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Research paper

# Differences in psychomotor activity and heart rate variability in patients with newly diagnosed bipolar disorder, unaffected relatives, and healthy individuals

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ABSTRACT

*Background:* Heart rate variability (HRV) and psychomotor activity have been found reduced in bipolar disorder (BD) but has never been investigated in newly diagnosed BD and unaffected relatives. The present study aimed to compare HRV and psychomotor activity between newly diagnosed patients with BD, their unaffected first-degree relatives (UR), and healthy control individuals (HC).
*Methods:* 20 newly diagnosed patients with BD, 20 of their UR, and 20 age- and sex-matched HC were included. Measurements of HRV for five minutes and heart rate and acceleration for seven days were conducted. Activity energy expenditure (AEE) was derived from the latter. Linear mixed effect regression models were conducted to compare the three groups.
*Results:* HRV did not differ in any measure between the three groups of participants. Similarly, AEE (kJ/day/kg) did not differ between the three groups in neither daily means (BD: 63.6, UR: 64.1, HC: 62.1) nor when divided into quarter-daily intervals.
*Limitations:* The relatively small size of the study may affect the validity of the results.
*Conclusion:* Patients with newly diagnosed BD and UR do not present with decreased HRV or AEE. These results contrast prior findings from BD patients with more advanced stages of the disorder, suggesting that these outcomes progress with illness duration.

## 1. Introduction

Bipolar disorder (BD) is a chronic disorder characterized by recurrent episodes of depression, (hypo)mania and mixed episodes with intervening periods of euthymia (Kessing, 2005). BD is estimated to be one of the most important causes of disability worldwide with great cost for the patients regarding overall disability, quality of life, socioeconomic status, and life expectancy (Laursen, 2011; Sajatovic, 2019). The life expectancy for patients with BD is approximately 12 years shorter than the background population, mainly on account of diseases of the cardiovascular system (Laursen, 2011). Furthermore, there is a high prevalence of misdiagnosis of patients with BD with approximately 40% of patients receiving a delayed diagnosis (Kessing, 2005; Sajatovic, 2019). A central feature in BD is abnormalities in psychomotor activity, and psychomotor retardation during depression as well as increased motor activity during mania have been described in the literature (Beigel and Murphy, 1971; Goldberg et al., 2009; Goodwin and Jamison, 1996; Judd et al., 2012; Kuhs and Reschke, 1992; Kupfer et al., 1974; Mitchell et al., 2011; Sobin and Sackeim, 1997). Moreover, psychomotor retardation has been shown to be a signature trait in BD, as it is present during euthymia and increased physical activity may decrease the risk of developing affective episodes and the risk of hospitalizations (Melo et al., 2019). Changes in the level of psychomotor activity could be a useful tool for monitoring differences between patients with BD, their unaffected first-degree relatives (UR), and healthy control individuals (HC).

Cardiovascular functioning is greatly influenced by autonomic regulation of the heart and dysfunction of the autonomic nervous system (ANS) has been associated with heart failure and sudden cardiac death (Alvares et al., 2016). Several studies have indicated dysfunction of the ANS in patients with BD (Levy, 2013; Wang et al., 2016). This displays as hyperarousal of the ANS and the hypothalamic-pituitary-adrenal axis, which increase the heart rate non-linearly (Levy, 2013). Heart rate variability (HRV) is the standard measurement of ANS

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dysfunction and is measured as variations of the instantaneous heart rate (frequency-domain analysis) or variations of the interval between consecutive heart beats (time-domain analysis) (Electrophysiology, 1996). Reduced HRV has been associated with diseases in the circulatory system such as coronary heart disease, atherosclerosis, heart failure, arrhythmias, and mortality following acute myocardial infarction (Faurholt-Jepsen et al., 2017). Our recent meta-analysis of HRV in BD showed reduced HRV regardless of affective state but with large between-study heterogeneity, highlighting a need for supporting studies (Faurholt-Jepsen et al., 2017). However, it is still unclear whether reduced HRV is a trait marker in BD being present in unaffected individuals at risk of developing BD and in the early stages of BD or whether reduced HRV is a consequence of the illness and its treatment.

The gold standard for HRV measurement is electrocardiography (e.g. Holter monitoring), but this type of monitoring can be complicated during long-term measurement and in free-living settings, which will provide more reliable data. Smaller portable heart rate monitors have been developed as a validated alternative (Kristiansen et al., 2011) with the advantage of also measuring psychomotor activity.

