Journal of Psychiatric Research 175 (2024) 437–445

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Cardiorespiratory fitness, perceived fitness and autonomic function in in-patients with different depression severity compared with healthy controls

Jan-Niklas Kreppke[a,*], Robyn Cody[a], Johannes Beck[b], Serge Brand[a,c,d,e,f], Lars Donath[g], Anne Eckert[c], Christian Imboden[h,i], Martin Hatzinger[j], Edith Holsboer-Trachsler[c], Undine E. Lang[c], Sarah Mans[h], Thorsten Mikoteit[j], Anja Oswald[b], Anja Rogausch[b], Nina Schweinfurth-Keck[c], Lukas Zahner[a], Markus Gerber[a], Oliver Faude[a]

[a] *Department for Sport, Exercise and Health, University of Basel, Basel, Switzerland*
[b] *Psychiatric Clinic Sonnenhalde, Riehen, Switzerland*
[c] *Adult Psychiatric Clinics (UPKE), University of Basel, Basel, Switzerland*
[d] *Substance Use Prevention Research Center and Sleep Disorder Research Center, Kermanshah University of Medical Sciences (KUMS), Kermanshah 6715847141, Iran*
[e] *School of Medicine, Tehran University of Medical Sciences (TUMS), Tehran, Iran*
[f] *Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah 6719851115, Iran*
[g] *German Sport University Cologne, Department of Intervention Research in Exercise Training, Cologne, Germany*
[h] *Private Clinic Wyss, Münchenbuchsee, Switzerland*
[i] *University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland*
[j] *Psychiatric Services, Solothurn, and Medical Faculty, University of Basel, Switzerland*

ARTICLE INFO

Keywords:
Major depressive disorder
Cardiorespiratory fitness
In-patients
Depression severity
Heart rate variability
Perceived fitness

ABSTRACT

Over 300 million individuals worldwide suffer from major depressive disorder (MDD). Individuals with MDD are less physically active than healthy people which results in lower cardiorespiratory fitness (CRF) and less favorable perceived fitness compared with healthy controls. Additionally, individuals with MDD may show autonomic system dysfunction. The purpose of the present study was to evaluate the CRF, perceived fitness and autonomic function in in-patients with MDD of different severity compared with healthy controls. We used data from 212 in-patients (age: 40.7 ± 12.6 y, 53% female) with MDD and from 141 healthy controls (age: 36.7 ± 12.7 y, 58% female). We assessed CRF with the Åstrand-Rhyming test, self-reported perceived fitness and autonomic function by heart rate variability (HRV). In specific, we used resting heart rate, time- and frequency-based parameters for HRV. In-patients completed the Beck Depression Inventory-II (BDI-II) to self-assess the subjectively rated severity of depression. Based on these scores, participants were grouped into mild, moderate and severe MDD. The main finding was an inverse association between depression severity and CRF as well as perceived fitness compared with healthy controls. Resting heart rate was elevated with increasing depression severity. The time-based but not the frequency-based autonomic function parameters showed an inverse association with depression severity. The pattern of results suggests that among in-patients with major depressive disorder, those with particularly high self-assessed severity scores show a lower CRF, less favorable perceived fitness and partial autonomic dysfunction compared to healthy controls. To counteract these conditions, physical activity interventions may be effective.

1. Background

According to the World Health Organization (WHO), over 300 million individuals worldwide (4.4% of the world's population) suffer from major depressive disorder (MDD) (World Health Organization, 2017). In addition to the acute effects of depression, such as lack of joy and pleasure, sadness or low mood, individuals with MDD are less physically active than healthy people. A meta-analysis by Schuch et al.

* Corresponding author. University of Basel, Department for Sport, Exercise and Health Grosse Allee 6, 4052, Basel, Switzerland.
E-mail address: jan-niklas.kreppke@unibas.ch (J.-N. Kreppke).

https://doi.org/10.1016/j.jpsychires.2024.05.044
Received 2 May 2023; Received in revised form 26 March 2024; Accepted 20 May 2024
Available online 21 May 2024

(2017) indicates that individuals with MDD are less likely to meet the physical activity guidelines and show higher sedentary behavior levels than healthy controls. Lower physical activity is a risk marker for lower cardiovascular health and consequently results in lower cardiorespiratory fitness (CRF) (Belvederi Murri et al., 2020). A meta-analysis by Papasavvas et al. (2016) shows a modest inverse relationship between depression severity and CRF which is slightly stronger in men compared with women. Low CRF is associated with cardiovascular events (Kodama et al., 2009), while MDD is associated with a higher cardiovascular risk (Correll et al., 2017) as well as an increased risk of non-communicable diseases (NCDs) and premature death (Carney and Freedland, 2017; Cuijpers et al., 2014; Laursen et al., 2016).

One link between MDD and cardiovascular health is the autonomic imbalance of the autonomic nervous system (ANS) (Herbsleb et al., 2020). Individuals with MDD may show a dysregulation of general homeostasis (Dhar and Barton, 2016) and an impaired function in the ANS (Correll et al., 2017; Jandackova et al., 2016; Kemp et al., 2010). A persistent autonomic imbalance is considered a risk factor for cardiovascular disease and leads to higher mortality (Thayer et al., 2010). The aforementioned imbalance in individuals with MDD is reflected by a continuous activation of the sympathetic nervous system without the normal counteraction by the parasympathetic nervous system (Stapelberg et al., 2012; Won and Kim, 2016). This depression-associated ANS dysfunction includes, for instance, elevated heart rate, exaggerated heart rate responses to physical stressors, low baroreceptor sensitivity, and low heart rate variability (HRV) (Carney et al., 2005; Kemp et al., 2010). HRV is often used to determine autonomic function and can be measured by time- and frequency-based parameters (Jandackova et al., 2016; Shaffer and Ginsberg, 2017). The time-based parameters indicate that individuals with MDD have lower parasympathetic and vagal activity. The frequency-based parameters indicate lower parasympathetic and higher sympathetic activity (Gullett et al., 2023; Herbsleb et al., 2020; Kemp et al., 2010). Nevertheless, HRV can be influenced by various factors like level of physical activity (Casanova-Lizon et al., 2022), age or body mass index (BMI) (Henje Blom et al., 2009). HRV can therefore be used alongside CRF to take a more holistic view of cardiovascular health in individuals with MDD.

In addition to objectively assessed parameters, self-reported parameters provide important information about health and well-being (Ortega et al., 2013). Perceived fitness is a reliable parameter to reflect the state of health and daily stress (Plante et al., 2000). It has been shown that individuals with lower CRF have lower perceived health and fitness levels (Eriksen et al., 2013), which makes perceived fitness an important marker of health. Poor perceived health and fitness are associated with depression and there is a higher risk to suffer from MDD with a dissatisfied self-perceived health (Hossain et al., 2020; Seo et al., 2018). Furthermore, individuals with MDD have lower CRF (Boettger et al., 2009) and less favorable perceived fitness than healthy controls (Van de Vliet et al., 2002).

Based on the background presented, it is clear that the three parameters CRF, ANS and perceived fitness can influence each other. A lower CRF is associated with impaired autonomic function (Correll et al., 2017) and poorer perceived fitness can be a marker for a lower CRF (Eriksen et al., 2013). However, it is not yet clear whether the above parameters are more strongly influenced by more severe symptoms of depression. We also do not yet know how much these parameters differ between individuals with different levels of depression symptoms and healthy individuals. Therefore, the purpose of this study was to evaluate the cardiorespiratory fitness (estimated maximal oxygen uptake; VO_2max), perceived fitness and autonomic function (resting heart rate as well as time- and frequency based HRV parameters) in in-patients with MDD with different depressive symptom severity (classified by Beck Depression Inventory-II (BDI-II) scores) compared with a healthy control group. Our hypotheses were that in-patients with more severe depression (i) will present with poorer estimated cardiorespiratory fitness (Papasavvas et al., 2016), (ii) will achieve lower scores for self-perceived fitness (Van de Vliet et al., 2002), and (iii) will have less favorable autonomic function profiles as indicated by higher resting heart rate and lower HRV (Kemp et al., 2010) always compared with healthy controls.

