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Heart rate vARiability and physical activity in inpatient treatMent of burnOut and DepressIon (HARMODI): protocol of a cross-sectional study with up to 8-week follow up

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ABSTRACT

Introduction Chronic stress can cause an imbalance within the autonomic nervous system, thereby affecting cardiovascular and mental health. Physical activity (PA) may have a positive effect on the autonomic nervous system and stress-related disorders, such as depression and burnout. Heart rate variability (HRV) is a non-invasive marker of the autonomic nervous system. However, limited and inconsistent data exist on the exact relationship between HRV, PA and depression and burnout symptoms. The HARMODI study aims to explore whether HRV is a feasible marker of depression and burnout symptoms and aims to evaluate the role of PA in the treatment of stress-related disorders.

Methods and analyses This is an observational study with a cross-sectional up to 8 week follow-up study design. A total of 153 patients, undergoing psychiatric inpatient treatment with burnout syndrome (Z73) and depressive episode (F32 or F33) or adjustment disorder (F43.2), will be recruited. Data on depression and burnout symptoms, HRV recordings (24-hour, supine, standing and exercise stress test), cognitive function, cardiorespiratory fitness, cardiovascular health, balance and strength will be collected at baseline (T1) and after up to 8 weeks (T2). Continuous data on PA and Ecological Momentary Assessments of exhaustion, mood and tension will be monitored daily throughout inpatient treatment. Multiple regression models, adjusted for potential confounders, will assess the association between HRV as the primary outcome, PA and depression and burnout severity score.

Ethics and dissemination The protocol has been approved by Swiss Ethics Committee, Cantonal Ethics Committee Zürich. Results of HARMODI will be disseminated through peer-reviewed journals and conference presentations.

Trial registration number NCT05874856.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This observational study aims to improve diagnosis and treatment of stress-related disorders by examining the role of heart rate variability under different recordings: 24-hour, supine, standing and exercise stress test.
⇒ While several studies have not investigated the role of physical activity in much detail, HARMODI study will monitor physical activity objectively throughout inpatient treatment.
⇒ Innovative methods, using smartphone-based Ecological Momentary Assessments of exhaustion, mood and tension, will assess symptom fluctuation throughout inpatient treatment.
⇒ This is an observational single-site study design that may limit generalisability and precludes causality.

INTRODUCTION

Stress is a major problem in society; the total cost of work-related stress in the Western World has been estimated to be up to US$187 billion per year.[1] Chronic stress can affect cardiovascular and mental health through an autonomic nervous system imbalance.[2] Generating knowledge about stress and its relationship with the autonomic nervous system is important for the diagnosis and treatment of stress-related disorders, such as depression and burnout. There is little published information on the treatment process of inpatients with stress-related disorders and international guidelines for the treatment of burnout have not been established yet.[3–6]

A non-invasive marker of the autonomic nervous system is heart rate variability (HRV), assessing the differences in time intervals between consecutive heartbeats.[7] HRV reflects the ability of the body's regulatory systems to adapt to psychological and environmental stress.[8] Extensive research has shown that HRV is not only linked to cardiovascular health,[9 10] but

also to cognitive performance,[11] emotion regulation[12] and social behaviour.[13] Thus, numerous studies have observed lower HRV in persons with depression and burnout.[14–17] To date, very few studies have investigated the association between HRV and severity of depression[18 19] and burnout.[15 20] However, other authors could not confirm an association between HRV and severity of depression.[21 22] In addition, limited[23 24] and inconsistent[25 26] findings are available on the impact of inpatient treatment on HRV and the recovery of HRV in parallel with improved clinical symptoms. The existing literature lacks clarity regarding which type of HRV recording and which HRV parameter is applicable in displaying certain symptoms of depression and burnout. Whether HRV changes after inpatient treatment of stress-related disorders remains unclear.

Physical activity (PA) in itself can also positively impact HRV[27] and is essential in the treatment of burnout and depression. On the one hand, individuals with mental illness engage in less PA and exhibit more sedentary behaviour.[28] Cardiorespiratory fitness is associated with burnout[29 30] and depression[31] severity. Furthermore, patients with depression have a higher risk to develop cardiovascular diseases.[32–36] On the other hand, PA can improve depression[37–39] and burnout symptoms.[40] Individuals with depression[41] and burnout[42] also suffer from cognitive deficits and PA has shown promising effects on cognitive function in inpatient treatment for major depression.[43 44] Nonetheless, little is known about the exact role of PA in inpatient treatment of stress-related disorders. Sports therapy is offered with varying scope as part of inpatient treatment of stress-related disorders.[45] Objective data on PA, cognitive function and physical fitness may show a potential association with HRV and symptoms of burnout and depression. New findings on HRV, PA, cognitive function, physical fitness and symptoms of burnout and depression will contribute to a deeper understanding of the role of sports therapy in inpatient treatment of stress-related disorders.

