ISMI and our intervention did not comprise all of the above-mentioned components to minimize drop-outs. Moreover, only one modality of exercise (e.g., treadmill) was used during the 6-month intervention. It might be possible that participants found this solely option quite less enjoyable with time, which could have influenced their adherence. However, future studies investigating the level of enjoyment may be warranted to confirm this. Finally, in the present study, a poorer social functioning was associated with higher drop-out rates and poor social functioning is known to negatively

Table 3
Comparison on baseline characteristics between compliant (>64% of exercise sessions completed) and non-compliant participants of the intervention group. Data are means ± standard deviation unless otherwise stated. Significant findings are in bold. Notes: SOFAS: Social and Occupational Assessment of Functioning; GAF: Global Assessment of Functioning; PANSS: Positive and Negative Symptoms Scale.

	Less than 64% (n = 17)	More than 64% (n = 21)	p value
Smokers (%)	20%	25.7%	0.68
Sex (%)			0.58
Females	13.2%	21.1%	
Males	31.6%	34.2%	
Age (years)	28.95 ± 6.30	30.31 ± 8.02	0.57
Waist circumference (cm)	105.79 ± 14.03	103.82 ± 9.82	0.61
Body mass index (kg/m^2)	33.08 ± 6.21	31.06 ± 4.20	0.25
SOFAS	49.71 ± 6.95	61.71 ± 11.86	**0.001**
GAF	50.59 ± 8.45	59.38 ± 12.80	**0.02**
PANSS - positive symptoms	12.56 ± 2.89	11.57 ± 5.88	0.54
PANSS - negative symptoms	17.63 ± 4.70	14.29 ± 7.17	0.11
PANSS - general psychopathology	32.19 ± 4.96	28.81 ± 10.36	0.24
Quality of life - physical component	55.52 ± 19.93	58.71 ± 15.81	0.61
Quality of life - mental component	65.71 ± 16.97	59.49 ± 13.12	0.24

Table 4
Effects of HIIT in ISMI compliant to the exercise program (>64% of sessions completed) vs ISMI on waiting-list control group - efficacy analyses. Data are estimated marginal means (standard errors). Significant findings are in bold.

