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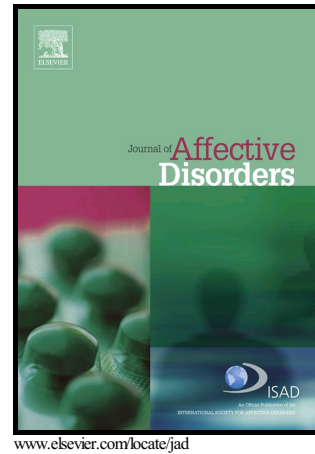
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Cardiorespiratory fitness in outpatients with bipolar disorder versus matched controls: an exploratory study

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Abstract

Background: Patients with bipolar disorder (BD) are approximately twice as likely to die prematurely due cardiovascular diseases (CVD) than the general population. Cardiorespiratory fitness (CRF) is an important health outcome measure, predictive for CVD and premature mortality.

Aims: The aim of the current study was to compare the CRF of outpatients with BD versus age-, gender-, and body mass index (BMI)-matched healthy controls (HC). A secondary aim was to assess potential correlates of CRF.

Methods: All participants underwent a maximal incremental exercise test to measure the maximum oxygen uptake ($VO_2\text{max}$, the golden standard assessment of cardiorespiratory fitness), wore a Body Sensewear Armband for 5 subsequent days to assess their physical activity behavior and completed the Positive-and-Negative-Affect-Schedule (PANAS).

Results: Outpatients with BD ($n=20$; 47.8 ± 7.6 years) had a significantly lower $VO_2\text{max}$ compared with HC ($n=20$; 47.8 ± 7.6 years) (26.0 ± 7.3 versus 30.4 ± 6.5 ml/min/kg, $P=0.047$). A higher $VO_2\text{max}$ was correlated with younger age, higher active energy expenditure, higher PANAS positive and lower PANAS negative affect scores and a lower antipsychotic medication dose.

Limitations: The limited sample and cross-sectional design preclude definitive conclusions.

Conclusions: Compared with HC, outpatients with BD have reduced CRF levels of approximately 4.4 ml/min/kg. In the general population such reductions are associated with a 20% increased premature mortality risk. Interventions targeting CRF in BD are required. Although more research is needed, clinicians should consider the utility of objective assessments of CRF for risk stratification in outpatient settings.

Keywords: fitness; physical activity; cardiovascular diseases; bipolar disorder

Introduction

Metabolic and cardiovascular diseases (CVD) have become a major concern in patients with bipolar disorder (BD) (Prieto et al., 2014; Vancampfort et al., 2015a). Patients with BD are known to have

nearly twice the normal risk of dying from CVD (Ösby et al., 2011, 2016). Genetic vulnerability (Ellingrod et al., 2012), illness-related inflammatory processes (Rosenblat et al., 2014), cardio-metabolic side-effects of pharmacotherapy (Correll et al., 2015), and lifestyle factors including a sedentary lifestyle (Janney et al., 2014), higher prevalence of substance abuse (Waxmonsky et al., 2005), and a poor diet (Bernstein et al., 2015) all contribute to the increased CVD risk.

In the general population, cardiorespiratory fitness (the ability of the circulatory and respiratory systems to supply oxygen to working muscles during sustained physical activity) is a strong and independent predictor for CVD [relative risk (RR)=1.56; 95% confidence interval (CI)=1.39-1.75; $p<0.001$] and all-cause mortality (RR=1.70; 95%CI=1.51-1.92; $P<0.001$) (Kodama et al., 2009). Also in people with severe mental illness, cardiorespiratory fitness testing has important clinical implications and can be used to help guide the prescription of exercise programs (Vancampfort et al., 2015b). Since CVD risk factors are already prevalent in the early stages of BD, even during childhood and adolescence (Goldstein et al., 2015), physical activity and cardiorespiratory fitness assessment should be initiated as early as possible, in particular since adolescents with BD participate in vigorous exercise less frequently than other adolescents (Jewell et al., 2015) and experience less improvements in energy following exercise (Subramaniapillai et al., 2016).