A growing body of research uses Ecological Momentary Assessments (EMA) to analyse symptom fluctuations and PA over time in real-time and real-life situations.[46] EMA is a research method to capture current state, feelings or behaviour of an individual with multiple assessments in their natural environment.[47] EMA complement retrospective self-report assessments that are frequently affected by recall bias.[48] Recently, EMA studies have demonstrated a link between PA and positive affect[49–51] and between PA and emotional exhaustion.[52] Nevertheless, our understanding of how symptoms may change over the treatment process is notably underdeveloped. To the best of our knowledge, no studies have examined EMA of psychological ratings and PA throughout inpatient treatment of stress-related disorders.

HARMODI study aims to give important insights into the tripart relationship between HRV, PA and symptoms of depression and burnout, to optimise treatment programmes and support public health policymaking. The main research questions for our three research projects are:

Project 1

Is there an association between HRV and depression severity at admission (baseline)?

Project 2

Is there a difference between HRV, cardiorespiratory fitness, PA, cardiovascular health, cognitive function, strength and balance performance at baseline (T1) and after an up to 8 week inpatient treatment of depression and burnout (T2)? Is there a difference between responders and non-responders regarding baseline HRV, cardiorespiratory fitness, PA, sleep, cognitive function, strength, balance performance and cardiovascular health?

Project 3

How do EMAs of exhaustion, mood and tension change throughout the 8 week inpatient treatment? Is there an association between PA and EMA of exhaustion, mood and tension?

METHODS

Study design and setting

This is an observational study with a cross-sectional up to 8 week follow-up study design, divided into three research projects. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations[53] will be used to report the HARMODI protocol.

The HARMODI study started in February 2023 at the Clinica Holistica Engiadina and will be conducted presumably until October 2024. The Clinica Holistica Engiadina is an inpatient psychiatric clinic, specialised in the treatment of stress-related disorders, such as depressive, anxiety, psychosomatic and stress disorders as well as burnout syndrome, with approximately 400 patients annually. All study participants are undergoing a similar multimodal treatment. The multimodal treatment generally consists of the following therapies, adjusted as needed: psychotherapy, sports therapy, art and dance therapy, psychopharmacotherapy, physical medicine, physiotherapy and selected interventions from traditional chinese medicine. A submaximal endurance test with lactate measurement and HRV recording are performed at the beginning and end of sports therapy. Sports therapy is based on an individual training plan for the medical training therapy, outdoor walking groups, Qi Gong, spinal gymnastics and relaxation exercises. Depending on indication, boxing, climbing or Escrima, a martial art originating from the Philippines, is prescribed. In addition, the clinic is located in a unique natural landscape that encourages patients to exercise independently in nature, that is, walking, hiking or cross-country skiing depending on season.

Study participants and recruitment

Patients referred to the psychiatric clinic will be screened for study participation. Inclusion criteria are as follows:

(1) diagnosis of depressive episode (F32 or F33), or adjustment disorder (F43.2) and burnout syndrome (Z73) without psychotic symptoms according to International Statistical Classification of Diseases and Related Health Problems (ICD)-10, (2) German language skills,[3] (3) smartphone ownership and[4] (4) age 18–65 years. Exclusion criteria are adapted from the Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH).[54] Exclusion criteria include, according to medical history, the following:

- Comorbid manifest psychiatric disorder, including post-traumatic stress disorder, anxiety disorder and panic disorder.
- Current treatment with antiarrhythmic drugs and tricyclic antidepressant medication.
- Factors precluding submaximal endurance test: history of cardiac diseases, such as myocardial infarction, stroke and unstable heart failure within the previous 6 months impairing exercise testing and training and heart failure (New York Heart Association functional classes III and IV).
- Factors severely affecting HRV parameters: type 1 and 2 diabetes mellitus with clinically proven cardiovascular autonomic neuropathy, chronic obstructive pulmonary disease Global Initiative for Obstructive Lung Disease stage≥III, ongoing cancer treatment, moderate to severe chronic kidney disease (estimated Glomerular Filtration Rate stage 3a (G3a) or worse (≤45 mL/min)), current eating disorders, such as anorexia nervosa and bulimia nervosa, excessive drug or alcohol abuse.
- Known pregnancy.
- Suicidal thoughts precluding informed consent.