	Control (N = 28)		N	Intervention (N = 21)		N	Cohen's d	p time * group
	PRE	POST		PRE	POST			
Physical characteristics								
Weight (g)	100.61 (3.79)	100.14 (3.49)	28	90.87 (4.37)	89.55 (4.02)	21	−0.03	0.59
BMI (kg/m^2)	33.58 (1.01)	33.21 (1.02)	28	31.07 (1.17)	30.99 (1.17)	21	0.04	0.66
Waist circumference (cm)	110.89 (2.34)	110.65 (2.21)	28	103.82 (2.70)	100.65 (2.54)	21	−0.20	**0.04**
Fat mass (%)	36.96 (1.75)	38.28 (1.74)	23	36.49 (1.87)	35.67 (1.86)	20	−0.25	0.11
Fat free mass (%)	29.13 (1.03)	28.41 (1.03)	23	29.67 (1.09)	30.05 (1.09)	20	0.22	0.09
Heart rate (bpm)	84.93 (2.65)	80.80 (2.15)	28	84.24 (3.06)	75.35 (2.38)	21	−0.32	0.25
Systolic blood pressure (mm Hg)	112.14 (2.74)	108.22 (2.21)	28	111.90 (3.16)	107.92 (2.46)	21	−0.004	0.98
Diastolic blood pressure (mm Hg)	72.18 (1.88)	65.64 (1.43)	28	69.19 (2.18)	66.58 (1.58)	21	0.39	0.18
Blood profile								
Total cholesterol (mmol/L)	5.04 (0.18)	4.86 (0.19)	28	4.84 (0.21)	4.69 (0.23)	21	0.03	0.88
HDL cholesterol (mmol/L)	1.27 (0.06)	1.18 (0.06)	28	1.18 (0.07)	1.22 (0.07)	21	0.38	0.09
LDL cholesterol (mmol/L)	2.88 (0.16)	2.92 (0.17)	28	2.89 (0.19)	2.72 (0.19)	21	−0.24	0.34
Triglycerides (mmol/L)	1.89 (0.23)	1.80 (0.23)	28	1.80 (0.27)	1.64 (0.27)	21	−0.06	0.76
HbA1C	0.055 (0.001)	0.053 (0.001)	27	0.053 (0.001)	0.053 (0.001)	20	0.25	0.16
ApoB (g/L)	0.94 (0.05)	0.92 (0.04)	28	0.88 (0.06)	0.90 (0.05)	20	0.14	0.50
Fasting glucose (mmol/L)	5.26 (0.11)	5.28 (0.09)	28	5.14 (0.12)	5.12 (0.11)	21	−0.07	0.72
Severity of symptoms/social functioning								
Global assessment of functioning (GAF)	58.75 (2.07)	57.21 (1.96)	28	59.38 (2.39)	63.22 (2.23)	21	0.54	**0.023**
Social and occupational functioning (SOFAS)	60.89 (1.98)	57.56 (1.98)	28	61.71 (2.29)	64.54 (2.27)	21	0.63	**0.001**
PANSS - positive symptoms	11.55 (0.93)	11.25 (0.83)	27	11.57 (1.06)	10.55 (0.91)	21	−0.17	0.55
PANSS - negative symptoms	15.02 (1.43)	16.23 (1.07)	27	14.28 (1.64)	11.78 (1.21)	21	−0.46	**0.01**
PANSS - general psychopathology	29.03 (1.69)	26.83 (1.44)	27	28.81 (1.93)	24.11 (1.57)	21	−0.32	0.32
Psychosocial outcomes								
Quality of life - physical component	59.02 (3.65)	69.63 (4.46)	23	59.36 (4.01)	66.76 (4.61)	19	−0.16	0.56
Quality of life - mental component	68.51 (2.49)	71.54 (3.36)	23	59.73 (2.74)	67.19 (3.46)	19	0.37	0.29
Self-esteem	25.54 (0.45)	25.23 (0.48)	21	24.80 (0.47)	23.89 (0.49)	20	−0.25	0.36

impair physical activity involvement in people with schizophrenia (Ohi et al., 2018). Strategies such as adapting the exercise intervention to ISMI showing more negative symptoms and lower functioning, as well as working on improving simultaneously exercise participation and social functioning (by a multidisciplinary mental health team), should be considered.

Even though our study has several strengths, some limitations should be underlined. First, the dropout rate was 10% higher than our expectation. Therefore, this may have decreased our statistical power to detect some effects. Also, evaluators were not blind to the RCT arm and were sometimes involved in the exercise supervision, which could have introduced biases in their evaluation. Indeed, many of the significant effects, although using validated scales, relied partly on the evaluator's subjective evaluation. In addition, HIIT was compared to a non-active control group, thus, we do not know whether this method of training is superior to another type of training. Indeed, at least one study comparing HIIT and continuous training in ISMI showed no difference (Chapman et al., 2017). Finally, despite the fact that we asked the participants to not change their dietary habits, there was no measure of the participant's food intake.

In conclusion, this study indicates that HIIT seems to be well accepted in overweight individuals with psychosis. When higher exercise compliance is achieved, results show that HIIT may improve waist circumference as well as negative symptoms and social functioning. These findings highlight the necessity to develop interventions facilitating adherence to exercise. Furthermore, social functioning may be a key factor for ISMI in the retention of exercise interventions. Our results provide support to the integration of physical activity interventions in mental health settings as early as possible in the rehabilitation process in order to manage metabolic complications and improve functioning (Curtis et al., 2016; Romain, 2017). Other intervention strategies such as nutrition, medication switching and smoking cessation should all be considered in the treatment efforts of ISMI. Finally, given that this study indicates that HIIT confers similar magnitude of physical and mental health benefits from other types of exercise (Chapman et al., 2017; Romain et al., 2009; Scheewe et al., 2013), future studies should consider to role of individualized exercise training programs; whereby participants are supported to engage in personally-preferred types of fitness training with which they feel most able to adhere. Such approaches may enable inactive individuals to engage in sufficiently intense and frequent physical activity to achieve the benefits observed from many different forms of exercise.

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