Measuring HRV and psychomotor activity combined can potentially be used as an objective marker when diagnosing BD, thereby reducing the diagnostic delay between first symptoms of mood episodes and the BD diagnosis (Kessing, 2005). Furthermore, HRV and physical activity could be used as a prognostic tool to characterize a subgroup of patients with BD and reduced life expectancy (Kessing et al., 2015b, 2015a). By identifying this group of patients, targeted care and treatment could potentially be provided.

### 1.1. Objectives and hypothesis

Our primary objective was to compare HRV and psychomotor activity measured for seven days in free-living settings between patients with newly diagnosed BD, their UR, and HC. We hypothesized that patients with newly diagnosed BD would have a reduced HRV compared to HC with their UR as an intermediary group.

Secondly, we hypothesized that patients with newly diagnosed BD would have psychomotor retardation as a signature trait and therefore present with more psychomotor retardation compared with HC, and again with the UR being an intermediary group.

## 2. Methods

### 2.1. Study design and setting

This cross-sectional study recruited participants already included in The Bipolar Illness Onset study (BIO, for further description see (Kessing et al., 2017)). The recruitment for the present study was done from February 2019 until June 2019 at the Copenhagen Affective Disorder research Centre (CADIC), Psychiatric Centre Copenhagen, Denmark.

### 2.2. Participants

#### 2.2.1. Patients with newly diagnosed BD

The patients were referred from the Copenhagen Affective Disorder Clinic. The clinic covers the entire Capital Region of Denmark with a catchment area of 1.6 million people and all psychiatric centers in the region (Kessing et al., 2017). Inclusion criteria for the present sub-study were being newly diagnosed with BD according to ICD-10 (Maier et al., 1990) and age between 18–55 years. The term newly diagnosed refers to newly diagnosed/first-episode patients with bipolar disorder, that is, onset of first manic or hypomanic episode or when the diagnosis of bipolar disorder is made for the first time (Kessing et al., 2017). Exclusion criterion was having an organic BD diagnosis secondary to brain injury. Patients were asked not change medication during the seven days study period.

#### 2.2.2. Unaffected first-degree relatives

UR were matched on gender and age to the patients. The UR included siblings or children to the patients. Information on the UR were gained after consent from participating patients. Inclusion criteria were being a sibling or child age 15–40 years of a participating patient of the BIO study with BD. Exclusion criteria were being diagnosed with any ICD-10 diagnosis below F34.

#### 2.2.3. Healthy controls

HC were recruited from the population of voluntary blood donors at the Blood Bank at Rigshospitalet, Copenhagen. They were matched on gender and age to the patients. Exclusion criteria were personally or a first-degree relative having a history of psychiatric illness requiring medical treatment.

### 2.3. Clinical assessments

Before being referred to the BIO-study, the patients were diagnosed with a BD diagnosis by a specialist in psychiatry at the Copenhagen Affective Disorder Clinic according to the ICD-10 (Maier et al., 1990). As part of the clinics initial diagnostic assessment, they were further categorized into BD type I or type II according to DSM-5 (Arlington, 2013). Before signing the informed consent form for the BIO study, the patients' diagnoses were validated by medical or psychology Ph.D. students using the Scale for Clinical Assessment in Neuropsychiatry (Wing et al., 1990).

At baseline, background characteristics were collected. The severity of depressive and manic symptoms for each participant was rated using Hamilton Depression Rating Scale 17-item (HDRS-17 (Hamilton, 1967)) and the Young Mania Rating Scale (YMRS (Young, 1978)). Clinical diagnosis on current affective state was given according to ICD-10. The physical activity of participants was self-reported using the International Physical Activity Questionnaire Short Form (IPAQ-SF (Lee et al., 2011)), a 9-item questionnaire that records activity by four intensity levels (vigorous-intensity, moderate-intensity, walking, and sitting) during the last seven days. From these, total volume of activity was calculated as the integrated measure of time (minutes per week) over intensity (metabolic equivalent task, MET). A systematic review has concluded that the correlation between IPAQ-SF and objective measures of activity at 0.29 were below the acceptable standard with the IPAQ-SF providing very complimentary data. (Lee et al., 2011).

### 2.4. Heart rate and activity assessment

A monitor measuring HRV and physical activity was used (Actiheart, Cambridge Neurotechnology Ltd, Papworth, UK). Validation and reliability of the monitor have been reported elsewhere for long-term HRV (Kristiansen et al., 2011) and heart rate and physical activity measurements (Brage et al., 2005). The method of estimating activity energy expenditure (AEE) from the combination of heart rate and movement monitoring has been validated to indirect calorimetry (Brage et al., 2015; Crouter et al., 2008; Thompson et al., 2006). The monitor was placed on the participants' thorax below the apex of the sternum with the wire in a horizontal line to the left. It was connected to the skin using Skintakt T-60 electrodes with micropores for long-term monitoring. The skin was prepared by using disinfecting wipes made for skin with 82% ethanol, 2% glycerol and 0,5% chlorhexidine. Participants were asked to change electrodes daily. Information on weight (kg), height (m), pulse, blood pressure, and respiratory frequency was collected for each participant.