Participant timeline and procedures

The investigator at site verbally presents the project to eligible patients 1 day after admission to the clinic. Interested patients have 1 day to consider study participation. Comorbid psychiatric exclusion criteria, suicidal thoughts, current eating disorders and drug or alcohol abuse will be screened with the German version of the Mini-International Neuropsychiatric Interview (MINI). The MINI is a structured diagnostic interview developed for 17 Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and ICD-10 axis I psychiatric disorders that can be assessed within 15 min.[55] Participants will be enrolled in baseline procedures if all of the criteria are met. Figure 1 presents an overview of the enrolment procedure. HRV recordings will be scheduled 5 days after admission to ensure acclimatisation as the clinic is located at 1438 m above sea level. Study appointments take place at the same time of the day for both admission and discharge to eliminate the influence of circadian rhythm on HRV.[56] HRV measurement will be performed according to GRAPH[54] by experienced sport scientists. All study appointments will be integrated into the clinic schedule to ensure a smooth process.

Questionnaires

Questionnaires at T1

PA performed 1 week before admission will be assessed with the 5-item German version of the Simple Physical

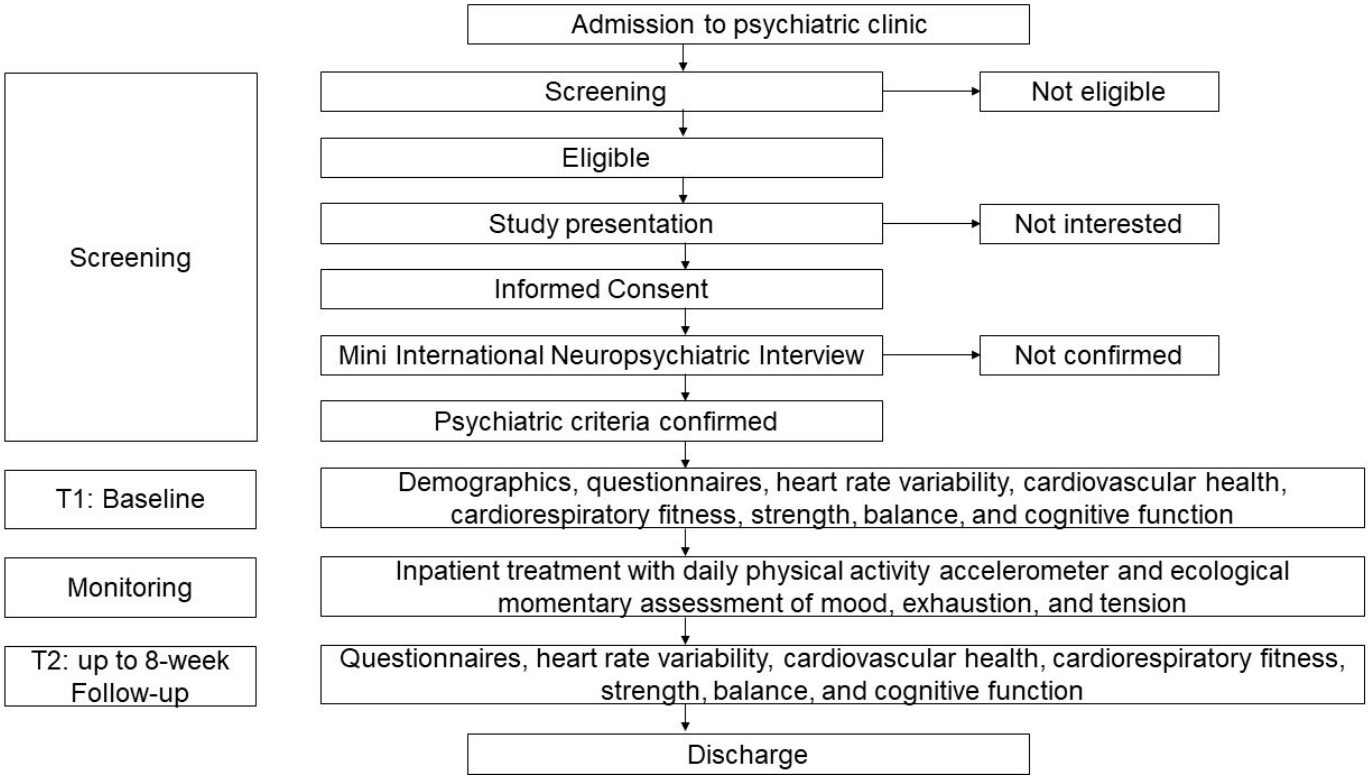

Figure 1 Study design and participant timeline.