Previous cross-sectional research using submaximal fitness tests showed that, compared with body mass index (BMI)-, age- and gender matched healthy controls (HC), patients with BD have a reduced speed of limb movement, leg muscle strength and abdominal muscular endurance (Vancampfort et al., 2015c) and a reduced functional exercise capacity (Vancampfort et al., 2015d). Although submaximal fitness tests (i.e. tests where the maximal cardiorespiratory fitness is estimated based on, for example, the heart rate obtained) are safe, relatively easy to administer and inexpensive, they only evaluate the global and integrated responses of the cardiorespiratory, peripheral circulation and neuromuscular systems involved during submaximal exercise or functional activities (Vanhees et al., 2005). Submaximal fitness tests do not provide more specific diagnostic and prognostic information about the function of each of the different systems involved in exercise or about the mechanism of exercise limitation as is possible with maximal cardiopulmonary exercise testing (Vanhees et al., 2005). To date, data comparing cardiorespiratory fitness of patients with BD versus matched controls using maximal incremental exercise tests is absent. Although a maximal incremental exercise test is more costly, needs highly specialized equipment, requires technical

expertise to supervise and interpret the test and is more demanding for the patients, the maximal oxygen uptake (VO_{2max}) assessed with a maximal incremental exercise test is the gold-standard to assess cardiorespiratory fitness (Vanhees et al., 2005).

Given the aforementioned, the aim of the current study was to compare the VO_{2max} of patients with BD with BMI-, age- and gender-matched HC. A secondary aim was to assess potential correlates (physical activity energy expenditure, sedentary behavior, medication use, positive and negative affect) of VO_{2max} .

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Methods

Participants and procedure

Over a 10-month period, adult (18-65 years) outpatients with a DSM-5 diagnosis of BD (American Psychiatric Association, 2013) of the UPC KU Leuven campus Kortenberg in Belgium were invited to participate. Diagnoses were made by a psychiatrist using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Patients with acute psychosis at the time of testing or a co-morbid DSM-5 diagnosis of substance abuse in the previous 6 months were excluded. Somatic exclusion criteria included evidence of severe cardiovascular, neuromuscular and endocrine disorders which according to the American College of Sports Medicine (2009) might prevent safe participation in the study. Healthy control subjects were recruited among family and friends of the researchers who were blinded from the test results of the patient population. All healthy controls were volunteers who received a general physical examination in the previous year and reported to be free of significant cardiovascular, neuromuscular and endocrine disorders that might hinder safe participation. An independent statistician performed the matching for age, gender and body mass index (BMI). The study was approved by the Scientific and Ethical Committee of the UPC KU Leuven, campus Kortenberg, Belgium and conducted in accordance with the principles of the Declaration of Helsinki. All participants gave their written informed consent. Patients did not receive any compensation for study participation.

Cardiorespiratory fitness: maximal incremental exercise testing

Graded exercise tests were performed according to International accepted standards (Gibbons et al., 2002) on a cycle ergometer (Siemens-Elema 380B; Ergometrics 800S, Ergometrics, Bitz, Germany) in an air-conditioned laboratory where the room temperature was regulated at 18-22°C. Participants were asked to cycle at a constant rate of 60 revolutions per minute. The initial workload of 20W was increased by 20W every minute. Blood pressure was measured at rest before the test, with the patient sitting on the bicycle, and every 2 minutes during graded exercise. Heart rate and a 12-lead electrocardiogram (Max Personal Exercise Testing®, Marquette, WI, USA) were registered continuously. In- and expired gasses were analyzed breath-by-breath by means of the Oxycon Pro (Jaeger, Mijhardt, The Netherlands). The gas analyzers and the flow meter were calibrated before each test according to the manufacturer's instructions. VO_2 max values were defined as the 30 seconds average at the highest workload achieved. All participants were asked and encouraged to perform a symptom-limited graded exercise test until exhaustion. In order to define a maximal effect

we followed the criteria described by the European Association for Cardiovascular Prevention and Rehabilitation (Mezzani et al., 2009). A maximal effort was assumed if the cardiopulmonary exercise testing was terminated by the patient due to exhaustion, dyspnea, pain or tiredness in the legs and if (1) a peak respiratory exchange ratio (RER) ≥ 1.10 and/or (2) a rating of perceived exertion ≥ 16 on the Borg Scale (Borg, 1998).