Frequency-domain analysis can be divided into three classes: very low frequency (VLF), low frequency (LF), and high frequency (HF), where HF is suggested to reflect parasympathetic activity and LF a combination of parasympathetic and sympathetic activity

(Billman, 2013).

The monitor was used for three sets of data collection. Firstly, a short-term (five minute) recording of HRV frequency bands (LF and HF) and HRV time-domain measures (Inter-beat interval and root mean square of successive distances (RMSSD)) was made with 15 s epochs during resting state. Measurements with a quality below 90% were discarded. Secondly, an eight minute step test with a two minute cooldown was conducted. This was used for individual calibration of heart rate to energy expenditure, significantly improving model accuracies (Brage et al., 2007). Thirdly, during the seven days long-term monitoring heart rate and acceleration was set up to collect data in 30 s epoch resolution. Participants were further asked to remove the monitor when showering or swimming. Data on sleeping heart rate (SHR) and hourly AEE was calculated by the software from the collected data. Psychomotor retardation is defined as a statistical significant reduction in AEE compared to HC. Data was collected for seven days per protocol but records were included if containing a minimum of three days of valid data. When participants returned the monitor, the data quality was assessed. If data was not accepted due to too low quantity or quality, participants were asked to repeat the long-term monitoring for another seven days.

### 2.5. Statistical analysis

The statistical analyses were decided á priori. Descriptive statistics were calculated using mean (standard deviation (SD)) or median values (interquartile range [IQR]). Differences in categorical data were analyzed with chi-square test, while differences in continuous data were analyzed with *t*-test and one-way analysis of variance.

Linear mixed effect regression models were used to compare group differences in HRV and psychomotor activity with familial relationship and participants ID number as random factors and group (newly diagnosed BD, UR, HC) as a fixed factor. In this way, mixed models were chosen to account for the relationship between patients with BD and UR and participant-specific correlations.

In the primary analysis we investigated differences in HRV in the three study groups (patients with newly diagnosed BD, UR, and HC). Secondly, we investigated differences in psychomotor activity in the three study groups (patients with newly diagnosed BD, UR, and HC). Additionally, we considered models on differences in six hours intervals of the dependent variables according to the three groups (patients with newly diagnosed BD, UR, and HC). Interactions between the six hours' time intervals and group were investigated for each of the considered models and reported accordingly.

For each comparison an unadjusted analysis was first conducted. Second, a model adjusted for age and sex was conducted; third, a model adjusted for age, sex, and BMI was conducted; fourth, a model adjusted for age, sex, BMI, HDRS-17 score, and YMRS score; and fifth, a model adjusted for age, sex, BMI, HDRS-17 score, YMRS score, and use of psychotropic medication were conducted. All HRV measures were further adjusted for resting heart rate in all models. Background data was collected in Excel sheets and SPSS version 25 was used for all analyses. P-values (two-sided) below 0.007 were considered statistically significant, since adjusting analyses for multiple analyses (on the variables RMSSD, IBI, LF, HF, LF/HF, SHR and AEE) would result in the given p-level (0.05/7).

### 2.6. Ethical considerations

The BIO-study was approved by the Committee on Health Research Ethics of the Capital region of Denmark (protocol No. H-7-2014-007) and the Danish Data Protection Agency, Capital Region of Copenhagen (RHP-2015-023). The study complied with the Declaration of Helsinki principles (Seoul, October 2008). All participants were free to withdraw from the study at any time.

## 3. Results

### 3.1. Demographic and background characteristics

A total of 28 patients with BD, 27 UR, and 26 HC already included in the BIO-study were invited to participate in the present study. Of these, seven patients with BD, seven UR, and four HC did not agree to participate with the main reasons being that the study was regarded too time consuming or a fear of being monitored. Of the eligible participants, one patient with BD and two HC were excluded, as they met exclusion criteria or had an allergic reaction to the electrodes during the seven days long-term measurements before our minimum requirements were met. Thus, a total of 20 patients with BD, 20 UR, and 20 HC were included in the present study. Of the included participants, two patients with BD had one of their own UR included, and two UR had another UR in their family included in the study. Of patients with BD, five had a diagnosis of BD type I, while 15 had a diagnosis of BD type II. Mean (SD) illness duration with a diagnosis of BD was 1.5 (1.4) years. The current affective state of patients with BD was distributed between 15 patients in euthymic state, 1 patient in hypomanic state, two patients in mild to moderate depressive state, and two patients in mixed state. A total of 17 patients with BD took psychotropic medication during the seven days measurements (10: anticonvulsive medication, seven: lithium, eight: antipsychotic medication, two: antidepressant medication). Table 1 presents further demographic and clinical characteristics for all study participants. There were no differences in clinical values (respiratory frequency, heart rate or blood pressure) between the three groups. The total IPAQ-SF score of self-reported physical activity did not differ between the three groups (Mean BD: 3390.7, mean UR: 3857.4, mean HC: 3013.1, $p = 0.75$).