Activity Questionnaire (SIMPAQ).[57] The SIMPAQ was developed to determine PA and sedentary behaviour in patients with mental illness.[58]

Whether participants exercise to avoid feeling tense, will be self-rated with one item of the German version[59] of the Exercise Dependence Scale (EDS),[60] with a 6-point Likert scale, ranging from 1 (*never*) to 6 (*always*).[59] Participants will be asked whether they continue to exercise when feeling tired with one item of the German version[61] of the Commitment to Exercise Scale (CES).[62] Rating will be performed on a visual analogue scale (*never to always*).[61]

Using the 40-item Hamburger Burnout Inventory (HBI), severity of burnout symptoms will be self-rated on a 9-point Likert scale, ranging from 1 (*not at all*) to 9 (*totally true*), with higher scores indicating worse outcome.[63] In addition, the 14-item German version of the Shirom-Melamed-Burnout-Measure (SMBM)[64] will be used to distinguish between physical, cognitive and emotional symptom severity. The SMBM has a 7-point Likert scale, ranging from 1 (*never*) to 7 (*always*),[65] with higher scores representing worse outcome and greater exhaustion.

Questionnaires at T1 and T2

Depression severity will be self-rated with the German version of the[66] 21-item Beck Depression Inventory-II (BDI-II).[67] Participants will be asked to describe their depressive symptoms over the past 2 weeks on a 4-point Likert scale, ranging from 0 (*no presence of a symptom*) to 3 (*strong presence of a symptom*),[68] with higher scores indicating worse depression.

The German version of the 9-item short form[69 70] of the original 21-item Maastricht Vital Exhaustion Questionnaire (MVEQ)[71] will measure change of exhaustion symptoms. Participants will report whether they feel exhausted 0 (*no*), 1 (*uncertain*) and 2 (*yes*), with total scores 4–10 indicating mild, 11–14 substantial and 15–18 severe vital exhaustion.[69]

Sleep quality will be evaluated with the German version of the 19-item Pittsburgh Sleep Quality Index (PSQI).[72] A total score >5 separates between good and poor sleep.[72]

The German version of the 21-item Beck Anxiety Inventory (BAI) will assess anxiety symptoms during the last 7 days on a 4-point Likert scale ranging from 0 (*not at all*) to 3 (*severely*).[73] The BAI is a user-friendly, valid international used inventory, with total scores 0–7 indicating minimal anxiety, 8–15 mild, 16–25 moderate and 26–63 clinical anxiety.[73 74]

The German version of the 53-item Brief Symptom Inventory (BSI) will be used to determine subjective symptoms during the past 7 days on a 5-point Likert scale, ranging from 0 (*not at all*) to 4 (*extremely*), with a higher total score indicating worse symptom severity.[75] The BSI is highly accepted and used worldwide.[76]

The 14-item German version of the Snaith-Hamilton-Pleasure Scale (SHAPS-D) will be used to assess anhedonia on a 4-point Likert scale, ranging from 1 (*I fully agree*) to 4 (*I do not agree at all*),[77] with higher scores indicating greater anhedonia. The SHAPS is a valid instrument to measure the experience of positive valence in depressed individuals.[78] Furthermore, current mood will be appraised before HRV supine recording with the 12-item short version of the Multidimensional Mood Questionnaire (MDMQ).[79] The MDMQ is a questionnaire with a 5-point Likert scale and three dimensions, with higher scores indicating a positive-toned pole, good mood, alertness, and calm state.[80]

Heart rate variability and cardiovascular health

Supine and standing HRV

HRV will be recorded in supine and standing position between 7.00 and 9.00 am in a room where light and temperature are stable within the range of 20–22 C°. Participants will be instructed to refrain from intense training 24 hours before recording, fast since 10 pm the day before and abstain from tobacco intake 30 min before recording. Women will be interviewed on the date of their last period or menopausal state. After 10 min of acclimatisation, the 5 min supine recording will start, followed by the 6 min standing recording. Using the ECG device Faros 180 (Bittium Biosignals, Kuopio, Finland) and HRV-Scanner software V.3.05.29 (BioSign GmbH, Ottenhofen, Germany), HRV will be measured with a sampling rate of 1000 Hz. Details on HRV recording procedure are described in online supplemental appendix 1.

