Efficacy of the exercise intervention “ImPuls” across diagnostically heterogenous mental disorders and its transdiagnostic mechanisms of action

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Abbreviations

ADHD/ADHS	Attention deficit hyperactivity disorder/ Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung
HRV	Heart rate variability/Herzratenvariabilität
PTSD	Post-traumatic stress disorder
OCD	Obsessive-compulsive disorder
DALYS	Disability-adjusted life years
vmHRV	Vagally-mediated heart rate variability
HRV-RMSSD	Root mean square of successive Differences between normal heartbeats
BCT	Behavior change technique
LMM	Linear mixed model
SEM	Structural equation modeling
RCT	Randomized controlled trial
TAU	Treatment as usual

Zusammenfassung

Psychische Erkrankungen treten sehr häufig auf und gehen mit starken persönlichen und gesamtgesellschaftlichen Beeinträchtigungen einher. Zu den häufigsten psychischen Erkrankungen in Deutschland zählen depressive Störungen, Angststörungen und Insomnie. Sie treten häufig komorbid untereinander und mit anderen Störungsbildern, wie beispielsweise der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS), auf. Die hohe Komorbidität könnte ein Hinweis darauf sein, dass diese Erkrankungen durch geteilte zugrundeliegende (transdiagnostische) Mechanismen entstehen und aufrechterhalten werden. Um diese Erkrankungen gleichzeitig wirksam behandeln zu können, braucht es daher Interventionen, die diese transdiagnostischen Mechanismen beeinflussen. Sportinterventionen können die Symptome von depressiven Störungen, Angststörungen, Insomnie sowie ADHS wirksam reduzieren. Wissenschaftliche Befunde weisen darauf, dass die Wirksamkeit über verschiedene Störungsbilder hinweg damit begründet werden kann, dass sportliche Aktivität eine positive Wirkung auf die Fähigkeit zur adaptiven Reaktion auf Stressoren (adaptive Stressbewältigung) haben kann. Maladaptive Stressbewältigung hingegen kann die genannten psychischen Erkrankungen bedingen und aufrechterhalten. Sportinterventionen scheinen nachhaltig wirksam zu sein, wenn sie Teilnehmende dazu befähigen langfristig sportlich aktiv zu sein und Sport bewusst gegen negativen Affekt (inklusive Stress) einzusetzen. Die Annahmen bezüglich der störungsbildübergreifenden Wirksamkeit von Sportinterventionen bzw. der transdiagnostischen Wirkmechanismen beruhen jedoch lediglich auf theoretischen Überlegungen, Longitudinal- bzw. Querschnittsstudien und experimentellen Studien mit gesunden oder störungsspezifischen Stichproben. Darüber hinaus gibt es wenige experimentelle Studien, die Wirkmechanismen von Sportinterventionen mit Mediationsanalysen untersucht haben. Daher kann geschlussfolgert werden, dass die störungsübergreifende Wirksamkeit von Sportinterventionen und deren transdiagnostischen Wirkmechanismen noch nicht ausreichend untersucht wurden. Dies ist jedoch wichtig, um die Wirksamkeit von Sportinterventionen zu verbessern und auf die Bedürfnisse diagnostisch heterogener psychischer Erkrankungen anzupassen. Es gibt es außerdem kaum Langzeitstudien von Sportinterventionen, die es erlauben, valide Aussagen über langfristig wirksame Komponenten von Sportinterventionen zu treffen. Anhand der selbstentwickelten Sportintervention ImPuls testeten wir die kurz- und langfristige Wirksamkeit einer Sportintervention in einer diagnostisch heterogenen

klinischen Stichprobe. Wir untersuchten transdiagnostische Wirkmechanismen, die der kurz- und langfristigen Wirksamkeit zugrunde liegen könnten. ImPuls integriert evidenz-basierte Komponenten für eine wirksame Symptomreduktion über verschiedene Störungsbilder hinweg. Wir nutzten Selbstberichte zu störungsspezifischer und globaler Symptomatik sowie zu transdiagnostischen Mechanismen. Außerdem wurde ein physiologischer Indikator für die Fähigkeit zur adaptiven Stressbewältigung (Herzratenvariabilität, HRV) eingesetzt. Zusammengefasst zeigen die Ergebnisse dieser Studie, dass eine Sportintervention gleichzeitig die störungsspezifische und globale Symptomatik von Depressionen, Angststörungen, Insomnie und ADHS verbessern kann (Manuskript 1). Diese Symptomverbesserung über alle Störungsbilder hinweg scheint durch eine Steigerung der sportlichen Aktivität (Manuskript 1) und insbesondere der Steigerung der adaptiven Stressbewältigung bedingt zu sein (Manuskript 2). Auch ein Jahr nach Interventionsende konnte die Symptomverbesserung und gesteigerte Sportaktivität aufrechterhalten werden. Verantwortlich für die langfristige Wirksamkeit scheint insbesondere das Lernen der bewussten Anwendung von sportlicher Aktivität als Affektregulation zu sein (Manuskript 3). Die vorliegende Arbeit erweitert den aktuellen Forschungsstand bezüglich des Einsatzes von Sportinterventionen als Behandlung bei psychischen Erkrankungen, indem eine diagnostisch heterogene klinische Stichprobe gewählt wurde und kurz- und langfristige transdiagnostische Wirkmechanismen mit robusten statistischen Methoden untersucht wurden. Die im Rahmen der Dissertation durchgeführte Studie weist auf die transdiagnostische und langfristige Wirksamkeit von Sportinterventionen hin, wenn die Intervention auf die Verbesserung der adaptiven Stressbewältigung abzielt und Teilnehmende dazu befähigt regelmäßige sportliche Aktivität als Affektregulations-Strategie zu nutzen. Stärken und Limitationen der Studie sowie praktische Implikationen der Ergebnisse werden in dieser Dissertation detailliert dargestellt. Es werden zudem relevante zukünftige Forschungsaufgaben diskutiert.

Summary

Mental disorders occur very frequently and are associated with severe personal and social impairment. Depressive disorders, anxiety disorders and insomnia are among the most common mental disorders. They often occur comorbidly with each other and with other mental disorders, such as attention deficit hyperactivity disorder (ADHD). The high comorbidity may indicate that these disorders are caused and maintained by shared underlying (transdiagnostic) mechanisms. Therefore, to effectively treat these disorders simultaneously, interventions that beneficially impact these transdiagnostic mechanisms are needed. Exercise interventions can efficaciously reduce symptoms of depressive disorders, anxiety disorders, insomnia, as well as ADHD. Scientific evidence indicates that the efficacy of exercise interventions across diagnostically heterogenous mental disorders may be due to their potential to increase the ability to adaptively respond to stressors (coping). In contrast, maladaptive stress coping can cause and maintain the aforementioned mental disorders. Beneficial effects of exercise interventions seem to be maintained if they enable participants to exercise regularly in the long-term and to use exercise intentionally to reduce negative affect (including stress). However, these assumptions regarding the efficacy of exercise interventions across disorders and transdiagnostic mechanisms of action are based only on theoretical considerations, longitudinal or cross-sectional studies, and experimental studies with healthy or disorder-specific samples. Moreover, experimental studies are needed that investigate these mechanisms of action by the conduction of mediation analyses. Therefore, it can be concluded that the efficacy of exercise interventions across heterogenous diagnoses and their transdiagnostic mechanisms of action have not been sufficiently investigated. However, this is important to improve the efficacy of exercise interventions and to tailor them to the needs of diagnostically heterogeneous mental disorders. Furthermore, follow-up periods of exercise trials have been rarely conducted which limits valid assumptions about long-term efficacious components of exercise interventions. Conducting the self-developed exercise intervention ImPuls, we tested the short- and long-term efficacy of an exercise intervention in a diagnostically heterogeneous clinical sample. We examined transdiagnostic mechanisms of action that might underlie short- and long-term efficacy of exercise interventions. ImPuls integrates the most efficacious evidence-based components for symptom reduction across diagnostically heterogenous outpatients. We used self-reported measures to assess disorder-

specific and global symptom severity as well as transdiagnostic mechanisms. We also used a physiological indicator of the ability to adaptively cope with stressors (heart rate variability, HRV). In summary, the results of this study demonstrated that an exercise intervention can simultaneously reduce disorder-specific and global symptom severity across depressive disorders, anxiety disorders, insomnia, and ADHD (Manuscript 1). Reductions of symptoms across all disorders seem to be due to an increase in exercise (Manuscript 1) and, particularly, an increase in the ability to adaptively cope with stressors (Manuscript 2). Symptom reductions and the increase in exercise were also maintained one year after the end of the intervention. Adopting the intentional use of exercise as an affect regulation strategy seems to underlie the long-term efficacy (Manuscript 3). The present dissertation extends the current state of research on the use of exercise interventions as a treatment for mental disorders by choosing a diagnostically heterogeneous clinical sample and examining short- and long-term transdiagnostic mechanisms of action with robust statistical methods. The study conducted in the context of this dissertation indicates transdiagnostic and long-term efficacy of exercise interventions when improvements of the ability to adaptively cope with stressors a major aim and when participants are enabled to use regular exercise as an affect regulation strategy. Limitations, strengths as well as future directions and practical implications of the present study are discussed in detail.

List of publications

a) Accepted publications

1) **Zeibig, J.-M.**, Seiffer, B., Sudeck, G., Rösel, I., Hautzinger, M., & Wolf, S. (2021). Transdiagnostic efficacy of a group exercise intervention for outpatients with heterogenous psychiatric disorders: a randomized controlled trial. *BMC Psychiatry*, 21(1), 313. https://doi.org/10.1186/s12888-21-03307-x
2) **Zeibig, J.-M.**, Seiffer, B., Frei, A. K., Takano, K., Sudeck, G., Rösel, I., Hautzinger, M., & Wolf, S. (2022). Long-term efficacy of exercise across diagnostically heterogenous mental disorders and the mediating role of affect regulation skills. *Psychol Sport Exerc*, 102340. https://doi.org/https://doi.org/10.1016/j.psychsport.2022.102340

b) Manuscript under review

3) **Zeibig, J.-M.**, Takano, K., Seiffer, B., Sudeck, G., Rösel, I., Hautzinger, M., & Wolf, S. (under review). An increase in heart rate variability mediates exercise effects on global symptom severity across heterogenous mental disorders: A secondary analysis of the ImPuls trial. *Ment Health Phys Act*.

c) Accepted manuscripts/book related to the dissertation

Wolf, S., **Zeibig, J.-M.**, Hautzinger, M., & Sudeck, G. (2020). *Psychische Gesundheit durch Bewegung. ImPuls: Ein sport- und bewegungstherapeutisches Programm für Menschen mit psychischen Erkrankungen*. Julius Beltz GmbH & Co. KG.

Wolf, S., Seiffer, B., **Zeibig, J.-M.**, Welkerling, J., Bauer, L. L., Frei, A. K., et al. (2021, Oct 30). Efficacy and cost-effectiveness of a Transdiagnostic group-based exercise intervention: study protocol for a pragmatic multi-site randomized controlled trial. *BMC Psychiatry, 21*(1), 540. https://doi.org/10.1186/s12888-021-03541-3

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Wolf, S., Seiffer, B., **Zeibig, J.-M.**, Welkerling, J., Brokmeier, L., Atrott, B., Ehring, T., & Schuch, F. B. (2021). Is Physical Activity Associated with Less Depression and Anxiety During the COVID-19 Pandemic? A Rapid Systematic Review. *Sports Medicine*, 51(8), 1771-1783. https://doi.org/10.1007/s40279-021-01468-z

Seiffer, B.*, Studnitz, T.*, **Zeibig, J.-M.**, Thiel, A., & Wolf, S. (in press). Sportliche Aktivität in der ambulanten Versorgung von Patient:innen mit psychischen Erkrankungen [Exercise in the outpatient care of patients with mental disorders]. In T. Thimme, H. Deimel, & C. Chermette (Eds.), *Bewegungstherapie bei psychischen Erkrankungen über die Lebensspanne*. Academia Verlag.

1 Introduction

1.1 Mental disorders in Germany

Mental disorders are a major health issue in Germany due to their high prevalence and substantial burden (Global Burden of Disease Collaborative Network, 2020). In 2019, the point prevalence of mental disorders (including substance use disorders) in the German adult population was 16.2% (Global Burden of Disease Collaborative Network, 2020). Depressive disorders[1] (4.8%), anxiety disorders[2] (7.3%), and insomnia (5.7%) were among the most common mental disorders (Global Burden of Disease Collaborative Network, 2020; Schlack et al., 2013). Correspondingly, 8.17% of all disability-adjusted life years (DALYS) in 2019 were attributed to mental disorders. Depressive disorders accounted for 2.1% and anxiety disorders for 1.8% of all DALYS (Global Burden of Disease Collaborative Network, 2020). Frequent comorbid physical diseases (e.g., cardiometabolic diseases, hypertension, diabetes) deteriorate this burden (Firth et al., 2019; Sutton, 2021). In addition to this personal burden, mental disorders result in considerable direct and indirect costs for society (Destatis, 2022). In 2020, the direct costs of mental disorders amounted to 56.4 billion euros in Germany, or about 13.1% of the total volume of medical costs. 9.5 billion euros were attributed to depressive disorders, 2.0 billion euros to anxiety disorders, and 96 million euros to insomnia (Destatis, 2022). In addition, mental disorders were responsible for 118 million days of incapacity to work (16.8% of all days) in Germany in 2020 (BAuA, 2022). Major depressive disorders (33.9 million days), anxiety disorders (29.2 million days) and insomnia (0.5 million days) caused the most days of incapacity to work (Rabe-Menssen et al., 2021). Similarly, individuals with ADHD are twice as likely to be absent at work as their healthy counterparts (Kessler et al., 2009).

The aforementioned mental disorders show a significant comorbidity with each other and with other mental disorders. For instance, insomnia occurs more often among depressive disorders and anxiety disorders versus healthy controls (Firth et al., 2019). 45.7% of individuals with lifetime major depression had one or more anxiety disorder in their lifetime (Kessler et al., 2015). Additionally, a diagnosis of a depressive

[1] Depressive disorders include major depressive disorder and dysthymia

[2] Anxiety disorders include generalized anxiety disorder, panic disorder, agoraphobia, social phobia, specific phobia, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD)

disorder increases the risk of a subsequent mental disorder (e.g., anxiety disorder) by 30% to 40% in the next five years (Plana-Ripoll et al., 2019). Furthermore, other mental disorders, such as ADHD, occur highly comorbid with depressive disorders, anxiety disorders and insomnia (Kessler et al., 2006). For example, an individual with ADHD has four to five times higher odds of developing any depressive disorder or anxiety disorder (Kessler et al., 2006). Therefore, multimorbidity is rather the norm in clinical practice. This multimorbidity may even exacerbate its negative effects by deteriorating symptoms and increasing the likelihood of comorbid physical disorders (Franzen et al., 2008; Klein Hofmeijer-Sevink et al., 2012; Ramsawh et al., 2009).

1.2 A transdiagnostic mechanism: Adaptive stress coping

The high likelihood of multimorbidity implies common (transdiagnostic) mechanisms associated with the development and persistence of depressive disorders, anxiety disorders, insomnia, and ADHD (Dalgleish et al., 2020). For instance, a reduced ability for adaptive responses to stressors (i.e., coping) has been discussed as one such transdiagnostic mechanism (Jacquart et al., 2019; Zorn et al., 2017). A high ability to adaptively cope with stressors can lead to a deliberate, goal-oriented, context-appropriate, and flexible response to internal (e.g., high personal performance demands) or external (e.g., workplace conflict) stressors. In contrast, a reduced ability to adaptively cope with stressors can lead to a context-inappropriate, not goal-oriented, exaggerated, or prolonged, and thus, maladaptive stress response (Charmandari et al., 2005; Thayer et al., 2012; Thayer et al., 2009). Excessive or prolonged activation of the stress system can reduce the ability to adaptively cope with stressors (Charmandari et al., 2005; McEwen, 1998). The onset, recurrence and exacerbation of depressive disorders, anxiety disorders, insomnia and AHDH can often be attributed to excessive or prolonged activation of the stress system due to severe or prolonged confrontation with stressful life events (e.g., abuse in early childhood) (Healey et al., 1981; Kendler et al., 1999; Moreno-Peral et al., 2014; Saccaro et al., 2021). Therefore, it is plausible that the aforementioned mental disorders tend to have a reduced ability to adaptively cope with stressors (Gross et al., 2019; Zorn et al., 2017).

Individual's ability to adaptively cope with stressors can be objectively measured via vagally-mediated heart rate variability (vmHRV) (Thayer et al., 2012). HRV reflects the variance of intervals between successive heart beats. The heart rate is controlled by the autonomic nervous system which consists of the parasympathetic and the

sympathetic nervous systems (Berntson et al., 1997; Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). Increased parasympathetic activity and reduced sympathetic activity decelerates the heart rate. Conversely, reduced parasympathetic activity and increased sympathetic activity accelerate the heart rate (Balzarotti et al., 2017; Rajendra Acharya et al., 2006). HRV parameters reflecting the vagal tone of the parasympathetic nervous system (vmHRV), such as the root mean square of successive differences between normal heartbeats (HRV-RMSSD), can be used to measure the activity of the parasympathetic nervous system (Laborde et al., 2017). According to the neurovisceral integration model (Thayer et al., 2000), increased levels of resting vmHRV are associated with the activation of higher-level executive functions involved in self-regulatory processes. The activation of these higher-level executive functions, thus high resting vmHRV, has been linked to the inhibition of the evolutionary “default” response to stressors known as the “fight or flight” response (Arnsten et al., 1998; Thayer et al., 2012; Thayer et al., 2009). In contrast, a low resting vmHRV gives free rein to the default response because higher-level executive functions are downregulated and cannot inhibit this automatic stress response (Thayer et al., 2012). The “fight or flight” response is usually not required in modern society and can lead to a context-inappropriate, not goal-oriented, exaggerated, or prolonged stress response (Thayer et al., 2009). Therefore, high levels of resting vmHRV are associated with a high ability to adaptively cope with stressors, whereas low levels of resting vmHRV are associated with a reduction in this ability (Bamert et al., 2022; Thayer et al., 2012).

Stress refers to a cognitive (e.g., increased alertness), emotional (e.g., anger, fear), behavioral (e.g., flight), and biological adaptation (e.g., increased heart rate and respiratory rate) induced by specific external and internal stressors. The goal is to adapt the organism as optimally as possible to the demands imposed by the stressor (Miller et al., 2002). According to the transactional model of stress and coping (Lazarus et al., 1984), stress occurs when a person cognitively evaluates the stressor as threatening and their own abilities to adaptively cope with it as inadequate. Consistent with this concept of stress, individuals with lower resting vmHRV reported higher levels of perceived stress (Chihaoui Mamlouk et al., 2021; Sin et al., 2016) compared with individuals with higher resting vmHRV.

Reduced resting vmHRV has been found in depressive disorders (Koch et al., 2019), anxiety disorders (Chalmers et al., 2014; Pole, 2007), insomnia (Spiegelhalder

et al., 2011; Werner et al., 2015) and ADHD (Christiansen et al., 2019). Patients with more severe, persistent, and comorbid symptoms have lower levels of resting vmHRV (Hartmann et al., 2018; Kemp et al., 2012; Toni et al., 2016). On the contrary, the absence of mental disorders has been associated with higher levels of resting vmHRV (Beauchaine et al., 2015). Accordingly, individuals diagnosed with depressive disorders, anxiety disorders, insomnia, and ADHD experience higher levels of stress (e.g., Schneider et al., 2020) compared to their healthy counterparts. Therefore, transdiagnostic treatments (i.e., affecting underlying mechanisms of mental disorders rather than specific diagnoses (McEvoy et al., 2009, p.21)) that positively affect resting vmHRV and concurrent perceived stress, rather than specific diagnoses, could simultaneously treat the common and burdensome mental disorders mentioned above (McEvoy et al., 2009).

1.3 Exercise as a transdiagnostic treatment

Numerous studies have demonstrated that exercise interventions represent an efficacious treatment for individuals with depressive disorders, anxiety disorders, insomnia and AHDH (Ashdown-Franks et al., 2020). Exercise is defined as “physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective” (Caspersen et al., 1985, p. 128). Robust meta-analytical evidence suggests a large antidepressant effect of exercise interventions in individuals with depressive disorders compared to active and non-active control conditions (Morres et al., 2019). Similarly, large effects of exercise interventions to improve sleep quality have been demonstrated in individuals with insomnia compared to inactive and active controls (Banno et al., 2018). Exercise interventions resulted in small to moderate anxiolytic effects for anxiety disorders over non-active controls (Ramos-Sanchez et al., 2021) and a small to moderate effect on ADHD core symptoms versus active and non-active control conditions (Cerrillo-Urbina et al., 2015; Seiffer et al., 2021). In addition, moderate to large effects of exercise interventions as an add-on treatment to psychological and psychopharmacological interventions have been reported in depressive disorders (Lee et al., 2021; Legrand et al., 2016), PTSD (Powers et al., 2015), and panic disorder (Gaudlitz et al., 2015) compared with standard treatment alone.

The efficacy of exercise interventions across these diagnostically heterogenous mental disorders could be explained by an improvement in their transdiagnostic

mechanisms (Jacquart et al., 2019). Exercise interventions are considered a promising treatment approach to increase resting vmHRV (Aubert et al., 2003; Mosley et al., 2022; Sandercock et al., 2005; Toni et al., 2016) and reduce perceived stress (Klaperski, 2018) in clinical and non-clinical samples. A meta-analysis of 13 studies examining the effects of exercise interventions on resting vmHRV in healthy subjects found a moderate effect of exercise on resting vmHRV (Sandercock et al., 2005). Physical fitness, which is positively correlated with regular exercise (Jackson et al., 2009), has also been associated with higher levels of resting vmHRV in healthy populations (Aubert et al., 2003; Mosley et al., 2022). At the same time, regular exercise has been linked to lower stress perception in healthy individuals, as shown by cross-sectional, longitudinal and experimental studies (Klaperski, 2018). Similarly, exercise interventions have shown to reduce stress reactivity (i.e., self-reported and physiological response to stressors) in non-clinical samples (Jacquart et al., 2019; Klaperski, 2018; Wunsch et al., 2019). Exercise interventions seem to be able to increase resting vmHRV in elderly individuals with depressive disorders with large effect size (Toni et al., 2016). Similarly, resting vmHRV can be increased by exercise interventions in individuals with anxiety disorders (Gaul-Alácová et al., 2005). We are not aware of any study that has investigated the effect of an exercise intervention on perceived stress in individuals with mental disorders. Among inpatients with depressive disorders, stress reactivity did not change after regular exercise (Gerber et al., 2020). However, the study included a small sample (N = 25), used per-protocol analyses and a short intervention period of six weeks which may not be sufficient to beneficially impact the stress response (Melanson et al., 2001). Therefore, study results need to be interpreted cautiously. In essence, some studies point towards the potential of using exercise interventions to improve the ability to adaptively cope with stressors across individuals with mental disorders. However, investigations among individuals with mental disorders are limited and based on few disorder-specific samples of depressive disorders and anxiety disorders (Gaul-Alácová et al., 2005; Jacquart et al., 2019; Toni et al., 2016). A reduced ability to adaptively cope with stressors seems to be a transdiagnostic mechanisms across depressive disorders, anxiety disorders, insomnia and ADHS (see *section 1.2*). Therefore, it seems necessary to investigate the effects of exercise interventions on the ability to adaptively cope with stressors in all of these mental disorders. This would provide valuable insight into the transdiagnostic efficacy of exercise interventions across diagnostically heterogeneous mental disorders with a

reduced ability to adaptively cope with stressors. Consequently, the efficacy of exercise interventions could be improved and tailored to the needs of diagnostically heterogeneous mental disorders.

1.4 Exercise interventions for the outpatient mental health care

According to the evidence- and consensus-based German health care guidelines (S3 guideline)[3], exercise should be considered as a treatment for major depression (recommendation level: B) (DGPPN et al., 2017), panic disorder or agoraphobia (recommendation level: expert consensus) (Bandelow et al., 2021) and ADHD (recommendation level: expert consensus) (DGPPN et al., 2018). In addition, exercise may be considered as a treatment for PTSD (recommendation level: 0) (Schäfer et al., 2019); for other anxiety disorders and insomnia, no recommendations are available yet. Recent meta-analyses and randomized controlled trials (RCTs) on the efficacy of exercise interventions for depressive disorders, anxiety disorders, insomnia, and ADHD, mentioned above (see *section 1.3*), have not yet been considered in these recommendations. If these were considered, it would be appropriate to include exercise interventions in the treatment for all the aforementioned mental disorders.

Despite of the guidelines and robust evidence about exercise interventions representing an efficacious transdiagnostic treatment, they are not used as a standard treatment in the outpatient mental health care in Germany (Nübling et al., 2014). Standard treatments for mental disorders in outpatient settings include psychological and psychopharmacological interventions (Nübling et al., 2014). However, these standard treatments seem to reach only a small percentage of individuals with mental disorders (i.e., treatment gap) (Patel, 2012), despite of their significant need for treatment (see *section 1.1*). In fact, only 17.6% of a large representative German sample with a 12-month diagnosis of a mental disorder, had accessed mental health care services during the past year (Mack et al., 2014). Furthermore, 90% of individuals with mental disorders do not receive evidence-based treatment and only 2.5% receive outpatient psychotherapeutic care in Germany (Nübling et al., 2014). Six to seven years pass between disorder onset and subsequent service use for any depressive or anxiety disorder (Mack et al., 2014). Even after initial treatment contact, individuals

[3] Recommendation levels: A = strong recommendation based on high quality randomized controlled trials; B = recommendation based on high quality studies; 0 = optional recommendation based on reports from expert circles or expert opinion; expert consensus = suggested as “good clinical practice” based on the clinical experience of the guideline group members

need to wait an average of 22.3 weeks for psychotherapeutic treatment in Germany (Singer et al., 2022). The absence or delay in treatment has actually deteriorated with COVID-19 which may be due to an increasing number of mental disorders, particularly anxiety disorders, depressive disorders and insomnia (American Psychological Association, 2020). However, the absence or delay of efficacious treatment may exacerbate symptoms of mental disorders and promote the onset of (additional) comorbid physical or mental disorders (Bundespsychotherapeutenkammer, 2018).

Compared to the effects of standard treatments for depressive disorders (Cipriani et al., 2018; Cuijpers et al., 2019), anxiety disorders (Mitte, 2005; Rosenbaum et al., 2015), insomnia (Koffel et al., 2015; Liu et al., 2017) and ADHD (Storebo et al., 2018; van der Oord et al., 2008), the effects of exercise interventions on symptom reduction seem to be comparable (Ashdown-Franks et al., 2020). Indeed, a recent meta-analysis by Recchia et al. (2022) showed no differences between antidepressant effects of exercise and antidepressants in individuals with non-severe depressive disorders. Psychological interventions are usually disorders-specific (Dalgleish et al., 2020) and delivered in individual formats (Mattke et al., 2020). In contrast, exercise interventions could be delivered in group format due to their efficacy across diagnostically heterogeneous mental disorders (Ashdown-Franks et al., 2020; Jacquart et al., 2019). Therefore, exercise interventions could efficiently treat a broad representative outpatient population (Kessler et al., 2005; Plana-Ripoll et al., 2019) and could be disseminated fast because only one treatment protocol can be generalized (Dalgleish et al., 2020). Furthermore, the conduction of exercise interventions for mental disorders could be delegated to other professional groups (e.g., exercise therapist) who are trained in their content and delivery which would reduce the treatment gap (Patel, 2012). In contrast to psychopharmacological treatments, they are available at low cost and are associated with few side effects (Fiuza-Luces et al., 2013). As a consequence, exercise interventions could represent a low-threshold treatment and could be easily integrated into standard mental health care in Germany. At the same time, they could directly reduce the burden of disease by beneficially preventing and treating comorbid physical diseases (Firth et al., 2019; Naci et al., 2015). Given the high efficacy, which is comparable to psychological and psychopharmacological interventions, and other multiple benefits, the use of exercise interventions as a standard (add-on or stand-alone) treatment could ameliorate the substantial treatment gap and its serious consequences. The potential of exercise

interventions to improve the outpatient mental health care in Germany is illustrated in Figure 1.