### 3.2. Differences in heart rate variability measures, sleeping heart rate, and activity energy expenditure between patients with newly diagnosed bipolar disorder, unaffected relatives, and healthy individuals

Differences between patients with BD, UR, and HC in heart rate variability, sleeping heart rate, and activity energy expenditure were estimated from linear mixed effect regression models. Results are

**Table 1**
Demographic and background characteristics for patients with bipolar disorder (BD), their unaffected first-degree relatives (UR), and healthy control individuals (HC).

| | BD ($n = 20$)[a] | UR ($n = 20$)[a] | HC ($n = 20$)[a] | *p*-values |
|---|---|---|---|---|
| Age (years) | 29.9 (7.8) | 27.5 (6.3) | 31.8 (8.6) | 0.22 |
| Sex (% female) | 10 (50) | 12 (60) | 11 (55) | 0.83 |
| Years of education[b] | 4.8 (2.8) | 5.9 (1.7) | 7.6 (1.3) | **<0.05** |
| HDRS[c] | 8.4 (5.2) | 1.9 (2.5) | 1.5 (1.6) | **<0.05** |
| YMRS[d] | 5.3 (5.0) | 0.75 (1.0) | 0.1 (0.3) | **<0.05** |
| Height (m) | 173.4 (9.4) | 171.8 (9.3) | 176.9 (6.5) | 0.17 |
| Weight (kg) | 78.6 (16.8) | 71.9 (11.7) | 80.9 (16.9) | 0.16 |
| BMI (kg/m$^2$) | 26.2 (5.8) | 24.3 (3.5) | 25.8 (4.9) | 0.45 |
| Systolic blood pressure (mmHg) | 120.7 (12.9) | 118.7 (9.8) | 117.8 (12.4) | 0.73 |
| Diastolic blood pressure (mmHg) | 71.2 (10.4) | 69.3 (10.1) | 69.9 (7.3) | 0.81 |
| Resting heart rate (bpm) | 65.8 (12.7) | 64.3 (11.8) | 61.6 (8.7) | 0.50 |
| Respiratory frequency (breath/min) | 15.3 (4.4) | 15.7 (3.9) | 14.1 (4.1) | 0.45 |
| Physical activity[e] (MET-minutes per week) | 3390.7 (3256.0) | 3857.4 (3722.0) | 3013.1 (3584.8) | 0.75 |

[a] Data are mean (SD) or proportions n (%) unless otherwise stated.
[b] Total years of finished education after primary school.
[c] Hamilton Depression Rating Scale score 17-items.
[d] Young Mania Rating Scale score.
[e] Self-reported using the International Physical Activity Questionnaire Short Form (IPAQ-SF).

**Table 2**
Differences in heart rate variability measures[f], sleeping heart rate (SHR), and activity energy expenditure (AEE) between patients with bipolar disorder (BD), their unaffected first-degree relatives (UR), and healthy control individuals (HC).

| | BD ($n$ = 20) | | UR ($n$ = 20) | | HC ($n$ = 20) | | BD/HC | BD/UR | UR/HC |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | 95% CI | Mean | 95% CI | Mean | 95% CI | $P$ | $p$ | $p$ |
| **Model 1**[e] | | | | | | | | | |
| RMSSD[a] (ms) | 55.8 | 46.2; 65.4 | 59.8 | 50.2; 69.4 | 48.0 | 38.4; 57.5 | 0.25 | 0.56 | 0.09 |
| IBI[b] (ms) | 970.1 | 931.6; 1008.6 | 938.2 | 899.8; 976.6 | 919.6 | 880.9; 958.3 | 0.07 | 0.25 | 0.50 |
| LF[c] ($ms^2$) | 1121.9 | 703.5; 1540.2 | 956.0 | 539.6; 1372.3 | 803.1 | 388.9; 1217.3 | 0.28 | 0.57 | 0.60 |
| HF[d] ($ms^2$) | 927.4 | 579.6; 1275.2 | 928.9 | 582.6; 1275.2 | 620.8 | 275.1; 966.5 | 0.22 | 0.99 | 0.21 |
| LF/HF (%) | 1.5 | 0.8; 2.3 | 1.2 | 0.5; 1.9 | 1.7 | 1.0; 2.5 | 0.68 | 0.54 | 0.30 |
| SHR (bpm) | 58.2 | 54.3; 62.1 | 55.5 | 51.6; 59.3 | 54.4 | 50.5; 58.3 | 0.17 | 0.33 | 0.70 |
| AEE (kJ/day/kg) | 63.6 | 53.6; 73.5 | 64.1 | 54.2; 73.9 | 62.1 | 52.3; 72.0 | 0.84 | 0.94 | 0.78 |