Cardiovascular health

Brachial systolic and diastolic blood pressure as well as pulse wave velocity measurements will be assessed after 15 min in supine position, three times at 1 min intervals, according to guidelines.[81 82] Using a valid oscillometric cuff-based sphygmomanometer on the left arm (Custo screen 310, custo med GmbH, Ottobrunn, Germany),[83] cardiovascular health measurements will be carried out.

Åstrand-ryhming test HRV

Using Faros 180 ECG with a sampling rate of 1000 Hz, Åstrand-Ryhming test HRV will be recorded during and 6 min post Åstrand-Ryhming test. A chest strap (Polar T31, H10 sensor; Polar Electro Oy, Kempele, Finland) will display participant's heart rate on the mechanically braked bicycle ergometer (motion cycle 800 med; Proxomed Medizintechnik GmbH, Alzenau, Germany). Cardiorespiratory fitness will be tested with the single-stage Åstrand-Ryhming test,[84] a submaximal test to estimate maximal oxygen uptake (VO_{2max}) over 6 min with a gender-sensitive nomogram and age-correction factor.[85] The Åstrand-Ryhming test is safe, one of the most common used,[86] valid submaximal tests[87] and has previously been used in stress-related disorders.[30 88] Participants will paddle with 60–70 rounds per minute at 25 watts for 3 min to warm-up. After warm-up, watts will be adjusted to keep participants' heart rate between 120 and 170 beats per minute (bpm) (age>40 years), respective 130–170 bpm (age<40 years). Heart rate and perceived exertion, based on Borg rating scale[89] will be documented every minute. After the Åstrand-Ryhming test, participants will be asked to

keep sitting on the bicycle for the 6 min recovery period, without talking and paddling.

24-hour HRV

Using Faros 180 ECG, HRV will be recorded for 24 hours with a sampling rate of 500 Hz; 24-hour recording will start in the afternoon. Participants will be asked to report their sleep onset and time of awakening, defined as 'switching off light' respectively 'switching on light'. Sleep latency will be taken into consideration in HRV analyses; 30 min after the reported sleep onset time will be considered as sleep onset. The accelerometer data of the ECG will be inspected to verify inactivity.

HRV parameter processing

Analyses of HRV data preparation and parameter calculation will follow recommendations of the GRAPH.[54] Raw HRV data will be imported into Kubios HRV Scientific (V.4.0.1.) to prepare data for artefact correction. Kubios offers a QRS detection algorithm, based on the Pan-Tompkins algorithm, to detect the R-wave of the imported raw ECG data.[90 91] ECG data will be analysed with automatic artefact correction,[92] inspected visually and corrected manually if needed.[93] Supine and standing HRV will be analysed in 5 min segments. Time (SDNN, RMSSD and pNN50), frequency (LF, LF(nu), HF, HF(nu) and total power) and non-linear parameters (DFA a1) will be calculated for supine and standing HRV.[7] Exercise stress test HRV will be described as event (during Åstrand-Ryhming test) and postevent in 5 min segments.[93] Postevent HRV will be analysed with time (SDNN and RMSSD), frequency (LF, LF(nu), HF, HF(nu) and total power) and non-linear parameters (SD1, SD2, DFA a1).[94] Event HRV will be analysed with DFA a1;[95] 24-hour HRV will be analysed in 18-hour segment.[7] Time domain parameters, such as SDNN, SDANN, RMSSD[7] and pNN50, will be calculated in the 24-hour recording.[96 97] Table 1 lists the planned HRV parameters.

Cognitive function

Cognitive function will be tested with THINC-Integrated Tool (THINC-it), a valid digitalised cognitive assessment battery that has already been utilised in depressed patients[98 99] and has demonstrated sensitivity to change.[100] THINC-it consists of a self-rated questionnaire, the Perceived Deficits Questionnaire and variants of four cognitive tests: One-Back Test, Digit Symbol Substitution

Table 1 Summary of the planned HRV parameter and their physiological explanation[7 93 129]