2. Methods

2.1. Study design

In this study, we evaluated baseline data from the multi-center two-arm randomized "Physical activity counselling in in-patients with major depressive disorders" (PACINPAT) trial. More detailed information about the PACINPAT trial has been published previously (Gerber et al., 2019). In addition to the in-patient population, we recruited an age- and gender-matched group of healthy individuals as a non-depressed control group. Recruitment and baseline assessments were finalized in October 2021. The same in-patient population was analyzed by Cody et al. (2022) with a particular focus on differences between groups with different depression severity and their psychosocial determinants of physical activity.

2.2. Participants and procedures

We recruited the in-patients from four Swiss psychiatric clinics (two private, two public) in the German speaking part of Switzerland. They were recruited between January 2019 and October 2021. For the purpose of the present study, we used data from 212 in-patients who had valid data for depression severity and data from 141 healthy controls. All in-patients had an interview with a psychiatrist at baseline to verify the inclusion criteria, which were: in-patients of both sexes; 18–65 years of age; presence of MDD based on the 10th version of the International Classification of Disease (ICD-10) diagnosis for a single episode (F32) or recurrent MDD (F33); currently not meeting the American College of Sports Medicine's (ACSM) physical activity recommendations, assessed with the International Physical Activity Questionnaire (IPAQ <150 min/week of moderate-to-vigorous physical activity) (Craig et al., 2017); written informed consent; and the ability to speak and read German. In-patients were excluded if: they had a history of bipolar disorder type I (F31 type 1); history of schizophrenia or schizoaffective disorder; current active alcohol or drug abuse/dependence; any significant medical condition that contra-indicated safe participation in physical activity; active suicidal intent; evidence of significant cardiovascular, neuromuscular, or endocrine disorders limiting regular physical activity as per ACSM absolute contra-indications to exercise or medical contra-indications to physical activity by the Physical Activity Readiness Questionnaire (PAR-Q) (Thomas et al., 1992); inability to speak and read German. We performed the screening in the first week after admission to in-patient treatment. We collected written informed consent from all participants before study entry. We informed that participation in the study was voluntary and withdrawing or discontinuing was possible at any time without further obligation or potential disadvantages. Baseline data-assessment was conducted 2–3 weeks after admission to in-patient treatment.

We recruited an age- and gender-matched sample of 151 healthy individuals for the control group via newspaper and online articles, as well as word-of-mouth recommendations. Inclusion criteria for healthy controls were the same as described above for in-patients with MDD, such as insufficient physical activity. The only exception was that depression diagnosis was not allowed. Exclusion criteria for this study were a BDI-II ≥ 17, inability to speak and read German and any significant medical condition that contra-indicated safe participation in physical activity. In total, we were able to include 141 individuals in the analysis (10 individuals had to be excluded due to missing BDI-II values, or BDI-II values ≥ 17 at baseline).

Study design and procedures were in accordance with the ethical principles described in the Declaration of Helsinki. Ethical approval was obtained from the Ethikkommission Nordwest-und Zentralschweiz (EKNZ; ref. approval no. 2018–00976) and from local ethical research boards from all study sites. The intervention study was registered in the WHO trial registry (trial number ISRCTN10469580).

2.3. Measures

2.3.1. Cardiorespiratory fitness, estimated VO_2max (ml/kg/min)

We assessed CRF with the Åstrand-Rhyming indirect test of maximal oxygen uptake (Åstrand et al., 2003). This submaximal test was performed between 8.00 and 10.00 a.m. on a bicycle ergometer (Bike Forma; Technogym, Lyss, Switzerland). We used a submaximal fitness test because it allowed us to measure CRF in a time-efficient way among a great number of in-patients and healthy controls with different fitness levels (Vancampfort et al., 2014; Vanhees et al., 2005). This test has been validated for the purposes of measuring submaximal fitness in normal populations (Macsween, 2001). The pedaling frequency was set at 50 to 55 rounds per minute (rpm), and the workload was adjusted so that the heart rate was kept between 130 min^{-1} and 160 min^{-1} in participants younger than 40 years and between 120 min^{-1} and 150 min^{-1} in participants older than 40 years. We ensured that participants maintained their exercise intensity level at 13 or 14 (slightly strenuous) by means of the Borg Rating of Perceived Exertion scale (Borg, 1970). We assumed a steady state when the heart rate remained stable ($\pm$5 min^{-1}) in minutes 5 and 6 or in the directly following minute. For estimating maximal oxygen uptake, we used a formula based on the original nomogram (Cink and Thomas, 1981).

The formula is based on sex, workload, and mean steady-state value of heart rate and is corrected for weight and age (men: VO_2max = ((0.00212 * workload * 6.12 + 0.299)/(0.769 * heart rate - 48.5) *100) * 1000/weight/age correction factor; women: VO_2max = ((0.00193 * workload * 6.12 + 0.326)/(0.769 * heart rate – 56.1) *100) * 1000/ weight/age correction factor). Maximal oxygen uptake is expressed relative to body mass (ml/min/kg). Participants using beta-blockers at the time of the assessments (in-patients: n = 14, healthy controls: n = 2) were excluded from the analysis because beta-blockers decrease heart rate and VO_2max and, thus, invalidate the described procedure (Prichard, 1987; Van Baak, 1988).

2.3.2. Perceived fitness

We used a one-item proxy ordinal scaled measure to assess subjectively perceived physical fitness (Plante et al., 2000). The validity of this item as an indicator of perceived fitness has been established previously with a sample of undergraduate students and high correlations were found with the 12-item Perceived Physical Fitness scale (Plante et al., 1998). We asked participants to respond to the following item: "Overall, how would you rate your physical fitness?". Answering options range from 1 (very poor fitness) to 10 (excellent fitness). Moreover, this measure proved to be reasonably associated with objective physical fitness, perceived well-being, and sleep (Gerber et al., 2013; Plante et al., 1998) and is a simplified variant for a complex parameter.

2.3.3. Autonomic function, heart rate variability parameters

We measured heart rate for 5 min at rest in a seated position to assess resting heart rate and heart rate variability (HRV). Prior to the measurement, the participants had to sit and rest for at least 5 min. We used a Polar watch (V800; Polar Electro Oy, Kempele, Finland) with chest strap which has previously been shown to allow a valid assessment (Giles et al., 2016). Resting heart rate was determined as the mean heart rate in beats per minute (bpm) during the 5-min assessment period. HRV was calculated from the variation of R–R intervals. Recorded R − R intervals were processed and analyzed with the freely available Kubios HRV software (Version 3.5.0) (Tarvainen et al., 2014). The validity of Kubios HRV software has been demonstrated (Rajalakshmi et al., 2015) and has already been used in analyses of HRV in individuals with MDD (Kemp et al., 2012; Singh and Mitra, 2022). In the time domain, the standard deviation of normal-to-normal intervals (SDNN) and the root mean square of standard deviation (RMSSD) were examined in milliseconds (ms). Low-frequency power (LF; bandwidth 0.04–0.15 Hz) and high-frequency power (HF; bandwidth 0.15–0.4 Hz), expressed as normalized units (n.u.), as well as the LF/HF ratio were examined as frequency-based HRV parameters. Because beta-blockers decrease resting heart rate and this affects R–R intervals, we excluded participants using beta-blockers (in-patients: n = 14, healthy controls: n = 2) from the analyses of HRV parameters (Prichard, 1987; Zhang et al., 2013).

2.3.4. Major depressive disorders, self-rating

We assessed the depression severity with the Beck Depression Inventory-II (Beck et al., 1996). The BDI-II consists of 21-items (Beck et al., 1988) to assess symptoms of unipolar depression such as somatic, affective, and cognitive symptoms (Vanheule et al., 2008). The BDI-II is widely used clinically and as a research tool that is particularly useful for categorizing the severity of depression and assessing the course of depression over time (García-Batista et al., 2018; Roelofs et al., 2013; Subica et al., 2014). There are four response options for each item (from 0 to 3) reflecting increasing levels of depressive symptomatology. The BDI-II total score ranges from 0 to 63, with higher scores reflecting stronger depressive symptoms. The reliability and validity of the BDI-II have been established elsewhere (Richter et al., 1998). In the present study, we compared three groups of in-patients with mild depression (BDI-II = 0–19), moderate depression (BDI-II = 20–28) and severe depression (BDI-II = 29–63), representing recognized depression severity categories (Beck et al., 1996; von Glischinski et al., 2019).