Physical activity and sedentary behaviour: Sensewear Armband (SWA)

All participants wore a Sensewear armband (SWA) for five consecutive days, except when showering, bathing or swimming. The SWA was worn over the right arm triceps muscle and assessed minute to minute movement through multiple sensors, namely a two-axis accelerometer and sensors measuring heat flux, galvanic skin and near body-temperature. Data were combined with gender, age, body weight and height, to estimate active energy expenditure using algorithms developed by the manufacturer (SenseWear Professional software, version 7.0). As behavioral modification often occurs on the first day of monitoring (Corder et al., 2008), data recorded on the initial day were discounted entirely and only the data obtained during the subsequent 4 full days (including 2 weekdays and 2 weekend days) were used. Several variables were calculated from the SWA data. Physical activity can be expressed in metabolic equivalents (MET; in kcal/hour/kg), an indicator of daily energy expenditure. The unit MET is used to estimate the amount of oxygen used by the body during physical activity. Daily average time spend in moderate (MPA) (3-6MET) and vigorous physical activity (VPA) (≥ 6 MET) were calculated from all minutes with a MET-value (American College of Sports Medicine, 2009). Active energy expenditure (AEE; in kcal: ≥ 3 MET) was calculated based on these 2 assessments. Next to this we also assessed the time spent sedentary (≤ 1.5 MET). Data were accepted when the average on-body measuring time was at least 1368 minutes per day (95% of a 24-hour bout). The SWA has been validated in clinical (Van Remoortel et al., 2012) and non-clinical (Reece et al., 2015) populations.

Positive and negative affect

The Positive-and-Negative-Affect-Schedule (PANAS) (Watson et al., 1988) is a 20-item questionnaire assessing positive and negative affect and was chosen as a measure of daily mood. Internationally, this instrument has received empirical support in the general population for its validity (e.g., Schmukle et al., 2002).

Smoking behavior

Participants were asked whether they smoked or not, and if so, how many cigarettes they smoked per day on average during the previous week.

Anthropometric assessments

Anthropometric measurements included body weight and height. Body weight was measured in light clothing to the nearest 0.1 kg using a SECA beam balance scale, and height to the nearest 0.1 cm using a wall-mounted stadiometer.

Medication use

Data on current use of antidepressants, mood stabilizers and antipsychotics was collected by checking the medical records. Daily dosage of each antipsychotic was converted into a daily equivalent dosage of chlorpromazine following the consensus of Gardner et al. (2010). If patients were treated with a combination of antipsychotics, all obtained equivalent dosages of chlorpromazine were summed together.

Statistical analysis

Data were assessed for normality using the Shapiro-Wilk test and found to be normally distributed. Descriptive statistics are therefore presented as mean \pm standard deviation (SD). Unpaired t-tests or Mann-Whitney U tests were used, when appropriate, to examine differences in characteristics between outpatients with BD and HC. Relationships between variables were calculated using Pearson correlation coefficients. A backward regression analysis was conducted in order to determine the variance explained in VO₂max. In order to prevent overfitting we only included significant correlates from the univariate tests (and only if the variable was available for all participants) in the model. To test for multicollinearity, a variance inflation factor was computed for each independent variable in the

model. Values above 3 were used to indicate a multicollinearity problem in the model (Kleinbaum et al., 2013). A priori, a two sided level of significance was set at $P \leq 0.05$. Statistical analyses were performed using the statistical package SPSS version 23.0 (SPSS Inc., Chicago, IL).