[a] Root mean square of successive distances.
[b] Average inter-beat interval.
[c] Low frequency heart rate variability.
[d] High frequency heart rate variability.
[e] Unadjusted.
[f] All heart rate variability measures are adjusted for resting heart rate.

presented in Table 2 from the unadjusted model 1. As can be seen, there were no differences in any HRV measure or AEE between patients with BD, UR, and HC. Model 2 adjusting for age and sex, model 3 adjusting for age, sex, and BMI, model 4 adjusting for age, sex, BMI, HDRS-17 score, and YMRS score, and model 5 adjusting for age, sex, BMI, HDRS-17 score, YMRS score, and use of psychotropic medication (lithium, anticonvulsive, antidepressant, and antipsychotic medication) did not significantly alter the results (results not presented). These results in AEE and HRV did not differ when excluding patients with BD in affective state.

### *3.3. Differences in quarter-daily intervals of activity energy expenditure between patients with newly diagnosed bipolar disorder, unaffected relatives, and healthy individuals*

Fig. 1 shows the diurnal profile of AEE (J/min/kg) which was collapsed into quarter-daily intervals (0–6 am, 6–12 am, 12–6 pm, and 6–12 pm) and compared between groups in linear mixed effect regression models. Results are presented in Table 3. from the unadjusted model 1. Results from model 2 adjusting for age and sex, a model 3 adjusting for age, sex, and BM, a model 4 adjusting for age, sex, BMI, HDRS-17 score, and YMRS score, and a model 5 adjusting for age, sex, BMI, HDRS-17 score, YMRS score, and use of psychotropic medication (lithium, anticonvulsive, antidepressant, and antipsychotic medication) did not significantly alter the pattern of findings (results not presented). There was no statistically significant difference in AEE between patients with BD, HC, and UR in any of the quarter-daily intervals.

## 4. Discussion

In this study, we compared measures of HRV and psychomotor activity between newly diagnosed patients with bipolar disorder, their unaffected first-degree relatives, and healthy control individuals. This is the first time HRV and psychomotor activity are investigated in both newly diagnosed patients with BD and UR.

Patients in the study were newly diagnosed with a median time of having a BD diagnosis of 1.5 years. The results show that HRV may not be decreased in newly diagnosed BD and UR, as we did not find reduced HRV in any time-domain or frequency-domain HRV measure. Similarly psychomotor retardation was not present in this sample of newly diagnosed patients with BD compared to HC or UR, neither in average daily AEE nor when this was divided into quarter-daily intervals.

A history of cardiovascular or respiratory diseases was not an exclusion criteria in the present study, though these diseases potentially may influence the outcomes of the study. BD is associated with obesity and cardiovascular diseases (Goldstein et al., 2011), and excluding patients with such diseases would result in a healthier subgroup of patients not representative of patients with newly diagnosed BD as a whole. Likewise, we did not exclude UR or HC with a history of or current cardiovascular or respiratory disease. Nevertheless, only three of the included patients (asthma, hypercholesterolemia) and two of the included UR (asthma) had a known cardiovascular or respiratory disease. The patients were treated with ICS/LABAs and/or SABAs, while both of the UR received ICSs and SABAs. The patient with hypercholesterolemia did not receive any medication. None of the HC had any cardiovascular or respiratory disease.