Parameter	Description	Physiological mechanism
Time		
SDNN	SD of all RR intervals in milliseconds	Reflects all cyclic components responsible for variability of heart rate
SDANN	SD of the averages of RR intervals in all 5 min segments of the entire recording in milliseconds	Long-term components of HRV, only applied in 24-hour recording
RMSSD	Root mean square of successive differences of RR intervals in milliseconds	Parasympathetic nervous system activity
pNN50	Percentage of successive normal sinus RR intervals more than 50 ms in %	Parasympathetic nervous system activity
Frequency		
HF	Power in high frequency: 0.15–0.40 Hz	Parasympathetic nervous system activity
HF (nu)	High frequency power in normalised units: HF/(total power–VLF) x 100	Represent relative value of HF to the total power minus the VLF
LF	Power in low frequency: 0.04–0.15 Hz	Combination of parasympathetic, sympathetic and baroreflex activity
LF (nu)	Low frequency power in normalised units: LF/(total power–VLF) x 100	Represent relative value of LF to the total power minus the VLF
Total power	Variance of RR intervals over the temporal segment<0.4 Hz	Overall HRV
Non-linear		
SD 1	SD in milliseconds, crosswise Poincaré plot	Quick and high frequent changes in HRV
SD 2	SD in milliseconds, lengthwise Poincaré plot	Long-term changes in HRV
DFA a1	Short-term scaling exponent alpha 1 of Detrended Fluctuation Analysis	Degree of fractal correlation properties, useful in exercise settings

DFA, detrended fluctuation analysis; HF, high frequency; HRV, heart rate variability; LF, low frequency; pNN, percentage of successive normal sinus RR intervals; RMSSD, root mean square of successive differences of RR intervals; SDANN, SD of the averages of RR intervals; SDNN, SD of all RR intervals; VLF, very low frequency.

Test, Trail Making Test-Part B and Choice Reaction Time Identification Task.[98]

Balance and strength

In order to better characterise the determinants of PA, balance and strength tests will be conducted. Balance performance will be screened with the reliable and feasible One-Leg Standing test (OLS).[101] The sport scientist will instruct participants to fold their hands behind the back, place the free foot on the knee of the standing leg and look at the wall marker. After 10 s, participants will be asked to close their eyes and after another 10 s, lay their head back. Time will be stopped, if the free foot loses contact with the standing leg, participants compensate an unstable stance with jumping, hands lose contact or eyes are open. The time in seconds for both legs until the stance cannot be maintained will be added.[101]

After the OLS, participants will perform the 10-time chair rise test[102] from a chair with 45 cm height and 38 cm depth. The reciprocal of time needed to fully rise 10 times without using the upper extremities will be multiplied by 100. Consequently, good performance will be represented by high scores.[103]

Hand grip strength will be tested with a handheld dynamometer (Jamar Smart Hand Dynamometer, Performance Health Supply, Cedarburg, USA) in a seated position, with shoulder adducted, elbow flexed at 90°, wrist position neutral and handle position 2.[104 105] Participant's dominant hand will be tested and the best out of the three attempts,[106] with 60 s rest in between,[107] will be chosen for analyses.

Physical activity

During up to 8 week inpatient treatment, participants will be asked to wear a GENEActiv accelerometer (Activinsights, Kimbolton, UK) on their non-dominant wrist. GENEActiv is a valid tool to monitor sedentary behaviour,[108] PA[109] as well as sleep[110] and has been used in depressed individuals before.[51] Data sampling frequency will be set to 87.5 Hz; 14 hours per day of wear time compliance will be necessary for statistical analyses.[111] A form with technical specifications of the accelerometer will address possible privacy concerns of the participant.[112]

EMA of exhaustion, tension and mood

Participants will download a customised app, developed by PsyMate (ECS International BV, Maastricht, Netherlands) on their smartphone. PsyMate has been frequently used to study self-reported symptoms, such as fatigue,[113] depression and mood.[48] Current mood,[114] physical tiredness,[79] mental exhaustion and tension level[115 116] will be rated on a 5-point Likert scale, ranging from 1 (*not at all*) to 5 (*completely*). Online supplemental appendix 2 describes the item wording in more detail. A prompt will remind the participants daily at eight pm to answer the questions. The app will be uninstalled, if daily rating is a burden for the participants. However, uninstalling the app does not qualify a participant as drop-out.

Outcomes

Primary endpoint will be HRV, expressed with the parameter root mean square of successive differences between normal heart beats (RMSSD) in milliseconds. Particular focus is the RMSSD, a robust parasympathetic nervous system parameter that is less influenced by breathing.[8 93] Secondary outcomes will be questionnaire symptom severity scores, cardiorespiratory fitness, cognitive function, balance, hand grip, leg strength, cardiovascular health, daily exhaustion, mood and tension level, self-reported PA preadmission as well as objective measured PA and sleep during treatment. Table 2 provides an overview of every outcome measure with respective timeframe.