Results

Participants

A total of 28 outpatients with BD agreed to participate in the study. Three patients with co-morbid substance abuse during the previous six months were excluded. Two more were excluded as a consequence of a cardiovascular or neuromuscular disorder that might prevent safe participation. Of the 23 eligible patients with BD, three declined to participate (i.e., were not interested anymore). None of the included patients dropped-out or were unable to complete the tests and twenty patients were included in the final analysis. Twenty HC, matched for age, BMI and gender completed the maximal incremental test, the PANAS and worn the SWA. Participants' characteristics are shown in Table 1. In both groups there were 6 men and 14 women. Two outpatients with BD smoked (10 and 20 cigarettes per day) compared to one of the HC (10 cigarettes per day). Ten patients were on antipsychotic medication (mean dose in chlorpromazine equivalents = 367 ± 217 mg/day) while nine patients took lithium carbonate (mean dose = 755 ± 292 mg/day) and eight patients were in receipt of lamotrigine (mean dose = 225 ± 128 mg/day). Five patients took antidepressants: escitalopram (n=2), venlafaxine (n=1), sertraline (n=1), trazodone (n=1). Somatic medication was taken by 9 patients. None were on beta-blockers.

[Add Table 1 about here]

Differences in clinical characteristics between outpatients with bipolar disorder and matched healthy controls

Outpatients with BD had a significantly ($P=0.047$) lower VO_2 max (26.0 ± 7.3 versus ml/min/kg) compared to HC (30.4 ± 6.5 ml/min/kg, $P=0.047$). Patients with BD also reported significantly higher Borg scores of perceived exertion during the test ($P=0.039$). While outpatients with BD were not significantly less physically active ($P=0.42$), they were more sedentary ($P=0.001$). The average on

body time of the SWA was 96.7% (range: 95.1%-99.9%) for outpatients with BD and 99.1% (96.7%-99.9%) for HC. Outpatients with BD scored significantly lower on the PANAS positive affect ($P=0.015$) score. Details are presented in Table 1.

Correlates of VO_2 max in patients with BD

Full details of the correlates with the obtained VO_2 max scores of outpatients with BD are summarized in Table 2. Briefly, higher VO_2 max score were significantly correlated with younger age, higher levels of active energy expenditure, higher PANAS positive affect and lower PANAS negative affect scores and a lower antipsychotic medication dose. There was also trend ($P=0.057$) for a lower VO_2 max in those patients taking antipsychotic medication (22.9 ± 6.9 versus 29.0 ± 6.7 ml/min/kg). Patients taking antipsychotic medication were also significantly less physically active (mean active energy expenditure= 510.6 ± 301.0 versus 791.3 ± 272.7 kcal/day) There were no other significant clinical differences between both groups. Although male patients with BD had a higher VO_2 max than female patients (28.7 ± 4.6 versus 24.7 ± 8.1 ml/min/kg), this difference was not significant ($P=0.18$).

[Add Table 2 about here]

All significant correlates which were available in all outpatients with BD (i.e. age, active energy expenditure, PANAS positive and negative affect) were included in a backward regression analysis. Within the fully adjusted VO_2 max-model, the unique significant predictors of a higher VO_2 max score were younger age and higher PANAS positive affect scores. The model explained 71.6% of the variance in the VO_2 max -score. Details of the final model are presented in Table 3.

[Add Table 3 about here]

Tolerability in outpatients with BD

Termination reason in BD was muscular soreness ($n=9$, 45%), shortness of breath ($n=2$, 10%), and physical fatigue ($n=9$, 45%). No patient with BD terminated the test due to exercise-induced rhythm abnormalities or other clinical symptoms warranting premature ending of the test.

Discussion

General findings

To the authors' knowledge, the present preliminary study is the first to compare the cardiorespiratory fitness using a maximal incremental exercise test in outpatients with BD with age, gender and BMI-matched HC. Our preliminary data suggest that outpatients with BD have a significantly reduced $VO_2\text{max}$, which is the gold-standard for assessing a person's cardiorespiratory fitness level. The mean difference in cardiorespiratory fitness is approximately $-4.4\text{ml}/\text{min}/\text{kg}$. Such a reduction is clinically important as in the general population each reduction of $3.5\text{ ml}/\text{kg}/\text{min}$ in $VO_2\text{max}$ increases the hazard ratio for premature CVD mortality with more than 20% higher while the hazard ratio for all-cause mortality increases with 15% in men and 8% in women (Nes et al., 2014).