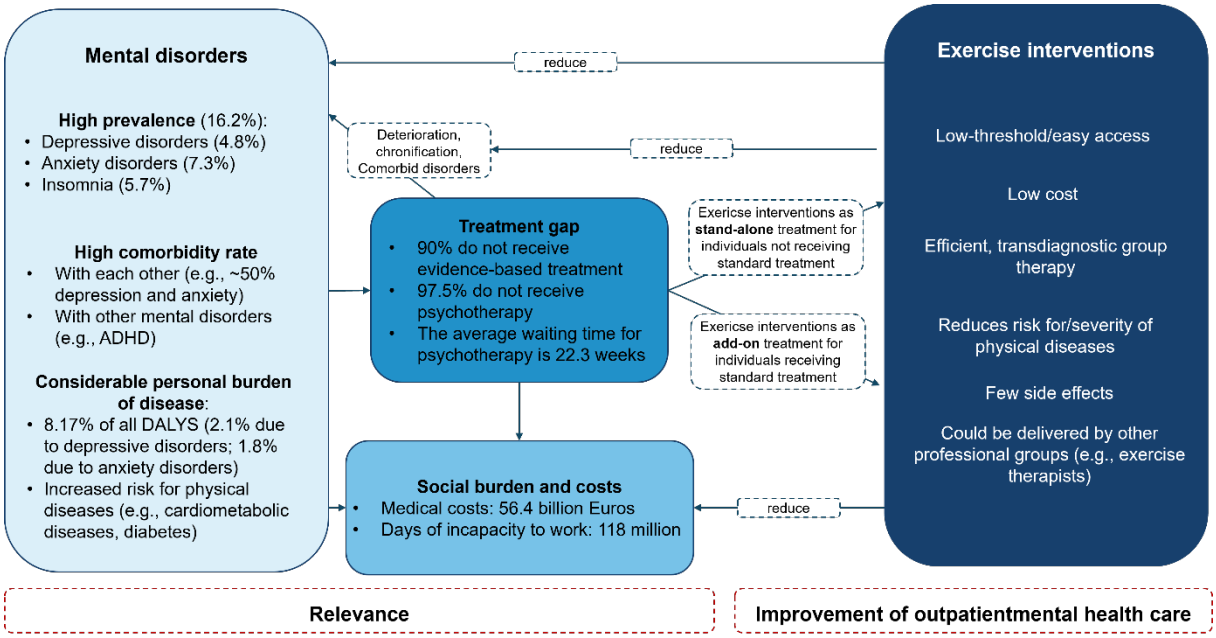

Figure 1. Deficits in outpatient mental health care in Germany and the and the opportunity to improve care through exercise interventions that are featured with optimal characteristics for long-lasting treatment efficacy.

1.5 Important characteristics of exercise interventions

Certain characteristics of exercise interventions have been associated with optimal efficacy in reducing symptoms across depressive disorders, anxiety disorders insomnia, and ADHD: 1) Aerobic exercise (optional combined with resistance training) (e.g., Banno et al., 2018; Morres et al., 2019), 2) partially supervised by qualified professionals (e.g., trained in exercise therapy and/or psychotherapy) (Firth et al., 2019; Ramos-Sanchez et al., 2021; Stubbs et al., 2018), 3) a minimum of moderate intensity (e.g., Melanson et al., 2001; Morres et al., 2019; Ramos-Sanchez et al., 2021; Seiffer et al., 2022; Stubbs et al., 2018), 4) a minimum total duration of 12 weeks (Melanson et al., 2001; Stubbs et al., 2018), 5) a minimum duration of 30 minutes of each session (e.g., Morres et al., 2019). Conducting exercise outdoors, in groups and addressing individual exercise preferences for exercise can further increase efficacy (Krogh et al., 2014; Morres et al., 2019).

Furthermore, behavior change techniques (BCTs) (Michie et al., 2011), seem to play a key role in exercise interventions for people with mental disorders, as they can sustainably increase exercise in this rather physically inactive population (Firth et al., 2019; Kramer et al., 2014). Despite beneficial effects of regular exercise on mental

health, individuals with depressive disorders (Schuch et al., 2017; Vancampfort et al., 2017), anxiety disorders (Goodwin, 2003; van den Berk-Clark et al., 2018), insomnia (Kline, 2014) and ADHD (Mercurio et al., 2019) engage in significant less exercise compared to their healthy counterparts. Lower levels of exercise among this population might be due to deficits in motivation (i.e., intention to perform a behavior) and volition (i.e., ability to perform the intended behavior) (Kramer et al., 2014). These deficits may be a result of their symptomatology, physical difficulties, and low social support (Firth et al., 2016). First, low energy levels, reduced interest or pleasure may diminish the motivation to exercise among patients with depressive disorders (Kramer et al., 2014) or insomnia (Fraser et al., 2015). Patients with anxiety disorders may avoid exercise because it can produce aversive symptoms similar to anxiety symptoms (e.g., increased heart rate) (Collimore et al., 2014). Dysregulation of executive functions in patients with ADHD can lead to deficits in goal-oriented and adaptive behaviors which is important for engagement in exercise (Hughes, 2013). Second, physical deficits due to medication (e.g., obesity, fatigue) and comorbid physical diseases (e.g., diabetes) may discourage from being physically active (Choi et al., 2017; McDevitt et al., 2006). Third, low social support due to stigma and social isolation is common in mental disorders and may discourage them from engaging in exercise (Firth et al., 2019; Mercurio et al., 2019). To address these motivational and volitional deficits of individuals with mental disorders, BCTs can be integrated into exercise interventions (Samdal et al., 2017). BCTs that can efficaciously increase exercise behavior in the short- and long-term include improving knowledge about beneficial effect of exercise, setting individual goals, self-monitoring of goal and behavior, barrier management, social support, autonomy-enhancing counselling and supportive phone calls (Ashdown-Franks et al., 2018; Gohner et al., 2015; Samdal et al., 2017).

The long-term increase in exercise appears to be essential for maintaining the treatment effects of exercise interventions (Babyak et al., 2000; Hoffman et al., 2011). Maintaining exercise during a 10-months (Babyak et al., 2000) or 12-months (Hoffman et al., 2011) follow-up period reduced the likelihood of a depression diagnosis by more than half at the end of that period among initially depressed participants (Babyak et al., 2000; Hoffman et al., 2011). Nevertheless, follow-up periods of exercise trials are rarely conducted, or follow-up periods are relatively short (e.g., three weeks) (Aylett et al., 2018; Cooney et al., 2013). However, this limits valid assumptions about long-term efficacious components of exercise interventions.

Nevertheless, not all exercise trials with follow-up periods showed sustained treatment effects (Aylett et al., 2018; Cooney et al., 2013). One possible reason for the conflicting results may be that the long-term effects of exercise are moderated by an increase in psychosocial mechanisms (e.g., affect regulation, self-efficacy, social support) rather than an increase in exercise per se (Thomas et al., 2020). According to the model of physical activity-related health competence (Pfeifer et al., 2013; Sudeck et al., 2016), to promote health and well-being, it is not only important to increase exercise, but also to increase the knowledge, motivation, and ability to intentionally use exercise to regulate affective well-being (i.e., exercise-specific affect regulation). Affect can be used as an umbrella term for emotions (e.g., feeling anxious), moods (e.g., feeling depressed), stress (e.g., feeling threatened) or impulses (e.g., the urge to smoke) (Gross et al., 2019). Individuals with a high exercise-specific affect regulation may particularly profit from potential mental health benefits of regular exercise (Sudeck et al., 2022). For example, individuals with high exercise-specific affect regulation have a stronger positive relationship between exercise and affective well-being (Sudeck et al., 2018). While low exercise-specific affect regulation has been associated with depressive disorders, anxiety disorders, insomnia and ADHD (Gross et al., 2019), high exercise-specific affect regulation appears to be associated with a lower likelihood of the onset of these mental disorders during stressful life events (Rösel et al., 2022). Moreover, the ability to respond adaptively to stressors, for example by using exercise as a coping strategy, seems to be one mechanism of action that underlies beneficial effects of exercise interventions on symptoms across these mental disorders (see *section 1.3*). Therefore, it seems necessary to promote exercise-specific affect regulation in exercise interventions for people with mental disorders in addition to sustained exercise behavior change. Exercise-specific affect regulation can be promoted by 1) increasing worry that motivates adaptive behavior (e.g., by raising awareness of the negative consequences of sedentary behavior), 2) reducing distress that inhibits adaptive behavior (e.g., by promoting positive exercise experiences) and 3) changing affect regulation behaviors (e.g., exercise) that influence well-being (e.g., by creating awareness of positive mood changes after exercise) (Cameron et al., 2020). In essence, exercise interventions should aim to promote a long-lasting increase in exercise and, equally important, the motivation and ability to intentionally use exercise as a strategy to regulate negative affect (Sudeck et al., 2018; Sudeck et al., 2016). However, studies are needed that experimentally evaluate these potential

long-term transdiagnostic mechanisms of action in a clinical sample of diagnostically heterogeneous mental disorders.

1.6 Current dissertation

On the one hand, evidence has pointed towards the potential of using exercise interventions as an efficacious transdiagnostic treatment; on the other hand, no exercise interventions had yet been developed for diagnostically heterogenous mental disorders until 2017. To address this gap, an exercise intervention, namely ImPuls, was developed prior to this dissertation. The initial intervention was invented by graduate students under the project supervision of Dr. Sebastian Wolf in 2017 at the University of Tübingen. Subsequently, it was progressed and finally published as a therapy manual in 2020 (Wolf, Zeibig, Hautzinger, et al., 2020). In addition, ImPuls was presented in German scientific journals (Wolf, Zeibig, et al., 2020a, 2020b).

1.6.1 ImPuls intervention

ImPuls is a standardized group exercise intervention for physically inactive outpatients in German outpatient health care settings. Individuals with depressive disorders, anxiety disorders, insomnia, and/or ADHD can participate. ImPuls is based on the latest scientific findings on the optimal criteria of exercise for sustained therapeutic efficacy (see *section 1.5*) Standardized materials and procedures can be found in the manual (Wolf, Zeibig, Hautzinger, et al., 2020). To test the feasibility of ImPuls in outpatient mental health care settings in Germany, the intervention was tested during waiting times for psychotherapy.

A temporal overview of ImPuls is displayed in Figure 2. BCTs that were conducted during the intervention can be found in Table 1. ImPuls aimed to encourage participants to perform exercise regularly and to integrate it into everyday life routines. In addition, it promoted the intentional use of exercise as an adaptive affect regulation strategy. A maximum of four participants could attend, supervised by two therapists (one licensed or in-training cognitive-behavioral psychotherapist and one graduate psychology student; trained in the background and content of ImPuls und supervised by one exercise therapist and one psychotherapist). ImPuls consisted of three core components: supervised running sessions, non-supervised exercise sessions and group meetings. The total duration of the intervention was twelve weeks. The first four weeks were the mainly supervised period. Participants took part in supervised running sessions combined with supervised group meetings. In addition, they participated in individually preferred, non-supervised exercise sessions once per week. The mainly

non-supervised period from week five to twelve contained non-supervised exercise sessions at least twice per week. This period was accompanied by an activity diary and weekly telephone contacts with one of the therapists. In addition, a supporter session (e.g., for participants' family, friends, partners) in week five was conducted to facilitate social support helping participants to exercise regularly during and after the non-supervised period.

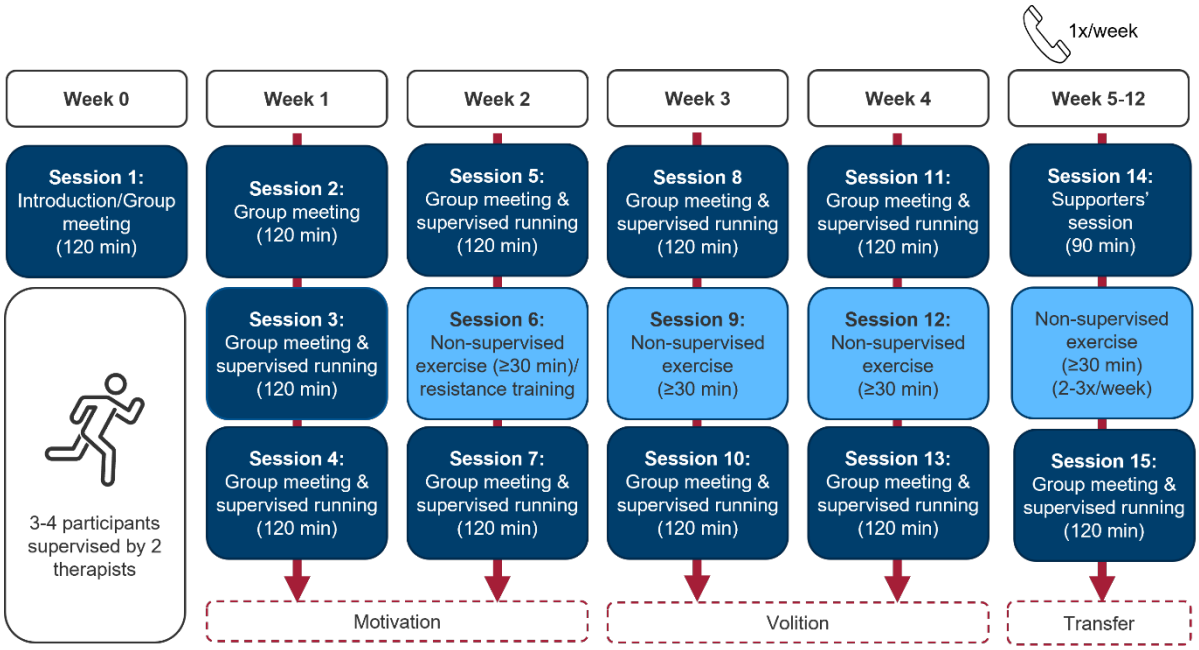

Figure 2. Intervention procedure of the exercise intervention ImPuls. Dark blue boxes represent group meetings combined with supervised running sessions (starting session 3) and the supporters' session (session 14 in week 5). Session 1 contains an introduction in the intervention. Session 15 is conducted in week 12. Light blue boxes represent non-supervised exercises or resistance training. The phone represents the weekly phone contact between weeks 5 and 12 (adapted from Zeibig et al. (2021)).

Table 1. Overview of behavior change techniques in ImPuls with motivation and volitional focus to promote long-lasting exercise and exercise-specific affect regulation (adapted from Wolf, Zeibig, Hautzinger, et al. (2020))

Focus	Behavior change technique	Brief definition
Motivational	Education about positive effects of regular exercise	Increasing knowledge about positive effects of exercise on reducing psychopathological symptoms (at emotional, cognitive, behavioral, and physical level)
	Education about negative effects of sedentary behavior	Increasing knowledge about negative effects of sedentary behavior on the development or persistence of psychopathological symptoms (at emotional, cognitive, behavioral, and physical level)
	Selection of a preferred activity	Participants find a preferred and enjoyable exercise activity with the support of the therapist; exercise activity needs to meet evidence-based criteria for optimal effects in reducing psychopathological symptoms
	Goal setting	Setting individualized concrete, measurable, attractive, realistic, and determined goals related to the reduction in psychopathological symptoms.
	Self-monitoring of goal achievement	Through visualizations (e.g., goal achievement scale) and therapists' questions, diary (goals and achievement of goals are noted)
	Visualization of goal achievement	Concrete visualization of goal achievement using an imagination technique
	Creating awareness about positive effects of exercise	Using a mood barometer prior and immediately after exercise engagement
Volitional	Education about optimal modalities of exercise	Evidence-based exercise recommendations about optimal modalities to reduce psychopathological symptoms
	Exercise self-monitoring (Optimal modality)	Participants estimate their perceived exertion using the Borg Rating of Perceived Exertion scale and compare this estimation with an objective measure (heart rate monitor) to enable realistic estimation of the physical exertion
	Identification of personal barriers	Identification of Individual barriers regarding regular exercise engagement
	Strategies to overcome barriers	Development of individual and realistic strategies to overcome barriers
	Social support (family, friends, intervention group, therapists)	Social support during the intervention period through the intervention group and therapists; conducting a supporters' session

Each supervised running session lasted 30 minutes with a previous warm-up (5-10 minutes) and a subsequent cool-down (5-10 minutes). Running was performed at moderate intensity and participants can choose between an endurance method (i.e., just running) or a standardized interval-based training (Eisenhut et al., 2013). The interval method transited to the endurance method after 13 weeks (i.e., alternating between running and walking with increasing bouts of running each week). Intensity was recorded using a heart rate monitor (Polar Electro GmbH; A 300) in combination

with a chest strap (Polar Electro GmbH; H7) and the Borg Rating of Perceived Exertion (RPE) scale (Borg, 1982). On the heart rate monitor, moderate intensity was defined as 60 to 80% of maximum heart rate (i.e., 220-age; Garber et al., 2011). On the RPE Scale, moderate intensity was defined on a scale of nine to 14 (Borg, 1982). Therefore, each participant ran on his/her own pace depending on objective and subjective exertion. The two therapists accompanied the group. Approximately every five minutes, they asked each participant about his/her intensity on the activity watch and RPE scale. If necessary, they instructed participants to reduce or increase pace to maintain moderate intensity on both measures. The aim of using an objective and subjective measure was to promote a realistic perception of moderate intensity. Furthermore, therapists supported participants with any other physical (e.g., stich, exhaustion) or psychological (e.g., negative affect, lack of motivation) difficulties during running sessions. Running was performed outdoors along a river. After 15 minutes, participants and therapists turned and took the same route back.

The non-supervised exercise activity could be chosen by each participant according to their personal preferences. A standardized strength training was developed for participants which they could use as the first non-supervised exercise training session (session 6). Prerequisites for the activity was a duration of minimum of 30 minutes and at least moderate intensity.

The group meetings had a duration of one to two hours. These "surrounded" the supervised running sessions by taking place prior and after the running session. The meeting always began with information about goals of the session and a debriefing of the last session. This was followed by specific BCTs to promote long-lasting exercise and exercise-specific affect regulation (see Table 1). At the end of the session, participants were given a homework assignment related to the content of the session.

1.6.2 Objectives of doctoral research

The overarching goal of the current dissertation was the investigation of the short- and long-term efficacy and transdiagnostic mechanisms of action of ImPuls across diagnostically heterogenous outpatients. The dissertation aimed to fill open research gaps: To the best of our knowledge, it is largely unknown whether a single exercise intervention can improve psychopathological symptoms and transdiagnostic mechanisms across diagnostically heterogenous mental disorders in the short- and long-term. In addition, there is a need for robust research on transdiagnostic mechanisms underlying the short- and long-term treatment effects of exercise

interventions across diagnostically heterogenous mental disorders. This resulted in eight sub-research questions that were addressed in three different manuscripts.

1.6.2.1 Research questions Manuscript I

1. Does the exercise intervention ImPuls reduce global symptom severity and disorder-specific symptoms from baseline to post-intervention compared to a passive control condition?
2. Does the exercise intervention ImPuls increase exercise from baseline to post-intervention compared to a passive control condition?
3. Does an increase in exercise from baseline to post-intervention mediate treatment effects on global symptom severity from baseline to post-intervention?

1.6.2.2 Research questions Manuscript 2

4. Does the exercise intervention ImPuls reduce perceived stress and increase resting vmHRV from baseline to post-intervention compared to a passive control condition?
5. Does a reduction in perceived stress and increase in resting vmHRV from baseline to post-intervention mediate treatment effects on global symptom severity from baseline to post-intervention?

1.6.2.3 Research questions Manuscript 3

6. Does the exercise intervention ImPuls reduce global symptom severity and disorder-specific symptoms from baseline to one-year follow-up compared to a passive control condition?
7. Does the exercise intervention ImPuls increase exercise and exercise-specific affect regulation from baseline to one-year follow-up compared to a passive control condition?
8. Do increases in exercise and exercise-specific affect regulation from baseline to one-year follow-up mediate treatment effects on global symptom severity and clinically significant changes from baseline to one-year follow-up?

2 Summary and results

An overview of the study design and selected measures relevant for the current dissertation can be found in Figure 3.

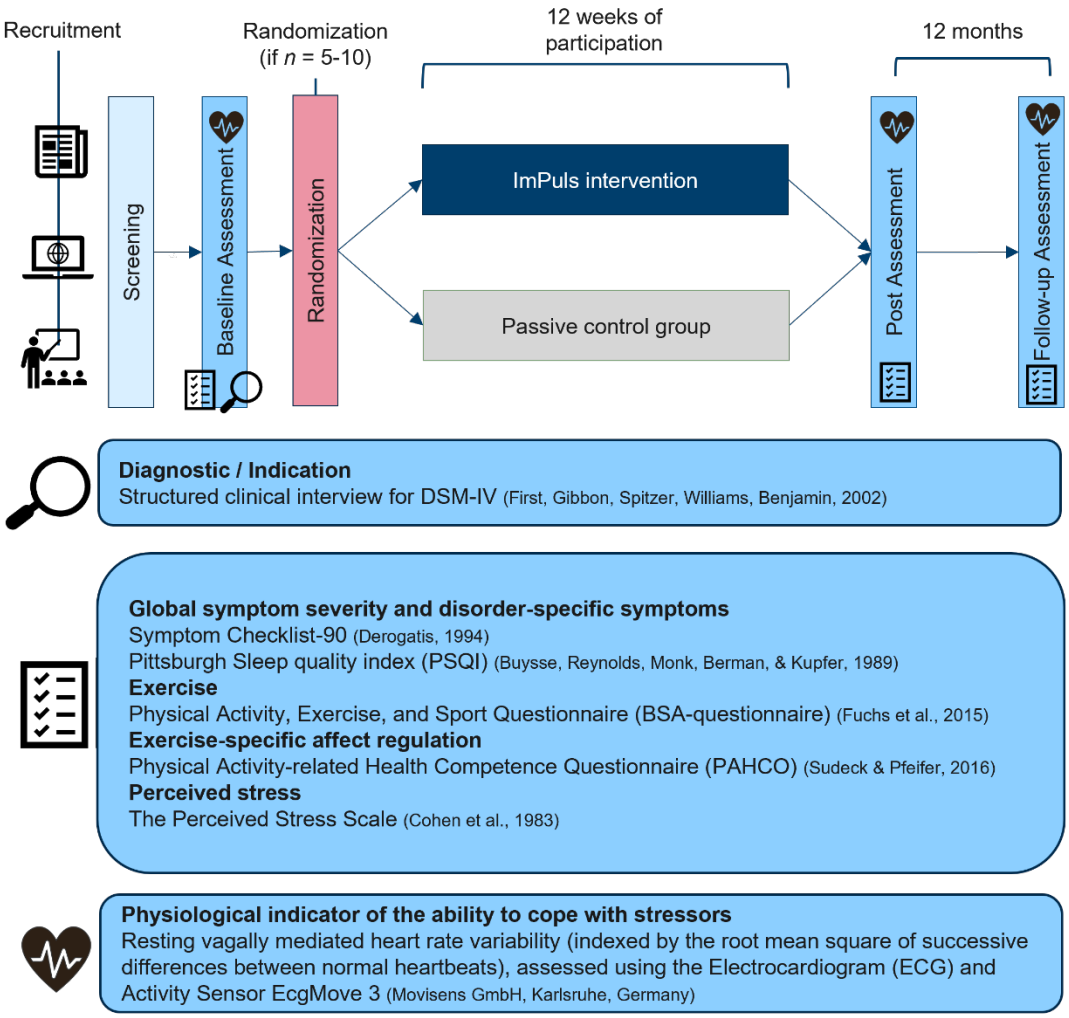

Figure 3. Overview of the study design and selected measures of manuscripts 1-3.

2.1 Manuscript I

"Transdiagnostic efficacy of a group exercise intervention for outpatients with heterogenous psychiatric disorders: a randomized controlled trial" (Zeibig et al., 2021)

Objectives and methods: Manuscript I investigated the effects of the 12-week exercise intervention ImPuls (Wolf, Zeibig, Hautzinger, et al., 2020) on the reduction in disorder-specific and global symptom severity as well as an increase in exercise immediately after treatment. Furthermore, it was of interest whether an increase in exercise would

underlie improved symptom severity. Groups of sedentary outpatients waiting for psychotherapy, with depressive disorders, anxiety disorders, insomnia, and ADHD were randomized to ImPuls (*n* = 38) or a passive control group (*n* = 36). Primary outcomes were global symptom severity and disorder-specific symptoms (i.e., depression, anxiety, sleep quality), measured with the Symptom Checklist-90 (Derogatis, 1994) and Pittsburgh Sleep Quality Index (Buysse et al., 1989) at baseline and post-treatment. Secondary outcome was the self-reported amount of exercise, assessed via the Physical Activity, Exercise, and Sport Questionnaire (Fuchs et al., 2015) at baseline, at week 9, and post-treatment. Adequate statistical power allowed a subgroup analysis examining effects of the intervention on depression among participants with depressive disorders.

Data analysis: To test differences between groups in changes of primary and secondary outcomes, linear mixed models (LMMs) were conducted among the intention-to-treat sample. Models included group allocation, assessment point and their interaction as predictors. Exploratory regression analyses (per-protocol analysis) tested the predictive value of changes in exercise on primary outcomes changes.

Results and discussion: From baseline to post-treatment, ImPuls led to an improvement of disorder-specific and global symptom severity compared to the control group with moderate to large effect sizes. Exercise increased from baseline to week 9 and from baseline to post-treatment in the intervention group compared to the control group with large effect sizes. Across both groups, the reduction in global symptom severity was significantly predicted by an increase in exercise. Major limitations of the study were the use of a passive control condition and the explorative regression analysis to prove a mediational pathway. We concluded that ImPuls showed efficacy across diagnostically heterogenous outpatients. The increase in exercise seemed to underlay treatment effects on global symptom severity. Exercise interventions may serve as an efficacious and efficient treatment option for the outpatient mental health care. Future studies are warranted to replicate findings with an active control condition and robust mediation analyses.

2.2 Manuscript II

“The increase in heart rate variability mediates exercise effects on global symptom severity across heterogenous mental disorders: A secondary analysis of the ImPuls trial” (Zeibig et al., under review)

Objectives and methods: Manuscript II investigated an increase in resting vmHRV and a reduction in perceived stress as potential transdiagnostic mechanisms mediating treatment effects of ImPuls on global symptom severity across diagnostically heterogenous outpatients (Manuscript I). At baseline and post-treatment, global symptom severity (Symptom Checklist-90) (Derogatis, 1994), resting vmHRV (indexed by HRV-RMSSD) and perceived stress (Perceived Stress Scale) (Cohen et al., 1983) were assessed.

Data analysis: To test differences between groups in the increase in resting vmHRV, LMMs were conducted. Models included group allocation, assessment point and their interaction as predictors. The mediation analysis was conducted using structural equation modeling (SEM) with the group allocation as the predictor and with the reduction in global symptom severity as the outcome. The increase in resting vmHRV was selected as mediator. Both statistical methods were conducted on the intention-to-treat sample.

Results and discussion: The intervention group increased in resting vmHRV with large effects size and did not significantly reduce perceived stress relative to the control group (i.e., small effect). An increase in resting vmHRV partially mediated the intervention effect on global symptom severity. Limitations of the study were the deficient control of certain factors that could have potentially influenced HRV parameters as well as participants’ low initial levels of perceived stress and high initial levels of resting vmHRV. Therefore, the included sample may not have been representative in terms of resting vmHRV levels and stress perception. We concluded that an exercise intervention can successfully increase the ability to adaptively cope with stressors which partially mediated its efficacy on reducing global symptom severity. Study results established evidence that improving the ability to adaptively cope with stressors may be a potential transdiagnostic mechanism mediating the treatment effects of exercise interventions across diagnostically heterogeneous mental disorders. Future studies are required to replicate findings with higher standardization of HRV assessments and a wider range of baseline levels of resting vmHRV and

perceived stress.

2.3 Manuscript III

“Long-term efficacy of exercise across diagnostically heterogenous mental disorders and the mediating role of affect regulation skills” (Zeibig et al., 2022)

Objectives and methods: Manuscript III investigated whether beneficial effects of ImPuls on disorder-specific global symptom severity (Manuscript 1) could be maintained over a one-year follow-up period. It was further investigated whether an increase in exercise and exercise-specific affect regulation from baseline to follow-up underlay long-lasting treatment effects. Primary outcome was global symptom severity (Symptom Checklist-90) (Derogatis, 1994), including clinically significant changes. Secondary outcomes were self-reported exercise (Physical Activity, Exercise, and Sport Questionnaire) (Fuchs et al., 2015), exercise-specific affect regulation (Physical Activity-related Health Competence Questionnaire) (Sudeck et al., 2016) and depression (Symptom Checklist-90). Primary and secondary outcomes were assessed at baseline, post-treatment, and follow-up (one-year after post-treatment).

Data analysis: To test differences between groups in changes of primary and secondary outcomes, LMMs were conducted. Models included group allocation, assessment point and their interaction as predictors. Mediation analyses were conducted using SEM with the group allocation as the predictor and with a reduction in global symptom severity and clinically significant changes (i.e., based on a reliable change index and clinical cut-off, participants are classified into four categories: recovered, improved, unchanged, deteriorated (Franke, 2013)) as outcomes. Increases in exercise and exercise-specific affect regulation were selected as mediators. Both statistical methods were conducted on the intention-to-treat sample.