2.4. Statistical analyses

We performed all analyses with the Jamovi software (The jamovi project, 2024). We reported descriptive statistics as means (M), standard deviations (SD), number of individuals (n) and percentage (%). In the case of data not being normally distributed, the median (Mdn) and interquartile range (IQR) are given and marked separately. We calculated the differences of all outcomes between the groups with different depression severities and healthy controls with linear regression models. We coded depression severity as a factor (healthy, mild, moderate, severe) and controlled our statistical model for the covariates sex, age, body mass index (BMI) and education status (number of years in education). Additionally, we treated depression severity as continuous BDI-II score against all outcomes across the entire sample. We assessed the effect of depression severity and calculated effect sizes for the differences between the groups (Cohen's d with 95% confidence intervals) based on the healthy populations' standard deviation. According to Cohen (1988), the following cut-off values were used: $d < 0.2$ negligible effect; $0.2 \leq d < 0.5$ small effect, $0.5 \leq d < 0.8$ medium effect, $d \geq 0.8$ large effect. Furthermore, we compared individuals with single or recurrent MDD using an ANCOVA including a post hoc test with Bonferroni correction in a subgroup analysis.

3. Results

3.1. Sample description

We present the population-describing parameters of the in-patients and the healthy control group in Table 1. Differences between the in-patients and the control group were found for age, BMI, years in education, and nationality. In addition, the in-patients' diagnoses as well as their prescribed medications are presented in Tables S1 and S2. Two participants from the healthy controls used beta-blockers, these were excluded for certain parameters as already mentioned. Otherwise, the healthy controls did not use any medication that influenced the study parameters. Recurrent depression with a current moderate episode (F33.1) was most prevalent in the in-patient sample (42 %, n = 88),

Table 1
Sample characteristics.

	Healthy control (n = 141)			Patients (n = 212)			Mild (n = 87)		Moderate (n = 74)		Severe (n = 51)	
	N	M	SD	N	M	SD	M	SD	M	SD	M	SD
Age (years)	141	36.7	14.1	212	40.7	12.6	42.3	12.9	39.9	13.0	39.1	11.4
Height (cm)	141	170.9	9.2	212	171.5	9.7	171.8	9.9	172.2	9.0	170.2	10.1
Weight (kg)	141	71.1	16.6	212	80.4	21.3	79.6	18.8	79.6	20.1	83	26.8
Body Mass Index (BMI; kg/m^2)[a]	140	24.3	5.2	211	27.1	6.2	26.9	5.9	26.7	6.2	27.9	6.6
Years of education[b]	141	15.8	3.9	210	14.4	3.3	14.8	3.6	13.9	3.0	14.6	3.2
Depression severity (BDI-II) at baseline	141	4.4	3.7	212	22.2	10.2	12.7	4.5	23.9	2.5	36.1	6.1
	N	*Mdn*	*IQR*	*N*	*Mdn*	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*	*Mdn*	*IQR*
Years of professional experience	*141*	*9*	*18*	*215*	*17*	*23.1*	*19*	*22.5*	*13.5*	*25*	*16*	*17*
Number of previous depressive episodes[c]	-	-	-	*196*	*1.5*	*3*	*1*	*2*	*2*	*2*	*2*	*3*
Age (years) at first depressive episode[d]	-	-	-	*197*	*27*	*24*	*30*	*24*	*26*	*23.5*	*27*	*23*
Number of antidepressants at baseline	*141*	*0*	*0*	*212*	*1*	*1*	*1*	*1*	*1*	*1*	*1*	*1*

	Healthy control (n = 141)		Patients (n = 212)		Mild (n = 87)		Moderate (n = 74)		Severe (n = 51)	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Sex										
Female	82	58	112	53	41	47	40	54	31	61
Male	59	42	100	47	46	53	34	46	20	39
Nationality										
Swiss	54	38	176	83	76	87	61	82	39	77
Foreign	87	62	36	17	11	13	13	18	12	24
Language										
German	120	85	185	87	80	92	64	87	41	80
Foreign	21	15	27	13	7	8	10	14	10	20
Civil status										
Single	92	65	154	73	64	74	51	69	39	77
Married/in a relationship	49	35	58	27	23	26	23	31	12	24
Children living at home										
Yes	29	21	51	24	24	28	16	22	11	22
No	112	79	161	76	63	72	58	78	40	78
Employment										
Yes	109	77	151	71	67	77	50	68	34	67
No	32	23	61	29	20	23	24	32	17	33
Income[e]										
<50′000 CHF/year	54	55	81	45	28	36	32	51	21	51
50′000 to 100′000 CHF/year	30	30	62	34	30	39	21	33	11	27
>100′000 CHF/year	15	15	39	21	20	26	10	16	9	22
Smoking status										
Smoking	29	21	85	40	40	46	24	32	21	41
Non-smoking	112	79	127	60	47	54	50	68	30	60

Notes.
N, *M*, *SD*, *Mdn* and *IQR* stands for sample size, mean, standard deviation, median and interquartile range.
[a] 1 healthy participant and 1 patient with missing values.
[b] 2 patients with missing values.
[c] 16 patients with missing values.
[d] 15 patients with missing values.
[e] 42 healthy participants and 30 patients with missing values.

followed by recurrent depression with current severe episode (F33.2; 22 %, n = 47) and moderate depressive episode (F32.1; 22 %, n = 46; Table S1). The antidepressants Trazadone (24 %, n = 51), Escitalopram (18 %, n = 39) and Vortioxetine (17 %, n = 36) were the most frequently drugs used by our participants (Table S2).

3.2. *Cardiorespiratory fitness, perceived fitness, resting heart rate and HRV in different depression severities*

The overall effects of the model show differences in perceived fitness, resting heart rate and the HRV parameter RMSSD between different depression severities and the healthy controls. The comparison of the three in-patient groups with different depression severity levels with the healthy control group as reference group are shown in Table 2 and Fig. 1, with Cohen's d as an effect size measure including the 95% confidence intervals. Severely depressed in-patients showed lower CRF (small effect), perceived fitness (large effect), RMSSD (moderate effect) and SDNN (small effect) and a higher resting heart rate (moderate effect) compared with healthy controls. The resting heart rate was higher (small to moderate effect) in each depression severity category than the resting heart rate of healthy controls. No obvious differences were detected in the frequency-based HRV parameters for low frequency, high frequency and LF/HF ratio. In addition, we found relationships that when depression severity as BDI-II increases by one point, CRF (−0.09 ml/kg/min [95% CI -0.17; −0.02]), perceived fitness (−0.05 [95% CI -0.06; −0.03]), RMSSD (−0.34 ms [95% CI -0.61; −0.06]), SDNN (−0.19 ms [95% CI -0.46; 0.09]) and high frequency (−0.12 n. u. [95% CI -0.32; 0.08]) decrease and resting heart rate (0.2 bpm [95% CI 0.08; 0.31]), low frequency (0.12 n. u. [95% CI -0.08; 0.32]) and LF/HF ratio (0.02 [95% CI -0.02; 0.06]) increase. The results of the subgroup analysis for single and recurrent MDD are presented in Table 3.

4. Discussion

4.1. *Main findings*

The main finding of this cross sectional study was the inverse association between depression severity and cardiorespiratory fitness as well

Table 2
Group comparison of healthy controls and in-patients with different depression severity.