Sample size

Based on relevant literature on inpatients with stress-related disorders and HRV,[18 24 25] correlation between RMSSD and BDI-II score at baseline (T1) was estimated with r=−0.25 (power 80%, two-sided α=0.05). Simulations showed a need for 123 participants at T1 for cross-sectional analysis between RMSSD and BDI-II. Due to various HRV measurement procedures,[23 117–119] literature does not provide suitable estimates for within subject differences in RMSSD at T1 and T2. However, HRV data from former patients at the Clinica Holistica Engiadina were used for estimation of within subject differences. Simulations showed a need for 135 participants for within subject differences in RMSSD at T1 and T2 (power 80%, two-sided α=0.05, paired t-test, correlation between groups=0.4). Based on reported dropout rates,[22 24 26] dropout rate was expected to be 13%. In conclusion, a total sample size of 153 participants will be planned for HARMODI.

Data management

Project data will be managed using REDCap electronic data capture tools hosted at the University of Basel, Switzerland[120 121] and will be double-checked to avoid human error. Data, generated by the customised PsyMate app, will be securely and anonymously stored on a server provided by PsyMate, with adherence to the General Data Protection Regulation Rules. Personal information will only be accessible to authorised personnel who require the data to fulfil their duties within the scope of the research project. The principle investigator will be responsible for the secure storage of the identification list. Adverse events, that occur as a result of participation in the study, will be documented and if necessary, reported to the Ethics Committee. Missing data will not be imputed, but will be documented for respective reasons. In the event of a withdrawal of consent, data already collected will be included in the data analyses. HARMODI project is classified in risk category A according to Human Research Ordinance, Article 7. Thus, data monitoring will be limited to a yearly monitoring visit at site by the sponsor. Data on statistical code, such as GENEActiv R script or HRV Kubios settings, will be available from a Zenodo repository.

Table 2 Outcome measures with respective time point

Outcome	Method of measurement	T1	T2	T1–T2
Questionnaires				
Preadmission physical activity in average hours	Simple Physical Activity Questionnaire	X	–	–
Attitude towards exercise score	Exercise Dependence Scale	X	–	–
Attitude towards training score	Commitment to Exercise Scale	X	–	–
Burnout severity score*	Hamburger Burnout Inventory	X	–	–
Physical, cognitive and emotional exhaustion score	Shirom-Melamed-Burnout-Measure	X	–	–
Depression score*	Beck Depression Inventory II	X	X	–
Vital exhaustion score*	Maastricht Vital Exhaustion Questionnaire	X	X	–
Sleep Quality score*	Pittsburgh Sleep Quality Index	X	X	–
Anxiety score*	Beck Anxiety Inventory	X	X	–
Symptom severity score*	Brief Symptom Inventory	X	X	–
Anhedonia score	Snaith-Hamilton-Pleasure Scale	X	X	–
Pre-HRV recording: mood, alertness and calmness score	Multidimensional Mood Questionnaire	X	X	–
HRV, balance, strength and cardiorespiratory fitness				
RMSSD in milliseconds	Supine, standing, 24-hour and Åstrand-Ryhming HRV	X	X	–
Balance performance in seconds	One-Leg Standing test	X	X	–
Leg strength in seconds	10-time chair rise test	X	X	–
Hand grip strength in kilogram	Jamar Smart Hand Dynamometer	X	X	–
Cardiorespiratory fitness in VO_{2max} in millilitres/kilogram/minute	Åstrand-Ryhming test	X	X	–
Cognitive function				
Self-rated cognitive function score	THINC-it: abbreviated Perceived Deficits Questionnaire	X	X	–
Attention function in mean latency in milliseconds	THINC-it: Choice Reaction Time Identification Task	X	X	
Working memory in number of correct responses	THINC-it: One-Back test	X	X	
Ability to concentrate in number of correct responses	THINC-it: Digit Symbol Substitution Test	X	X	
Executive function in time in seconds	THINC-it: Trail Making Test-Part B	X	X	
Cardiovascular health				
Brachial systolic and diastolic blood pressure in millimetres of mercury	Sphygmomanometer	X	X	–
Central systolic and diastolic blood pressure in millimetres of mercury	Sphygmomanometer	X	X	
Pulse wave velocity in metres/second	Sphygmomanometer	X	X	
Daily monitoring				
Physical activity and sleep in average minutes per day	GENEActiv accelerometer	–	–	X
Exhaustion, tension and mood score	PsyMate app	–	–	X

*Part of clinical assessments routine.
HRV, heart rate variability; RMSSD, root mean square of successive differences between normal heart beats; T1, time point baseline; T2, time point up to 8-week follow-up; $VO_{2\ max}$, maximal oxygen uptake.