Results and discussion: From baseline to follow-up, the exercise intervention led to a reduction in global symptom severity compared to the control group with moderate effect size. The intervention group was more likely to reveal clinically significant changes compared to the control group. Considering the subsample of participants with depressive disorders, depression was reduced in the intervention group compared to the control group with moderate effect size. Exercise increased in the intervention group compared to the control group with moderate effect size. Exercise-specific affect regulation increased in the intervention group compared to the control group with

moderate to large effect size. An increase in exercise-specific affect regulation mediated the intervention effect on global symptom severity and clinically relevant changes from baseline to follow-up. One major limitation of this study was the high attrition rate at follow-up. We concluded that treatment gains of ImPuls immediately after the intervention (Manuscript 1) were maintained long after the end of the intervention. Results suggest that ImPuls might be a long-term efficacious treatment across diagnostically heterogenous outpatients due to its long-lasting promotion of exercise-specific affect regulation. Future studies are needed to replicate findings including strategies to reduce the attrition rate.

3 Discussion

3.1 Summary

Exercise interventions represent an efficacious treatment across depressive disorders, anxiety disorders, insomnia and ADHD (Ashdown-Franks et al., 2020). Scientific evidence suggests that the efficacy of exercise interventions across these diagnostically heterogenous mental disorders may be due their beneficial effects on shared underlying (transdiagnostic) mechanisms leading to their onset and maintenance (Jacquart et al., 2019). Improving the ability to adaptively cope with stressors seems to mediate treatment effects of exercise interventions across these mental disorders (e.g., Jacquart et al., 2019). The beneficial effects of exercise interventions seem to be maintained when they enable participants to engage in regular, long-term exercise (Hoffman et al., 2011) and to intentionally use exercise to reduce negative affect (Bernstein et al., 2018; Rösel et al., 2022).

However, assumptions about the efficacy of exercise interventions across diagnostically heterogenous mental disorders as well as transdiagnostic mechanisms of action are based on theoretical considerations (e.g., Ekkekakis, 2003), longitudinal or cross-sectional studies (e.g., Klaperski, 2018) or experimental studies with non-clinical or disorder-specific samples (Jacquart et al., 2019). Moreover, in experimental studies, mechanisms of action are usually investigated by correlational analyses rather than by appropriate mediation analyses (e.g., Jacquart et al., 2019). In addition, long-term effects of exercise interventions for mental disorders have been studied infrequently or with short follow-up periods (Aylett et al., 2018; Cooney et al., 2013). To fill these research gaps, the aim of the current dissertation was the investigation of the short- and long-term efficacy of an exercise intervention across diagnostically heterogenous outpatients and its transdiagnostic mechanisms of action.

For this investigation, an exercise intervention for diagnostically heterogenous mental disorders was developed prior to this dissertation (Wolf, Zeibig, Hautzinger, et al., 2020). The intervention, namely ImPuls, integrates the most recent evidence on efficacious components for sustained symptom improvement across depressive disorders, anxiety disorders, insomnia, and ADHD. In this dissertation, ImPuls was evaluated in an RCT among 72 initially physically inactive outpatients with the aforementioned mental disorders. Participants were randomly assigned to the intervention or a passive control condition.

From baseline to post-treatment, ImPuls led to a reduction in global symptom

severity with moderate to large effect size as well as disorder-specific symptoms (depression with moderate effect size, anxiety with large effect size, sleep quality with large effect size) compared to the control group. Considering a subsample of participants with depressive disorders, depression was reduced with moderate to large effect size in the intervention group compared to the control group. Exercise was increased among the intervention group with large effect size compared to the control group. Resting vmHRV (indexed by HRV-RMSSD) increased with large effect size and self-reported stress reduced with small but non-significant effect size in the intervention group compared with the control group. Across both conditions, an increase in exercise significantly predicted a reduction in global symptom severity. An increase in resting vmHRV partially mediated the intervention effect on global symptom severity. We concluded that an exercise intervention can be efficacious across diagnostically heterogenous outpatients. An increase in exercise and particularly the improved ability to adaptively cope with stressors (as indexed by resting vmHRV) may be transdiagnostic mechanisms that underlie beneficial effects of exercise interventions on symptoms across diagnostically heterogenous mental disorders.

From baseline to follow-up, ImPuls led to a reduction in global symptom severity with moderate effect size compared to the control group. The intervention group was more likely to reveal clinically significant changes than the control group. Considering a subsample of participants with depressive disorders, depression was reduced with moderate effect size in the intervention group compared to the control group. Exercise was increased among the intervention group with moderate effect size compared to the control group. Exercise-specific affect regulation increased with moderate to large effect size in the intervention group compared with the control group. An increase in exercise-specific affect regulation mediated the intervention effect on global symptom severity (statistically and clinically relevant changes) from baseline to follow-up. We concluded that an exercise intervention can be a long-term efficacious treatment across diagnostically heterogenous outpatients. The improved ability to intentionally use exercise as an affect regulation strategy seems to underlie long-lasting treatment effects.

3.2 Discussion of the main findings

3.2.1 Short-term intervention effects and transdiagnostic mechanisms

The results presented above (see *section 2.1*) suggest that ImPuls might be an

efficacious treatment in reducing global symptom severity and disorder-specific symptoms across a diagnostically heterogenous outpatient sample. These findings corroborate previous results about beneficial effects of disorder-specific exercise interventions on symptoms of depressive disorders, anxiety disorders, insomnia and ADHD in disorder-specific samples (Ashdown-Franks et al., 2020). The finding of a moderate to large intervention effect on reducing depression among participants with depressive disorders is consistent with previous meta-analytical findings of a large antidepressant effect of exercise (Morres et al., 2019). Comorbidity might reduce treatment effects (Vittengl et al., 2019). Therefore, the slightly inferior effect size in our study might be attributed to the inclusion of individuals with depressive disorders with and without comorbid anxiety disorders. However, authors did not state whether participants had comorbid diagnoses (Morres et al., 2019). Participants' comorbidity is usually not reported in exercise trials (Bond et al., 2020). Hence, this interpretation needs to be considered with caution. Additionally, results on depression across the entire sample provide novel evidence for a moderate antidepressant effect of exercise among a diagnostically heterogenous sample with and without depression. Evidence about the anxiolytic effect of exercise across anxiety disorders suggests a small to moderate effect over non-active controls (Ramos-Sanchez et al., 2021). In contrast, the anxiolytic effect of ImPuls among our mixed sample was large. In their meta-analysis, individuals with PTSD, OCD and mixed anxiety disorders yielded the smallest effect sizes (Ramos-Sanchez et al., 2021). We included only a small percentage of these diagnoses in our study: three individuals with PTSD (7.3% from all participants with any anxiety disorders), no individual with OCD and two individuals with mixed anxiety disorders (4.9% from all participants with any anxiety disorders). This might explain the larger effect size that we found in our study. A meta-analysis about effects of exercise interventions on improving sleep quality across mental disorders (Lederman et al., 2019) demonstrated moderate to large effects versus active or non-active controls. This is consistent with our finding indicating a large effect of the exercise intervention on improving sleep quality across the entire sample. In contrast to our study, the meta-analysis did not include a primary diagnosis of insomnia (Lederman et al., 2019). However, the effect sizes for the improvement of sleep quality seem to be larger for individuals diagnosed with insomnia compared to their non-diagnosed counterparts (Banno et al., 2018). This might explain the slightly larger effect size in our study. Slightly superior effect sizes in our study compared to previous

meta-analytical evidence for anxiety and insomnia need to be considered with caution due to the use of different control conditions. In contrast to our study, which used a passive control condition, previous meta-analyses (Lederman et al., 2019; Ramos-Sanchez et al., 2021) have compared exercise interventions with inactive control conditions (e.g., treatment as usual (TAU), time- and attention-matched control activities) and active control conditions (e.g., talking therapy) which may also reduce psychopathological symptoms. Nevertheless, a possible superiority of transdiagnostic treatments over disorder-specific treatments can be assumed (Newby et al., 2016; Păsărelu et al., 2017). While disorder-specific interventions focus on the primary clinical diagnosis, transdiagnostic treatments, such as ImPuls, also address comorbid mental disorders or elevated symptoms (Dalgleish et al., 2020). Mental disorders usually occur with comorbid mental disorders (Kessler et al., 2005) which can deteriorate symptom severity (Franzen et al., 2008; Klein Hofmeijer-Sevink et al., 2012; Ramsawh et al., 2009). In addition, secondary diagnoses often persists even after efficacious treatment of the primary diagnosis (e.g., Riemann et al., 2015). Therefore, ImPuls may be more efficacious in improving symptom severity than previous disorder-specific exercise interventions.

Results extend previous findings by assessing effects on global symptom severity in a diagnostically heterogenous sample. In addition, exercise trials usually do not account for comorbid presentations of mental disorders (Bond et al., 2020). For example, in a sample of patients with depressive disorders and comorbid anxiety disorders, only changes of depression were assessed as outcome (Bond et al., 2020). In contrast, the current measure of global symptom severity assesses the reduction in global symptom severity independent of a specific diagnosis. Thus, we established evidence for the efficacy of exercise interventions across diagnostically heterogenous mental disorders (with and without comorbid mental disorders).

In essence, the current results provide novel evidence for the efficacy of exercise interventions across diagnostically heterogenous mental disorders using a clinical valid measure of global symptom severity. Additionally, we demonstrated that an exercise intervention designed for diagnostically heterogenous mental disorders can reveal comparable disorder-specific effects on depression, anxiety, and insomnia as exercise interventions designed for a single mental disorder (Ashdown-Franks et al., 2020).

Current results suggest that ImPuls was efficacious in increasing participants'

exercise behavior during and after the intervention period. At post-treatment, participants in the intervention group reported higher levels of exercise during the non-supervised period of ImPuls compared to the control group. Therefore, it can be assumed that the exercise intervention led to independent exercise behavior regardless of personal supervision. Thus, participants may have already incorporated regular exercise into their daily lives. This finding supports the results of a recent systematic review (Thomas et al., 2020) showing that exercise interventions combined with BCTs are more efficacious than exercise alone in increasing exercise in people with and without mental disorders. Nevertheless, only 25% of exercise interventions with BCTs seem to efficaciously increase exercise (Ashdown-Franks et al., 2018). It might be possible that previous exercise interventions and BCTs were not adequately tailored to the needs of outpatients. For instance, they might not have addressed specific deficits in motivation and volition (see *section 1.5*). In contrast, the current results suggest that ImPuls was adequately tailored to the needs of outpatients. The increase in exercise was essential because it was predictive of the reduction in global symptom severity. This finding suggests that the increase in exercise leads, at least partially, to treatment effects. This mechanism of action is often assumed in the previous studies but rarely investigated (Ashdown-Franks et al., 2020).

The results presented above (see *section 2.2*) suggest that ImPuls might be an efficacious transdiagnostic treatment by increasing the ability to adaptively cope with stressors across a diagnostically heterogenous sample. Nevertheless, the intervention did only increase resting vmHRV and not perceived stress with statistical significance. A significant positive correlation between an increase in resting vmHRV and a reduction in perceived stress in the current study proposes that both measures may be associated. This is in accordance with the transactional model of stress and coping of stress (Lazarus et al., 1984) which states that perceived stress occurs when one's ability to adaptively cope with a particular stressor (as indexed by resting vmHRV) is appraised to be insufficient. The non-significant result for perceived stress might be caused by the power-calculation that was based on moderate to large (d = 0.74) effects of exercise on disorder-specific symptoms for depressive disorders, anxiety disorders and insomnia (Kelley et al., 2017; Powers et al., 2015; Schuch et al., 2016). Effects of exercise on resting vmHRV have been considered as large (median of effect sizes: d = 0.93) (Sandercock et al., 2005; Toni et al., 2016) which is comparable to the disorder-specific effects of exercise. In contrast, effects of exercise on perceived stress have

been demonstrated to be small (median of effect sizes: d = 0.27) in previous literature (Jacquart et al., 2019). Therefore, the sample size might have been too small to detect a significant small effect of exercise on perceived stress.

Available evidence of the effects of exercise interventions on resting vmHRV among individuals with mental disorders is consistent with our results (Gaul-Alácová et al., 2005; Toni et al., 2016). In an RCT, Toni et al. (2016) demonstrated that an exercise intervention (in combination with antidepressant use) efficaciously increased resting vmHRV in elderly depressed participants with a large effect size compared with antidepressant use alone. A meta-analysis of the effects of regular exercise on HRV indices among non-clinical samples (Sandercock et al., 2005) demonstrated a moderate within-group effect size on increasing resting vmHRV. These comparisons indicate that the results about an exercise-induced increase in resting vmHRV among disorder-specific and non-clinical samples might be transferable to samples with diagnostically heterogenous mental disorders.

The current finding about the small (non-significant) effect of the exercise intervention on perceived stress is in line with previous meta-analytical findings (Jacquart et al., 2019). Authors demonstrated a small effect on self-reported stress reactivity among healthy samples and a small but not-significant effect on self-reported distress tolerance (i.e., the perceived ability to tolerate stressors) among healthy samples and samples with anxiety disorders. Effects can be compared to our study results of the effects on perceived stress because self-reported stress reactivity and distress tolerance are strongly correlated with perceived stress (Felton et al., 2017; Schlotz et al., 2011). Study results expand on limited evidence about effects of exercise interventions on resting vmHRV and perceived stress by investigating this effect in a clinical sample of diagnostically heterogenous mental disorders.

The increase in resting vmHRV seem to be a transdiagnostic mechanism of action that underlies immediate beneficial effects of exercise interventions on global symptom severity across diagnostically heterogenous mental disorders. The finding of a *partial* mediation assumes additional underlying mechanisms (e.g., reduction in rumination, increase in self-efficacy) of treatment effects. We are aware of only one study that also investigated an increase in resting vmHRV as a mechanism that mediates treatment effects of exercise in a clinical sample (Toni et al., 2016). In the exercise trial of elderly depressed patients (Toni et al., 2016), the authors examined the effects of resting vmHRV on depression status using a correlational analysis. An

increase in resting vmHRV and remission from depression were not significantly associated. Although based on an exploratory analysis, the results suggest that factors other than an increase in resting vmHRV may have mediated the treatment effects. Contrasting results in our study could have been caused by a different outcome and sample. While the authors used a cut-off score of the Hamilton Depression Rating Scale to define remission (yes/no), we used a continuous variable as the study outcome. Continuous variables contain more information than dichotomous ones. Thus, it could be assumed that our findings about vmHRV as a partial mediator of treatment outcomes of exercise might be more valid. Similar to the statistical analysis of Toni et al. (2016), mechanisms of action are often investigated using correlation analyses (e.g., Jacquart et al., 2019). A correlation analysis, however, is not sufficient to make assumptions about mediators of treatment effects (Kazdin, 2007).

Study results extend the current state of research regarding transdiagnostic mechanisms mediating treatment effects of exercise interventions by using a diagnostically heterogenous clinical sample and mediation analyses. To date, very little research has been established about transdiagnostic mechanisms that may mediate treatment effects of exercise interventions across diagnostically heterogenous mental disorders. They are either assumed based on theoretical considerations (e.g., Ekkekakis, 2003), longitudinal or cross-sectional studies (e.g., Klaperski, 2018). Moreover, limited experimental studies are usually conducted with healthy and disorder-specific samples (Jacquart et al., 2019). Therefore, we established valid empirical evidence about transdiagnostic mechanisms of action of exercise interventions across diagnostically heterogeneous mental disorders. Results are important to improve the efficacy of exercise interventions and to tailor them to the needs of diagnostically heterogeneous mental disorders.

3.2.2 Long-term intervention effects and transdiagnostic mechanisms

The results presented above (see *section 2.3*) suggest that ImPuls might be a long-term efficacious treatment by reducing global symptom severity and revealing clinically significant changes one year after the intervention had ended. Hence, treatment gains of ImPuls immediately after the intervention (Manuscript 1) were maintained after the intervention period. The current results support previous meta-analytical evidence about follow-up effects of disorder-specific exercise interventions (Siu et al., 2021). Previous studies suggest small follow-up effect sizes of exercise interventions for improving depression (Cooney et al., 2013), anxiety (Aylett et al.,

2018) and insomnia (Siu et al., 2021) over active and non-active controls. Slightly inferior effect sizes in previous studies might be due to the comparison to active control groups or a potential superiority of transdiagnostic interventions over disorder-specific ones (see section 3.2.1). Exercise trials often include no or relatively short follow-up periods (e.g., three weeks) (Aylett et al., 2018; Cooney et al., 2013; Siu et al., 2021). Therefore, we expand previous research by demonstrating the maintenance of symptom improvement even one year after participating in an exercise intervention. In addition, to the best of our knowledge, this is the first study that examined follow-up effects of an exercise intervention on global symptom severity in a diagnostically heterogenous sample with mental disorders.

Furthermore, the intentional use of exercise to cope with negative affect seems to play a key role for remaining treatment effects (Sudeck et al., 2022). An increase in exercise-specific affect regulation mediated long-lasting treatment effects on global symptom severity and clinically significant changes. Therefore, our results support theoretical considerations (Pfeifer et al., 2013; Sudeck et al., 2016) and empirical evidence about the importance of exercise-specific affect regulation to improve mental health (Sudeck et al., 2022). We extent the previous evidence by experimentally investigating its mediating role on long-lasting effects of exercise and by using a diagnostically heterogenous clinical sample that shared affect regulation deficits (Gross et al., 2019). Furthermore, results challenge previous empirical evidence suggesting that long-term exercise behavior alone is responsible for treatment effects (Babyak et al., 2000; Hoffman et al., 2011). Even though ImPuls led to long-lasting exercise, the increase in exercise did not mediate long-lasting treatment effects. Results are in accordance with findings from Manuscript 2 (see *section 2.2*) demonstrating that the increase in the ability to adaptively cope with stressors partially mediate immediate treatment effects. Hence, maintaining the ability to reduce negative affect (including stress), by using exercise as an affect regulation strategy during a follow-up period, seems to be important for remaining treatment effects. Results suggest that BCTs which particularly aimed to promote exercise-specific affect regulation might be a key component of exercise interventions to reveal reliable treatment gains. Mechanisms that underlie long-lasting treatment effects of exercise interventions had been relatively unknown. Therefore, results provide important evidence regarding the identification of essential components of exercise interventions for long-lasting efficacy.

Although the assessment of clinically significant changes (Jacobson et al., 1991) has been considered as the most encompassing method to assess treatment gains (Loerinc et al., 2015), it has been rarely included within exercise trials. Hence, results provide novel insights into the long-term efficacy of exercise trials on global symptom severity with respect to both, statistical significance based on group level and individual clinically meaningful treatment responses.

3.3 Strength and limitations

3.3.1 Strengths

The strengths of the study are manifold. First, the design of the study can be mentioned as a major strength. The use of an RCT (i.e., random assignment to intervention or control group, concealment, intention-to-treat analysis, pre-specified primary outcomes, ethical approval, registration in a clinical trials database) increased validity of study results (Kunz et al., 2007). Therefore, an RCT is considered the gold standard for evaluating the efficacy of interventions. In addition, equality of treatment arms and allocation maximized internal validity (Hey et al., 2014). By establishing strict inclusion and exclusion criteria, factors that could bias outcome measures were controlled for (Stanley, 2007). Furthermore, the long-term follow-up period of one year after post-treatment contributes to evidence about long-term effects of exercise long beyond a treatment period. Long-term follow-up effects had been rarely investigated or only with short-term follow-up periods (Aylett et al., 2018; Cooney et al., 2013).

Second, the mechanisms of action underlying the treatment effects of exercise have never been studied in this way: 1) assessments of transdiagnostic mechanisms across a diagnostically heterogenous sample, 2) mechanisms that underlie short-term and long-term treatment effects, 3) conduction of valid and reliable mediation analyses using SEMs and the intention-to-treat sample. Previous experimental studies have either investigated potential mechanisms of action in non-clinical or disorder-specific samples (e.g., Jacquart et al., 2019) which do not allow to draw conclusions about transdiagnostic mechanisms of action across diagnostically heterogenous mental disorders. Similarly, mechanisms of action are often investigated using correlation analyses (e.g., Jacquart et al., 2019). A correlation analysis, however, is not sufficient to make assumptions about mediators of treatment effects (Kazdin, 2007).

Third, the implementation of the exercise intervention ImPuls among realistic groups of outpatients (i.e., the proportion of mental disorders in the current sample corresponds to the prevalence of these mental disorders in Germany (Global Burden

of Disease Collaborative Network, 2020), comorbid and non-comorbid clinical diagnoses (Kessler et al., 2005), a large number of included patients with severe, clinically elevated symptomatology, wide age range) within a naturalistic outpatient setting (i.e., during waiting periods for psychotherapy) is another strength. Hence, study results may predict a successful applicability of ImPuls in outpatient mental health care settings in Germany.

Fourth, the inclusion of global symptom severity with clinically significant changes as primary outcome and the use of resting vmHRV as a physiological indicator of the ability to adaptively cope with stressors can be mentioned as an additional strength. The Global Severity Index of the SCL-90 was used to measure global symptom severity. The SCL-90 is an instrument that can reliably and validly assess global symptom severity and clinically significant changes across diagnostically heterogeneous mental disorders (Derogatis et al., 2010). In addition, the use of this instrument is widespread internationally (Derogatis, 1994). Therefore, the results of the study can be compared with international findings on the effects of different treatments on symptom severity. A global measure of symptom severity and the assessment of clinical significance have rarely been applied in exercise trials. Therefore, our study results provide new insights into the efficacy of exercise on global symptom severity across diagnostically heterogenous mental disorders as well as into the efficacy on individual clinically meaningful responses to treatment. Furthermore, the physiological measure of the ability to adaptively cope with stressors (i.e., HRV-RMSSD) might have reduced potential bias (e.g., recall bias) of retrospective self-report measures.

3.3.2 Limitations

The dissertation has several limitations that need to be considered when interpreting results. First, the high attrition rate can be mentioned as a major limitation. The high number of dropouts at post-treatment and at follow-up combined with a significant differential dropout between conditions at post-treatment might have biased results. To reduce this potential source of bias, we handled missing data in each manuscript as follows: 1) Mechanisms of missingness were assessed using Little's test of missing completely at random, 2) analyses were performed on the intention-to-treat sample using the (full-information) maximum likelihood method that is offered in the R package *lme4* for LMMs (Bates et al., 2015) and *lavaan* for SEM (Rosseel, 2012), 3) per-protocol analyses (completers only) assessed whether the inclusion and exclusion of dropouts influenced results, 4) baseline values between completers and dropouts

were compared. Missing data were missing at random, sensitivity analyses yielded largely identical results and we found no differences between completers versus dropouts which mitigates the source of bias.

Second, by using a passive control condition, we could not control for non-specific treatment effects. Nevertheless, we could demonstrate that an increase in exercise (exploratory assessed; Manuscript 1) and an increase in the ability to adaptively cope with stressors (Manuscript 2) might be transdiagnostic mechanisms of action of the immediate reduction in global symptom severity. In addition, an increase in exercise-specific affect regulation might be a transdiagnostic mechanism of action of the long-term reduction in global symptom severity (Manuscript 3). These results propose that the increase in exercise and exercise-specific affect regulation as well as the increase in the ability to adaptively cope with stressors might mediate treatment effects of the exercise intervention across diagnostically heterogenous mental disorders and not (only) other non-specific effects of treatment.

Third, the power calculation was based on disorder-specific effects of exercise (depression, anxiety, sleep quality) (Kelley et al., 2017; Powers et al., 2015; Schuch et al., 2016) of immediate intervention effects. Therefore, the sample size was not intended to detect effects of transdiagnostic mechanisms (e.g., perceived stress) or long-term treatment effects. Hence, it might be possible that the power was not appropriate to find certain effects (e.g., a reduction in perceived stress).

Fourth, the sample was selective which might have diminished the external validity of results: 1) the sample took part voluntarily, 2) only one participant was diagnosed with ADHD which limits the generalizability of results to individuals with that particular mental disorder, 3) participants' mean baseline resting vmHRV and perceived stress levels were not lower compared with non-clinical samples (Nunan et al., 2010; Schneider et al., 2020). Thus, levels of resting vmHRV and perceived stress in the current sample may not be representative of a broader population of individuals with mental disorders (e.g., Koch et al., 2019; Schneider et al., 2020).

Fifth, even though there was a high standardization in HRV assessment (Manuscript 3), we did not control for some factors that could have potentially influenced HRV parameters. For instance, we did not standardize the timing of the assessment (van Eekelen et al., 2004) or participants’ posture (e.g., knees at 90◦ angle, both feet flat on the floor, hands on thighs) (Laborde et al., 2017). Furthermore, we did not objectively measure potentially confounding variables that we controlled for

(e.g., normal sleep routine), as recommended (Laborde et al., 2017).

3.4 Future directions

Future research is warranted to replicate results by addressing the limitations of the current study. First, it would be important to incorporate strategies that could reduce the attrition rate in the entire sample and particularly in the control group. We propose the following strategies to reduce attrition rates in exercise trials with mental disorders: 1) the comparison of the exercise intervention plus TAU versus TAU alone would reduce the necessity of excluding participants due to administrative reasons (e.g., change in treatment during the intervention period), 2) to ensure participants' willingness to take part in the assessments, financial incentives could be raised (Khadjesari et al., 2011), 3) regular reminders of upcoming assessments would allow to increase participants' awareness of this assessment point. To avoid high attrition rates, particularly among the control group, it might be useful to 1) replicate findings with an active control condition (e.g., psychotherapeutic treatment) with similar duration and regularity of meetings, or 2) increase the attractiveness to continue participating in the study, for instance by providing intervention materials after the last assessment point. The use of an appropriate active control condition would also allow to control for non-specific factors of treatment. In addition, it would allow better comparability with previous interventions because active controls are predominantly used.

Second, study results need to be replicated with an a priori power calculation for mediation analyses, follow-up analyses, or oriented on the variable on which exercise interventions showed the smallest effect (e.g., perceived stress). The resulting larger sample size would allow to investigate the efficacy of exercise among further subgroups (e.g., only anxiety disorders, comorbid vs. non-comorbid diagnoses, high vs. low levels of resting vmHRV or perceived stress, medicated vs. non-medicated). Thus, a larger sample size would provide novel insights into potential differences in the efficacy of exercise interventions across specific subgroups. Furthermore, a larger sample size would allow the testing of additional transdiagnostic mechanisms of actions (e.g., anxiety sensitivity, self-efficacy) (Jacquart et al., 2019) and their individual contribution to treatment effects. This would provide valuable insights into essential components of exercise interventions for diagnostically heterogenous mental disorders. This knowledge could be used to increase efficacy of exercise interventions that can be used for diagnostically heterogenous mental

disorders that share similar transdiagnostic mechanisms. A follow-up project with a larger sample size is currently being conducted to further investigate transdiagnostic mechanisms of ImPuls (Wolf et al., 2021).

Third, to reduce selection bias, it might be useful to select participants who do not participate in the intervention only voluntarily. For example, ImPuls could be conducted as a standard treatment in a psychiatric hospital. Participants could also be screened according to a certain characteristic (e.g., motivation for exercise) to ensure that a large variance of this characteristic (e.g., low, moderate, and high motivation for exercise) is present in the study. Pre-selection would also avoid that shared characteristics (e.g., high motivation for exercise) influence results. In addition, the efficacy of ImPuls could be examined among a sample with different characteristics. For example, ImPuls could be conducted with children, adolescents or older adults since evidence suggests that exercise interventions can reduce psychopathological symptoms across all age groups (Ashdown-Franks et al., 2020; Seiffer et al., in press). Furthermore, the sample might be extended to other mental disorders for which exercise has shown to be efficacious, such as schizophrenia (Ashdown-Franks et al., 2020). To further reduce selection bias, the intervention could be extended to individuals receiving TAU (e.g., psychotherapy). The follow-up project (Wolf et al., 2021), mentioned in the previous paragraph, compares ImPuls (plus TAU) with TAU alone.

Fourth, the standardization of the HRV assessment could be increased. For example, one could control for participants' sitting position during the assessment or conduct questionnaires prior to assessment that control for specific factors (e.g., previous caffeine intake) that could potentially influence HRV results. It would be interesting to measure not only the effects of exercise on the ability to adaptively cope with stressors but also on general physiological stress levels. To measure physiological stress levels, sympathetic activity (e.g., via pre-ejection period) and the activity of the hypothalamus-pituitary-adrenal (HPA) axis (e.g., via cortisol or alpha amylase, in addition to vmHRV and perceived stress, need to be assessed (Charmandari et al., 2005). To gain a more comprehensive understanding of the effects of exercise on the ability to cope with stressors, stress reactivity and recovery could additionally be examined (Laborde et al., 2018). Stress reactivity and stress recovery could be investigated using valid stress tests, such as the Trier Social Stress Test (Kirschbaum et al., 1993), or using ecological momentary assessments (Shiffman et

al., 2008) for investigations in natural settings. In addition, to be able to draw clearer causal conclusions about mechanisms of action, studies are needed that manipulate those mechanisms and measure them prior the outcome (Kazdin, 2007; Kraemer et al., 2002).