	Healthy controls (n = 141)	Mild (*n* = 87)		Moderate (*n* = 74)		Severe (*n* = 51)		Overall effect of BDI-II severity
	M (*SD*)	*M* (*SD*)	*d* (95% *CI*)	*M* (*SD*)	*d* (95% *CI*)	*M* (*SD*)	*d* (95% *CI*)	p
Estimated VO_2max[a] (ml/kg/min)	38.2 (9.1)	34.6 (10.0)	−0.07 (−0.32; 0.18)	34.0 (9.5)	−0.09 (−0.35; 0.17)	30.6 (8.5)	−0.38 (−0.68; −0.08)	0.09
Perceived fitness[b]	4.6 (1.8)	4.1 (1.6)	−0.21 (−0.45; 0.04)	3.7 (1.6)	−0.40 (−0.66; −0.14)	2.9 (1.3)	−0.83 (−1.13; −0.54)	<0.001
HRV parameters								
Resting heart rate (bpm)	73.1 (11.9)	76.0 (12.1)	0.32 (0.02; 0.60)	79.0 (13.3)	0.51 (0.21; 0.82)	81.0 (11.7)	0.60 (0.25; 0.95)	<0.001
RMSSD (ms)	46.0 (27.8)	36 (25.1)	−0.33 (−0.63; −0.04)	44.0 (33.0)	−0.1 (−0.41; 0.21)	33.1 (29.0)	−0.63 (−0.97; −0.26)	0.004
SDNN (ms)	50.6 (26.0)	41.9 (28.2)	−0.29 (−0.61; 0.03)	47.1 (31.9)	−0.15 (−0.49; 0.18)	43.3 (34.5)	−0.40 (−0.76; −0.00)	0.15
Low frequency (n.u.)	60.0 (20.2)	57.1 (23.4)	−0.14 (−0.44; 0.16)	56.8 (21.8)	−0.1 (−0.41; 0.22)	63.1 (22.4)	0.25 (−0.10; 0.61)	0.21
High frequency (n.u.)	39.9 (20.1)	42.8 (23.3)	0.14 (−0.16; 0.45)	43.0 (21.5)	0.09 (−0.23; 0.40)	36.8 (22.3)	−0.27 (−0.61; 0.10)	0.22
LF/HF Ratio	2.8 (3.4)	3.3 (6.5)	0.09 (−0.28; 0.45)	2.4 (3.0)	−0.11 (−0.48; 0.27)	3.7 (4.4)	0.31 (−0.12; 0.74)	0.33

Notes.
[c] 5 healthy participants and 5 patients with missing values (mild: 4, moderate: 1). *M*, *SD*, *d*, 95% *CI*, *p*, *n*, ml, kg, min, bpm, ms and n.u. stand for mean, standard deviation, effect size (Cohen's *d*), 95% confidence interval, probability, sample size, milliliter, kilogram, minute, beats per minute, millisecond and normalized units.
[a] 7 healthy participants and 6 patients with missing values (mild: 2, moderate: 3, severe: 1).
[b] 1 healthy participant and 1 patient with missing value (moderate: 1).

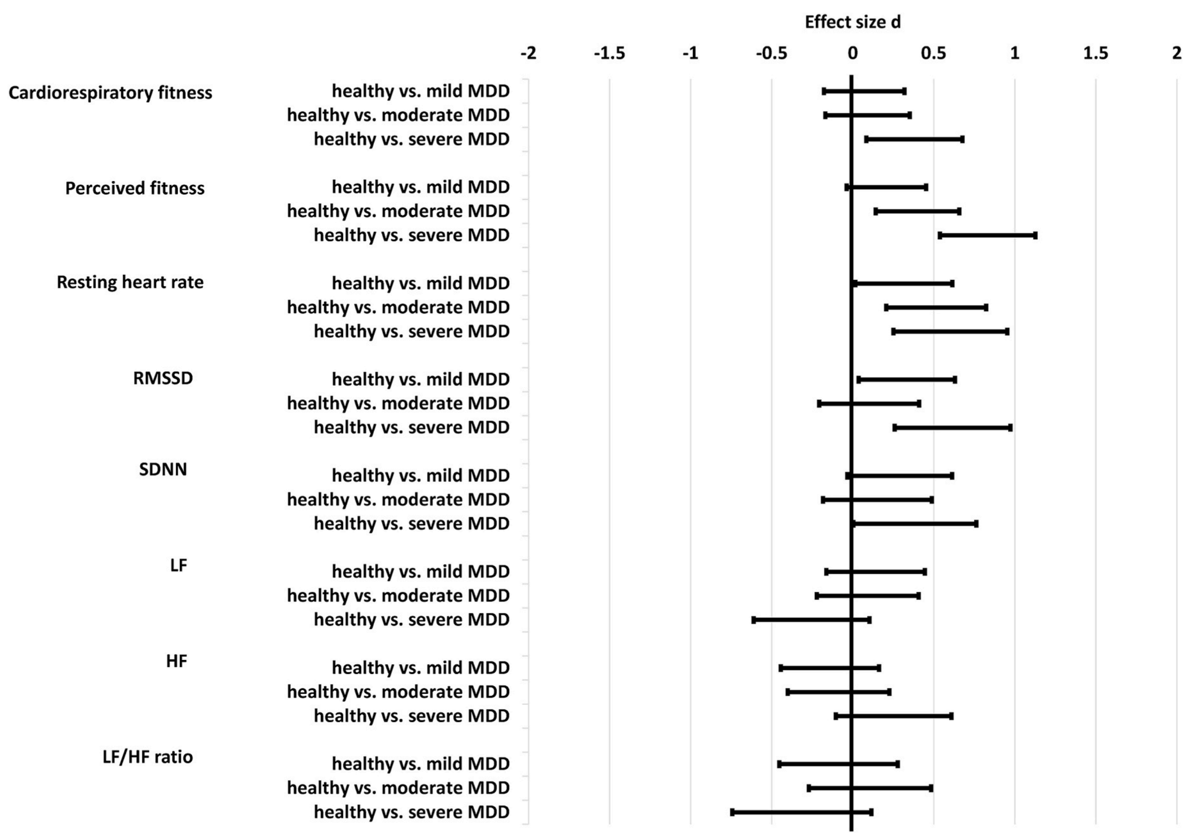

Fig. 1. Group comparison bar chart with healthy controls and patients with different depression severity
The "zero" axis represents the healthy control group. The bars show the effect sizes (Cohen's d including the 95% confidence intervals) of the groups with different depression severity compared to the healthy control group.

as perceived fitness. Furthermore, we found that resting heart rate was elevated with increasing severity of depression. Similarly, the time-based but not the frequency-based HRV parameters showed an inverse association with depression severity.

First, we hypothesized that in-patients with more severe depression would present poorer estimated CRF compared with healthy controls. The hypothesis is confirmed with the difference in cardiorespiratory fitness between the group with MDD and severe symptoms and the healthy control group. This is in agreement with findings of the meta-analysis of Papasavvas et al. (2016) with an inverse association

Table 3
Differences between in-patients with single or recurrent episodes of MDD.

	Single episode of MDD (n = 76)	Recurrent episodes of MDD (n = 136)	Effect size	Level of significance
	M (SD)	*M (SD)*	*d (95% CI)*	*P*
Depression severity (BDI-II score)	20.4 (10.3)	23.3 (10.0)	−0.34 (−0.63;-0.05)	0.02
Estimated VO_2max[a] (ml/kg/min)	34.9 (11.0)	32.9 (8.6)	0.26 (−0.04; 0.56)	0.08
Perceived fitness[b]	3.7 (1.5)	3.6 (1.7)	0.00 (−0.29; 0.29)	1.0
HRV parameters[c]				
Resting heart rate (bpm)	80.5 (14.2)	77.2 (11.4)	0.22 (−0.09; 0.52)	0.16
RMSSD (ms)	39.9 (33.7)	37.3 (26.7)	0.04 (−0.27; 0.34)	0.81
SDNN (ms)	45.3 (33.5)	43.4 (29.8)	0.00 (−0.3; 0–3)	0.99
Low frequency (n.u.)	57.3 (21.6)	59.1 (23.2)	−0.15 (−0.45; 0.16)	0.34
High frequency (n.u.)	42.4 (21.3)	40.8 (23.1)	0.14 (−0.162; 0.44)	0.36
LF/HF Ratio	2.3 (2.7)	3.5 (5.8)	−0.29 (−0.59; 0.02)	0.06

Notes.
M, *SD*, *d*, 95% *CI*, *p*, *n*, ml, kg, min, bpm, ms and n.u. stand for mean, standard deviation, effect size (Cohen's *d*), 95% confidence interval, probability, sample size, milliliter, kilogram, minute, beats per minute, millisecond and normalized units.
[a] 6 patients with missing values (single episode: 3, recurrent episodes: 3).
[b] 1 patient with missing value (recurrent episodes: 1).
[c] 5 patients with missing values (single episode: 1, recurrent episodes: 4).