Statistical methods

Multiple regression analyses adjusted for potential confounders (age, sex, body mass index (BMI), PA level, blood pressure with intake of beta-adrenoreceptor antagonists and average nicotine consumption) will examine the association between primary outcome (RMSSD) and symptom severity (total score of BDI-II questionnaire) at T1 and T2. Analyses will be performed,

respectively, for supine, standing, 24-hour and exercise stress test HRV.

Paired t-tests will be used to analyse changes between HRV, exhaustion symptoms, cardiorespiratory fitness, sleep, cognitive function, strength, balance and PA between T1 and T2. A Wilcoxon signed-rank test will be performed if data are not normally distributed. For a group comparison, responders will be defined as >50% BDI-II score reduction and non-responders as <50% BDI-II score reduction. Unpaired t-tests will be carried out to compare psychophysiological and behavioural parameters (HRV, cardiorespiratory fitness, self-reported and objectively measured PA, sleep, cognitive function, strength, balance and cardiovascular health) between responders and non-responders. T-tests will be corrected for multiple testing.[122 123]

In the explorative analyses, multilevel vector autoregressive models will be computed to detect between-time and changes in PA, sleep and EMA of exhaustion, mood, and tension.

Statistical analyses will be performed using R, V.4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Level of significance will be two-sided α=0.05. Missing data will not be imputed. Drop-out rate was considered in the sample size calculation.

Patient and public involvement

Patients and the public were not involved in the design of the study.

ETHICS AND DISSEMINATION

Swiss Ethics Committee, Cantonal Ethics Committee Zürich, approved HARMODI protocol on 9 January 2023 (no. 2022-01871). Before recruitment, written informed consent (see online supplemental appendix 3) will be obtained by the investigator at site. Findings of HARMODI will be published in peer-reviewed journals, presented at conferences, described in local newspapers and posted on website of Clinica Holistica Engiadina.

DISCUSSION

HARMODI study will demonstrate whether HRV is a suitable diagnostic marker in the treatment of stress-related disorders. Monitoring HRV, physical and cognitive performance, PA and psychological symptoms will gain a better understanding of the treatment process of inpatients with stress-related disorders.

HARMODI study has an explorative and pragmatic design with the strength that findings can in future be directly implemented in the treatment of stress-related disorders. However, this cross-sectional single-site design has some limitations. It is important to bear in mind that study participants will be recruited from a psychiatric clinic, where a control group cannot be implemented. Therefore, causality is precluded and generalisability of study results are compromised. To overcome this obstacle, we will compare outcome variables between responders and non-responders. Another limitation is the expected variability of the primary outcome, HRV. HRV parameters are influenced by age,[124] gender,[125] BMI,[126] PA level,[27] blood pressure,[21] caffeine[127] and nicotine intake[128] and will be considered as covariates. Other confounders, in particular change of medication and different PA levels throughout inpatient treatment cannot be completely excluded, but will be monitored.

To the best of our knowledge, HARMODI is the first study combining follow-up data from (1) subjective psychological symptom ratings and (2) objective HRV recordings, cardiovascular health measurements, cognitive function tests and physical fitness assessments, with (3) daily objective PA data and subjective EMA of psychological symptoms throughout inpatient treatment. Results of HARMODI will provide valuable information on optimising treatment programmes for patients with stress-related disorders. These findings will strengthen the knowledge base on HRV as a health marker and demonstrate the role of PA in the treatment of stress-related disorders. In this regard, HARMODI project might underscore the importance of PA, as a cost-effective treatment option, for public decision-makers.

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Competing interests WT is funded through an industry-sponsored PhD by the Clinica Holistica Engiadina and represents the role of the investigator at site. Clinica Holistica Engiadina employed Dr MP (until 30 June 2023) and KM (until 1 January 2024). Clinica Holistica Engiadina also employs Dr TR (since 1 July 2023) and Dr RLM. Professor AS-T, Professor HB and Dr BS are members of the scientific advisory board of the Clinica Holistica Engiadina. Other conflicts of interest are not declared.

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