3.5 Practical implications

Exercise interventions such as ImPuls could be implemented as a standard (stand-alone or add-on) treatment in the outpatient mental health care in Germany because they could contribute significantly to improve the outpatient mental health care. The long-term efficacy suggests that ImPuls is a sustainable treatment that could improve the course of mental disorders in the long-term. Consequently, no or fewer follow-up treatments might be needed after participating in exercise intervention. As a result, exercise interventions as a standard outpatient treatment would improve the large treatment gap in Germany and its severe consequences (see Figure 1 and *section 1.4*). To reveal short- and long-term efficacy, exercise interventions designed for outpatient mental health settings need to integrate key components of ImPuls: 1) characteristics of exercise interventions that have been associated with optimal efficacy in in treating diagnostically heterogenous mental disorders and 2) the inclusion of BCTs that promote long-lasting exercise behavior and exercise-specific affect regulation (see *section 1.5*).

3.6 Conclusion

The present dissertation demonstrates that the exercise intervention ImPuls, combining regular exercise with BCTs and designed for diagnostically heterogeneous outpatients, has the potential to improve disorder-specific symptoms and global symptom severity across depressive disorders, anxiety disorders, insomnia and ADHD compared to a passive control condition. Treatment gains were maintained one-year after the end of the intervention. Potential mechanisms of immediate intervention effects were increases in exercise and the ability to adaptively cope with stressors; the potential mechanism of long-lasting treatment effects was an increase in exercise-specific affect regulation. Thus, exercise interventions such as ImPuls could provide a feasible, efficacious, and sustainable evidence-based treatment for a broad range of outpatients. Consequently, defining exercise interventions as a standard outpatient treatment could help to close the treatment gap that exists in the German mental health care system. Results of the present dissertation make an important contribution to the understanding of the transdiagnostic mechanisms of exercise interventions which are

still poorly investigated. In addition, they demonstrate that exercise interventions can be used in the treatment of diagnostically heterogenous patients that share similar transdiagnostic mechanisms. This will allow for progress in the treatment of diagnostically heterogeneous mental disorders as essential treatment components may have been identified. Future studies are needed to replicate the results with an active control condition as well as a larger, broader, and less-selective sample to increase external validity. Future research should focus on the investigations of other transdiagnostic mechanisms of action to further strengthen the efficacy of exercise interventions for diagnostically heterogenous mental disorders.

References

American Psychological Association. (2020). *Patients with Depression and Anxiety Surge as Psychologists Respond to the Coronavirus Pandemic*. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjeitfdzsv7AhXeRvEDHbdxDl0QFnoECBQQAw&url=https%3A%2F%2Fwww.apa.org%2Fnews%2Fpress%2Freleases%2F2020%2F11%2Ftelehealth-survey-summary.pdf&usg=AOvVaw0W_7yKK0Qn7UM0mgmNMUST

Arnsten, A. F., & Goldman-Rakic, P. S. (1998). Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. *Arch Gen Psychiatry, 55*(4), 362-368. https://doi.org/10.1001/archpsyc.55.4.362

Ashdown-Franks, G., Firth, J., Carney, R., Carvalho, A. F., Hallgren, M., Koyanagi, A., Rosenbaum, S., Schuch, F. B., Smith, L., & Solmi, M. (2020). Exercise as medicine for mental and substance use disorders: a meta-review of the benefits for neuropsychiatric and cognitive outcomes. *Sports Med, 50*(1), 151-170.

Ashdown-Franks, G., Williams, J., Vancampfort, D., Firth, J., Schuch, F., Hubbard, K., Craig, T., Gaughran, F., & Stubbs, B. (2018). Is it possible for people with severe mental illness to sit less and move more? A systematic review of interventions to increase physical activity or reduce sedentary behaviour. *Schizophr Res, 202*, 3-16. https://doi.org/10.1016/j.schres.2018.06.058

Aubert, A. E., Seps, B., & Beckers, F. (2003). Heart rate variability in athletes. *Sports Med, 33*(12), 889-919. https://doi.org/10.2165/00007256-200333120-00003

Aylett, E., Small, N., & Bower, P. (2018). Exercise in the treatment of clinical anxiety in general practice - a systematic review and meta-analysis. *BMC Health Serv Res, 18*(1), 559. https://doi.org/10.1186/s12913-018-3313-5

Babyak, M., Blumenthal, J. A., Herman, S., Khatri, P., Doraiswamy, M., Moore, K., Craighead, W. E., Baldewicz, T. T., & Krishnan, K. R. (2000). Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom Med, 62*(5), 633-638. https://doi.org/10.1097/00006842-200009000-00006

Balzarotti, S., Biassoni, F., Colombo, B., & Ciceri, M. R. (2017). Cardiac vagal control as a marker of emotion regulation in healthy adults: A review. *Biol Psychol, 130*, 54-66. https://doi.org/10.1016/j.biopsycho.2017.10.008

Bamert, M., & Inauen, J. (2022). Physiological stress reactivity and recovery: Some laboratory results transfer to daily life. *Front Psychol, 13*, 943065. https://doi.org/10.3389/fpsyg.2022.943065

Bandelow, B., Wiltink, J., Alpers, G. W., Benecke, A., Benecke, C., Deckert, J., Domschke, K., Eckhardt-Henn, A., Geiser, F., Gerlach, A. L., Harfst, T., Hau, S., Hoffmann, S., Hoyer, J., Hunger-Schoppe, Kellner, M., Köllner, V., Kopp, I., Langs, G., & Beutel, M. E. (2021). *Deutsche S3-Leitlinie Behandlung von Angststörungen*. https://www.awmf.org/uploads/tx_szleitlinien/051-028l_S3_Behandlung-von-Angststoerungen_2021-06.pdf

Banno, M., Harada, Y., Taniguchi, M., Tobita, R., Tsujimoto, H., Tsujimoto, Y., Kataoka, Y., & Noda, A. (2018). Exercise can improve sleep quality: a systematic review and meta-analysis. *PeerJ, 6*, e5172. https://doi.org/10.7717/peerj.5172

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *J Stat Softw, 67*(1), 1-48.

https://doi.org/10.18637/jss.v067.i01
BAuA. (2022). *Volkswirtschaftliche Kosten durch Arbeitsunfähigkeit 2020*. https://www.baua.de/DE/Themen/Arbeitswelt-und-Arbeitsschutz-im-Wandel/Arbeitsweltberichterstattung/Kosten-der-AU/pdf/Kosten-2020.pdf?__blob=publicationFile&v=1
Beauchaine, T. P., & Thayer, J. F. (2015). Heart rate variability as a transdiagnostic biomarker of psychopathology. *Int J Psychophysiol, 98*(2 Pt 2), 338-350. https://doi.org/10.1016/j.ijpsycho.2015.08.004
Bernstein, E. E., & McNally, R. J. (2018). Exercise as a buffer against difficulties with emotion regulation: A pathway to emotional wellbeing. *Behav Res Ther, 109*, 29-36. https://doi.org/10.1016/j.brat.2018.07.010
Berntson, G. G., Bigger, J. T., Jr., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., Nagaraja, H. N., Porges, S. W., Saul, J. P., Stone, P. H., & van der Molen, M. W. (1997). Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology, 34*(6), 623-648. https://doi.org/10.1111/j.1469-8986.1997.tb02140.x
Bond, G., Stanton, R., Wintour, S.-A., Rosenbaum, S., & Rebar, A. (2020). Do exercise trials for adults with depression account for comorbid anxiety? A systematic review. *Ment Health Phys Act*, 100320. https://doi.org/10.1016/j.mhpa.2020.100320
Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Med Sci Sports Exerc, 14*(5), 377-381. https://www.ncbi.nlm.nih.gov/pubmed/7154893
Bundespsychotherapeutenkammer. (2018). *Ein Jahr nach der Reform der Psychotherapie-Richtlinie*. https://www.bptk.de/wp-content/uploads/2019/01/20180411_BPtK-Studie_Wartezeiten_2018.pdf
Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res, 28*(2), 193-213. https://doi.org/https://doi.org/10.1016/0165-1781(89)90047-4
Cameron, L. D., Fleszar-Pavlović, S., & Khachikian, T. (2020). Changing Behavior Using the Common-Sense Model of Self-Regulation. In K. Hamilton, L. D. Cameron, M. S. Hagger, N. Hankonen, & T. Lintunen (Eds.), *The Handbook of Behavior Change* (pp. 60-76). Cambridge University Press. https://doi.org/DOI: 10.1017/9781108677318.005
Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep, 100*(2), 126-131.
Cerrillo-Urbina, A. J., García-Hermoso, A., Sánchez-López, M., Pardo-Guijarro, M. J., Santos Gómez, J. L., & Martínez-Vizcaíno, V. (2015). The effects of physical exercise in children with attention deficit hyperactivity disorder: a systematic review and meta-analysis of randomized control trials. *Child Care Health Dev, 41*(6), 779-788. https://doi.org/10.1111/cch.12255
Chalmers, J. A., Quintana, D. S., Abbott, M. J., & Kemp, A. H. (2014). Anxiety Disorders are Associated with Reduced Heart Rate Variability: A Meta-Analysis. *Front Psychiatry, 5*, 80. https://doi.org/10.3389/fpsyt.2014.00080
Charmandari, E., Tsigos, C., & Chrousos, G. (2005). Endocrinology of the stress response. *Annu Rev Physiol, 67*, 259-284. https://doi.org/10.1146/annurev.physiol.67.040403.120816
Chihaoui Mamlouk, A., Younes, M., Zarrouk, F., Shephard, R., & Bouhlel, E. (2021). Heart rate variability and stress perception: The influence of physical fitness. *Science & Sports, 36*(4), 276-283.

https://doi.org/https://doi.org/10.1016/j.scispo.2021.02.001
Choi, J., Lee, M., Lee, J. K., Kang, D., & Choi, J. Y. (2017). Correlates associated with participation in physical activity among adults: a systematic review of reviews and update. *BMC Public Health, 17*(1), 356. https://doi.org/10.1186/s12889-017-4255-2
Christiansen, H., Hirsch, O., Albrecht, B., & Chavanon, M.-L. (2019). Attention-Deficit/Hyperactivity Disorder (ADHD) and Emotion Regulation Over the Life Span. *Curr Psychiatry Rep, 21*(3), 17. https://doi.org/10.1007/s11920-019-1003-6
Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., Leucht, S., Ruhe, H. G., Turner, E. H., Higgins, J. P. T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J. P. A., & Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet, 391*(10128), 1357-1366. https://doi.org/10.1016/s0140-6736(17)32802-7
Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *J Health Soc Behav*, 385-396.
Collimore, K. C., & Asmundson, G. J. (2014). Fearful responding to interoceptive exposure in social anxiety disorder. *J Anxiety Disord, 28*(2), 195-202. https://doi.org/10.1016/j.janxdis.2013.10.003
Cooney, G. M., Dwan, K., Greig, C. A., Lawlor, D. A., Rimer, J., Waugh, F. R., McMurdo, M., & Mead, G. E. (2013). Exercise for depression. *Cochrane Database Syst Rev, 9*(9), CD004366. https://doi.org/10.1002/14651858.CD004366.pub6
Cuijpers, P., Karyotaki, E., Reijnders, M., & Ebert, D. D. (2019). Was Eysenck right after all? A reassessment of the effects of psychotherapy for adult depression. *Epidemiol Psychiatr Sci, 28*(1), 21-30. https://doi.org/10.1017/S2045796018000057
Dalgleish, T., Black, M., Johnston, D., & Bevan, A. (2020). Transdiagnostic approaches to mental health problems: Current status and future directions. *J Consult Clin Psychol, 88*(3), 179-195. https://doi.org/10.1037/ccp0000482
Derogatis, L. R. (1994). *SCL-90-R: Administration, scoring and procedures manual* (3rd ed.). NCS Pearson.
Derogatis, L. R., & Unger, R. (2010). Symptom Checklist-90-Revised. In *The Corsini Encyclopedia of Psychology* (pp. 1-2). https://doi.org/10.1002/9780470479216.corpsy0970
Destatis. (2022). *Krankheitskosten, Krankheitskosten je Einwohner: Deutschland, Jahre, Krankheitsdiagnosen (ICD-10)*. https://www-genesis.destatis.de/genesis/online?operation=abruftabelleBearbeiten&levelindex=1&levelid=1659943712868&auswahloperation=abruftabelleAuspraegungAuswaehlen&auswahlverzeichnis=ordnungsstruktur&auswahlziel=werteabruf&code=23631-0001&auswahltext=&werteabruf=starten&wertauswahl=643&wertauswahl=2843#abreadcrumb
DGPPN, & ÄZQ. (2017). *S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression - Kurzfassung* [S3 Guideline/National Health Care Guideline Unipolar Depression - Abridged Version] (2nd ed.). Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN) Bundesärztekammer (BÄK) Kassenärztliche Bundesvereinigung (KBV) Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen

Fachgesellschaften (AWMF). https://doi.org/10.6101/azq/000366
DGPPN, DGKJP, & DGSPJ. (2018). *S3-Leitlinie ADHS bei Kindern, Jugendlichen und Erwachsenen*. AWMF online. https://www.awmf.org/uploads/tx_szleitlinien/028-045l_S3_ADHS_2018-06.pdf
Eisenhut, A., & Zintl, F. (2013). *Ausdauertraining* [Aerobic exercise]. BLV.
Ekkekakis, P. (2003). Pleasure and displeasure from the body: Perspectives from exercise. *Cogn Emot, 17*(2), 213-239. https://doi.org/10.1080/02699930302292
Felton, J. W., Banducci, A. N., Shadur, J. M., Stadnik, R., MacPherson, L., & Lejuez, C. W. (2017). The developmental trajectory of perceived stress mediates the relations between distress tolerance and internalizing symptoms among youth. *Dev Psychopathol, 29*(4), 1391-1401. https://doi.org/10.1017/s0954579417000335
Firth, J., Rosenbaum, S., Stubbs, B., Gorczynski, P., Yung, A. R., & Vancampfort, D. (2016). Motivating factors and barriers towards exercise in severe mental illness: a systematic review and meta-analysis. *Psychol Med, 46*(14), 2869-2881. https://doi.org/10.1017/S0033291716001732
Firth, J., Siddiqi, N., Koyanagi, A., Siskind, D., Rosenbaum, S., Galletly, C., Allan, S., Caneo, C., Carney, R., Carvalho, A. F., Chatterton, M. L., Correll, C. U., Curtis, J., Gaughran, F., Heald, A., Hoare, E., Jackson, S. E., Kisely, S., Lovell, K., Maj, M., McGorry, P. D., Mihalopoulos, C., Myles, H., O'Donoghue, B., Pillinger, T., Sarris, J., Schuch, F. B., Shiers, D., Smith, L., Solmi, M., Suetani, S., Taylor, J., Teasdale, S. B., Thornicroft, G., Torous, J., Usherwood, T., Vancampfort, D., Veronese, N., Ward, P. B., Yung, A. R., Killackey, E., & Stubbs, B. (2019). The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. *Lancet Psychiatry, 6*(8), 675-712. https://doi.org/10.1016/S2215-0366(19)30132-4
Fiuza-Luces, C., Garatachea, N., Berger, N., & Lucia, A. (2013). Exercise is the real polypill. *Physiology, 28*(5), 330-358. https://doi.org/10.1152/physiol.00019.2013
Franke, G. (2013). *Die Symptom-Checkliste SCL-90®* (Vol. 41). Hogrefe.
Franzen, P. L., & Buysse, D. J. (2008). Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. *Dialogues Clin Neurosci, 10*(4), 473-481. https://www.ncbi.nlm.nih.gov/pubmed/19170404
Fraser, S. J., Chapman, J. J., Brown, W. J., Whiteford, H. A., & Burton, N. W. (2015). Physical activity attitudes and preferences among inpatient adults with mental illness. *Int J Ment Health Nurs, 24*(5), 413-420. https://doi.org/10.1111/inm.12158
Fuchs, R., Klaperski, S., Gerber, M., & Seelig, H. (2015). Assessment of Exercise and Physical Activity with the BSA Questionnaire: A Methodical Interim Assessment [Messung der Bewegungs-und sportaktivität mit dem BSA-Fragebogen: Eine Methodische Zwischenbilanz]. *Zeitschrift für Gesundheitspsychologie, 23*(3), 60-76. https://doi.org/https://doi.org/10.1026/0943-8149/a000137
Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I. M., Nieman, D. C., Swain, D. P., & American College of Sports, M. (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc, 43*(7), 1334-1359.

https://doi.org/https://doi.org/10.1249/MSS.0b013e318213fefb
Gaudlitz, K., Plag, J., Dimeo, F., & Strohle, A. (2015). Aerobic exercise training facilitates the effectiveness of cognitive behavioral therapy in panic disorder. *Depress Anxiety, 32*(3), 221-228. https://doi.org/10.1002/da.22337
Gaul-Alácová, P., Boucek, J., Stejskal, P., Kryl, M., Pastucha, P., & Pavlík, F. (2005). Assessment of the influence of exercise on heart rate variability in anxiety patients. *Neuro Endocrinol Lett, 26*(6), 713-718.
Gerber, M., Imboden, C., Beck, J., Brand, S., Colledge, F., Eckert, A., Holsboer-Trachsler, E., Pühse, U., & Hatzinger, M. (2020). Effects of Aerobic Exercise on Cortisol Stress Reactivity in Response to the Trier Social Stress Test in Inpatients with Major Depressive Disorders: A Randomized Controlled Trial. *J Clin Med, 9*(5). https://doi.org/10.3390/jcm9051419
Global Burden of Disease Collaborative Network. (2020). *Global Burden of Disease Study 2019 (GBD 2019) Results* Institute for Health Metrics and Evaluation (IHME). http://ghdx.healthdata.org/gbd-results-tool
Gohner, W., Dietsche, C., & Fuchs, R. (2015). Increasing physical activity in patients with mental illness--A randomized controlled trial. *Patient Educ Couns, 98*(11), 1385-1392. https://doi.org/10.1016/j.pec.2015.06.006
Goodwin, R. D. (2003). Association between physical activity and mental disorders among adults in the United States. *Prev Med, 36*(6), 698-703. https://doi.org/10.1016/s0091-7435(03)00042-2
Gross, J. J., Uusberg, H., & Uusberg, A. (2019). Mental illness and well-being: an affect regulation perspective. *World Psychiatry, 18*(2), 130-139.
Hartmann, R., Schmidt, F. M., Sander, C., & Hegerl, U. (2018). Heart Rate Variability as Indicator of Clinical State in Depression. *Front Psychiatry, 9*, 735. https://doi.org/10.3389/fpsyt.2018.00735
Healey, E. S., Kales, A., Monroe, L. J., Bixler, E. O., Chamberlin, K., & Soldatos, C. R. (1981). Onset of insomnia: role of life-stress events. *Psychosom Med, 43*(5), 439-451. https://doi.org/10.1097/00006842-198110000-00007
Hey, S. P., & Kimmelman, J. (2014). The questionable use of unequal allocation in confirmatory trials. *Neurology, 82*(1), 77-79. https://doi.org/10.1212/01.wnl.0000438226.10353.1c
Hoffman, B. M., Babyak, M. A., Craighead, W. E., Sherwood, A., Doraiswamy, P. M., Coons, M. J., & Blumenthal, J. A. (2011). Exercise and pharmacotherapy in patients with major depression: one-year follow-up of the SMILE study. *Psychosom Med, 73*(2), 127-133. https://doi.org/10.1097/PSY.0b013e31820433a5
Hughes, C. (2013). Executive Function. In J. L. R. Rubenstein & P. Rakic (Eds.), *Neural Circuit Development and Function in the Brain* (pp. 429-445). Academic Press. https://doi.org/10.1016/b978-0-12-397267-5.00062-5
Jackson, A. S., Sui, X., Hebert, J. R., Church, T. S., & Blair, S. N. (2009). Role of lifestyle and aging on the longitudinal change in cardiorespiratory fitness. *Arch Intern Med, 169*(19), 1781-1787. https://doi.org/10.1001/archinternmed.2009.312
Jacobson, N. S., & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol, 59*(1), 12-19. https://doi.org/10.1037//0022-006x.59.1.12
Jacquart, J., Dutcher, C. D., Freeman, S. Z., Stein, A. T., Dinh, M., Carl, E., & Smits, J. A. J. (2019). The effects of exercise on transdiagnostic treatment targets: A meta-analytic review. *Behav Res Ther, 115*, 19-37. https://doi.org/10.1016/j.brat.2018.11.007

Kazdin, A. E. (2007). Mediators and mechanisms of change in psychotherapy research. *Annu Rev Clin Psychol, 3*, 1-27. https://doi.org/10.1146/annurev.clinpsy.3.022806.091432

Kelley, G. A., & Kelley, K. S. (2017). Exercise and sleep: a systematic review of previous meta-analyses. *J Evid Based Med, 10*(1), 26-36. https://doi.org/10.1111/jebm.12236

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. https://doi.org/10.1371/journal.pone.0030777

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry, 156*(6), 837-841. https://doi.org/10.1176/ajp.156.6.837

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., Faraone, S. V., Greenhill, L. L., Howes, M. J., Secnik, K., Spencer, T., Ustun, T. B., Walters, E. E., & Zaslavsky, A. M. (2006). The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry, 163*(4), 716-723. https://doi.org/10.1176/ajp.2006.163.4.716

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry, 62*(6), 617-627. https://doi.org/10.1001/archpsyc.62.6.617

Kessler, R. C., Lane, M., Stang, P. E., & Van Brunt, D. L. (2009). The prevalence and workplace costs of adult attention deficit hyperactivity disorder in a large manufacturing firm. *Psychol Med, 39*(1), 137-147. https://doi.org/10.1017/S0033291708003309

Kessler, R. C., Sampson, N. A., Berglund, P., Gruber, M. J., Al-Hamzawi, A., Andrade, L., Bunting, B., Demyttenaere, K., Florescu, S., de Girolamo, G., Gureje, O., He, Y., Hu, C., Huang, Y., Karam, E., Kovess-Masfety, V., Lee, S., Levinson, D., Medina Mora, M. E., Moskalewicz, J., Nakamura, Y., Navarro-Mateu, F., Browne, M. A., Piazza, M., Posada-Villa, J., Slade, T., Ten Have, M., Torres, Y., Vilagut, G., Xavier, M., Zarkov, Z., Shahly, V., & Wilcox, M. A. (2015). Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiol Psychiatr Sci, 24*(3), 210-226. https://doi.org/10.1017/S2045796015000189

Khadjesari, Z., Murray, E., Kalaitzaki, E., White, I. R., McCambridge, J., Thompson, S. G., Wallace, P., & Godfrey, C. (2011). Impact and costs of incentives to reduce attrition in online trials: two randomized controlled trials. *J Med Internet Res, 13*(1), e26. https://doi.org/10.2196/jmir.1523

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test'--a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology, 28*(1-2), 76-81. https://doi.org/10.1159/000119004

Klaperski, S. (2018). Exercise, stress and health: The stress-buffering effect of exercise. In *Handbuch Stressregulation und Sport* (pp. 227-249). Springer.

Klein Hofmeijer-Sevink, M., Batelaan, N. M., van Megen, H. J. G. M., Penninx, B. W., Cath, D. C., van den Hout, M. A., & van Balkom, A. J. L. M. (2012). Clinical relevance of comorbidity in anxiety disorders: A report from the Netherlands Study of Depression and Anxiety (NESDA). *J Affect Disord, 137*(1), 106-112. https://doi.org/https://doi.org/10.1016/j.jad.2011.12.008

Kline, C. E. (2014). The bidirectional relationship between exercise and sleep: Implications for exercise adherence and sleep improvement. *Am J Lifestyle Med, 8*(6), 375-379. https://doi.org/10.1177/1559827614544437

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. https://doi.org/10.1017/S0033291719001351

Koffel, E. A., Koffel, J. B., & Gehrman, P. R. (2015). A meta-analysis of group cognitive behavioral therapy for insomnia. *Sleep Med Rev, 19*, 6-16. https://doi.org/10.1016/j.smrv.2014.05.001

Kraemer, H. C., Wilson, G. T., Fairburn, C. G., & Agras, W. S. (2002). Mediators and Moderators of Treatment Effects in Randomized Clinical Trials. *Arch Gen Psychiatry, 59*(10), 877-883. https://doi.org/10.1001/archpsyc.59.10.877

Kramer, L. V., Helmes, A. W., Seelig, H., Fuchs, R., & Bengel, J. (2014). Correlates of reduced exercise behaviour in depression: the role of motivational and volitional deficits. *Psychol Health, 29*(10), 1206-1225. https://doi.org/10.1080/08870446.2014.918978

Krogh, J., Lorentzen, A. K., Subhi, Y., & Nordentoft, M. (2014). Predictors of adherence to exercise interventions in patients with clinical depression – A pooled analysis from two clinical trials. *Ment Health Phys Act, 7*, 50-54.

Kunz, R., Vist, G., & Oxman, A. D. (2007). Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*(2), MR000012. https://doi.org/https://doi.org/10.1002/14651858.MR000012.pub2

Laborde, S., Mosley, E., & Mertgen, A. (2018). Vagal Tank Theory: The Three Rs of Cardiac Vagal Control Functioning – Resting, Reactivity, and Recovery [Hypothesis and Theory]. *Front Neurosci, 12*. https://doi.org/10.3389/fnins.2018.00458

Laborde, S., Mosley, E., & Thayer, J. F. (2017). Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for Experiment Planning, Data Analysis, and Data Reporting. *Front Psychol, 8*, 213. https://doi.org/10.3389/fpsyg.2017.00213

Lazarus, R. S., & Folkman, S. (1984). *Stress, Appraisal, and Coping*. Springer Publishing Company.

Lederman, O., Ward, P. B., Firth, J., Maloney, C., Carney, R., Vancampfort, D., Stubbs, B., Kalucy, M., & Rosenbaum, S. (2019). Does exercise improve sleep quality in individuals with mental illness? A systematic review and meta-analysis. *J Psychiatr Res, 109*, 96-106. https://doi.org/10.1016/j.jpsychires.2018.11.004

Lee, J., Gierc, M., Vila-Rodriguez, F., Puterman, E., & Faulkner, G. (2021). Efficacy of exercise combined with standard treatment for depression compared to standard treatment alone: A systematic review and meta-analysis of randomized controlled trials. *J Affect Disord, 295*, 1494-1511. https://doi.org/10.1016/j.jad.2021.09.043

Legrand, F. D., & Neff, E. M. (2016). Efficacy of exercise as an adjunct treatment for clinically depressed inpatients during the initial stages of antidepressant pharmacotherapy: An open randomized controlled trial. *J Affect Disord, 191*, 139-144. https://doi.org/10.1016/j.jad.2015.11.047

Liu, Y., Xu, X., Dong, M., Jia, S., & Wei, Y. (2017). Treatment of insomnia with tricyclic antidepressants: a meta-analysis of polysomnographic randomized controlled trials. *Sleep Med, 34*, 126-133. https://doi.org/10.1016/j.sleep.2017.03.007

Loerinc, A. G., Meuret, A. E., Twohig, M. P., Rosenfield, D., Bluett, E. J., & Craske,

M. G. (2015). Response rates for CBT for anxiety disorders: Need for standardized criteria. *Clin Psychol Rev, 42*, 72-82. https://doi.org/10.1016/j.cpr.2015.08.004

Mack, S., Jacobi, F., Gerschler, A., Strehle, J., Hofler, M., Busch, M. A., Maske, U. E., Hapke, U., Seiffert, I., Gaebel, W., Zielasek, J., Maier, W., & Wittchen, H. U. (2014). Self-reported utilization of mental health services in the adult German population--evidence for unmet needs? Results of the DEGS1-Mental Health Module (DEGS1-MH). *Int J Methods Psychiatr Res, 23*(3), 289-303. https://doi.org/10.1002/mpr.1438

Mattke, D., & Pröstler, M. (2020). *Formen ambulanter Gruppentherapie* [Forms of outpatient group therapy [] (first ed.). Springer-Verlag GmbH https://doi.org/10.1007/978-3-662-59092-8

McDevitt, J., Snyder, M., Miller, A., & Wilbur, J. (2006). Perceptions of barriers and benefits to physical activity among outpatients in psychiatric rehabilitation. *J Nurs Scholarsh, 38*(1), 50-55. https://doi.org/10.1111/j.1547-5069.2006.00077.x

McEvoy, P. M., Nathan, P., & Norton, P. J. (2009). Efficacy of Transdiagnostic Treatments: A Review of Published Outcome Studies and Future Research Directions. *J Cogn Psychother*(1), 20-33. https://doi.org/10.1891/0889-8391.23.1.20

McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Ann N Y Acad Sci, 840*, 33-44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x

Melanson, E. L., & Freedson, P. S. (2001). The effect of endurance training on resting heart rate variability in sedentary adult males. *Eur J Appl Physiol, 85*(5), 442-449. https://doi.org/10.1007/s004210100479

Mercurio, L. Y., Amanullah, S., Gill, N., & Gjelsvik, A. (2019). Children With ADHD Engage in Less Physical Activity. *J Atten Disord*, 1087054719887789. https://doi.org/10.1177/1087054719887789

Michie, S., Ashford, S., Sniehotta, F. F., Dombrowski, S. U., Bishop, A., & French, D. P. (2011). A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: The CALO-RE taxonomy. *Psychol Health, 26*(11), 1479-1498. https://doi.org/10.1080/08870446.2010.540664

Miller, D. B., & O'Callaghan, J. P. (2002). Neuroendocrine aspects of the response to stress. *Metabolism, 51*, 5-10.