between cardiorespiratory fitness and depression symptom severity. Our findings are also in line with a study by Boettger et al. (2009) who found that patients with MDD have lower peak oxygen uptake (VO_2peak) than a healthy control group matched for age, sex, BMI and weekly physical activity. In this study, the testing was done with a maximal exercise test and participants were out-patients in treatment. Similarly, a longitudinal study from Hollenberg et al. (2003) showed that women with depressive symptoms had decreased VO_2peak and a shorter test duration on a treadmill test compared with non-depressed women. Voderholzer et al. (2011) compared 51 depressed patients with a sex, age and BMI matched group of 51 healthy individuals. Depressed patients had lower performance at the individual anaerobic threshold and lower maximum power output on a bicycle ergometer test than the healthy individuals. Thus, there is convincing evidence that individuals with depression exhibit lower fitness scores compared with non-depressed controls. Our study additionally showed a gradual decline in fitness with an increase in depression severity. Therefore, it is especially important that people with MDD increase their physical activity, as physical activity is an important factor in increasing CRF (Isath et al., 2023). A higher CRF has many different health benefits (Isath et al., 2023). For example, an increase of 1 MET in exercise capacity, which stands for the maximum amount of physical exertion (Goldstein, 1990), has been shown to reduce all-cause mortality by an average of 15% (Kokkinos et al., 2009). This underscores the benefits of adequate CRF and PA in everyday life.

Second, we hypothesized that in-patients with more severe depression would achieve lower scores for self-perceived fitness compared with healthy controls. Our data confirm this hypothesis. We observed that perceived fitness decreased with increasing depression severity. In addition, as indicated by the larger effect sizes, our in-patients rated their perceived fitness worse than their actually measured cardiorespiratory fitness compared with the healthy control group. Although perceived fitness is a simple marker for estimating actual cardiorespiratory fitness (Germain and Hausenblas, 2006; Phillips et al., 2010), MDD patients usually underestimate themselves (Germain and Hausenblas, 2006). This may be due to poorer body sensation or cognitive dysfunction caused by depression (Görgülü et al., 2021; Köhler et al., 2015). With higher depression severity, there may also be a higher cognitive dysfunction, which can also have a negative effect on therapy success and treatment outcomes (Köhler et al., 2015). We have already been able to show in our data that in-patients with a higher depression severity have negative outcome expectations and lower self-efficacy (Cody et al., 2022). These assumptions are consistent with previous findings, as patients with MDD have been found to have lower self-efficacy and self-perception than healthy controls, which can negatively impact perceived fitness (Krämer et al., 2014; Van de Vliet et al., 2002). This is where we need to start, as poor physical self-perception and perceived fitness increase the risk of physical inactivity, which is, like mentioned before, a health risk factor (Inchley et al., 2011; Kohl et al., 2012). This is particularly important to consider because it is known that individuals with MDD generally exercise less than healthy controls (Schuch et al., 2017), which can have a negative impact on various health parameters (Isath et al., 2023).

Third, we hypothesized that in-patients with more severe depression would have less favorable autonomic function profiles indicated by higher resting heart rate and lower HRV compared with healthy controls. Our data conform an increased resting heart rate in in-patients with MDD as a marker of cardiovascular health (Carney and Freedland, 2017), which is also indicative of the already described lower cardiorespiratory fitness. This accords well with a systematic review, in which Zeiher et al. (2019) found an inverse correlation between cardiorespiratory fitness and resting heart rate. Moreover, an increased resting heart rate proved to be a predictor for increased cardiovascular mortality in prior research (Cook et al., 2006). Autonomic dysregulation in heart rate can also be observed in other studies after exercising, in which patients with MDD showed poorer heart rate recovery compared with healthy controls (Boettger et al., 2009). The time-based HRV parameters SDNN as well as RMSSD are lower in in-patients with MDD than in the healthy control group and more pronounced with severe depression. The lower values of SDNN show a sympathetic overdrive and parasympathetic withdrawal (Malik et al., 1996; Shaffer and Ginsberg, 2017) as well as lower RMSSD a parasympathetic withdrawal (Kleiger et al., 2005; Shaffer and Ginsberg, 2017). These impairments can also be observed in the frequency-based data, albeit not with significant deviations. In our data, HF power is slightly elevated in mild and moderate depression, but lower in cases with severe symptoms. Low HF power is associated with stress, panic, anxiety, or worry, which is consistent with the results of the severely depressed in-patients in our study (Thayer et al., 2010). According to Koch et al. (2019), LF power is also lower in individuals with depression. This applies in our study for the values of mild and moderate depression severity, but not for severe depression. This variation in LF power is also shown by Udupa et al. (2007), where LF values are higher in patients with MDD than in healthy controls. Regular physical activity is an effective way to positively influence HRV (Casanova-Lizon et al., 2022; Grässler et al., 2021). For example, three 30-min sessions of moderate to vigorous intensity can improve several HRV parameters (Casanova-Lizon et al., 2022). The meta-analysis by Chen et al. (2022) confirm that physical activity is one of several ways to improve HRV in individuals with MDD, whether in combination with antidepressants or not.

So far, it is unclear whether a lower CRF or a sympathetic overdrive together with a parasympathetic withdrawal influences depression severity or depression severity influences the mentioned parameters (Papasavvas et al., 2016). The relationship between MDD and ANS imbalances, for example, involves a complex interaction in which both could potentially influence each other. However, establishing a clear causal direction between depression and ANS imbalances is difficult due to the complexity of these interactions. Nevertheless, it is clear that there are biologically measurable symptoms between CRF or HRV as and depression severity, which are considered markers for all-cause and cardiovascular mortality (Cuijpers et al., 2014), even if the underlying biological mechanisms require further investigation.

4.2. Methodological considerations

Compared with other studies with MDD patients, a particular strength of our study is the large sample size of in-patients (Boettger et al., 2009; Görgülü et al., 2021), representing the situation during their therapy in a real-life clinical setting. This is underscored by the fact that in-patients in our study also have several comorbid psychiatric and physical diagnoses. The risk of comorbidities in MDD is increased and the number of comorbidities in individuals with MDD has risen in recent years (Arnaud et al., 2022; Walrave et al., 2022). Due to the large sample size, we were able to build three comparably large groups with different depression severity based on established norm values (von Glischinski et al., 2019). This provides the opportunity to shed light on the manifestation of the examined parameters at different levels of depression severity and allows conclusions to be drawn for therapy. With regard to the depression severity groups, it is important to note that these were formed using the BDI-II, a questionnaire focusing on affective, cognitive, and somatic symptoms of depression (Vanheule et al., 2008). The BDI-II is, however, very common and allows for good comparability clinically and for research purposes (Subica et al., 2014; von Glischinski et al., 2019). Using a different depression severity tool could have resulted in different group compositions. The included in-patients should represent a naturalistic sample as possible. Therefore, attention was paid to the main diagnosis of MDD and the in- and exclusion criteria, but previous episodes of alcohol or drug dependence or personality disorders were not recorded. These could have an influence on the reported parameters. In addition to the aforementioned inclusion and exclusion criteria, the BDI-II score was used to categorize the healthy control group. Here, short structured interviews (e.g. the mood episode module of the Structured Clinical Interview for the DSM-IV Axis I, SCID-I) could have supported the inclusion and exclusion in order to better exclude an MDD diagnosis (Regier et al., 2009).

There were major differences in nationality between in-patients and the healthy control group. They exist because in-patients were recruited in 4 clinics located in the Northwestern, German-speaking part of Switzerland. The healthy control group was recruited mainly in the area of Basel. Basel is close to the German border with a large fraction of people commuting between countries. Thus, a larger proportion of the control group was of German nationality. For this reason, we found no relevant difference in language between groups.

In order to reduce the potential influence of motivation and fatigue in testing cardiorespiratory fitness, a submaximal test was used to estimate the VO_2max. The estimation of the VO_2max by the Åstrand-Rhyming cycling test shows a good correlation with the actually measured VO_2max in validation studies (Macsween, 2001).