Our data also demonstrate that next to age, higher active energy expenditure levels, lower antipsychotic medication doses, higher positive affect and lower negative affect levels might be associated with higher cardiorespiratory fitness levels. More research is however needed to explore all these possible determinants. Although the antipsychotic medication dose might be a measure-of-proxy for the presence and level of psychotic symptoms, acute psychosis at the time of the testing was an exclusion criterion. To the best of our knowledge, studies exploring the effect of antipsychotics but also of mood stabilizers on cardiorespiratory parameters is currently absent in the literature and should become a research priority. Future research should in particular explore the effect of mood symptoms on the level of cardiorespiratory fitness. A more positive affect might be associated with higher levels of self-efficacy, a more active lifestyle, more motivation to perform well, and less negative outcome expectations which on their turn might be associated with better physical fitness test performances. In the opposite way, a more negative affect might be associated with lower levels of self-efficacy, a more sedentary lifestyle, and less motivation to perform well which on their turn might be associated with worse physical fitness test performances. Outpatients with BD perceived the exercise tests as more exhausting on the Borg scale than HC. Also the low-grade inflammation associated with mood fluctuations (Leboyer et al., 2012) might be a hypothesis which should be tested more in detail. Inflammatory processes may cause pathological microvascular changes that can affect gas transfer across the alveolar-capillary membrane, which in turn may affect the circulatory, respiratory, and muscular systems involved in supplying oxygen to the body (Ostermann et al., 2012). Finally, future research should explore in more detail the role of physical activity and a sedentary lifestyle. One should note that in our exploratory analysis higher levels of sedentary behavior per day was not

associated with lower cardiorespiratory fitness levels. It might be hypothesized that the time spent actively at moderate to high intensity will most directly influence the cardiorespiratory fitness, however an increased time spent in sedentary activities is related with worsening of several cardio-metabolic functions, and might eventually also negatively influence cardiorespiratory fitness. Longitudinal and interventional studies are therefore needed to explore more rigorously the role of physical activity and a sedentary lifestyle on cardiorespiratory fitness levels in outpatients with BD. Recent meta-analyses in patients with schizophrenia (Vancampfort et al., 2015e) and major depressive disorder (Stubbs et al., 2016) clearly demonstrate that patients with severe mental illness can achieve clinically relevant improvements in cardiorespiratory fitness in response to exercise interventions.

Practical implications

Low cardiorespiratory fitness, as measured by maximal cardiorespiratory exercise testing, is a potent predictor of CVD and premature all-cause mortality (Kodama et al., 2009) and even a stronger predictor than traditional risk factors such as overweight, dyslipidemia, high blood pressure, and smoking (Myers et al., 2002). In addition, a single measurement of CRF considerably improves risk classification beyond traditional risk factors (Gupta et al., 2011). As outpatients with BD have impaired cardiorespiratory fitness levels, the objective assessment of cardiorespiratory fitness (i.e., by ventilatory gas analysis) is an appealing approach for risk stratification in outpatient settings.

Limitations

The present findings need to be interpreted with caution because of some methodological limitations. Firstly, the study is a pilot with a limited sample size and included volunteers and our results should be considered with this in mind. Moreover, due to the inclusion of volunteers our data may overestimate the cardiorespiratory fitness level in outpatients with BDs and in HC. Nevertheless, there was a good response rate in the BD group which should prevent serious distortion of the results due to selection bias. Although in the healthy controls' group SWA scores were in agreement with a large-scale Belgian general population study (Scheers et al., 2013), a selection bias in favor of healthier control volunteers cannot be excluded. Second, most outpatients were on poly-pharmacy making it impossible to investigate the role of specific medications on the cardiorespiratory fitness level. Third, we did not collect data on physical activity and sedentary behavior in the weeks prior to the testing, any physical