Mitte, K. (2005). A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. *J Affect Disord, 88*(1), 27-45. https://doi.org/10.1016/j.jad.2005.05.003

Moreno-Peral, P., Conejo-Ceron, S., Motrico, E., Rodriguez-Morejon, A., Fernandez, A., Garcia-Campayo, J., Roca, M., Serrano-Blanco, A., Rubio-Valera, M., & Bellon, J. A. (2014). Risk factors for the onset of panic and generalised anxiety disorders in the general adult population: a systematic review of cohort studies. *J Affect Disord, 168*, 337-348. https://doi.org/10.1016/j.jad.2014.06.021

Morres, I. D., Hatzigeorgiadis, A., Stathi, A., Comoutos, N., Arpin-Cribbie, C., Krommidas, C., & Theodorakis, Y. (2019). Aerobic exercise for adult patients with major depressive disorder in mental health services: A systematic review and meta-analysis. *Depress Anxiety, 36*(1), 39-53. https://doi.org/10.1002/da.22842

Mosley, E., & Laborde, S. (2022). A scoping review of heart rate variability in sport

and exercise psychology. *Int Rev Sport Exerc Psychol*. https://doi.org/10.1080/1750984X.2022.2092884

Naci, H., & Ioannidis, J. P. A. (2015). Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *BJSM, 49*(21), 1414-1422. https://doi.org/10.1136/bjsports-2015-f5577rep

Newby, J., Twomey, C., Li, S., & Andrews, G. (2016). Transdiagnostic computerised cognitive behavioural therapy for depression and anxiety: A systematic review and meta-analysis. *J Affect Disord, 199*. https://doi.org/10.1016/j.jad.2016.03.018

Nübling, R., T, B., Jeschke, K., M, O., Sarubin, N., & Juergen, S. (2014). Versorgung psychisch kranker Erwachsener in Deutschland - Bedarf und Inanspruchnahme sowie Effektivität und Effizienz von Psychotherapie [Care of Mentally Ill Adults in Germany - Need and Utilization as well as Effectiveness and Efficiency of Psychotherapy]. *Psychotherapeutenjournal, 13*, 389-397.

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. https://doi.org/10.1111/j.1540-8159.2010.02841.x

Păsărelu, C. R., Andersson, G., Bergman Nordgren, L., & Dobrean, A. (2017). Internet-delivered transdiagnostic and tailored cognitive behavioral therapy for anxiety and depression: a systematic review and meta-analysis of randomized controlled trials. *Cogn Behav Ther, 46*(1), 1-28. https://doi.org/10.1080/16506073.2016.1231219

Patel, V. (2012). Global mental health: from science to action. *Harv Rev Psychiatry, 20*(1), 6-12. https://doi.org/10.3109/10673229.2012.649108

Pfeifer, K., Sudeck, G., Geidl, W., & Tallner, A. (2013). Bewegungsforderung und Sport in der Neurologie - Kompetenzorientierung und Nachhaltigkeit [Exercise Challenge and Sport in Neurology - Competence Orientation and Sustainability]. *NEUROLOGIE UND REHABILITATION*, 7-19.

Plana-Ripoll, O., Pedersen, C. B., Holtz, Y., Benros, M. E., Dalsgaard, S., de Jonge, P., Fan, C. C., Degenhardt, L., Ganna, A., Greve, A. N., Gunn, J., Iburg, K. M., Kessing, L. V., Lee, B. K., Lim, C. C. W., Mors, O., Nordentoft, M., Prior, A., Roest, A. M., Saha, S., Schork, A., Scott, J. G., Scott, K. M., Stedman, T., Sørensen, H. J., Werge, T., Whiteford, H. A., Laursen, T. M., Agerbo, E., Kessler, R. C., Mortensen, P. B., & McGrath, J. J. (2019). Exploring Comorbidity Within Mental Disorders Among a Danish National Population. *JAMA Psychiatry, 76*(3), 259-270. https://doi.org/10.1001/jamapsychiatry.2018.3658

Pole, N. (2007). The psychophysiology of posttraumatic stress disorder: a meta-analysis. *Psychol Bull, 133*(5), 725-746. https://doi.org/10.1037/0033-2909.133.5.725

Powers, M. B., Medina, J. L., Burns, S., Kauffman, B. Y., Monfils, M., Asmundson, G. J., Diamond, A., McIntyre, C., & Smits, J. A. (2015). Exercise Augmentation of Exposure Therapy for PTSD: Rationale and Pilot Efficacy Data. *Cogn Behav Ther, 44*(4), 314-327. https://doi.org/10.1080/16506073.2015.1012740

Rabe-Menssen, C., Dazer, A., & Maaß, E. (2021). *Report Psychotherapie 2021* [Report Psychotherapy] (2nd ed.). Deutsche Psychotherapeuten Vereinigung (DPtV).

Rajendra Acharya, U., Paul Joseph, K., Kannathal, N., Lim, C. M., & Suri, J. S. (2006). Heart rate variability: a review. *Med Biol Eng Comput, 44*(12), 1031-1051. https://doi.org/10.1007/s11517-006-0119-0

Ramos-Sanchez, C. P., Schuch, F. B., Seedat, S., Louw, Q. A., Stubbs, B., Rosenbaum, S., Firth, J., van Winkel, R., & Vancampfort, D. (2021). The anxiolytic effects of exercise for people with anxiety and related disorders: An update of the available meta-analytic evidence. *Psychiatry Res, 302*, 114046. https://doi.org/10.1016/j.psychres.2021.114046

Ramsawh, H. J., Stein, M. B., Belik, S. L., Jacobi, F., & Sareen, J. (2009). Relationship of anxiety disorders, sleep quality, and functional impairment in a community sample. *J Psychiatr Res, 43*(10), 926-933. https://doi.org/10.1016/j.jpsychires.2009.01.009

Recchia, F., Leung, C. K., Chin, E. C., Fong, D. Y., Montero, D., Cheng, C. P., Yau, S. Y., & Siu, P. M. (2022). Comparative effectiveness of exercise, antidepressants and their combination in treating non-severe depression: a systematic review and network meta-analysis of randomised controlled trials. *BJSM*, bjsports-2022-105964. https://doi.org/10.1136/bjsports-2022-105964

Riemann, D., Nissen, C., Palagini, L., Otte, A., Perlis, M. L., & Spiegelhalder, K. (2015). The neurobiology, investigation, and treatment of chronic insomnia. *The Lancet Neurology, 14*(5), 547-558. https://doi.org/10.1016/S1474-4422(15)00021-6

Rösel, I., Bauer, L. L., Seiffer, B., Deinhart, C., Atrott, B., Sudeck, G., Hautzinger, M., & Wolf, S. (2022). The effect of exercise and affect regulation skills on mental health during the COVID-19 pandemic: A cross-sectional survey. *Psychiatry Res, 312*, 114559. https://doi.org/10.1016/j.psychres.2022.114559

Rosenbaum, S., Vancampfort, D., Steel, Z., Newby, J., Ward, P. B., & Stubbs, B. (2015). Physical activity in the treatment of Post-traumatic stress disorder: A systematic review and meta-analysis. *Psychiatry research, 230*(2), 130–136. https://doi.org/10.1016/j.psychres.2015.10.017

Rosseel, Y. (2012). lavaan: An R Package for Structural Equation Modeling. *J Stat Softw, 48*(2), 1 - 36. https://doi.org/10.18637/jss.v048.i02

Saccaro, L. F., Schilliger, Z., Perroud, N., & Piguet, C. (2021). Inflammation, Anxiety, and Stress in Attention-Deficit/Hyperactivity Disorder. *Biomedicines, 9*(10). https://doi.org/10.3390/biomedicines9101313

Samdal, G. B., Eide, G. E., Barth, T., Williams, G., & Meland, E. (2017). Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses. *Int J Behav Nutr Phys Act, 14*(1), 42. https://doi.org/10.1186/s12966-017-0494-y

Sandercock, G. R., Bromley, P. D., & Brodie, D. A. (2005). Effects of exercise on heart rate variability: inferences from meta-analysis. *Med Sci Sports Exerc, 37*(3), 433-439. https://doi.org/10.1249/01.mss.0000155388.39002.9d

Schäfer, I., Gast, U., Hofmann, A., Knaevelsrud, C., Lampe, A., Liebermann, P., Lotzin, A., Maercker, A., Rosner, R., & Wöller, W. (2019). *S3-Leitlinie Posttraumatische Belastungsstörung* [S3 Guideline Posttraumatic Stress Disorder]. Springer Verlag. https://www.awmf.org/uploads/tx_szleitlinien/155-001l_S3_Posttraumatische_Belastungsstoerung_2020-02_1.pdf

Schlack, R., Hapke, U., Maske, U., Busch, M., & Cohrs, S. (2013). Frequency and distribution of sleep problems and insomnia in the adult population in Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1). *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz, 56*(5-6), 740-748. https://doi.org/10.1007/s00103-013-1689-2 (Haufigkeit und Verteilung von Schlafproblemen und Insomnie in der deutschen Erwachsenenbevolkerung: Ergebnisse der Studie zur Gesundheit

Erwachsener in Deutschland (DEGS1).)
Schlotz, W., Yim, I., Zoccola, P., Jansen, L., & Schulz, P. (2011). The Perceived Stress Reactivity Scale: Measurement Invariance, Stability, and Validity in Three Countries. *Psychol Assess, 23*, 80-94. https://doi.org/10.1037/a0021148
Schneider, E. E., Schönfelder, S., Domke-Wolf, M., & Wessa, M. (2020). Measuring stress in clinical and nonclinical subjects using a German adaptation of the Perceived Stress Scale. *Int J Clin Health Psychol*. https://doi.org/10.1016/j.ijchp.2020.03.004
Schuch, F. B., 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. https://doi.org/10.1016/j.jad.2016.10.050
Schuch, F. B., Vancampfort, D., Richards, J., Rosenbaum, S., Ward, P. B., & Stubbs, B. (2016). Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. *J Psychiatr Res, 77*, 42-51. https://doi.org/10.1016/j.jpsychires.2016.02.023
Seiffer, B., Hautzinger, M., Ulrich, R., & Wolf, S. (2021). The Efficacy of Physical Activity for Children with Attention Deficit Hyperactivity Disorder: A Meta-Analysis of Randomized Controlled Trials. *J Atten Disord*, 10870547211017982. https://doi.org/10.1177/10870547211017982
Seiffer, B., Hautzinger, M., Ulrich, R., & Wolf, S. (2022). The Efficacy of Physical Activity for Children with Attention Deficit Hyperactivity Disorder: A Meta-Analysis of Randomized Controlled Trials. *J Atten Disord, 26*(5), 656-673. https://doi.org/10.1177/10870547211017982
Seiffer, B., Studnitz, T., Zeibig, J.-M., Thiel, A., & Wolf, S. (in press). Sportliche Aktivität in der ambulanten Versorgung von Patient:innen mit psychischen Erkrankungen [Exercise in the outpatient care of patients with mental disorders]. In T. Thimme, H. Deimel, & C. Chermette (Eds.), *Bewegungstherapie bei psychischen Erkrankungen über die Lebensspanne*. Academia Verlag.
Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annu Rev Clin Psychol, 4*, 1-32. https://doi.org/10.1146/annurev.clinpsy.3.022806.091415
Sin, N. L., Sloan, R. P., McKinley, P. S., & Almeida, D. M. (2016). Linking Daily Stress Processes and Laboratory-Based Heart Rate Variability in a National Sample of Midlife and Older Adults. *Psychosom Med, 78*(5), 573-582. https://doi.org/10.1097/psy.0000000000000306
Singer, S., Maier, L., Paserat, A., Lang, K., Wirp, B., Kobes, J., Porsch, U., Mittag, M., Toenges, G., & Engesser, D. (2022). Wartezeiten auf einen Psychotherapieplatz vor und nach der Psychotherapiestrukturreform. *Psychotherapeut, 67*(2), 176-184. https://doi.org/10.1007/s00278-021-00551-0
Siu, P. M., Yu, A. P., Tam, B. T., Chin, E. C., Yu, D. S., Chung, K. F., Hui, S. S., Woo, J., Fong, D. Y., Lee, P. H., Wei, G. X., & Irwin, M. R. (2021). Effects of Tai Chi or Exercise on Sleep in Older Adults With Insomnia: A Randomized Clinical Trial. *JAMA Netw Open, 4*(2), e2037199. https://doi.org/10.1001/jamanetworkopen.2020.37199
Spiegelhalder, K., Fuchs, L., Ladwig, J., Kyle, S. D., Nissen, C., Voderholzer, U., Feige, B., & Riemann, D. (2011). Heart rate and heart rate variability in subjectively reported insomnia. *J Sleep Res, 20*(1 Pt 2), 137-145. https://doi.org/10.1111/j.1365-2869.2010.00863.x

Stanley, K. (2007). Design of randomized controlled trials. *Circulation, 115*(9), 1164-1169. https://doi.org/10.1161/CIRCULATIONAHA.105.594945

Storebo, O. J., Pedersen, N., Ramstad, E., Kielsholm, M. L., Nielsen, S. S., Krogh, H. B., Moreira-Maia, C. R., Magnusson, F. L., Holmskov, M., Gerner, T., Skoog, M., Rosendal, S., Groth, C., Gillies, D., Buch Rasmussen, K., Gauci, D., Zwi, M., Kirubakaran, R., Hakonsen, S. J., Aagaard, L., Simonsen, E., & Gluud, C. (2018). Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of adverse events in non-randomised studies. *Cochrane Database Syst Rev, 5*, Cd012069. https://doi.org/10.1002/14651858.CD012069.pub2

Stubbs, B., Vancampfort, D., Hallgren, M., Firth, J., Veronese, N., Solmi, M., Brand, S., Cordes, J., Malchow, B., Gerber, M., Schmitt, A., Correll, C. U., De Hert, M., Gaughran, F., Schneider, F., Kinnafick, F., Falkai, P., Möller, H., & Kahl, K. G. (2018). EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and Position Statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH). *Eur Psychiatry, 54*, 124-144. https://doi.org/https://doi.org/10.1016/j.eurpsy.2018.07.004

Sudeck, G., Jeckel, S., & Schubert, T. (2018). Individual Differences in the Competence for Physical-Activity-Related Affect Regulation Moderate the Activity-Affect Association in Real-Life Situations. *J Sport Exerc Psychol, 40*(4), 196-205. https://doi.org/10.1123/jsep.2018-0017

Sudeck, G., & Pfeifer, K. (2016). Physical activity-related health competence as an integrative objective in exercise therapy and health sports – conception and validation of a short questionnaire. *Sportwissenschaft, 46*(2), 74-87. https://doi.org/10.1007/s12662-016-0405-4

Sudeck, G., Rosenstiel, S., Carl, J., & Pfeifer, K. (2022). Bewegungsbezogene Gesundheitskompetenz – Konzeption und Anwendung in Gesundheitsförderung, Prävention und Rehabilitation [Physical activity-related health competence - conception and application in health promotion, prevention and rehabilitation]. In K. Rathmann, K. Dadaczynski, O. Okan, & M. Messer (Eds.), *Gesundheitskompetenz* (pp. 1-12). Springer. https://doi.org/10.1007/978-3-662-62800-3_135-1

Sutton, E. L. (2021). Insomnia. *Ann Intern Med, 174*(3), ITC33-ITC48. https://doi.org/10.7326/AITC202103160

Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology. (1996). Heart Rate Variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation, 93*(5), 1043-1065. https://doi.org/doi:10.1161/01.CIR.93.5.1043

Thayer, J. F., Ahs, F., Fredrikson, M., Sollers, J. J., 3rd, & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev, 36*(2), 747-756. https://doi.org/10.1016/j.neubiorev.2011.11.009

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Ann Behav Med, 37*(2), 141-153. https://doi.org/10.1007/s12160-009-9101-z

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord, 61*(3), 201-216.

https://doi.org/10.1016/s0165-0327(00)00338-4
Thomas, J., Thirlaway, K., Bowes, N., & Meyers, R. (2020). Effects of Combining Physical Activity with Psychotherapy on Mental Health and Well-being: A Systematic Review. *J Affect Disord, 265*. https://doi.org/10.1016/j.jad.2020.01.070
Toni, G., Belvederi Murri, M., Piepoli, M., Zanetidou, S., Cabassi, A., Squatrito, S., Bagnoli, L., Piras, A., Mussi, C., Senaldi, R., Menchetti, M., Zocchi, D., Ermini, G., Ceresini, G., Tripi, F., Rucci, P., Alexopoulos, G. S., & Amore, M. (2016). Physical Exercise for Late-Life Depression: Effects on Heart Rate Variability. *Am J Geriatr Psychiatry, 24*(11), 989-997. https://doi.org/10.1016/j.jagp.2016.08.005
van den Berk-Clark, C., Secrest, S., Walls, J., Hallberg, E., Lustman, P. J., Schneider, F. D., & Scherrer, J. F. (2018). Association between posttraumatic stress disorder and lack of exercise, poor diet, obesity, and co-occuring smoking: A systematic review and meta-analysis. *Health Psychol, 37*(5), 407-416. https://doi.org/10.1037/hea0000593
van der Oord, S., Prins, P. J., Oosterlaan, J., & Emmelkamp, P. M. (2008). Efficacy of methylphenidate, psychosocial treatments and their combination in school-aged children with ADHD: a meta-analysis. *Clin Psychol Rev, 28*(5), 783-800. https://doi.org/10.1016/j.cpr.2007.10.007
van Eekelen, A. P., Houtveen, J. H., & Kerkhof, G. A. (2004). Circadian variation in cardiac autonomic activity: reactivity measurements to different types of stressors. *Chronobiol Int, 21*(1), 107-129. https://doi.org/10.1081/cbi-120027983
Vancampfort, D., Firth, J., Schuch, F. B., Rosenbaum, S., Mugisha, J., Hallgren, M., Probst, M., Ward, P. B., Gaughran, F., De Hert, M., Carvalho, A. F., & Stubbs, B. (2017). Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. *World Psychiatry, 16*(3), 308-315. https://doi.org/10.1002/wps.20458
Vittengl, J. R., Clark, L. A., Smits, J. A. J., Thase, M. E., & Jarrett, R. B. (2019). Do comorbid social and other anxiety disorders predict outcomes during and after cognitive therapy for depression? *J Affect Disord, 242*, 150-158. https://doi.org/10.1016/j.jad.2018.08.053
Werner, G. G., Ford, B. Q., Mauss, I. B., Schabus, M., Blechert, J., & Wilhelm, F. H. (2015). High cardiac vagal control is related to better subjective and objective sleep quality. *Bio Psychol, 106*, 79-85. https://doi.org/https://doi.org/10.1016/j.biopsycho.2015.02.004
Wolf, S., Seiffer, B., Zeibig, J. M., Welkerling, J., Bauer, L. L., Frei, A. K., Studnitz, T., Rosenstiel, S., Fiedler, D. V., Helmhold, F., Ray, A., Herzog, E., Takano, K., Nakagawa, T., Kropp, S., Franke, S., Peters, S., El-Kurd, N., Zwanzleitner, L., Sundmacher, L., Ramos-Murguialday, A., Hautzinger, M., Sudeck, G., & Ehring, T. (2021). Efficacy and cost-effectiveness of a Transdiagnostic group-based exercise intervention: study protocol for a pragmatic multi-site randomized controlled trial. *BMC Psychiatry, 21*(1), 540. https://doi.org/10.1186/s12888-021-03541-3
Wolf, S., Zeibig, J.-M., Giel, K., Granz, H., Sudeck, G., & Thiel, A. (2020a). Sportliche Aktivität und psychische Erkrankungen [Exercise and mental disorders]. *Psychother Psych Med, 70*(Georg Thieme Verlag KG Stuttgart · New York), 412-428. https://doi.org/10.1055/a-0973-1982
Wolf, S., Zeibig, J.-M., Giel, K., Granz, H., Sudeck, G., & Thiel, A. (2020b). Sportliche

Aktivität und psychische Erkrankungen [Exercise and mental disorders]. *PSYCH up2date, 14*(Georg Thieme Verlag KG Stuttgart · New York), 255-271. https://doi.org/10.1055/a-0973-1982

Wolf, S., Zeibig, J.-M., Hautzinger, M., & Sudeck, G. (2020). *Psychische Gesundheit durch Bewegung. ImPuls: Ein sport- und bewegungstherapeutisches Programm für Menschen mit psychischen Erkrankungen* [Mental health through exercise. ImPuls: An exercise intervention for individuals with mental disorders]. Julius Beltz GmbH & Co. KG.

Wunsch, K., Wurst, R., von Dawans, B., Strahler, J., Kasten, N., & Fuchs, R. (2019). Habitual and acute exercise effects on salivary biomarkers in response to psychosocial stress. *Psychoneuroendocrinology, 106*, 216-225. https://doi.org/10.1016/j.psyneuen.2019.03.015

Zeibig, J.-M., Seiffer, B., Frei, A. K., Takano, K., Sudeck, G., Rösel, I., Hautzinger, M., & Wolf, S. (2022). Long-term efficacy of exercise across diagnostically heterogenous mental disorders and the mediating role of affect regulation skills. *Psychol Sport Exerc*, 102340. https://doi.org/https://doi.org/10.1016/j.psychsport.2022.102340

Zeibig, J.-M., Seiffer, B., Sudeck, G., Rösel, I., Hautzinger, M., & Wolf, S. (2021). Transdiagnostic efficacy of a group exercise intervention for outpatients with heterogenous psychiatric disorders: a randomized controlled trial. *BMC Psychiatry, 21*(1), 313. https://doi.org/10.1186/s12888-021-03307-x

Zeibig, J.-M., Takano, K., Seiffer, B., Sudeck, G., Rösel, I., Hautzinger, M., & Wolf, S. (under review). An increase in heart rate variability mediates exercise effects on global symptom severity across heterogenous mental disorders: A secondary analysis of the ImPuls trial. *Ment Health Phys Act*.

Zorn, J. V., Schur, R. R., Boks, M. P., Kahn, R. S., Joels, M., & Vinkers, C. H. (2017). Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology, 77*, 25-36. https://doi.org/10.1016/j.psyneuen.2016.11.036

Appendix A: Manuscript I

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RESEARCH Open Access

Transdiagnostic efficacy of a group exercise intervention for outpatients with heterogenous psychiatric disorders: a randomized controlled trial

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Abstract

Background: Exercise efficaciously reduces disorder-specific symptoms of psychiatric disorders. The current study aimed to examine the efficacy of a group exercise intervention on global symptom severity and disorder-specific symptoms among a mixed outpatient sample.

Methods: Groups of inactive outpatients, waiting for psychotherapy, with depressive disorders, anxiety disorders, insomnia, and attention-deficit/hyperactivity disorders were randomized to a manualized 12-week exercise intervention, combining moderate to vigorous aerobic exercise with techniques for sustainable exercise behaviour change ($n = 38$, female = 71.1% ($n = 27$), $M_{age} = 36.66$), or a passive control group ($n = 36$, female = 75.0% ($n = 27$), $M_{age} = 34.33$). Primary outcomes were global symptom severity and disorder-specific symptoms, measured with the Symptom Checklist-90-Revised and Pittsburgh Sleep Quality Index pre- and post-treatment. Secondary outcome was the self-reported amount of exercise (Physical Activity, Exercise, and Sport Questionnaire), measured pre-treatment, intermediate-, and post-treatment. Intention-to-treat analyses were conducted using linear mixed models. Linear regressions were conducted to examine the effect of the change of exercise behaviour on the change of symptoms.

Results: The intervention significantly improved global symptom severity ($d = 0.77$, $p = .007$), depression ($d = 0.68$, $p = .015$), anxiety ($d = 0.87$, $p = .002$), sleep quality ($d = 0.88$, $p = .001$), and increased the amount of exercise ($d = 0.82$, $p < .001$), compared to the control group. Post-treatment differences between groups were significant for depression ($d = 0.63$, $p = .031$), sleep quality ($d = 0.61$, $p = .035$) and the amount of exercise ($d = 1.45$, $p < .001$). Across both groups, the reduction of global symptom severity was significantly predicted by an increase of exercise ($b = .35$, $p = .012$).

Conclusions: The exercise intervention showed transdiagnostic efficacy among a heterogeneous clinical sample in a realistic outpatient setting and led to sustained exercise behaviour change. Exercise may serve as an efficacious and feasible transdiagnostic treatment option improving the existing treatment gap within outpatient mental health care settings.

Trial registration: The study was registered on ClinicalTrials.gov (ID: NCT03542396, 25/04/2018).

Keywords: Exercise, Transdiagnostic efficacy, Depression, Anxiety disorders, Insomnia

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Background

In 2019, psychiatric disorders affected about 15.6% (point prevalence) of the population in Germany [1]. Psychiatric disorders result in a considerable burden of disease, accounting for 6.4% of disability-adjusted life years (DALYS) [1] and increasing the risk for cardiovascular diseases [2]. The most frequent and burdensome psychiatric disorders are depressive disorders (point prevalence: 4.3%), anxiety disorders (point prevalence: 7.1%), including obsessive compulsive disorders (OCD) and posttraumatic-stress disorder (PTSD), and insomnia (point prevalence: 4%) [1, 3]. Epidemiological studies demonstrated that comorbidity across these disorders is rather the rule than the exception [4]. Additionally, these disorders show a comorbidity with other psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD) [5]. Comorbidity is related to an increased impairment, a worse prognosis and stronger chronicity of symptoms compared to people affected by one single mental disorder [6–8]. The high prevalence and burden of psychiatric disorders as well as their comorbid occurrence, emphasize the substantial need for treating psychiatric disorders. However, in Germany, only 10% of all individuals with psychiatric disorders receive evidence-based treatment and only 2.5% receive psychotherapy [9]. Furthermore, in 2018, the average waiting time for psychotherapeutic treatment was approximately 5 months [10]. The high necessity for treatment, on the one hand, and deficits in mental health care, on the other hand, illustrates the severe gap between people in need for treatment and those actually receiving it [11]. This treatment gap aggravates the burden of psychiatric disorders because the absence or delay in treatment can lead to worsening and chronicity of symptoms and additionally to the development of comorbid diagnoses [10]. Thus, there is a demand for treatment that can improve this treatment gap by being applicable and efficacious to individuals who meet criteria for one or more clinical diagnoses and also for groups of heterogenous disorders. In addition, this treatment would need to be easily and fast accessible (i.e., efficient) to increase the number of people receiving treatment.

The mental health care is dominated by treatments, that are tailored to specific disorders (i.e., disorder-specific treatments) [12] and are usually conducted in individual format rather than in group format [13]. However, considering clinical reality with heterogenous and also comorbid presentations of diagnoses [4], the conduction of those treatments is not efficient because multiple treatment protocols for different specific disorders need to be applied [12]. Furthermore, disorder-specific treatments no longer correspond to recent evidence supposing that underlying shared common etiological and maintenance processes rather than specific diagnoses should be considered when treating psychiatric disorders [12, 14].

To address these underlying mechanisms instead of specific disorders, transdiagnostic psychological treatments, that "[…] apply the same underlying treatment principles across mental disorders without tailoring the protocol to specific diagnoses" ([26], p.21) have been developed [27, 28, 29, 30, 31]. Recent meta-analyses [27–31], that evaluated the efficacy of transdiagnostic psychological treatments, such as transdiagnostic cognitive behavior therapy (CBT) [27], among patients with depressive disorders and/or anxiety disorders over comparison or control interventions (i.e., diagnosis-specific intervention control, treatment-as-usual, or a waitlist control), demonstrated moderate to large effect sizes. This suggests that transdiagnostic treatments can efficaciously augment dominating disorder-specific treatments [12].