Prior studies have shown reduced HRV in patients with BD in later stages of the illness compared to HC (Bassett et al., 2016; Chang et al., 2014; Cohen et al., 2003; Henry et al., 2010; Lee et al., 2012; Levy, 2014; Moon et al., 2013; Quintana et al., 2016; Voggt et al., 2015), and a recent meta-analysis found reduced LF-HRV, but not HF-HRV and LF/HF-HRV between such patients with BD and HC (Faurholt-Jepsen et al., 2017). Similarly, the same meta-analysis found reduced HRV in time-domain measures in patients with BD in later stages, which was not reproduced in our sample of newly diagnosed BD. While our population of patients with BD mostly included BD type II, most prior studies exclusively investigated HRV in BD type I (Bassett et al., 2016; Chang et al., 2014; Cohen et al., 2003; Henry et al., 2010; Howells et al., 2014; Levy, 2014), while some did not specify the subtype of BD (Faurholt-Jepsen et al., 2016; Lee et al., 2012; Moon et al., 2013; Voggt et al., 2015). BD type II have been characterized to have more affective symptoms and overall lower functioning than BD type I (Vinberg et al., 2017), and we would therefore not expect a significant alteration of our results by including a higher percentage of BD type I. Furthermore, this study included patients with BD in different states, which possible could influence our results on HRV and AEE. However, only five patient were in an affective state, and excluding these five patients, did not significantly alter the results of neither AEE nor HRV.

BD has long been associated with psychomotor retardation during euthymia and depression (Beigel and Murphy, 1971; Goldberg et al., 2009; Goodwin and Jamison, 1996; Kuhs and Reschke, 1992; Kupfer et al., 1974; Mitchell et al., 2011; Sobin and Sackeim, 1997), which we did not find in these patients with newly diagnosed BD. Our results are in accordance with findings from a previous study comparing patients with BD with high severity illness and low severity illness assessed by factors such as number of previous psychotic episodes, affective episode recurrence, and hospitalizations, and finding lower HRV with higher severity of illness (Levy, 2014). However, additional studies investigating this subject are needed.