comorbidities nor on mental health parameters such as comorbid anxiety, motivational level and number of previous bipolar episodes. BD is uniquely characterized by instability, mood and activity fluctuations, course variability and unpredictability, ongoing symptoms and ongoing fluctuations, even during the remitted phase, disruption of circadian rhythms that may all be part of a common diathesis that may lead to a reduced ability to perform daily life activities (Frank et al., 2000). Future research in patients with BD should explore the role of these parameters, including a rigorous assessment of manic and depressive symptoms, on the cardiorespiratory fitness level. Future research should also explore the role of cardio-metabolic risk factors such as hypertension and abdominal obesity on the cardiorespiratory fitness level of people with BD. Fourth, our data are cross-sectional and cannot establish cause and effect. Nevertheless, our study is the first to establish that outpatients with BD have a reduced cardiorespiratory fitness level compared with age-, gender- and BMI-matched controls. Future larger scale research is required to replicate our study in order to establish if our results are generalizable to other populations of patients with BD in other settings and countries.

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Table 1. Comparisons in baseline characteristics between outpatients with bipolar disorder and healthy controls

Variables	Bipolar disorder	Healthy controls	P
	(n=20)	(n=20)	
Gender (men/women)	6/14	6/14	1.0
Age (years)	47.9±7.9	47.8±7.6	0.95
BMI (kg/m ²)	26.4±5.2	25.6±5.0	0.60
VO ₂ max (ml/min/kg)	26.0±7.3	30.4±6.5	0.047*
Borg score	17.2±1.1	16.3±1.5	0.039*
SWA AEE (kcal/day)	650.9±314.5	731.2±306.0	0.42
SWA sedentary time (min/day)	1062.4±136.2	898.2±161.8	0.001*
PANAS positive affect (0-50)	30.5±9.1	36.9±6.8	0.015*
PANAS negative affect (0-50)	19.9±8.1	15.4±7.4	0.072

Data expressed as mean ± standard deviation, BMI = body mass index, VO₂max= maximum oxygen uptake, SWA AEE= Sensewear armband active energy expenditure, PANAS= Positive and Negative Affect Schedule, *significant when P≤0.05.

Table 2. Associations of the maximum oxygen uptake ($VO_2\text{max}$) with demographical and clinical variables in outpatients with bipolar disorder (n=20)

Variables	Pearson's r	P
Age (years)	-0.66	0.002*
BMI (kg/m^2)	-0.64	0.002*
SWA AEE (kcal/day)	0.63	0.003*
SWA sedentary time (min/day)	-0.24	0.31
PANAS positive affect (0-50)	0.78	0.001*
PANAS negative affect (0-50)	-0.60	0.005*
Chlorpromazine equivalent (mg/day)	-0.64	0.044*

Data expressed as mean \pm standard deviation, BMI = body mass index, SWA AEE= Sensewear armband active energy expenditure, PANAS = Positive and Negative Affect Schedule, *significant when $P \leq 0.05$.

Table 3. Backward stepwise regression analysis with the maximum oxygen uptake ($VO_2\max$) as dependent variable (final model)

Variables ^o	B	SE	β	t	VIF	P
(Constant)	27.7	9.1		3.0		0.007*
Age	-0.3	0.1	-0.4	-2.4	1.3	0.024*
PANAS positive affect	0.5	0.1	0.6	4.0	1.3	0.001*

^oSignificant correlates (i.e. age, active energy expenditure, PANAS positive and negative affect and SF-36 physical and psychological subcomponents) were included in the models, B=unstandardized coefficient, SE = standard error, β =standardized coefficient, VIF = variance inflation factor, PANAS= Positive and Negative Affect Scale, *significant when $P \leq 0.05$.

Highlights

- Outpatients with bipolar disorder have a lower cardiorespiratory fitness than healthy controls.
- Maximal incremental exercise tests are safe and well tolerated by outpatients with bipolar disorder.
- Future research should explore the role of mood symptoms and antipsychotics on fitness levels.