There is a body of evidence assuming that exercise, defined as physical activity that is planned, structured, and repetitive, with the primary aim to improve or maintain physical fitness [32] might represent a potential transdiagnostic treatment for depressive disorders, anxiety disorders, insomnia and ADHD. Findings of a recent meta-analysis [33] investigating the effects of exercise on underlying processes of these psychiatric disorders (i.e., anxiety sensitivity, distress tolerance, stress reactivity, and general self-efficacy) revealed a large effect of exercise on reducing anxiety sensitivity, a moderate effect on increasing general self-efficacy and a small effect on reducing stress reactivity. Similarly, a recent meta-analysis of randomized controlled trials (RCTs) [34], which examined the impact of exercise on sleep quality among people with psychiatric disorders, revealed a large beneficial effect on the improvement of sleep quality. Supporting the assumption of the transdiagnostic efficacy of exercise, results of numerous systematic reviews and meta-analyses have suggested moderate to large disorder-specific effects of exercise on depressive disorders [35, 36], anxiety disorders [37, 38], insomnia [39, 40] and ADHD [41, 42] over non-active [37, 39], or active and non-active controls [35, 36, 38, 40, 41].

Exercise conducted two to three times per week, for approximately 10 weeks, at a minimum of moderate intensity and a duration of 30 min, partially supervised or non-supervised, solely aerobic or aerobic combined with resistance training, are key components of previous disorder-specific exercise interventions and seem to be associated with optimal therapeutic efficacy among patients with specific disorders [33, 35,37, 43]. These beneficial effects, such as the reduction of depressive symptoms, seem to be only sustainable when exercise is conduced and maintained on a regular base. In an exercise trial [44], the antidepressant effect of exercise was compared to those of psychopharmacotherapy in patients with depressive disorders. Both

conditions showed similar improvements in depressive symptoms. In the one-year follow up study, however, this effect was only maintained for those participants who engaged in exercise on a regular base [45]. Exercise interventions combined with behavior change techniques (BCTs), that increase motivation and volition for exercise seem to increase the initiation and maintenance of exercise among healthy and psychiatric samples [46, 47, 48, 49].

Despite of the promising evidence of the efficacy of exercise among specific disorders and underlying processes across disorders, to the best of our knowledge, the effects of exercise have never been investigated across a broad range of diagnostically heterogeneous and a highly comorbid clinical sample in a realistic outpatient setting. Furthermore, as far as we know, there is no exercise trial that includes heterogenous disorders and assessed global symptom severity with a reliable and clinical measure.

Therefore, the manualized group exercise intervention, named "ImPuls" [50], was developed. The intervention was developed for inactive outpatients, waiting for psychotherapeutic treatment in German health care settings in outpatient units and practices, suffering from one or more diagnoses of depressive disorders, anxiety disorders, insomnia, and ADHD. The exercise intervention integrates the most recent findings about optimal modalities of exercise for therapeutic efficacy for the targeted disorders and sustainable behavior change by integrating behavior change techniques (BCTs). All components of this intervention are tailored to the care reality of outpatients with psychiatric disorders to offer an efficient treatment option in the outpatient mental health care setting: 1) including a broad range of heterogenous diagnoses for which prior research has demonstrated therapeutic efficacy, 2) conducting the intervention in group format, 3) short duration (i.e., 4 weeks of supervised sessions, 8 weeks non-supervised exercise) to be feasible during waiting times for psychotherapy.

The primary hypothesis was that participants of the intervention group would demonstrate lower global symptom severity and disorder-specific symptoms (depression, anxiety, sleep quality) at post-treatment assessment compared to a passive control group. The secondary hypothesis was that participants of the intervention group would demonstrate a significant larger amount of exercise at intermediate- and post-treatment assessment compared to the control group. It was further hypothesized that the increase of the amount of exercise from pre- to post-treatment assessment would predict the reduction of global symptom severity and disorder-specific symptoms from pre- to post-treatment assessment across both treatment arms.

Methods

Study design

The study was conducted at the University of Tuebingen. Active enrollment lasted from April 2018 to October 2019. The study was registered on ClinicalTrials.gov (ID: NCT03542396, 25/04/2018) and approved by the local ethics committee for psychological research (Az_Wolf_2018_0108_99). A block-randomized (allocation ratio 1:1) parallel trial with two treatment arms (intervention group, control group) and three measurement points (pre-, intermediate-, post-treatment assessment) was conducted. Primary outcomes were assessed at pre- and post-treatment assessment; secondary outcome at pre-, intermediate- and post-treatment assessment. The study was reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement [51].

Recruitment and participants

Recruiting was performed at the outpatient clinic of the University of Tuebingen, medical and psychotherapist's offices, and by media advertising. Inclusion criteria were age between 18 and 65 years, fluent in German, no medical contraindications for exercise (participants needed to receive a medical consultation prior to the intervention that confirmed participant's ability to exercise), on a waiting-list for outpatient psychotherapy and diagnosed according to DSM-IV-TR with at least one of the following disorders: depressive disorders (F32, F33, F34.1), anxiety disorders (F40.0, F40.1, F40.2, F41.0, F41.1, F41.2, F42, F43.1, insomnia (F51.0), and ADHD (F90.0, F90.1, F98.8). Exclusion criteria included: acute substance use disorders (F10.2, F11.2, F12.2, F13.2, F14.2, F15.2, F16.2, F18.2, F19.2), chronic pain disorder (F45.1), eating disorders (lifetime; F50), bipolar disorder (lifetime; F31), antisocial personality disorder (F60.2), borderline personality disorder (F60.3), acute suicidal tendencies, regular exercise (≥ 30 min/week), change (i.e., reduction and increase) of psychopharmaceuticals (≤ 2 months). Any change in treatment led to a withdrawal from the study.

The sample size was determined a-priori through power analysis, using G*Power ([52], v. 3.1.9.7.). A moderate to large effect (Cohen's $d = 0.74$) of the mean post-difference between the two groups for the primary outcome was expected. Effect estimation was the median of the effect of exercise on disorder-specific symptoms of depressive disorders, anxiety disorders and insomnia. Since a small number of eligible participants with ADHD was expected, the effect of exercise on symptoms of ADHD was not included in the effect estimation. Effect sizes were derived from the most recent meta-analyses and RCTs available at the time of trial design [36, 40, 53]. With significance level: $\alpha = .05$, Power: $1-\beta = .80$, allocation ratio N2/N1: $\varepsilon = 1$, the required

sample size for a two-tailed t-test for independent samples was $N = 60$. With an expected dropout rate of 18% for a clinical sample in an RCT [38], the total sample resulted in $N = 71$. This resulted in a group size of approximately $n = 36$ for each group.

Randomization

Randomization was performed when the maximum of participants for one treatment group ($n = 5–10$) was eligible and/or when remaining waiting time for psychotherapy was shorter than intervention period (≤3 months). Participants were assigned a code, which was sent to a research assistant. They were randomly assigned to a group, based on a randomization table, stratified by age and symptom severity (Global Assessment of Functioning Scale, GAF) for each group, using MATLAB (9.6.0, R2019a). The study therapist received the allocation information, matched the codes to participants and informed them of their group allocation.

Procedure

Psychologists performed a preliminary telephone screening of eligibility criteria. Eligible participants were invited to the University of Tuebingen where they first completed a demographic questionnaire. Research assistants, who were trained in the conduction of structured clinical interviews, conducted the structured clinical interview for DSM-IV (SCID) [54] for eligibility criteria. ADHD was diagnosed by DSM-IV criteria through the Homburg ADHD Scales for Adults (HASE) [55]. Primary insomnia was diagnosed by DSM-IV criteria combined with the Pittsburgh Sleep Quality Index (PSQI) [56]. Participants signed an informed consent form and completed online questionnaires via a secure online survey software Sosci Survey [57] prior to randomization. This *pre-treatment assessment* was conducted on an average of 23.15 days ($SD = 22.19$) prior to the start of the intervention.

Ten groups of five-to-ten participants were sequentially allocated to the intervention group or control group. The intervention group completed the exercise intervention, while the control group did not receive any treatment. At week 9 of the intervention (*intermediate-treatment assessment*), participants' amount of exercise was assessed. No other assessments were conducted at this assessment point. Intermediate-treatment assessment was scheduled at week 9 of the intervention because it was middle of the non-supervised time. The non-supervised intervention period started at week 5 of the intervention and lasted 8 weeks in total.

One-to-two weeks after intervention (*post-treatment assessment*), the same procedure of the pre-treatment assessment was performed. The SCID was also conducted again at post-treatment assessment by an outcome assessor (research assistants, who were trained in the conduction of structured clinical interviews) that was blind to group assignment. Afterwards, the control group received 50€ as a compensation for their time. All participants were offered preferential psychotherapy at the outpatient clinic in Tuebingen after post-treatment assessment. The final post-treatment assessment was conducted in October 2019.

Assessments

Primary outcomes

Global symptom severity Global symptom severity was measured by the Global Severity Index (GSI) of the German version of the self-reported questionnaire Symptom Checklist-90-Revised (SCL-90-R [58];). The GSI comprises the average distress rating on all symptom scales and ranges from 0 to 4. Higher scores indicate higher distress. Clinically relevant changes are defined as a change on the GSI of at least 0.26 [58]. Among patients with affective disorders, the GSI has demonstrated good internal consistency ($\alpha = .97$) and construct validity ($r = .77$) [59]. The internal consistency in the current study was $\alpha = .97$ for the GSI.

Depression and anxiety Depression and Anxiety were measured by the sub scores Depression and Anxiety of the self-reported questionnaire SCL-90-R [58]. Items of the depression sub score ask participants for symptoms of depression (e.g., "How much did you suffer from a decrease in your interest or pleasure in sexuality in the past few days?") and items of the anxiety sub score for symptoms of anxiety (e.g., "How much did you suffer from nervousness or inner trembling in the past days?"). Scales ranges from 0 to 4 with higher scores indicating higher distress. Symptoms are clinically raised when T-values are ≥60. Among patients with affective disorders, the depression scale ($\alpha = .89$) and anxiety scale ($\alpha = .87$) have demonstrated internal consistency and construct validity ($r = .80$ for depression and $r = .61$ for anxiety) [59]. The internal consistency in the current study was $\alpha = .91$ for depression and $\alpha = .90$ for anxiety.

Sleep quality Sleep Quality was measured by the global sleep quality score of the German version of the self-reported questionnaire Pittburgh Sleep Quality Index (PSQI [56];). The global sleep quality score is the sum of seven sleep component scores (range of component scores: 0–3): subjective sleep quality ("Over the last four weeks, how would you rate your overall sleep quality?"), sleep latency (e.g., "Over the last four weeks, how long have had it usually take you to fall asleep at night?), sleep duration (e.g., "Over the last four weeks, how many hours have you actually slet per night?"), habitual sleep

efficiency (e.g., "Over the last four weeks, what time have you usually gotten up in the morning?"), sleep disturbances (e.g., "Over the last four weeks, how often have you had a bad night's sleep because you couldn't fall asleep within 30 minutes?"), use of sleeping medications (e.g., "Over the last four weeks, how often have you taken sleeping pills (prescribed by a doctor or over-the-counter)?"), and daytime dysfunction (e.g., "Over the last four weeks, how often have you had difficulty staying awake, such as while driving, eating, or attending social events?"). The global sleep quality score can vary from 0 to 21 with a cut-off score of 5, identifying clinically raised sleep impairment [56]. It has shown a high sensitivity (98.7%) and specificity (84.4%) in identifying insomnia [60]. In the literature, the internal consistency for the global sleep quality score was $\alpha = .77$ [61]. In the current study, it was $\alpha = .67$.

Secondary outcome: exercise

The amount of exercise was measured using the self-reported exercise activity index of the physical activity, exercise, and sport questionnaire (BSA questionnaire [62];). Participants specify whether they have engaged in regular exercise in the past 4 weeks ("Have you engaged in regular exercise in the past 4 weeks?"). If they have engaged in regular exercise, participants were asked to specify the type ("What kind of exercise activity (ies) have you engaged in?"), frequency and duration ("I have engaged in activity x approximately … times in the past four weeks, every time for approximately … minutes") of it. The exercise activity index indicates the average minutes of exercise per week. The BSA questionnaire can validly assess changes in exercise behavior. Data of reliability is not available [62] and could not be analyzed for the current study it because this scale consists of one item only.

Further assessments

Further measures (self-reported questionnaires), described in the trial registration, but not included in the current evaluation, were the Sleep Questionnaire B-Revised version (SF-B [63];), Perceived Stress Scale (PSS [64];), 36-Item Short Form Health Survey (SF-36) (SF-36 [65];), Self Concordance of Sport- and Exercise-related Goals Scale (SKK-Scale [66];), Scales that assess motivation and volition for exercise [67], and Physical Activity-related Health Competence Questionnaire [68]. Accelerometer derived exercise at seven consecutive days was assessed. 5-min resting heart rate variability was assessed by a trained research assistant.

Exercise intervention

The 12-week exercise intervention "ImPuls" [69] was conducted in a group format of three to four participants and divided into a supervised and non-supervised period. Behaviour change techniques (BCTs), such as self-efficacy, goal setting, self-monitoring, formation of concrete exercise plans and coping planning, were integrated to promote sustained exercise behaviour change [49, 70]. Intervention contents are displayed in Fig. 1 and Table 1.

Supervised period (week 0–4)

Participants took part in a combination of supervised running session and group meetings with a total duration of 120 min. One supervised session is conducted during week 0 (introduction to the intervention), three supervised sessions during the second week, two supervised sessions plus one non-supervised exercise during week 2–4, respectively. Running lasted 30 min and participants could choose a standardized interval-based training or endurance training. Both training methods were conducted with moderate intensity, which was tracked by a heart rate monitor (Polar Electro GmbH; A 300) combined with a chest strap (Polar Electro GmbH; H7) and the Borg Rating of Perceived Exertion (RPE) Scale [71]. Moderate intensity was defined as 60 to 80% of maximum heart rate, subtracting age from 220 [72] and from nine to 14 on the RPE Scale [71]. Participants engaged in additional 30-min, moderate-intensity, non-supervised exercise.

Non-supervised period (week 5–12)

During the non-supervised period, participants engaged in 30-min, moderate-intensity, non-supervised exercise two to three times a week, which was accompanied by an activity diary and weekly phone calls with one study therapist, intending to maintain motivation, volition, and adherence to exercise. A session for participant's supporters (e.g., friends, partner) was scheduled in week 5 to inform them about the possibilities to aid the participants in transforming their intentions into action. A final group meeting with a running session took place in week 12 in order to exchange experiences and to encourage participants to maintain regular exercising.

Attendance and adherence

Participants performed 30 min non-supervised exercise if they missed a supervised running session. Contents of group meetings were repeated in one-to-one sessions (by phone or face-to-face). The assessment of the amount of exercise (see Procedure) served as a measure of adherence during the non-supervised period (see Table 3).

Therapists

All main therapists were master's degree psychologists with either fully approved in psychological

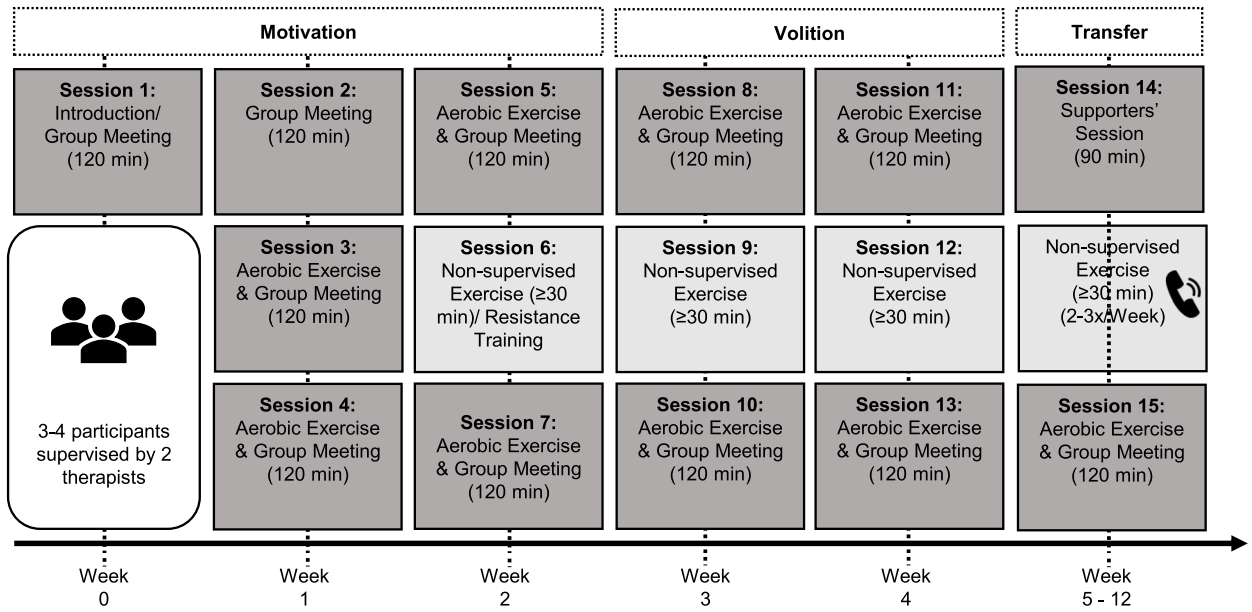

Fig. 1 Intervention procedure of the group exercise intervention. Dark grey boxes represent group meetings combined with supervised aerobic exercise (starting session 3) and the supporters' session (session 14 in week 5). Session 1 contains an introduction into the intervention. Session 15 is conducted in week 12. Light grey boxes represent non-supervised exercises or resistance training, which can be conducted as participants' first non-supervised exercise (session 6). The phone represents the weekly phone contact from week 5–12. Week 1–2 mainly aimed to increase motivation, week 2–4 mainly increase volition. Week 5–12 aimed to transfer motivation and volition for exercise into participants' daily life routines

psychotherapy or in advanced postgraduate training for CBT. Assistant therapists were graduate students of psychology. All therapists were trained in the background and contents of ImPuls und supervised by an exercise therapist and a psychotherapist.

Table 1 Overview of behaviour change techniques of the group exercise intervention

Focus	Technique
Motivational (mainly week 1–2)	Education about positive and negative effects of exercise
	Education about optimal modalities of exercise to experience positive psychological effects
	Selection of a preferred activity
	Goal setting
	Self-monitoring of goal achievement
	Reflection about positive experiences/effects with/of exercise
Volitional (mainly week 3–4)	Identification of barriers to exercise
	Techniques to overcome barriers
	Social support (intervention group and trainers)
	Exercise self-monitoring (optimal modality)
Motivational and volitional (week 5–12)	Social support (family, friends, trainer)
	Self-monitoring of goal achievement
	Exercise self-monitoring (optimal modality)

Potential risks and benefits of the intervention

Most common risks associated with exercise are cardiovascular events and musculoskeletal injuries [73]. Intermediate and long-term potential benefits of exercise are improved physical health, such as prevention of diabetes (e.g., [74]) and improved mental health, such as the reduction of depressive symptoms (e.g., [75]). Furthermore, majority of individuals are exposed to greater risk by not exercising. Indeed, sedentary behavior seem to be associated with a higher risk to develop mental disorders [76, 77] and reduced physical health [78]. Since all participants of the current intervention needed to receive a medical consultation prior to the intervention, the potential risk of exercise on physical health was minimized. Therefore, potential benefits seemed to outweighs the risks of participation in the study.

Data diagnostics

Individuals from both study arms, who fulfilled any exclusion criteria (i.e., change of treatment, contraindications for exercise) during the intervention, were excluded from post-data collection, 18.1% ($n = 13$). Since the current study contained exclusion criteria that could change during study participation (e.g., change of treatment), data from participants, who did no longer meet eligibility criteria needed to be excluded from post-data collection in order to reduce the risk of bias in the intervention effect estimate [79]. Missing data was assessed at

scale level. Linear mixed models, using maximum likelihood estimations, were conducted to handle missing data (also participants' data of those who were excluded from post-data-collection). Linear mixed models, based on all observed data, can be a valid and unbiased method to handle data that is missing at random [80].

Potential outliers were identified through three measures: Leverage, Cook's Distance, and Studentized Residuals. Cases with greater than three time the average leverage, cook's distance greater than 1, and studentized residuals greater than 3 [81, 82], were considered as potential outliers or influential data points. To evaluate the influence of potential outliers on results of linear mixed models, they were calculated again without cases that either exceeded the cut-off value of all three measures, or exceeded the cut-off values of cook's distance and leverage, or exceeded the cut-off value of cook's distance. Post-difference and interaction-effect sizes were then compared to those of linear mixed models including the complete data set.

Assumptions of linear mixed models and linear regressions (i.e., linearity, normality of the residuals, homoscedasticity, and multicollinearity) were visually inspected. If residuals of linear mixed models were not normally distributed, data was log-transformed.

Analytic strategy

For data preparation the Statistical Package for Social Science (IBM SPSS, Inc., Chicago, IL, USA, version 26) was used. Statistical analyses were carried out using R (version 4.0.3) and RStudio (version 1.1.453). Descriptive statistics were used to analyze sample characteristics and dropout rates. Baseline differences between groups and between those that completed the study versus dropped out were analyzed using two-tailed t-tests for independent samples (continuous variables), Chi-scared tests or fisher's exact tests (categorical variables).

Differences between groups on primary and secondary outcomes changes were analyzed as intention-to-treat (ITT) analysis with linear mixed models using the lme4 package [83] in R. Models used maximum likelihood as the estimation technique. Models included *treatment group*, *time point* and *time point-by-treatment group* interaction as fixed effects. Intercepts were included as random effects. An unstructured covariance matrix was assumed. Post-hoc tests for post-treatment-differences between groups were carried out using two-tailed t-test for independent samples. For post-hoc tests of the secondary outcome, a Bonferroni correction was used. Effect sizes for differences between groups (intermediate-, post-treatment-difference effects and interaction effects) were calculated according to Cohen's d [84].

An additional analysis inspected clinically relevant changes of participants' symptomatology. Clinically relevant changes were defined as a change on the GSI from pre-treatment to post-treatment assessment of at least 0.26 [58].

Sufficient statistical power enabled exploratory analyses that examined the efficacy of exercise on depression for subgroups of participants diagnosed with depressive disorders. Additional exploratory analysis (per-protocol analysis) tested the predictive value of the change of the amount of exercise on primary outcomes changes. Linear regressions were calculated with change of exercise (post-treatment assessment – pre-treatment assessment) as a predictor variable and primary outcomes changes (pre-treatment assessment – post-treatment assessment) as criterion variables.

Results

Participant flow during the study

In total, 106 individuals were assessed for eligibility. Of those assessed, 30.2% ($n = 32$) were excluded and 69.8% ($n = 74$) were eligible for participation. Those eligible were randomly assigned to the intervention group, 51.3% ($n = 38$), or control group, 48.7% ($n = 36$). 5.3% ($n = 2$) of participants of the intervention group were removed from the analysis due to a wrong diagnosis at pre-treatment assessment (comorbid lifetime eating disorder, 2.6% ($n = 1$), and a comorbid alcohol use disorder, 2.6% ($n = 1$) [79]. This led to an ITT efficacy group of $N = 72$ (50.0% ($n = 36$) of patients in the intervention group vs. 50.0% ($n = 36$) in the control group) (see Fig. 2).

Participant characteristics at baseline

Baseline characteristics of the studied sample are reported in Table 2. There were no significant baseline differences between intervention group and control group. Dropout rates of the control group were higher compared to the intervention group, but not statistically different. Compared to the intervention group, participants of the control group dropped out more frequently due to treatment change without reaching statistical significance (see Table 2 and Fig. 2). There were no significant baseline differences between study completers and dropouts (Additional file 1). There were no serious adverse events.

Statistics and data analysis

Missing data was missing completely at random (MCAR) (χ^2 (14) = 12.33, $p = .580$). 106 (14.7%) values of primary and secondary outcomes were incomplete. Per-protocol analyses for each primary and secondary outcome were conducted as sensitivity analyses, using linear mixed models (Additional file 2), to examine the robustness of the results.

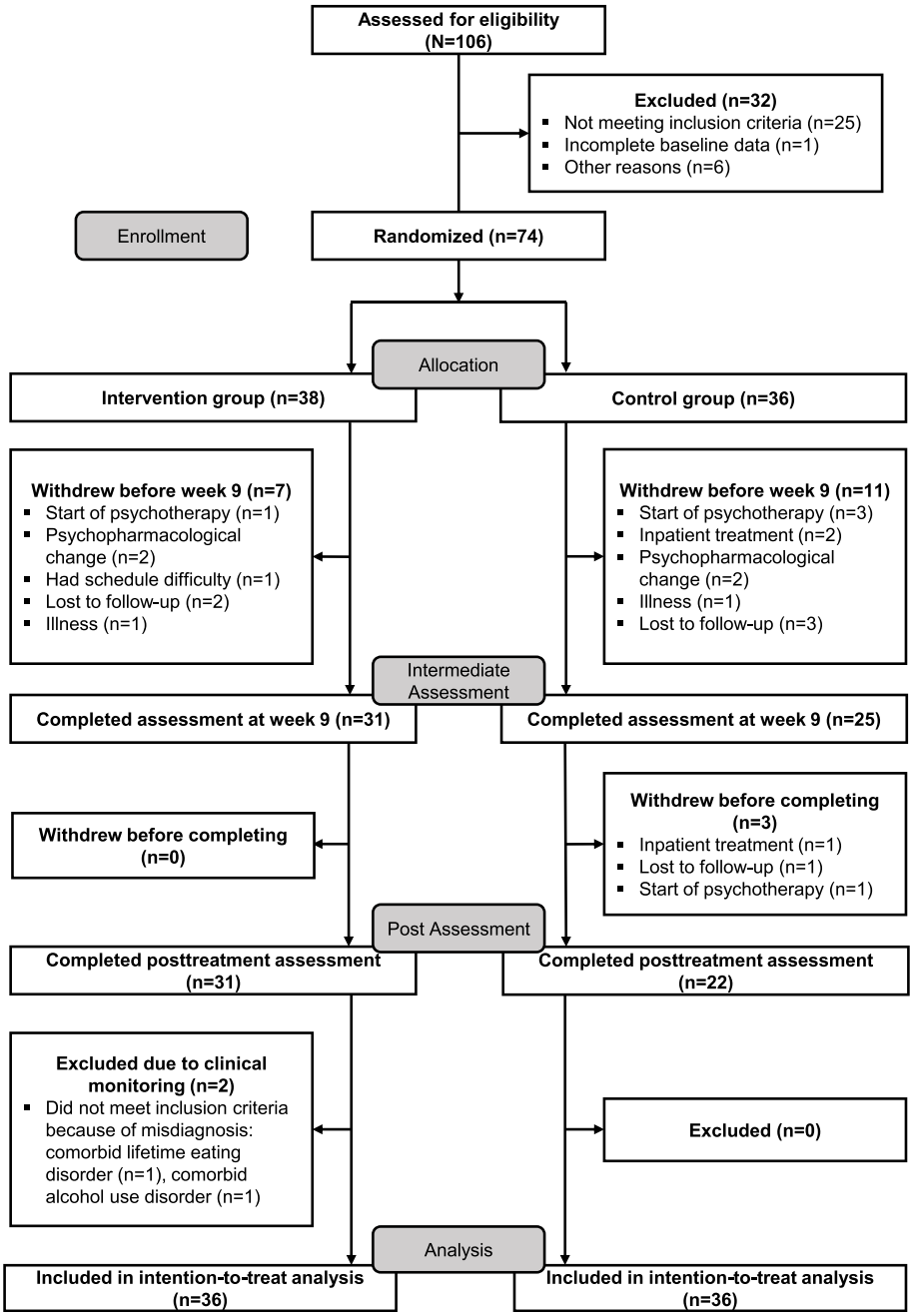

Fig. 2 CONSORT flow diagram: profile and enrollment and flow through the randomized controlled trial of group exercise intervention versus a passive control group for individuals with mental disorders

Ten cases were detected as potential outliers in the linear mixed model with the GSI (SCL-90-R) as criterion variable and four cases in the linear mixed model with the global sleep quality score (PSQI) as criterion variable. No cases were detected as potential outliers in the mixed models with exercise (BSA questionnaire) as criterion variable. Excluding potential outliers did not change direction, nor significance of intervention effects (Additional file 4). Intervention effects on the global sleep quality score increased from moderate to large effect size (cohen's d for post-treatment-difference between groups) when potential outliers were excluded. Therefore, potential outliers were not excluded from analyses.