A limitation refers to the body position while measuring resting heart rate and HRV. The measurement was carried out in a sitting instead of a supine position (Udupa et al., 2007). With a supine position, there would have been a higher probability of relaxation and, thus, a more standardized assessment. Similarly, a longer resting time before the assessment may have resulted in more standardized resting conditions. The recording time of 5 min for the HRV parameter was rather short, as there are studies that recommend longer recordings (Shaffer et al., 2014). This type of measurement of 5 min belongs to the short-term measurements and it was shown that this method is simple to implement and has been widely used in studies for many years (Berntson et al., 1997; Nunan et al., 2010; Shaffer and Ginsberg, 2017).

The present study is of cross-sectional nature and, therefore, we cannot draw any conclusion on potential causal relationships between fitness, autonomic function and depression severity.

4.3. Conclusion and practical implications

Our study shows that in depression, and especially in severe depression, cardiorespiratory fitness is impaired. In addition to the objectively estimated VO_2max, a lower perceived fitness is present in physically less active depressed in-patients and this effect is more pronounced in in-patients with severe symptoms. Furthermore, autonomic dysregulation is present, which is evident from the higher resting heart rate and the time-domain parameters of HRV. Especially, in in-patients with severe depression, the effects are typically stronger. Physical activity can positively influence depression severity and the above-mentioned parameters, so interventions to increase physical activity may be helpful for in-patients with MDD (Sant'Ana et al., 2020; Stubbs et al., 2016). When implementing physical activity, the severity of depression should be taken into account, as there is an increased risk of poorer fitness and poorer perceived fitness with more severe symptoms. In this way, treatment can be more targeted and effective.

Declarations

Ethical approval and consent to participate

The PACINPAT trial was approved by the "Ethikkommission Nordwest-und Zentralschweiz" (EKNZ, project number 2018-00976). The PACINPAT trial has also been registered in the WHO trial register (ISRCTN10469580). Before participation in the trial, participants were informed about the goals, their right to withdraw from the study at any time without negative consequences and signed an informed consent form.

Consent for publication

Consent for the publication of the collected data was provided in the informed consent signed by the participants.

Availability of data and materials

The data and materials will be made available by the authors upon request.

Author's contributions

JB, MH, CI, UEL, SM, TM, AO, AR and NS supported the patient screening and recruitment processes on the four study sites. JNK and RC recruited the participants and collected the data. EHT, LD, AE, SB, LZ and MG offered thematic support. JNK and OF were responsible for conceptualizing the manuscript. JNK conducted the statistical analyses. JNK wrote the first draft of the manuscript with assistance of OF. All listed co-authors read, contributed to and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

The PACINPAT trial is funded by the Swiss National Science Foundation (grant number: 321003B-179353).

CRediT authorship contribution statement

Jan-Niklas Kreppke: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing. **Robyn Cody:** Conceptualization, Data curation, Investigation, Writing – review & editing. **Johannes Beck:** Investigation, Writing – review & editing. **Serge Brand:** Methodology, Writing – review & editing. **Lars Donath:** Methodology, Writing – review & editing. **Anne Eckert:** Methodology, Writing – review & editing. **Christian Imboden:** Investigation, Writing – review & editing. **Martin Hatzinger:** Investigation, Writing – review & editing. **Edith Holsboer-Trachsler:** Methodology, Writing – review & editing. **Undine E. Lang:** Investigation, Writing – review & editing. **Sarah Mans:** Investigation, Writing – review & editing. **Thorsten Mikoteit:** Investigation, Writing – review & editing. **Anja Oswald:** Investigation, Writing – review & editing. **Anja Rogausch:** Investigation, Writing – review & editing. **Nina Schweinfurth-Keck:** Investigation, Writing – review & editing. **Lukas Zahner:** Methodology, Writing – review & editing. **Markus Gerber:** Funding acquisition, Methodology, Writing – review & editing. **Oliver Faude:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no competing interests. The PACINPAT trial is funded by the Swiss National Science Foundation (grant number: 321003B-179353). The authors JB, MH, CI, UEL, SM, TM, AO, AR and NS supported the patient screening and recruitment processes on the four study sites. JNK and RC recruited the participants and collected the data. EHT, LD, AE, SB, LZ and MG offered thematic support. JNK and OF were responsible for conceptualizing the manuscript. JNK conducted the statistical analyses. JNK wrote the first draft of the manuscript with assistance of OF. All listed co-authors read, contributed to and approved the final manuscript.

Acknowledgements

Thanks go to all clinicians who supported the recruitment process and participants who were a part of the PACINPAT trial.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.05.044.