Using the exact same methods and procedures as in the present

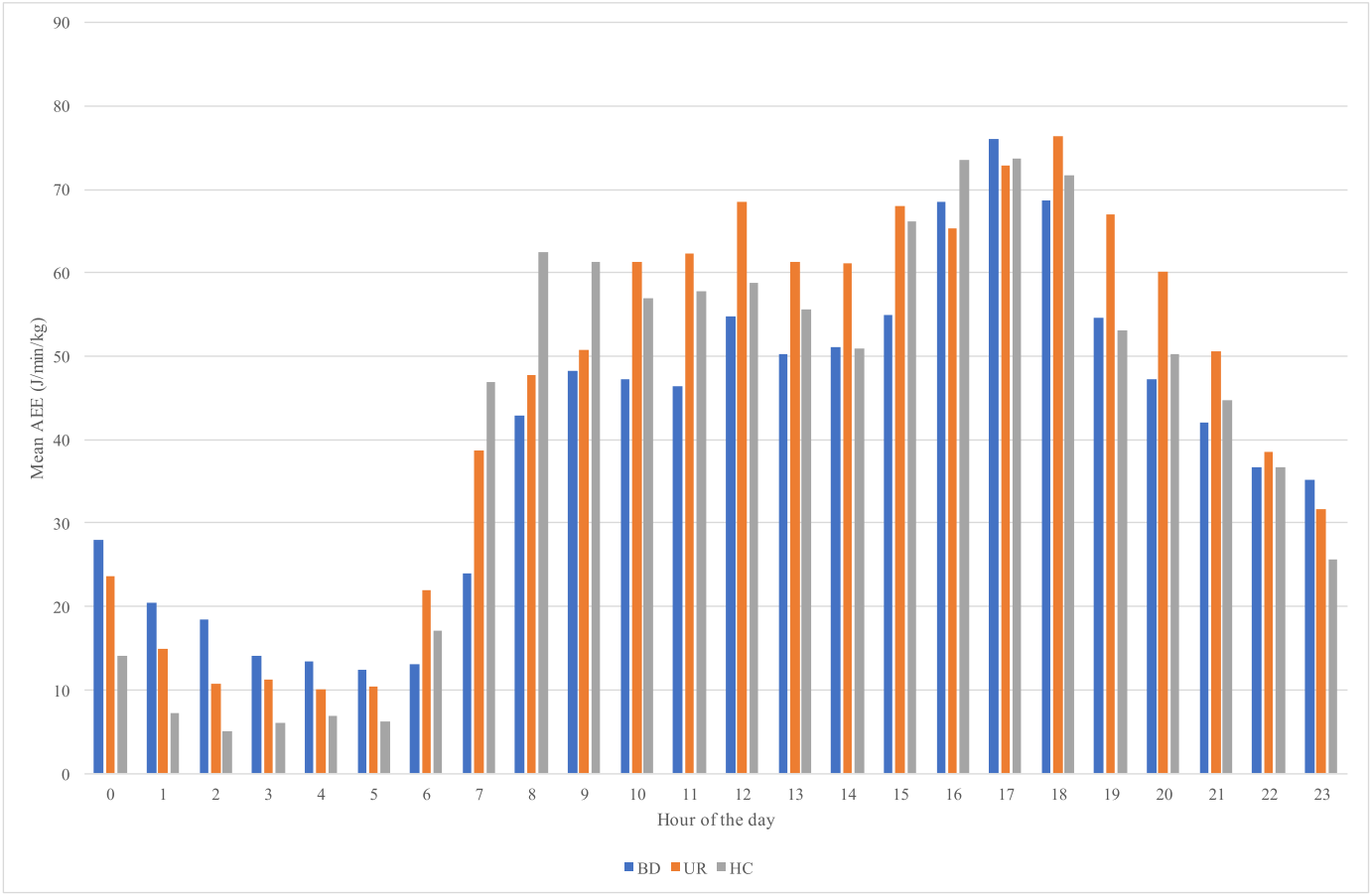


**Fig. 1.** Unadjusted mean AEE (J/min/kg) illustrated hour by hour for patients with bipolar disorder (BD), their unaffected first-degree relatives (UR), and healthy control individuals (HC).

study, we have previously found increased HRV during the manic state compared with a depressed state and the euthymic state in patients with more progressed BD (Faurholt-Jepsen et al., 2016).

### *4.1. Limitations*

There are some limitations to our study. This study has a relatively small number of participants in each group (BD = 20, UR = 20, HC = 20), which may affect the validity of the results. Since few exploratory studies have been published within the area of differences in HRV between patients with BD and HC, and none within the area of differences in HRV between patients with BD and UR, we were not able to perform power analyses prior to the study. Nevertheless, due to the small number of participants included, interpretation of the findings should be made with caution. It is possible that a larger sample with repeated measurements during follow-up period could have resulted in other findings. Further, had the study had a larger set-up with a higher number of patients, it would have made it possible to investigate HRV in different affective states or by use of different psychotropic medications.

Secondly, the control individuals in this study were recruited from volunteer blood donors. This may result in a super healthy control group, as they have the mental reserve to volunteer for blood donation and the BIO-study. Indeed, the activity level of this group did appear to be higher than observed for other healthy controls of similar age sampled from the general population (Lindsay et al., 2019). We also found, that they had a statistically significantly higher level of education. However, this volunteering group was matched on age and sex, and it was recruited from the same catchment area as the BD patients which makes it a valid control group, when considering the common challenges with identifying an appropriate control group (Grimes and Schulz, 2002).

Thirdly, recruitment of UR to the BIO-study has been difficult due to lacking consent from the patients with BD to contact their family or from the UR having major psychiatric illness themselves. As many patients did not give consent to contact their family, the UR in this study might be relatives of patients with higher levels of resources, making the included UR not entirely representative of the group as a whole.

## 5. Conclusion

Patients with newly diagnosed BD and UR do not appear to present with decreased HRV or AEE. These results contrast prior findings from BD patients with more advanced stages of the disorder, suggesting that these outcomes progress with illness duration. However, due to the small number of participants included, interpretation of the findings should be made with caution.

## Author statement

All authors have seen and approved the final version of the manuscript being submitted. This manuscript presents original material, has not been published and is not under consideration for publication elsewhere.

## CRediT authorship contribution statement

**Josefine Freyberg:** Data curation, Formal analysis, Writing - original draft. **Søren Brage:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing - review &

**Table 3**
Differences in six hours intervals per day of activity energy expenditure (AEE) between patients with bipolar disorder (BD), their unaffected first-degree relatives (UR), and healthy control individuals (HC).