References

Arnaud, A.M., Brister, T.S., Duckworth, K., Foxworth, P., Fulwider, T., Suthoff, E.D., Werneburg, B., Aleksanderek, I., Reinhart, M.L., 2022. Impact of major depressive disorder on comorbidities: a systematic literature review. J. Clin. Psychiatr. 83 (6), 43390.
Åstrand, P.-O., Rodahl, K., Dahl, H.A., Strømme, S.B., 2003. Textbook of Work Physiology: Physiological Bases of Exercise. Human Kinetics.
Beck, A.T., Steer, R.A., Brown, G., 1996. Beck depression inventory–II. Psychol. Assess. https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft00742-000.
Beck, A.T., Steer, R.A., Carbin, M.G., 1988. Psychometric properties of the Beck depression inventory: twenty-five years of evaluation. Clin. Psychol. Rev. 8 (1), 77–100.
Belvederi Murri, M., Folesani, F., Zerbinati, L., Nanni, M.G., Ounalli, H., Caruso, R., Grassi, L., 2020. Physical activity promotes health and reduces cardiovascular mortality in depressed populations: a literature overview. Int. J. Environ. Res. Publ. Health 17 (15), 5545.
Berntson, G.G., Thomas Bigger Jr., J., Eckberg, D.L., Grossman, P., Kaufmann, P.G., Malik, M., Nagaraja, H.N., Porges, S.W., Saul, J.P., Stone, P.H., 1997. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 34 (6), 623–648.
Boettger, S., Wetzig, F., Puta, C., Donath, L., Müller, H.-J., Gabriel, H.H.W., Bär, K.-J., 2009. Physical fitness and heart rate recovery are decreased in major depressive disorder. Psychosom. Med. 71 (5), 519–523.
Borg, G., 1970. Perceived exertion as an indicator of somatic stress. Scand. J. Rehabil. Med. 2(2), 92-98.
Carney, R.M., Freedland, K.E., 2017. Depression and coronary heart disease. Nat. Rev. Cardiol. 14 (3), 145–155.
Carney, R.M., Freedland, K.E., Veith, R.C., 2005. Depression, the autonomic nervous system, and coronary heart disease. Psychosom. Med. 67 (Suppl. 1), S29–S33.
Casanova-Lizon, A., Manresa-Rocamora, A., Flatt, A.A., Sarabia, J.M., Moya-Ramon, M., 2022. Does exercise training improve cardiac-parasympathetic nervous system activity in sedentary people? A systematic review with meta-analysis. Int. J. Environ. Res. Publ. Health 19 (21) (no pagination).
Chen, S., Wang, H., Yue, J., Guan, N., Wang, X., 2022. Intervention methods for improving reduced heart rate variability in patients with major depressive disorder: a systematic review and meta-analysis. Compr. Psychiatr., 152347
Cink, R., Thomas, T., 1981. Validity of the Astrand-Ryhming nomogram for predicting maximal oxygen intake. Br. J. Sports Med. 15 (3), 182–185.
Cody, R., Beck, J., Brand, S., Donath, L., Eckert, A., Faude, O., Hatzinger, M., Holsboer-Trachsler, E., Imboden, C., Kreppke, J.-N., Lang, U., Ludyga, S., Mans, S., Mikoteit, T., Oswald, A., Pühse, U., Schweinfurth, N., Zahner, L., Gerber, M., 2022. Depression severity and psychosocial determinants of physical activity behavior in in-patients with major depressive disorders. Psychol. Sport Exerc. 63, 102294.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences {Ind Cd. Hillsdale. NJ: Erihaum.
Cook, S., Togni, M., Schaub, M.C., Wenaweser, P., Hess, O.M., 2006. High heart rate: a cardiovascular risk factor? Eur. Heart J. 27 (20), 2387–2393.
Correll, C.U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., 2017. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatr. 16 (2), 163–180.
Craig, C., Marshall, A., Sjostrom, M., Bauman, A., Lee, P., Macfarlane, D., Lam, T., Stewart, S., 2017. International physical activity questionnaire-short form. J. Am. Coll. Health 65 (7), 492–501.
Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., Penninx, B.W., 2014. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. Am. J. Psychiatr. 171 (4), 453–462.
Dhar, A.K., Barton, D.A., 2016. Depression and the link with cardiovascular disease. Front. Psychiatr. 7, 33.
Eriksen, L., Curtis, T., Grønbæk, M., Helge, J.W., Tolstrup, J.S., 2013. The association between physical activity, cardiorespiratory fitness and self-rated health. Prev. Med. 57 (6), 900–902.
García-Batista, Z.E., Guerra-Peña, K., Cano-Vindel, A., Herrera-Martínez, S.X., Medrano, L.A., 2018. Validity and reliability of the Beck depression inventory (BDI-II) in general and hospital population of Dominican republic. PLoS One 13 (6), e0199750.
Gerber, M., Beck, J., Brand, S., Cody, R., Donath, L., Eckert, A., Faude, O., Fischer, X., Hatzinger, M., Holsboer-Trachsler, E., Imboden, C., Lang, U., Mans, S., Mikoteit, T., Oswald, A., Pühse, U., Rey, S., Schreiner, A.-K., Schweinfurth, N., Spitzer, U., Zahner, L., 2019. The impact of lifestyle Physical Activity Counselling in IN-PATients with major depressive disorders on physical activity, cardiorespiratory fitness, depression, and cardiovascular health risk markers: study protocol for a randomized controlled trial. Trials 20 (1), 367.
Gerber, M., Kellmann, M., Elliot, C., Hartmann, T., Brand, S., Holsboer-Trachsler, E., Pühse, U., 2013. Perceived fitness protects against stress-based mental health impairments among police officers who report good sleep. J. Occup. Health 55 (5), 376–384.
Germain, J.L., Hausenblas, H.A., 2006. The relationship between perceived and actual physical fitness: a meta-analysis. J. Appl. Sport Psychol. 18 (4), 283–296.
Giles, D., Draper, N., Neil, W., 2016. Validity of the Polar V800 heart rate monitor to measure RR intervals at rest. Eur. J. Appl. Physiol. 116 (3), 563–571.
Goldstein, R., 1990. Exercise capacity. In: Walker, H., Hall, W., Hurst, J. (Eds.), Clinical Methods: the History, Physical, and Laboratory Examinations. Butterworths, Boston.
Görgülü, E., Bieber, M., Engeroff, T., Zabel, K., Etyemez, S., Prvulovic, D., Reif, A., Oertel, V., 2021. Physical activity, physical self-perception and depression symptoms in patients with major depressive disorder: a mediation analysis. Eur. Arch. Psychiatr. Clin. Neurosci. 271 (7), 1205–1215.
Grässler, B., Thielmann, B., Böckelmann, I., Hökelmann, A., 2021. Effects of different exercise interventions on heart rate variability and cardiovascular health factors in older adults: a systematic review. European review of aging and physical activity : official journal of the European Group for Research into Elderly and Physical Activity 18 (1), 24.
Gullett, N., Zajkowska, Z., Walsh, A., Harper, R., Mondelli, V., 2023. Heart rate variability (HRV) as a way to understand associations between the autonomic nervous system (ANS) and affective states: a critical review of the literature. Int. J. Psychophysiol. 192, 35–42.
Henje Blom, E., Olsson, E.M., Serlachius, E., Ericson, M., Ingvar, M., 2009. Heart rate variability is related to self-reported physical activity in a healthy adolescent population. Eur. J. Appl. Physiol. 106, 877–883.
Herbsleb, M., Schumann, A., Lehmann, L., Gabriel, H.H., Bär, K.-J., 2020. Cardio-respiratory fitness and autonomic function in patients with major depressive disorder. Front. Psychiatr. 10, 980.
Hollenberg, M., Haight, T., Tager, I.B., 2003. Depression decreases cardiorespiratory fitness in older women. J. Clin. Epidemiol. 56 (11), 1111–1117.
Hossain, S., Anjum, A., Hasan, M.T., Uddin, M.E., Hossain, M.S., Sikder, M.T., 2020. Self-perception of physical health conditions and its association with depression and anxiety among Bangladeshi university students. J. Affect. Disord. 263, 282–288.

Inchley, J., Kirby, J., Currie, C., 2011. Longitudinal Changes in Physical Self-Perceptions and Associations With Physical Activity During Adolescence. Pediatric Exercise Science 23 (2), 237–249.
Isath, A., Koziol, K.J., Martinez, M.W., Garber, C.E., Martinez, M.N., Emery, M.S., Baggish, A.L., Naidu, S.S., Lavie, C.J., Arena, R., Krittanawong, C., 2023. Exercise and cardiovascular health: a state-of-the-art review. Prog. Cardiovasc. Dis. 79, 44–52.
Jandackova, V.K., Britton, A., Malik, M., Steptoe, A., 2016. Heart rate variability and depressive symptoms: a cross-lagged analysis over a 10-year period in the Whitehall II study. Psychol. Med. 46 (10), 2121–2131.
Kemp, A.H., Quintana, D.S., Felmingham, K.L., Matthews, S., Jelinek, H.F., 2012. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. PLoS One 7 (2), e30777.
Kemp, A.H., Quintana, D.S., Gray, M.A., Felmingham, K.L., Brown, K., Gatt, J.M., 2010. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. Biol. Psychiatr. 67 (11), 1067–1074.
Kleiger, R.E., Stein, P.K., Bigger Jr., J.T., 2005. Heart rate variability: measurement and clinical utility. Ann. Noninvasive Electrocardiol. 10 (1), 88–101.
Koch, C., Wilhelm, M., Salzmann, S., Rief, W., Euteneuer, F., 2019. A meta-analysis of heart rate variability in major depression. Psychol. Med. 49 (12), 1948–1957.
Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., Sugawara, A., Totsuka, K., Shimano, H., Ohashi, Y., Yamada, N., Sone, H., 2009. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA 301 (19), 2024–2035.
Kohl, Craig, C.L., Lambert, E.V., Inoue, S., Alkandari, J.R., Leetongin, G., Kahlmeier, S., Group, L.P.A.S.W., 2012. The pandemic of physical inactivity: global action for public health. The Lancet 380 (9838), 294–305.
Köhler, S., Unger, T., Hoffmann, S., Mackert, A., Ross, B., Fydrich, T., 2015. Dysfunctional cognitions of depressive inpatients and their relationship with treatment outcome. Compr. Psychiatr. 58, 50–56.
Kokkinos, P., Myers, J., Doumas, M., Faselis, C., Manolis, A., Pittaras, A., Kokkinos, J.P., Singh, S., Fletcher, R.D., 2009. Exercise capacity and all-cause mortality in prehypertensive men. Am. J. Hypertens. 22 (7), 735–741.
Krämer, L.V., Helmes, A.W., Bengel, J., 2014. Understanding activity limitations in depression. Eur. Psychol. 19 (4), 278–288.
Laursen, T.M., Musliner, K.L., Benros, M.E., Vestergaard, M., Munk-Olsen, T., 2016. Mortality and life expectancy in persons with severe unipolar depression. J. Affect. Disord. 193, 203–207.
Macsween, A., 2001. The reliability and validity of the Astrand nomogram and linear extrapolation for deriving VO (2max) from submaximal exercise data. J. Sports Med. Phys. Fit. 41 (3), 312.
Malik, M., Bigger, J.T., Camm, A.J., Kleiger, R.E., Malliani, A., Moss, A.J., Schwartz, P.J., 1996. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Eur. Heart J. 17 (3), 354–381.
Nunan, D., Sandercock, G.R., Brodie, D.A., 2010. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. Pacing Clin. Electrophysiol. 33 (11), 1407–1417.
Ortega, F.B., Sánchez-López, M., Solera-Martínez, M., Fernandez-Sanchez, A., Sjöström, M., Martinez-Vizcaino, V., 2013. Self-reported and measured cardiorespiratory fitness similarly predict cardiovascular disease risk in young adults. Scand. J. Med. Sci. Sports 23 (6), 749–757.
Papasavvas, T., Bonow, R.O., Alhashemi, M., Micklewright, D., 2016. Depression symptom severity and cardiorespiratory fitness in healthy and depressed adults: a systematic review and meta-analysis. Sports Med. 46 (2), 219–230.
Phillips, A.C., Der, G., Carroll, D., 2010. Self-reported health, self-reported fitness, and all-cause mortality: prospective cohort study. Br. J. Health Psychol. 15 (2), 337–346.
Plante, T.G., Lantis, A., Checa, G., 1998. The influence of perceived versus aerobic fitness on psychological health and physiological stress responsivity. Int. J. Stress Manag. 5 (3), 141–156.
Plante, T.G., LeCaptain, S.E., McLain, H.C., 2000. Perceived fitness predicts daily coping better than physical activity. J. Appl. Biobehav. Res. 5 (1), 66–79.
Prichard, B., 1987. Pharmacologic aspects of intrinsic sympathomimetic activity in beta-blocking drugs. Am. J. Cardiol. 59 (13), F13–F17.
Rajalakshmi, R., Akila, B., Tharion, E., 2015. Intra-class correlation among heart rate variability analysis softwares across different physiological postures. Indian J. Physiol. Pharmacol. 59 (1), 2–8.
Regier, D.A., Narrow, W.E., Kuhl, E.A., Kupfer, D.J., 2009. The conceptual development of DSM-V. Am. J. Psychiatr. 166 (6), 645–650.
Richter, P., Werner, J., Heerlein, A., Kraus, A., Sauer, H., 1998. On the validity of the Beck depression inventory. Psychopathology 31 (3), 160–168.
Roelofs, J., van Breukelen, G., de Graaf, L.E., Beck, A.T., Arntz, A., Huibers, M.J.H., 2013. Norms for the Beck depression inventory (BDI-II) in a large Dutch community sample. J. Psychopathol. Behav. Assess. 35 (1), 93–98.
Sant'Ana, L.D.O., Machado, S., Ribeiro, A.A.D.S., Reis, N.R.D., Campos, Y.D.A.C., Silva, J.G.V.D., Scartoni, F.R., Brown, A.F., Monteiro, E.R., Novaes, J.D.S., Vianna, J. M., Budde, H., 2020. Effects of cardiovascular interval training in healthy elderly subjects: a systematic review. Front. Physiol. 11 no pagination).
Schuch, F., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P., Reichert, T., Bagatini, N. C., Bgeginski, R., Stubbs, B., 2017. Physical activity and sedentary behavior in people with major depressive disorder: a systematic review and meta-analysis. J. Affect. Disord. 210, 139–150.
Seo, E.H., Kim, S.-G., Kim, S.H., Kim, J.H., Park, J.H., Yoon, H.-J., 2018. Life satisfaction and happiness associated with depressive symptoms among university students: a cross-sectional study in Korea. Ann. Gen. Psychiatr. 17 (1), 52.
Shaffer, F., Ginsberg, J.P., 2017. An overview of heart rate variability metrics and norms. Front. Public Health 5, 258-258.
Shaffer, F., McCraty, R., Zerr, C.L., 2014. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. Front. Psychol. 5, 1040.
Singh, V., Mitra, S., 2022. Psychophysiological impact of spinal cord injury: depression, coping and heart rate variability. The Journal of Spinal Cord Medicine 1–9.
Stapelberg, N.J., Hamilton-Craig, I., Neumann, D.L., Shum, D.H., McConnell, H., 2012. Mind and heart: heart rate variability in major depressive disorder and coronary heart disease-a review and recommendations. Aust. N. Z. J. Psychiatr. 46 (10), 946–957.
Stubbs, B., Rosenbaum, S., Vancampfort, D., Ward, P.B., Schuch, F.B., 2016. Exercise improves cardiorespiratory fitness in people with depression: a meta-analysis of randomized control trials. J. Affect. Disord. 190, 249–253.
Subica, A.M., Fowler, J.C., Elhai, J.D., Frueh, B.C., Sharp, C., Kelly, E.L., Allen, J.G., 2014. Factor structure and diagnostic validity of the Beck Depression Inventory-II with adult clinical inpatients: comparison to a gold-standard diagnostic interview. Psychol. Assess. 26 (4), 1106–1115.
Tarvainen, M.P., Niskanen, J.-P., Lipponen, J.A., Ranta-Aho, P.O., Karjalainen, P.A., 2014. Kubios HRV–heart rate variability analysis software. Comput. Methods Progr. Biomed. 113 (1), 210–220.
Thayer, J.F., Yamamoto, S.S., Brosschot, J.F., 2010. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int. J. Cardiol. 141 (2), 122–131.
The jamovi project, 2024. Jamovi 2, 5 ed.
Thomas, S., Reading, J., Shephard, R.J., 1992. Revision of the physical activity readiness questionnaire (PAR-Q). Can. J. Sport Sci. 17 (4), 338–345.
Udupa, K., Sathyaprabha, T., Thirthalli, J., Kishore, K., Lavekar, G., Raju, T., Gangadhar, B., 2007. Alteration of cardiac autonomic functions in patients with major depression: a study using heart rate variability measures. J. Affect. Disord. 100 (1–3), 137–141.
Van Baak, M., 1988. β-adrenoceptor blockade and exercise an update. Sports Med. 5 (4), 209–225.
Van de Vliet, P., Knapen, J., Onghena, P., Fox, K., Van Coppenolle, H., David, A., Pieters, G., Peuskens, J., 2002. Assessment of physical self-perceptions in normal Flemish adults versus depressed psychiatric patients. Pers. Indiv. Differ. 32 (5), 855–863.
Vancampfort, D., Guelinckx, H., De Hert, M., Stubbs, B., Soundy, A., Rosenbaum, S., De Schepper, E., Probst, M., 2014. Reliability and clinical correlates of the Astrand–Rhyming sub-maximal exercise test in patients with schizophrenia or schizoaffective disorder. Psychiatr. Res. 220 (3), 778–783.
Vanhees, L., Lefevre, J., Philippaerts, R., Martens, M., Huygens, W., Troosters, T., Beunen, G., 2005. How to assess physical activity? How to assess physical fitness? Eur. J. Cardiovasc. Prev. Rehabil. 12 (2), 102–114.
Vanheule, S., Desmet, M., Groenvynck, H., Rosseel, Y., Fontaine, J., 2008. The factor structure of the Beck Depression Inventory-II: an evaluation. Assessment 15 (2), 177–187.
Voderholzer, U., Dersch, R., Dickhut, H., Herter, A., Freyer, T., Berger, M., 2011. Physical fitness in depressive patients and impact of illness course and disability. J. Affect. Disord. 128 (1–2), 160–164.
von Glischinski, M., von Brachel, R., Hirschfeld, G., 2019. How depressed is "depressed"? A systematic review and diagnostic meta-analysis of optimal cut points for the Beck Depression Inventory revised (BDI-II). Qual. Life Res. 28 (5), 1111–1118.
Walrave, R., Beerten, S.G., Mamouris, P., Coteur, K., Van Nuland, M., Van Pottelbergh, G., Casas, L., Vaes, B., 2022. Trends in the epidemiology of depression and comorbidities from 2000 to 2019 in Belgium. BMC Primary Care 23 (1), 163.
Won, E., Kim, Y.-K., 2016. Stress, the autonomic nervous system, and the immune-kynurenine pathway in the etiology of depression. Curr. Neuropharmacol. 14 (7), 665–673.
World Health Organization, 2017. Depression and Other Common Mental Disorders: Global Health Estimates. World Health Organization.
Zeiher, J., Ombrellaro, K.J., Perumal, N., Keil, T., Mensink, G.B.M., Finger, J.D., 2019. Correlates and determinants of cardiorespiratory fitness in adults: a systematic review. Sports Medicine - Open 5 (1), 39.
Zhang, Y., de Peuter, O.R., Kamphuisen, P.W., Karemaker, J.M., 2013. Search for HRV-parameters that detect a sympathetic shift in heart failure patients on β-blocker treatment. Front. Physiol. 4, 81.