| | BD ($n$ = 20) | | UR ($n$ = 20) | | HC ($n$ = 20) | | BD/HC | BD/UR | UR/HC |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | 95% CI | Mean | 95% CI | Mean | 95% CI | $p$ | $p$ | $p$ |
| **Model 1**[a] | | | | | | | | | |
| *AEE* | | | | | | | | | |
| 0–6 am (J/min/kg) | 17.7 | 10.3; 25.2 | 13.5 | 6.2; 20.8 | 7.6 | 0.4; 14.9 | 0.06 | 0.42 | 0.26 |
| 6–12 am (J/min/kg) | 37.9 | 27.9; 47.9 | 46.9 | 37.0; 56.8 | 52.3 | 42.5; 62.1 | 0.045 | 0.21 | 0.44 |
| 12–6 pm (J/min/kg) | 60.4 | 49.5; 71.2 | 67.1 | 56.3; 77.8 | 63.8 | 55.1; 74.4 | 0.65 | 0.38 | 0.67 |
| 6–12 pm (J/min/kg) | 48.3 | 36.8; 59.7 | 54.9 | 43.5; 66.2 | 47.4 | 36.2; 58.6 | 0.91 | 0.42 | 0.35 |
| **Model 2**[b] | | | | | | | | | |
| *AEE* | | | | | | | | | |
| 0–6 am (J/min/kg) | 17.9 | 10.7; 25.0 | 12.9 | 5.7; 20.1 | 9.2 | 2.2; 16.2 | 0.09 | 0.33 | 0.47 |
| 6–12 am (J/min/kg) | 38.1 | 28.0; 48.2 | 45.6 | 35.4; 55.8 | 52.7 | 42.7; 62.8 | 0.043 | 0.30 | 0.33 |
| 12–6 pm (J/min/kg) | 60.4 | 50.0; 70.8 | 66.1 | 55.5; 76.6 | 66.1 | 55.8; 76.4 | 0.44 | 0.45 | 0.99 |
| 6–12 pm (J/min/kg) | 48.2 | 38.8; 57.6 | 53.4 | 44.0; 62.9 | 51.3 | 42.1; 60.5 | 0.64 | 0.43 | 0.75 |
| **Model 3**[c] | | | | | | | | | |
| *AEE* | | | | | | | | | |
| 0–6 am (J/min/kg) | 18.2 | 11.1; 25.4 | 12.5 | 5.4; 19.7 | 9.0 | 2.0; 16.0 | 0.07 | 0.27 | 0.49 |
| 6–12 am (J/min/kg) | 38.6 | 28.5; 48.7 | 45.1 | 34.9; 55.4 | 52.5 | 42.5; 62.5 | 0.055 | 0.37 | 0.31 |
| 12–6 pm (J/min/kg) | 61.1 | 50.8; 71.5 | 65.4 | 55.0; 75.9 | 65.8 | 55.6; 76.0 | 0.52 | 0.56 | 0.96 |
| 6–12 pm (J/min/kg) | 48.7 | 39.4; 58.0 | 53.0 | 43.6; 62.4 | 51.1 | 41.9; 60.3 | 0.72 | 0.52 | 0.77 |
| **Model 4**[d] | | | | | | | | | |
| *AEE* | | | | | | | | | |
| 0–6 am (J/min/kg) | 19.4 | 9.88; 29.0 | 11.9 | 4.2; 19.6 | 8.4 | 0.6; 16.3 | 0.12 | 0.27 | 0.49 |
| 6–12 am (J/min/kg) | 38.3 | 24.8; 51.8 | 45.0 | 34.1; 56.0 | 52.8 | 41.5; 64.0 | 0.15 | 0.48 | 0.30 |
| 12–6 pm (J/min/kg) | 66.7 | 53.2; 80.3 | 63.1 | 52.1; 74.1 | 62.8 | 51.5; 74.0 | 0.69 | 0.71 | 0.97 |
| 6–12 pm (J/min/kg) | 54.9 | 42.7; 67.1 | 50.8 | 50.9; 60.6 | 47.7 | 37.7; 57.7 | 0.42 | 0.64 | 0.64 |
| **Model 5**[e] | | | | | | | | | |
| *AEE* | | | | | | | | | |
| 0–6 am (J/min/kg) | 6.2 | −8.6; 20.9 | 17.7 | 8.8; 20.6 | 14.7 | 5.3; 24.0 | 0.43 | 0.28 | 0.55 |
| 6–12 am (J/min/kg) | 25.7 | 3.4; 48.0 | 50.3 | 37.0; 63.7 | 58.6 | 44.5; 72.7 | 0.048 | 0.12 | 0.28 |
| 12–6 pm (J/min/kg) | 52.1 | 30.5; 73.7 | 69.3 | 56.3; 82.3 | 69.4 | 55.8; 83.0 | 0.28 | 0.27 | 0.99 |
| 6–12 pm (J/min/kg) | 40.2 | 21.7; 58.8 | 56.9 | 45.8; 68.1 | 54.5 | 42.8; 66.2 | 0.30 | 0.21 | 0.70 |

[a] unadjusted;.
[b] adjusted for age and sex.
[c] adjusted for age, sex and BMI.
[d] adjusted for age, sex, BMI, Hamilton Depression Rating Scale 17-items score, and Young Mania Rating Scale score.
[e] adjusted for age, sex, BMI, Hamilton Depression Rating Scale 17-items score, Young Mania Rating Scale score, and use of psychotropic medication (lithium, anticonvulsive, antidepressant, and antipsychotic medication).

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## Declaration of Competing Interest

JF, SB and MFJ declare no conflicts of interest. LVK has within recent three years been a consultant for Lundbeck.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.01.110.

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