Efficacy of the intervention

Results of all primary and secondary outcomes and subgroup analysis, including effect sizes, are presented in

Table 2 Baseline demographic and clinical characteristics of participants

	Intervention Group (*N* = 36)		Control Group (*N* = 36)		Intervention Group Compared With Control Group (*N* = 72)		
Measure	N	%	N	%	χ^2	df	*p*
Female	25	69.4	27	75.0	0.28	1	.599
Married or partnered	25	69.4	24	66.7	0.06	1	.801
High school	31	86.1	25	69.4	2.89	1	.089
Employment[a]	33	94.3	31	88.6			.673[h]
Diagnosis							.866[h]
Depressive disorders (single)[b]	13	36.1	11	30.6			
Depressive disorders (comorbid with anxiety disorders)[c]	10	27.8	13	36.1			
Panic disorder	2	5.6	2	5.6			
Social anxiety disorder	2	5.6	2	5.6			
Specific anxiety disorder	2	5.6	0	0.0			
Generalized anxiety disorder	1	2.8	0	0.0			
Agoraphobia	1	2.8	1	2.8			
Obsessive-compulsive disorder	0	0.0	0	0.0			
Obsessive-compulsive disorder and social anxiety disorder	0	0.0	2	5.6			
Post-traumatic stress disorder	1	2.8	2	5.6			
Primary insomnia	3	8.3	3	8.3			
Attention deficit hyperactivity disorder	1	2.8	0	0.0			
Clinically raised symptoms (SCL-90-R, PSQI)	36	100.0	34	94.1			.493[h]
Depression[d], anxiety[d], insomnia[e]	21	58.3	17	47.2	0.89	1	.345
Receiving psychiatric drugs[f]	18	50.0	20	57.1	0.36	1	.546
Dropout	7	19.4	14	38.9	3.29	1	.070
Treatment change[g]	3	8.3	9	25.0			.111[h]
	Mean	SD	Mean	SD	t	df	p
Age (years)	37.33	14.23	34.33	12.39	0.95	68.69	.343
Global Severity Index (SCL-90-R)	1.06	0.63	1.02	0.61	0.27	69.91	.790
Sleep Quality (PSQI)[e]	9.67	3.66	8.62	3.15	1.28	68.04	.204
Latency pre-treatment – initiation (days)	21.94	17.21	24.36	26.44	−0.46	60.15	.648

Note. *SCL-90-R* Symptom Checklist-90-Revised, *PSQI* Pittsburgh Sleep Quality Index

[a] For employment, the number of participants was *n* = 35 for the intervention group and *n* = 35 for the control group because of incomplete data at pre-treatment assessment.

[b] Depressive disorders (single) includes all participants diagnosed with a single depressive disorder.

[c] Depressive disorders (comorbid with anxiety disorders) includes all participants diagnosed with depressive disorder and comorbid anxiety disorders.

[d] Depression and anxiety levels were classified as clinically raised when t-values of the sub-scales depression and anxiety of the SCL-90-R were greater or equal to 60 (reference group: healthy men, aged between 35 and 44).

[e] Symptoms of insomnia were classified as clinically raised when the cut-off value of five of the total sum score of the PSQI were reached. For clinically raised symptoms and sleep quality, the number of participants was 36 for the intervention group and 35 for the control group because of incomplete data at pre-treatment assessment on the PSQI.

[f] For receiving psychiatric drugs, the number of participants was *n* = 36 for the intervention group and *n* = 35 for the control group because of incomplete data at pre-treatment assessment.

[g] Treatment change is defined as the start of psychotherapy, inpatient treatment or psychopharmacological change.

[h] Fisher's exact test was used as a replacement for the chi-square test because the frequency of one or more cells was less than 5

Table 3. The interaction effect of group by time was significant for global symptom severity, F (1, 53) = 7.93, p = .007, 95%CI[− 0.50,- 0.08], depression, F (1, 55) = 6.30, p = .015, 95%CI[− 0.82, − 0.09], anxiety, F (1, 54) = 10.12, p = .002, 95%CI[− 0.36, − 0.08], and sleep quality, F (1, 58) = 11.24, p = .001, 95%CI[− 4.68, − 1.19], with larger decreases in the intervention group. Post-treatment difference effects were significant for depression, t

(114) = 2.18, $p = .031$, and sleep quality, t (121) = 2.13, $p = .035$, with lower scores in the intervention group. Post-treatment difference effects for global symptom severity, t (105) = 1.68, $p = .096$, and anxiety, t (110) = 1.88, $p = .063$, were moderate, with lower scores in the intervention group, without reaching significance.

The interaction effect of group by time was significant for the mean amount of exercise, F (2, 115) = 16.50, $p < .001$, 95%CI [1.41, 3.61], with larger increases in the intervention group. Bonferroni-corrected intermediate-treatment difference effect, t (167) = − 5.83, $p < .001$, and post-treatment difference effect, t (170) = − 5.04, $p < .001$, were significant, with higher scores in the intervention group.

Compared to participants of the control group, more participants of the intervention group revealed clinically significant changes of symptomatology, without reaching statistical significance (χ^2 (1) = 3.61, $p = .058$.

In a subgroup of participants with depressive disorders, the interaction effect was significant for depression, F (1, 37.48) = 5.74, $p = .022$, 95%CI[− 1.01, − 0.09], with larger decreases in the intervention group. The Post-treatment difference in this subgroup was significant, t (75) = 2.75, $p = .008$, with lower scores in the intervention group (see Table 3). Across both groups, the change of the mean amount of exercise from pre- to post-treatment assessment significantly predicted the change of global symptom severity, $b = .35$, t (49) = 2.61, $p = .012$]. Predictions

Table 3 Marginal means, confidence intervals, effect sizes, and results of linear mixed models analyses

	Intervention Group (*N* = 36)			**Control Group (*N* = 36)**				**Change from Baseline in Intervention Group Compared With Control Group (*N* = 72)**		
Measure and Assessment Point	**Mean**	**SD**	**95% CI**	**Mean**	**SD**	**95% CI**	**d[a]**	**B**	**95% CI**	**d[b]**
Global Severity Index (SCL-90-R)								−0.30	−0.50,-0.08	0.77**
Pre-treatment	1.06	0.59	0.87,1.26	1.02	0.59	0.83,1.22				
Post-treatment	0.67	0.55	0.47,0.87	0.93	0.51	0.71,1.14	0.48			
Depression (SCL-90-R)								−0.46	−0.82,-0.09	0.68*
Pre-treatment	1.57	0.85	1.29,1.85	1.60	0.85	1.32,1.88				
Post-treatment	0.94	0.80	0.65,1.24	1.43	0.76	1.11,1.76	0.63*			
Anxiety (SCL-90-R)[c]								−0.22	−0.36,-0.08	0.87**
Pre-treatment	0.60	0.35	0.49,0.72	0.56	0.35	0.44,0.67				
Post-treatment	0.36	0.33	0.24,0.48	0.53	0.31	0.40,0.67	0.53			
Sleep Quality (PSQI)								−2.94	−4.68,-1.19	0.88**
Pre-treatment	9.67	3.31	8.57,10.76	8.67	3.29	7.57,9.77				
Post-treatment	6.47	3.21	5.29,7.65	8.41	3.12	7.09,9.73	0.61*			
Exercise (BSA questionnaire)[c]								2.51	1.41,3.61	0.82***
Pre-treatment	1.82	1.82	1.22,2.42	1.72	1.82	1.12,2.33				
week 9	4.68	1.80	4.00,5.35	1.74	1.79	1.04,2.45	1.64***			
Post-treatment	4.12	1.80	3.46,4.78	1.53	1.77	0.78,2.27	1.45***			
	Exploratory Analysis (*N* = 47)									
	Intervention Group (*N* = 23)			**Control Group (*N* = 24)**				**Change from Baseline in Intervention Group Compared With Control Group (*N* = 47)**		
Depression (single and with comorbid anxiety disorders) (SCL-90-R)[d]								−0.55	−1.01,−0.09	0.78*
Pre-treatment	1.84	0.79	1.51,2.17	2.00	0.78	1.68,2.32				
Post-treatment	1.10	0.77	0.77,1.44	1.81	0.71	1.42,2.20	0.95**			

Note. SCL-90-R Symptom Checklist-90-Revised, *PSQI* Pittsburgh Sleep Quality Index, *BSA questionnaire* Exercise Activity Index of the Physical Activity, Exercise, and Sport Questionnaire

[a] Cohen's d for post- and intermediate-treatment effect.

[b] Cohen's d for the interaction effect.

[c] Log-transformed data due to a skewed data distribution.

[d] Participants with depression with and without comorbidities.

*$p < .05$. **$p < .01$. ***$p < .001$

from the change of exercise on the change of disorder-specific symptoms across both groups and for each group are displayed in Additional file 3.

Discussion

This RCT compared a group exercise intervention with a passive control group among 72 inactive outpatients, suffering from one or more diagnoses of depressive disorders, anxiety disorders, insomnia, and ADHD. Compared to the control group, the intervention was efficacious in improving global symptom severity, depression, anxiety and sleep quality as well as the amount of exercise with moderate to large effect sizes. Post-treatment difference effects were moderate to large on depression, sleep quality and the amount of exercise. Among participants diagnosed with depressive disorders, the antidepressant effect of the exercise intervention was larger compared to the entire mixed sample. Across both groups, an increase in the amount of exercise predicted the reduction of global symptom severity, indicating that those patients who engaged in more exercise showed decreased symptom severity.

Efficacy of the intervention

Beneficial effects of the intervention on global symptom severity suggest that the exercise intervention efficaciously reduced symptoms across the included heterogenous sample. On the one hand, there are few studies that investigated the efficacy of exercise among outpatients with heterogenous psychiatric diagnoses [75]. On the other hand, the few existing studies assessed physical health, rather than mental health as primary outcomes [85]. Two RCTs assessed quality of life [86] and general mental health [87] as secondary outcome. Their results suggested improvements on quality of life (i.e., physical function score, social function, emotional role) [86] but not on general mental health (i.e., psychological distress and well-being) [87]. To the best of our knowledge, there exists no study investigating the effects of exercise among a sample with heterogenous diagnoses that include a clinical valid and reliable measure to assess global symptom severity. Whereas the intervention group revealed stronger improvements on global symptom severity, compared to the control group, the post-treatment effect between both groups was not significant. Since sample size calculation was based on large effects of exercise on disorder-specific symptoms among included disorders, power might have been to small to detect treatment effects on global symptom severity across disorders at post-treatment assessment.

Interaction effects of the current intervention on global symptom severity are similar to those of recent meta-analyses [27, 28, 29, 30, 31], evaluating the efficacy of transdiagnostic psychological treatments among patients with depressive disorders and/or anxiety disorders over comparison or control interventions (i.e., diagnosis-specific intervention control, treatment-as-usual, or a waitlist control). Results of these previous studies revealed moderate to large effects on clinical measures assessing symptom severity across included disorders (i.e., depression-anxiety scales, quality of life).

Supporting the assumption of the transdiagnostic efficacy of the intervention, our results demonstrated that the intervention improved one underlying process across included disorders with large effect size: poor sleep quality [21, 22]. This result is similar to a recent meta-analysis of RCTs [34] which demonstrated large beneficial effect of exercise on sleep quality among people with various psychiatric disorders. Nonetheless, the analysis included primarily RCTs assessing the effects of exercise on sleep quality among study samples with specific diagnoses. Only one RCT [88] included participants with a primary diagnosis of a depressive disorder with and without comorbid anxiety disorders. Similarly, another recent meta-analysis [89] that investigated the effects of exercise on various underlying processes across psychiatric disorders, mostly included participants with specific diagnoses or even non-clinical samples. Thus, the findings of our study therefore expand on the results of recent meta-analyses by demonstrating effects on one underlying process across a clinical sample with heterogenous psychiatric disorders.

Correspondingly, our results suggest disorder-specific efficacy by improving symptoms of depression, anxiety and insomnia. The moderate antidepressant effect of the intervention at post-treatment assessment is smaller compared to prior meta-analytical findings suggesting a large antidepressant effect of exercise, over non-active controls [36]. In contrast to our study, prior studies included samples with a primary diagnosis of a depressive disorder only [36]. Although the large antidepressant effect among patients with a primary depressive disorder have been consistently demonstrated in prior studies [35, 36], to the best of our knowledge, the antidepressant effect of exercise among anxiety disorders, insomnia, and ADHD has not been investigated yet. When analyzing the antidepressant efficacy of our exercise intervention among the subsample with a primary diagnosis of a depressive disorder, the effect size is comparable to prior studies [36]. The mean change of anxiety symptoms among the intervention group across the entire mixed sample was large, compared to the control group. Prior exercise trials have reported moderate interaction effects of exercise on anxiety symptoms among patients with anxiety disorders, over non-active controls [38]. This result may suggest that the current exercise intervention might have been more efficacious in reducing anxiety

across heterogenous disorders than prior exercise trials that included only anxiety disorders [38]. However, this assumption needs to be considered with caution due to different sample characteristics and exercise modalities.

The post-treatment difference effect between the intervention group and control group on anxiety was not statistically significant. As stated above, the power analysis was based on the median effect size for disorder-specific effects of exercise across depressive disorders, anxiety disorders, and insomnia. Beneficial effects of exercise on anxiety seem to be smaller than those for depression [35] and insomnia symptoms [39]. Furthermore, it appears that effect sizes differ across different anxiety disorders [37]. Therefore, the a-priori determined sample size might have been underestimated to detect treatment effects on anxiety across the heterogenous sample. The large post-treatment effect of exercise on sleep quality among the intervention group, compared to the control group, is comparable to prior meta-analytical findings investigating the effect of exercise on sleep quality in patients with insomnia, over non-active controls [40]. In comparison to meta-analytical findings investigating disorder-specific effects of CBT, over non-active controls, our results showed similar efficacy for depression among depressed participants [90] and sleep quality among the entire mixed sample [91].

The efficacy on global symptom severity and underlying mechanisms across the sample as well as disorder-specific efficacy of the current exercise intervention, suggests that exercise might be able treat a broad range of heterogenous diagnoses with and without comorbidities. Our study results further suggest, that exercise interventions do not necessarily be tailored to a specific psychiatric disorder referring to exercise modalities (i.e., type, frequency) to efficaciously treat disorder-specific symptoms or underlying processes across disorders. Rather, exercise modalities, that have shown therapeutic efficacy among single psychiatric disorders (i.e., two to three times per week, for 10 weeks, at a minimum of moderate intensity and a duration of 30 min, partially supervised or non-supervised, solely aerobic or aerobic combined with resistance training [33, 35, 37, 43]) seem to be adoptable to the treatment of heterogenous diagnoses with and without comorbidities. Similar to the efficacy of transdiagnostic psychological interventions, this may result in a faster and easier dissemination, compared to disorder-specific treatments, because there is no need to learn and apply multiple treatment protocols for different specific disorders [12]. Thus, exercise interventions may improve the existing treatment gap in mental health care [11] by offering an efficacious and effective treatment.

Effects on exercise behavior

Study results demonstrated that the current exercise intervention was highly efficacious in increasing the amount of exercise, even when participants were not supervised. This is in line with a recent systematic review [46] and Editorial [48], suggesting that exercise interventions, combined with BCTs, are efficacious in increasing the amount of exercise. To date, there are only a few exercise interventions for individuals with psychiatric disorders integrating BCTs [46, 85] and only approximately one quarter of those seem to efficaciously increasing participant's amount of exercise [85]. The frequent failure to increase exercise behavior among patients with psychiatric disorders may be related to a lack of motivation and exercise-related self-regulatory skills (i.e., volition) in this population [49]. A large proportion of outpatients in Germany do not exercise on a regular base [92]. Thus, the integrated BCTs in our intervention seem to be adequately tailored to outpatients to improve their deficiencies in motivation and volition regarding exercise.

Results of our explorative analyses demonstrated a prediction of symptom reduction by an increase of the performed amount of exercise, indicating that the change of exercise might indeed be one specific mode of action of the therapeutic effects. This moderation effect is often assumed in the exercise literature, however only very few trials do report such effects. As far as we know, only one of the recently published high quality RCTs [45] did show changes of exercise as the specific mode of action of the effects of exercise interventions. In addition to the increase of exercise, results suggest also a maintenance of exercise behavior because participants were still exercising even when they were not supervised. Since there is a lack of follow-up studies of exercise interventions or an absence of measures for exercise behavior, little is known about the maintenance of exercise behavior due to the conduction of exercise interventions combined or without BCTs [85]. As mentioned in the introduction, beneficial effects of exercise seem to be maintained only when exercise behavior has changed sustainably [45]. Since participants were still exercising during the non-supervised period of the intervention, participants might have integrated regular exercise into their daily life routines. Since the amount of exercise was assessed 5 weeks and 2 months after the supervised period, no general conclusions can be drawn about the long-lasting exercise behavior.

Feasibility of the intervention

Results of this study not only suggest efficacy of the current exercise intervention but also its feasibility in a realistic outpatient setting. First, the study sample included a realistic outpatient sample, waiting for

psychotherapeutic treatment, with heterogenous, highly prevalent psychiatric disorders with and without comorbid diagnoses. Second, approximately half of the participants of the intervention group revealed clinically relevant changes of global symptom severity, compared to less than one quarter of the control group. Third, the dropout quote among participants of the intervention group was low. Additionally, only 5.2% ($n = 2$) of the intervention group dropped out due to lost to follow up. Hence, a strong acceptance and few adherence issues regarding the intervention can be assumed. The dropout rate is similar to prior exercise interventions [38, 93] and lower than other health behaviour change interventions (e.g., exercise, health education) for individuals with psychiatric disorders, in which the medium average dropout rate was 45% [94]. The current dropout rate was lower than those of individual and group CBT interventions (35%). Most dropouts were reported in outpatient settings [95]. The lower dropout rate in the current exercise intervention over CBT, might suggest equivalent acceptance of exercise than CBT among outpatients. Forth, the latency between pre-treatment assessment and initiation of the intervention was low, compared to waiting times for psychotherapy of approximately 5 months in Germany [10]. As stated in the introduction, prolonged waiting times for treatment are associated with worsening and chronicity of symptoms and the development of comorbid diagnoses. Consequently, the current intervention could be conducted to improve negative consequences of delayed treatment in Germany. Lastly, in comparison to an average duration of 19 weeks of prior exercise intervention for patients with psychiatric disorders [96], the current exercise intervention was short (12 weeks), including a very short supervised period of 4 weeks. The total number of 12 supervised sessions is equivalent to the average treatment duration of CBT among depressive disorders and anxiety disorders [97, 98].

Hence, in addition to the suggested transdiagnostic and disorder-specific efficacy of the intervention, current results demonstrated that the exercise intervention might be feasible treatment among outpatients, that were waiting for psychotherapeutic treatment in German health care settings in outpatient units and practices.

Limitations

One limitation of the current study is the use of a passive control group, which does not allow to control for non-specific effects of therapy, such as relationship building or social support. However, the results of our explorative analyses demonstrated a prediction of symptom reduction by an increase of the performed amount of exercise, indicating that the change of exercise might indeed be one specific mode of action of the therapeutic effects. Second, the measure for global symptom severity symptoms was comprised of symptoms that were not characteristic for all included disorders (e.g., aggression). Therefore, the validity of this metric to assess global symptom severity among the current sample is disputable. However, the GSI is a reliable and valid instrument to assess clinical global symptom severity across heterogenous psychiatric disorders and allows to rate clinically relevant changes of symptomatology [99]. Therefore, the use of this measure was reasonable in this study because of the inclusion of heterogenous and highly comorbid psychiatric disorders. Furthermore, the internationally widespread use of this measure [58] allows to compare study results with international publications on the effect of various treatments on symptom severity. Third, eligibility criteria of the current study allowed for a wide age range. However, participants had a low average age, which might limit the generalizability of results to older individuals. Large standard deviations around the mean value, a large age range (19–63 years) of the current sample as well as a similar average age of prior exercise trials [36] might increase the generalizability of results to older individuals. Forth, although the SCID was conducted at pre-treatment and post-treatment assessment, we did not include results of the SCID from post-treatment assessment in our analyses. We intended to assess clinically relevant changes of symptomatology. If a diagnosis, that was present at pre-treatment assessment, had still been present at post-treatment assessment, relevant changes on symptomatology would not have been able to assess. Therefore, we considered self-reported outcomes (GSI of the SCL-90-R) as a more valid measure to assess clinically relevant changes of symptomatology. Moreover, one eligible participant could meet multiple inclusion diagnoses. Thus, the comparison of the number of inclusion diagnoses between pre-treatment and post-treatment assessment did not seem as a valid indicator of treatment responders vs. non-responders. Alternative indicators of treatment responders vs. non-responders, resulting from analyses of the SCID (e.g., counting of symptom criteria for depressive disorders) seem to be an arbitrary and not valid approach.

Strengths

First, the high methodological standard is an important strength of the study. The study involved an RCT design with stratified block-randomization, which is considered as the gold standard to evaluate intervention efficacy [100]. Equal treatment arms and allocation maximized internal validity [101]. Strict inclusion and exclusion criteria controlled for factors that may obfuscate outcome measures [102]. Second, the inclusion of a heterogeneous sample with a broad age range and various psychiatric disorders allowed for a high generalizability of the results. The conduction of the intervention in a realistic outpatient setting, the large number of included patients

with severe, clinically raised symptoms and comorbid presentations of psychiatric disorders suggest a valid representation of the clinical reality [12].

Conclusions

In conclusion, our findings suggest the transdiagnostic efficacy of exercise across heterogenous psychiatric disorders with comparable effects to transdiagnostic psychological interventions. The transdiagnostic efficacy of the group exercise intervention "ImPuls", tailored to and conducted with heterogenous psychiatric disorders, is comparable to disorder-specific exercise interventions or established treatments, such as CBT. The increase of exercise behavior seemed to be responsible for the therapeutic effects of the intervention. The low dropout rate, the short latency from first meeting to intervention initiation, the small number of supervised sessions, and the successful increase and maintenance of exercise by integrating BCTs, may indicate a high feasibility and acceptance of the current exercise intervention. Due to the transdiagnostic efficacy and its feasibility within a real-world outpatient setting, the current exercise intervention may represent a treatment option that could improve the existing treatment gap in the outpatient mental health care in Germany. Future research is required to replicate findings with an active control condition, among older individuals, and additional measures of global symptom severity. A follow-up study will allow to assess the maintenance of treatment effects.

Abbreviations

DALYS: Disability-adjusted life years; OCD: Obsessive compulsive disorders; PTSD: Posttraumatic-stress disorder; ADHD: Attention deficit hyperactivity disorder; CBT: Cognitive behavioural therapy; RCT: Randomized controlled trial; BCT: Behaviour change technique; CONSORT: Consolidated Standards of Reporting Trials; GAF: Global Assessment of Functioning Scale; SCID: Structured Clinical Interview for DSM-IV (SCID); HASE: Homburg ADHD Scales for Adults; PSQI: Pittsburgh Sleep Quality Index; GSI: Global Severity Index; SCL-90-R: Symptom Checklist-90-Revised; BSA questionnaire: Physical Activity, Exercise, and Sport Questionnaire; SF-B: Sleep Questionnaire B-Revised version; PSS: Perceived Stress Scale; SF-36: 36-Item Short Form Health Survey; SKK-Scale: Self Concordance of Sport- and Exercise-related Goals Scale; RPE Scale: Rating of Perceived Exertion Scale; IBM SPSS: Statistical Package for Social Science; ITT: Intention-to-treat; MCAR: Missing completely at random

Supplementary Information

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Additional file 1. Characteristics of treatment completers versus dropouts.

Additional file 2. Sensitivity Analysis using Study Completers.

Additional file 3. Additional Explorative Analyses of the Predictive Value of Exercise on Primary Outcomes.

Additional file 4. Linear mixed models excluding potential outliers.

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Authors' contributions

J.-M.Z., B.-A.S., G.S., I.R., M.H. and S.W. contributed to the conception and the design of the study. J.-M.Z., B.-A.S., M.H., and S.W. completed the acquisition of data. J.-M.Z., S.W. and I.R. performed the data analysis. J.-M.Z., B.-A.S., G.S., I.R., M.H. and S.W. assisted with the interpretation. Original draft preparation was done by J.-M.Z. and S.W. J.-M.Z., B.-A.S., G.S., I.R., M.H. and S.W. contributed to the drafting and revision of the final article. J.-M.Z., B.-A.S., G.S., I.R., M.H. and S.W. have read and agreed to the published version of the manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are available in the PsychArchives repository, https://doi.org/10.23668/psycharchives.4625.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee for psychological research of the University of Tuebingen, Department of Psychology (Az_Wolf_2018_0108_99, February 22nd, 2018). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. United States: Institute for Health Metrics and Evaluation (IHME); 2020. http://ghdx.healthdata.org/gbd-results-tool. Accessed 1 Nov 2020
2. De Hert M, Detraux J, Vancampfort D. The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin Neurosci. 2018; 20(1):31–40.
3. Hajak G. Epidemiology of severe insomnia and its consequences in Germany. Eur Arch Psychiatry Clin Neurosci. 2001;251(2):49–56. https://doi.org/10.1007/s004060170052.
4. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National

Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617–27. https://doi.org/10.1001/archpsyc.62.6.617.
5. Erskine HE, Norman RE, Ferrari AJ, Chan GC, Copeland WE, Whiteford HA, et al. Long-term outcomes of attention-deficit/hyperactivity disorder and conduct disorder: a systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2016;55(10):841–50. https://doi.org/10.1016/j.jaac.2016.06.016.
6. Klein Hofmeijer-Sevink M, Batelaan NM, van Megen HJGM, Penninx BW, Cath DC, van den Hout MA, et al. Clinical relevance of comorbidity in anxiety disorders: a report from the Netherlands study of depression and anxiety (NESDA). J Affect Disord. 2012;137(1):106–12. https://doi.org/10.1016/j.jad.2011.12.008.
7. Franzen PL, Buysse DJ. Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. Dialogues Clin Neurosci. 2008;10(4):473–81.
8. Ramsawh HJ, Stein MB, Belik SL, Jacobi F, Sareen J. Relationship of anxiety disorders, sleep quality, and functional impairment in a community sample. J Psychiatr Res. 2009;43(10):926–33. https://doi.org/10.1016/j.jpsychires.2009.01.009.
9. Nübling R, Bär T, Jeschke K, Ochs M, Sarubin N, Schmidt J. Care of mentally ill adults in Germany - need and utilization as well as effectiveness and efficiency of psychotherapy [Versorgung psychisch kranker Erwachsener in Deutschland - Bedarf und Inanspruchnahme sowie Effektivität und Effizienz von Psychotherapie]. Psychotherapeutenjournal. 2014;13:389–97.
10. Bundespsychotherapeutenkammer. One year after psychotherapy guideline reform [Ein Jahr nach der Reform der Psychotherapie-Richtlinie]. Berlin: BPtK; 2018.
11. Patel V. Global mental health: from science to action. Harv Rev Psychiatry. 2012;20(1):6–12. https://doi.org/10.3109/10673229.2012.649108.
12. Dalgleish T, Black M, Johnston D, Bevan A. Transdiagnostic approaches to mental health problems: current status and future directions. J Consult Clin Psychol. 2020;88(3):179–95. https://doi.org/10.1037/ccp0000482.
13. Mattke D, Pröstler M. Forms of outpatient group therapy [Formen ambulanter Gruppentherapie], first edn: springer-Verlag GmbH Deutschland; 2020. https://doi.org/10.1007/978-3-662-59092-8.
14. Haslam N, Holland E, Kuppens P. Categories versus dimensions in personality and psychopathology: a quantitative review of taxometric research. Psychol Med. 2012;42(5):903–20. https://doi.org/10.1017/s0033291711001966.
15. Öster C, Ramklint M, Meyer J, Isaksson J. How do adolescents with ADHD perceive and experience stress? An interview study. Nord J Psychiatry. 2020;74(2):123–30. https://doi.org/10.1080/08039488.2019.1677771.
16. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry. 1999;156(6):837–41. https://doi.org/10.1176/ajp.156.6.837.
17. Moreno-Peral P, Conejo-Ceron S, Motrico E, Rodriguez-Morejon A, Fernandez A, Garcia-Campayo J, et al. Risk factors for the onset of panic and generalised anxiety disorders in the general adult population: a systematic review of cohort studies. J Affect Disord. 2014;168:337–48. https://doi.org/10.1016/j.jad.2014.06.021.
18. Hall M, Thayer JF, Germain A, Moul D, Vasko R, Puhl M, et al. Psychological stress is associated with heightened physiological arousal during NREM sleep in primary insomnia. Behav Sleep Med. 2007;5(3):178–93. https://doi.org/10.1080/15402000701263221.
19. Maciejewski PK, Prigerson HG, Mazure CM. Self-efficacy as a mediator between stressful life events and depressive symptoms. Differences based on history of prior depression. Br J Psychiatry. 2000;176(4):373–8. https://doi.org/10.1192/bjp.176.4.373.
20. Iancu I, Bodner E, Ben-Zion IZ. Self esteem, dependency, self-efficacy and self-criticism in social anxiety disorder. Compr Psychiatry. 2015;58:165–71. https://doi.org/10.1016/j.comppsych.2014.11.018.
21. Wahl K, Ehring T, Kley H, Lieb R, Meyer A, Kordon A, et al. Is repetitive negative thinking a transdiagnostic process? A comparison of key processes of RNT in depression, generalized anxiety disorder, obsessive-compulsive disorder, and community controls. J Behav Ther Exp Psychiatry. 2019;64:45–53. https://doi.org/10.1016/j.jbtep.2019.02.006.
22. Harvey AG. A cognitive model of insomnia. Behav Res Ther. 2002;40(8):869–93. https://doi.org/10.1016/S0005-7967(01)00061-4.
23. Naragon-Gainey K. Meta-analysis of the relations of anxiety sensitivity to the depressive and anxiety disorders. Psychol Bull. 2010;136(1):128–50. https://doi.org/10.1037/a0018055.
24. Coles ME, Schubert JR, Nota JA. Sleep, circadian rhythms, and anxious traits. Curr Psychiatry Rep. 2015;17(9):73. https://doi.org/10.1007/s11920-015-0613-x.
25. Olatunji BO, Wolitzky-Taylor KB. Anxiety sensitivity and the anxiety disorders: a meta-analytic review and synthesis. Psychol Bull. 2009;135(6):974–99. https://doi.org/10.1037/a0017428.
26. McEvoy PM, Nathan P, Norton PJ. Efficacy of Transdiagnostic treatments: a review of published outcome studies and future research directions. J Cogn Psychother. 2009;1(1):20–33. https://doi.org/10.1891/0889-8391.23.1.20.
27. Andersen P, Toner P, Bland M, McMillan D. Effectiveness of Transdiagnostic cognitive behaviour therapy for anxiety and depression in adults: a systematic review and meta-analysis. Behav Cogn Psychother. 2016;44(6):673–90. https://doi.org/10.1017/S1352465816000229.
28. Newby JM, McKinnon A, Kuyken W, Gilbody S, Dalgleish T. Systematic review and meta-analysis of transdiagnostic psychological treatments for anxiety and depressive disorders in adulthood. Clin Psychol Rev. 2015;40:91–110. https://doi.org/10.1016/j.cpr.2015.06.002.
29. Pearl SB, Norton PJ. Transdiagnostic versus diagnosis specific cognitive behavioural therapies for anxiety: a meta-analysis. J Anxiety Disord. 2017;46:11–24. https://doi.org/10.1016/j.janxdis.2016.07.004.
30. Newby JM, Twomey C, Yuan Li SS, Andrews G. Transdiagnostic computerised cognitive behavioural therapy for depression and anxiety: a systematic review and meta-analysis. J Affect Disord. 2016;199:30–41. https://doi.org/10.1016/j.jad.2016.03.018.
31. Reinholt N, Krogh J. Efficacy of transdiagnostic cognitive behaviour therapy for anxiety disorders: a systematic review and meta-analysis of published outcome studies. Cogn Behav Ther. 2014;43(3):171–84. https://doi.org/10.1080/16506073.2014.897367.
32. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126–31.
33. Jacquart J, Dutcher CD, Freeman SZ, Stein AT, Dinh M, Carl E, et al. The effects of exercise on transdiagnostic treatment targets: a meta-analytic review. Behav Res Ther. 2019;115:19–37. https://doi.org/10.1016/j.brat.2018.11.007.
34. Lederman O, Ward PB, Firth J, Maloney C, Carney R, Vancampfort D, et al. Does exercise improve sleep quality in individuals with mental illness? A systematic review and meta-analysis. J Psychiatr Res. 2019;109:96–106. https://doi.org/10.1016/j.jpsychires.2018.11.004.
35. Morres ID, Hatzigeorgiadis A, Stathi A, Comoutos N, Arpin-Cribbie C, Krommidas C, et al. Aerobic exercise for adult patients with major depressive disorder in mental health services: a systematic review and meta-analysis. Depress Anxiety. 2019;36(1):39–53. https://doi.org/10.1002/da.22842.
36. Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB, Stubbs B. Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. J Psychiatr Res. 2016;77:42–51. https://doi.org/10.1016/j.jpsychires.2016.02.023.
37. Aylett E, Small N, Bower P. Exercise in the treatment of clinical anxiety in general practice - a systematic review and meta-analysis. BMC Health Serv Res. 2018;18(1):559. https://doi.org/10.1186/s12913-018-3313-5.
38. Stubbs B, Vancampfort D, Rosenbaum S, Firth J, Cosco T, Veronese N, et al. An examination of the anxiolytic effects of exercise for people with anxiety and stress-related disorders: a meta-analysis. Psychiatry Res. 2017;249:102–8. https://doi.org/10.1016/j.psychres.2016.12.020.
39. Banno M, Harada Y, Taniguchi M, Tobita R, Tsujimoto H, Tsujimoto Y, et al. Exercise can improve sleep quality: a systematic review and meta-analysis. PeerJ. 2018;6:e5172. https://doi.org/10.7717/peerj.5172.
40. Kelley GA, Kelley KS. Exercise and sleep: a systematic review of previous meta-analyses. J Evid Based Med. 2017;10(1):26–36. https://doi.org/10.1111/jebm.12236.
41. Cerrillo-Urbina AJ, García-Hermoso A, Sánchez-López M, Pardo-Guijarro MJ, Santos Gómez JL, Martínez-Vizcaíno V. The effects of physical exercise in children with attention deficit hyperactivity disorder: a systematic review and meta-analysis of randomized control trials. Child Care Health Dev. 2015;41(6):779–88. https://doi.org/10.1111/cch.12255.
42. Seiffer B, Hautzinger M, Ulrich R, Wolf S. Efficacy of regular moderate to vigorous physical activity in children with ADHD: a meta-analysis of randomized controlled trials. J Atten Disord. 2021:108705472110179. https://doi.org/10.1177/10870547211017982.

43. Stubbs B, Vancampfort D, Hallgren M, Firth J, Veronese N, Solmi M, et al. EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and position statement from the European psychiatric association (EPA), supported by the International Organization of Physical Therapists in mental health (IOPTMH). Eur Psychiatry. 2018;54:124–44. https://doi.org/10.1016/j.eurpsy.2018.07.004.
44. Blumenthal JA, Babyak MA, Doraiswamy PM, Watkins L, Hoffman BM, Barbour KA, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom Med. 2007;69(7):587–96. https://doi.org/10.1097/PSY.0b013e318148c19a.
45. Hoffman BM, Babyak MA, Craighead WE, Sherwood A, Doraiswamy PM, Coons MJ, et al. Exercise and pharmacotherapy in patients with major depression: one-year follow-up of the SMILE study. Psychosom Med. 2011;73(2):127–33. https://doi.org/10.1097/PSY.0b013e31820433a5.
46. Thomas J, Thirlaway K, Bowes N, Meyers R. Effects of combining physical activity with psychotherapy on mental health and well-being: a systematic review. J Affect Disord. 2020;265:475–85. https://doi.org/10.1016/j.jad.2020.01.070.
47. Fuchs R, Seelig H, Göhner W, Burton NW, Brown WJ. Cognitive mediation of intervention effects on physical exercise: causal models for the adoption and maintenance stage. Psychol Health. 2012;27(12):1480–99. https://doi.org/10.1080/08870446.2012.695020.
48. Rosenbaum S, McKeon G, Stubbs B, Teychenne M, Parker A, Stanton R, et al. Redefining mental healthcare: going multidisciplinary to manage multimorbidity. Br J Sports Med. 2020;55(1):7–8. https://doi.org/10.1136/bjsports-2019-101691.
49. Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP. A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. Psychol Health. 2011;26(11):1479–98. https://doi.org/10.1080/08870446.2010.540664.
50. Wolf S, Zeibig J-M, Hautzinger M, Sudeck G. Psychische Gesundheit durch Bewegung. ImPuls: Ein sport- und bewegungstherapeutisches Programm für Menschen mit psychischen Erkrankungen. Weinheim: Julius Beltz GmbH & Co. KG; 2020.
51. Schulz K, Altman D, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726–32. https://doi.org/10.7326/0003-4819-152-11-201006010-00232%m20335313.
52. Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G*power 3.1: tests for correlation and regression analyses. Behav Res Methods. 2009;41(4):1149–60. https://doi.org/10.3758/BRM.41.4.1149.
53. Powers MB, Medina JL, Burns S, Kauffman BY, Monfils M, Asmundson GJ, et al. Exercise augmentation of exposure therapy for PTSD: rationale and pilot efficacy data. Cogn Behav Ther. 2015;44(4):314–27. https://doi.org/10.1080/16506073.2015.1012740.
54. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. Structured clinical interview for DSM-IV Axis I disorders (SCID-I), clinician version (SCID-CV). Washington: American Psychiatric Press; 2002.
55. Rösler M, Retz-Junginger P, Retz W, Stieglitz R-D. HASE – Homburg ADHD scales for adults [HASE – Homburger ADHS-Skalen für Erwachsene]. Göttingen: Hogrefe; 2008.
56. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193–213. https://doi.org/10.1016/0165-1781(89)90047-4.
57. Leiner DJ. SoSci Survey [Computer Software]. In., 2.6.00 edn; 2016.
58. Derogatis LR. SCL-90-R: administration, scoring and procedures manual. 3rd ed. Minneapolis: NCS Pearson; 1994.
59. Prinz U, Nutzinger D, Schulz H, Petermann F, Braukhaus C, Andreas S. Comparative psychometric analyses of the SCL-90-R and its short versions in patients with affective disorders. BMC Psychiatry. 2013;13(1):104. https://doi.org/10.1186/1471-244X-13-104.
60. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test-retest reliability and validity of the Pittsburgh sleep quality index in primary insomnia. J Psychosom Res. 2002;53(3):737–40. https://doi.org/10.1016/S0022-3999(02)00330-6.
61. Doi Y, Minowa M, Uchiyama M, Okawa M, Kim K, Shibui K, et al. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh sleep quality index (PSQI-J) in psychiatric disordered and control subjects. Psychiatry Res. 2000;97(2–3):165–72. https://doi.org/10.1016/s0165-1781(00)00232-8.
62. Fuchs R, Klaperski S, Gerber M, Seelig H. Assessment of exercise and physical activity with the BSA questionnaire: a methodical interim assessment [Messung der Bewegungs-und sportaktivität mit dem BSA-Fragebogen: Eine Methodische Zwischenbilanz]. Zeitschrift für Gesundheitspsychologie. 2015;23(3):60–76. https://doi.org/10.1026/0943-8149/a000137.
63. Görtelmeyer R. SF-A/R and SF-B/R. sleep questionnaire a and B - revised version [SF-A/R und SF-B/R. Schlaffragebogen a und B - revidierte Fassung]. Götting: Hogrefe; 2005.
64. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385–96. https://doi.org/10.2307/2136404.
65. Morfeld M, Kirchberger I, Bullinger M. Short Form-36 Health Survey: German Version [SF-36 Fragebogen zum Gesundheitszustand: Deutsche Version des Short Form-36 Health Survey]. Göttingen: Hogrefe; 2011.
66. Seelig H, Fuchs R. Assessment of exercise and physical activity-related self-concordance [Messung der sport- und bewegungsbezogenen Selbstkonkordanz]. Zeitschrift Fur Sportpsychologie. 2006;13(4):121–39. https://doi.org/10.1026/1612-5010.13.4.121.
67. Göhner W, Seelig H, Fuchs R. Intervention effects on cognitive antecedents of physical exercise: a 1-year follow-up study. Appl Psychol Health Well Being. 2009;1(2):233–56. https://doi.org/10.1111/j.1758-0854.2009.01014.x.
68. Sudeck G, Pfeifer K. Physical activity-related health competence as an integrative objective in exercise therapy and health sports - conception and validation of a short questionnaire. Ger J Exerc Sport Res. 2016;46(2):74–87. https://doi.org/10.1007/s12662-016-0405-4.
69. Wolf S, Zeibig J-M, Hautzinger M, Sudeck G: Mental health through exercise. ImPuls: an exercise intervention for individuals with psychiatric disorders [Psychische gesundheit durch Bewegung. ImPuls: Ein sport- und bewegungstherapeutisches Programm für menschen mit psychischen Erkrankungen], first edn. Weinheim: Julius Beltz GmbH & Co. KG; 2020.
70. Abraham C, Kelly MP, West R, Michie S. The UK National Institute for health and clinical excellence public health guidance on behaviour change: a brief introduction. Psychol Health Med. 2009;14(1):1–8. https://doi.org/10.1080/13548500802537903.
71. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377–81.
72. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334–59. https://doi.org/10.1249/MSS.0b013e318213fefb.
73. Copley JB, Lindberg JS. The risks of exercise. Adv Ren Replace Ther. 1999;6(2):165–71. https://doi.org/10.1016/s1073-4449(99)70035-x.
74. Firth J, Siddiqi N, Koyanagi A, Siskind D, Rosenbaum S, Galletly C, et al. The lancet psychiatry commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatry. 2019;6(8):675–712. https://doi.org/10.1016/S2215-0366(19)30132-4.
75. Ashdown-Franks G, Firth J, Carney R, Carvalho AF, Hallgren M, Koyanagi A, et al. Exercise as medicine for mental and substance use disorders: a meta-review of the benefits for neuropsychiatric and cognitive outcomes. Sports Med. 2020;50(1):151–70. https://doi.org/10.1007/s40279-019-01187-6.
76. Yang Y, Shin JC, Li D, An R. Sedentary behavior and sleep problems: a systematic review and meta-analysis. Int J Behav Med. 2017;24(4):481–92. https://doi.org/10.1007/s12529-016-9609-0.
77. Allen MS, Walter EE, Swann C. Sedentary behaviour and risk of anxiety: a systematic review and meta-analysis. J Affect Disord. 2019;242:5–13. https://doi.org/10.1016/j.jad.2018.08.081.
78. Patterson R, McNamara E, Tainio M, de Sá TH, Smith AD, Sharp SJ, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. Eur J Epidemiol. 2018;33(9):811–29. https://doi.org/10.1007/s10654-018-0380-1.
79. Fergusson D, Aaron SD, Guyatt G, Hébert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. The BMJ. 2002;325(7365):652–4. https://doi.org/10.1136/bmj.325.7365.652.
80. Bell ML, Fiero M, Horton NJ, Hsu CH. Handling missing data in RCTs; a review of the top medical journals. BMC Med Res Methodol. 2014;14(1):118. https://doi.org/10.1186/1471-2288-14-118.

81. Pituch KA, Stevens JP. Multiple regression of prediction. In: Applied multivariate statistics for the social sciences. 6th ed. Hillsdale: Erlbaum; 2016.
82. Cook RD, Weisberg S. Residuals and influence in regression. New York: Chapman & Hall; 1982.
83. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw. 2015;67(1):1–48. https://doi.org/10.18637/jss.v067.i01.
84. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale: Erlbaum; 1988.
85. Ashdown-Franks G, Williams J, Vancampfort D, Firth J, Schuch F, Hubbard K, et al. Is it possible for people with severe mental illness to sit less and move more? A systematic review of interventions to increase physical activity or reduce sedentary behaviour. Schizophr Res. 2018;202:3–16. https://doi.org/10.1016/j.schres.2018.06.058.
86. Masa-Font R, Fernández-San-Martín MI, Martín López LM, Alba Muñoz AM, Oller Canet S, Martín Royo J, et al. The effectiveness of a program of physical activity and diet to modify cardiovascular risk factors in patients with severe mental illness after 3-month follow-up: CAPiCOR randomized clinical trial. Eur Psychiatry. 2015;30(8):1028–36. https://doi.org/10.1016/j.eurpsy.2015.09.006.
87. Goldberg RW, Reeves G, Tapscott S, Medoff D, Dickerson F, Goldberg AP, et al. "MOVE!" outcomes of a weight loss program modified for veterans with serious mental illness. Psychiatr Serv. 2013;64(8):737–44. https://doi.org/10.1176/appi.ps.201200314.
88. Strid C, Andersson C, Forsell Y, Öjehagen A, Lundh L-G. Internet-based cognitive behaviour therapy and physical exercise – effects studied by automated telephone assessments in mental ill-health patients; a randomized controlled trial. Br J Clin Psychol. 2016;55(4):414–28. https://doi.org/10.1111/bjc.12111.
89. LeBouthillier DM, Asmundson GJG. The efficacy of aerobic exercise and resistance training as transdiagnostic interventions for anxiety-related disorders and constructs: a randomized controlled trial. J Anxiety Disord. 2017;52:43–52. https://doi.org/10.1016/j.janxdis.2017.09.005.
90. Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJ. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. World Psychiatry. 2016;15(3):245–58. https://doi.org/10.1002/wps.20346.
91. van Straten A, van der Zweerde T, Kleiboer A, Cuijpers P, Morin CM, Lancee J. Cognitive and behavioral therapies in the treatment of insomnia: a meta-analysis. Sleep Med Rev. 2018;38:3–16. https://doi.org/10.1016/j.smrv.2017.02.001.
92. Petzold MB, Bischoff S, Rogoll J, Plag J, Teran C, Brand R, et al. Physical activity in outpatients with mental disorders: status, measurement and social cognitive determinants of health behavior change. Eur Arch Psychiatry Clin Neurosci. 2017;267(7):639–50. https://doi.org/10.1007/s00406-017-0772-3.
93. Herring MP, Herring MP, Jacob ML, Suveg C, Dishman RK, O'Connor PJ. Feasibility of exercise training for the short-term treatment of generalized anxiety disorder: a randomized controlled trial. Psychother Psychosom. 2012;81(1):21–8. https://doi.org/10.1159/000327898.
94. van Hasselt FM, Krabbe PF, van Ittersum DG, Postma MJ, Loonen AJ. Evaluating interventions to improve somatic health in severe mental illness: a systematic review. Acta Psychiatr Scand. 2013;128(4):251–60. https://doi.org/10.1111/acps.12096.
95. Fernandez E, Salem D, Swift JK, Ramtahal N. Meta-analysis of dropout from cognitive behavioral therapy: magnitude, timing, and moderators. J Consult Clin Psychol. 2015;83(6):1108–22. https://doi.org/10.1037/ccp0000044.
96. Ashdown-FranksG, Williams J, Vancampfort D, Firth J, Schuch FB, Hubbard K, Craig T, GaughranF, Stubbs B. Is it possible for people with severe mental illness to sit lessand move more? A systematic review of interventions to increase physicalactivity or reduce sedentary behaviour. Schizophrenia Research 2018; 202:3-16. https://doi.org/10.1016/j.schres.2018.06.058.
97. Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JAJ, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: a meta-analysis of randomized placebo-controlled trials. Depress Anxiety. 2018;35(6):502–14. https://doi.org/10.1002/da.22728.
98. Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. Can J Psychiatr. 2013;58(7):376–85. https://doi.org/10.1177/070674371305800702.
99. Derogatis LR, Unger R. Symptom Checklist-90-Revised. In: The Corsini Encyclopedia of Psychology; 2010. p. 1–2.
100. Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. Cochrane Database Syst Rev. 2007;2:MR000012. https://doi.org/10.1002/14651858.MR000012.pub2.
101. Hey SP, Kimmelman J. The questionable use of unequal allocation in confirmatory trials. Neurology. 2014;82(1):77–9. https://doi.org/10.1212/01.wnl.0000438226.10353.1c.
102. Stanley K. Design of randomized controlled trials. Circulation. 2007;115(9):1164–9. https://doi.org/10.1161/CIRCULATIONAHA.105.594945.

Publisher's Note

Appendix B: Manuscript II

Zeibig, J.-M., Takano, K., Seiffer, B., Sudeck, G., Rösel, I., Hautzinger, M., & Wolf, S. (under review). An increase in heart rate variability mediates exercise effects on global symptom severity across heterogenous mental disorders: A secondary analysis of the ImPuls trial. *Ment Health Phys Act*.

Abstract

Background: The reduced ability to adaptively respond to stressors (coping) has been proposed as an underlying mechanism across psychopathology. It is associated with a reduced vagally-mediated HRV (vmHRV) at rest and increased perceived stress. The present study investigated the increase in vmHRV and the reduction in perceived stress as potential mediators on the previously demonstrated intervention effect of exercise on global symptom severity across diagnostically heterogenous stress-related mental disorders.

Methods: Sedentary outpatients with depressive disorders, anxiety disorders, insomnia and attention deficit hyperactivity disorder were randomized to a 12-week standardized exercise intervention (n = 38), or passive control condition (n = 36). At baseline and post-treatment, global symptom severity (Symptom Checklist-90) as well as resting vmHRV (root mean square of successive differences between normal heartbeats) and perceived stress (Perceived Stress Scale) were assessed. Linear mixed models and structural equations modeling were used for intention-to-treat analyses.

Results: Among the intervention group resting vmHRV increased (d = 0.89, p = .001) but perceived stress did not significantly reduce (d = -0.31, p = .277) relative to the control group. The increase in vmHRV partially mediated the intervention effect on global symptom severity (β = -0.05, p = .013).

Conclusion: Study results established evidence for the improved ability to cope with stressors as a transdiagnostic mechanism of action through which exercise interventions achieve their beneficial effects on symptoms across stress-related mental disorders.

The study was registered on ClinicalTrials.gov (ID: NCT03542396, 25/04/2018).

Keywords: Exercise, vagally-mediated heart rate variability, stress coping, mental disorders, outpatient mental health care, transdiagnostic efficacy

Introduction

Prolonged exposure to stressors or severe acute stressful life events are considered as a major risk factor for the onset, recurrence, and exacerbation of severe and debilitating mental disorders, including depressive disorders (Kendler et al., 1999; Kessler, 1997), anxiety disorders (Francis et al., 2012; Moreno-Peral et al., 2014), insomnia (Healey et al., 1981) and attention deficit hyperactivity disorder (ADHD) (Saccaro et al., 2021). Simultaneously, individuals with these mental disorders perceive higher levels of stress compared with the healthy population (e.g., Schneider et al., 2020). Due to this reciprocal relationship of stress and depressive disorders, anxiety disorders, insomnia as well as ADHD, they are often referred to as stress-related mental disorders (e.g., Smoller, 2016).

This reciprocal relationship could be explained by a vicious circle of stress and mental disorders. First, excessive, or persistent activation of the stress system can lead to a reduced ability to respond adaptively (i.e., deliberate, context-appropriate and flexible) to internal and external stressors (Charmandari et al., 2005; McEwen, 1998) which is also referred to as “coping” (Carver, 2011). However, maladaptive responses to stressors (i.e., context-inappropriate, exaggerated, or prolonged), hinder successful adaptation and self-regulation in daily life (Charmandari et al., 2005; Thayer et al., 2009). Therefore, a reduced ability to cope with stressors has been associated with psychopathology (Charmandari et al., 2005). In addition, the appraisal that one's ability to cope with stressors is inadequate contributes significantly to the perception of stress (Lazarus & Folkman, 1984). This would explain the high level of perceived stress reported by individuals with stress-related mental disorders (e.g., Schneider et al., 2020).

The ability to cope with stressors can be indexed by the functioning of the autonomous nervous system (ANS) (Charmandari et al., 2005). The ANS is divided into the sympathetic nervous system and the parasympathetic nervous system (Charmandari et al., 2005). Heart rate variability (HRV), the variance of the intervals between successive heartbeats (Berntson et al., 1997; Malik, 1996), is a result of the balancing action of the parasympathetic and the sympathetic nervous systems. Parasympathetic activity can be indexed by HRV parameters that reflect the cardiac vagal tone of the parasympathetic activity (i.e., vagally-mediated HRV, vmHRV) (Laborde et al., 2017). According to the neurovisceral integration model (Thayer & Lane, 2000), resting vmHRV is associated with higher-level executive functions that are essential for self-regulation in the presence of internal and external stressors. This model proposes that a low resting vmHRV is associated with inactivation of higher-level executive functions during emotional stress, whereas high resting vmHRV inhibits this inactivation. Therefore, low resting vmHRV is associated with a reduced ability to cope with stressors, whereas high resting vmHRV facilitates adaptive and flexible responses to stressors (Arnsten & Goldman-Rakic, 1998; Thayer et al., 2012; Thayer et al., 2009). Consistent with the psychological concept of stress (Lazarus & Folkman, 1984), individuals with lower resting vmHRV report higher levels of perceived stress compared with those with higher resting vmHRV (Chihaoui Mamlouk et al., 2021; Sin et al., 2016).

Accordingly, a low resting vmHRV has been found in depressive disorders (Koch et al., 2019), anxiety disorders (Chalmers et al., 2014), insomnia (Spiegelhalder et al., 2011) and ADHD (Christiansen et al., 2019). Resting vmHRV is lower in individuals with higher symptom severity, longer duration of illness and higher number of psychiatric comorbidities (Hartmann et al., 2018; Kemp et al., 2012; Toni et al., 2016). In contrast, high resting

vmHRV has been linked to mental health (Beauchaine & Thayer, 2015). Hence, offering treatments that increase resting vmHRV while also reducing perceived stress would be an efficient approach to improve symptoms across stress-related mental disorders.

Exercise, defined as "physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective" (Caspersen et al., 1985, p. 128), seems to be one promising method for increasing resting vmHRV (Aubert et al., 2003; Mosley & Laborde, 2022; Sandercock et al., 2005; Toni et al., 2016) and reducing perceived stress (Klaperski, 2018). Regular exercise or high physical fitness has been associated with high resting vmHRV in healthy individuals (Aubert et al., 2003; Mosley & Laborde, 2022; Sandercock et al., 2005). Although evidence about the impact of exercise on resting vmHRV among individuals with stress-related mental disorders is sparse, preliminary evidence suggests an exercise-induced increase of resting vmHRV in elderly depressed individuals (Toni et al., 2016) and patients with anxiety disorders (Gaul-Alácová et al., 2005). Simultaneously, regular exercise is associated with lower levels of perceived stress and lower stress reactivity (i.e., self-reported and physiological reaction to a stressor) among non-clinical samples (Jacquart et al., 2019; Klaperski, 2018; Wunsch et al., 2019). Furthermore, individuals who exercise regularly seem to be protected from the negative consequences of acute stressful life events on mental health (Gerber et al., 2014). In essence, limited evidence suggests that exercise interventions may improve the ability to cope with stressors in individuals with stress-related mental disorders. However, this evidence is based on a small number of studies, non-clinical samples or disorder-specific samples of depressive disorders and anxiety disorders (Gaul-Alácová et al., 2005; Jacquart et al., 2019; Toni et al., 2016). Despite evidence suggesting that a reduced ability to cope with stressors may be a transdiagnostic mechanism across depressive

disorders, anxiety disorders, insomnia and AHDH, little is known about the impact of exercise interventions on this ability across these stress-related mental disorders.

The transdiagnostic efficacy (i.e., addressing underlying mechanisms of mental disorders rather than specific diagnoses (McEvoy et al., 2009, p.21)) of exercise is supported by evidence demonstrating efficacy in reducing symptoms across stress-related mental disorders (Ashdown-Franks et al., 2020; Zeibig et al., 2021). Meta-analyses of randomized controlled trials found a large antidepressant effect in depressive disorders (Morres et al., 2019), a small to moderate anxiolytic effect in patients with anxiety disorders (Ramos-Sanchez et al., 2021), a large effect in improving sleep quality in individuals with insomnia (Banno et al., 2018) and a small effect on ADHD core symptoms (among children and adolescents) (Seiffer et al., 2021) versus non-active or active control conditions.

Based on the cited evidence, improving the ability to cope with stressors can be considered a potential transdiagnostic mechanism of action through which exercise achieves its beneficial effects on symptoms across stress-related mental disorders. Nevertheless, the mediational mechanism is largely unknown, especially in a clinical population and across heterogenous diagnoses. Therefore, we aimed to investigate whether an exercise intervention would increase resting vmHRV and reduce perceived stress across diagnostically heterogeneous stress-related mental disorders. In addition, it was of interest whether the increase in resting vmHRV or the reduction in perceived stress would mediate intervention effects of exercise on global symptom severity across the sample.

The present study is a secondary analysis on the data collected as part of a randomized clinical trial examining the efficacy of an exercise intervention, namely ImPuls, across depressive disorders, anxiety disorders, insomnia, and ADHD (Zeibig et al., 2021). This trial targeted to investigate the efficacy of a 12-week standardized exercise intervention

that combines moderate aerobic exercise with techniques for sustained exercise behaviour change (Wolf, Zeibig, Giel, et al., 2020; Wolf, Zeibig, Hautzinger, et al., 2020). Compared with a passive control condition (i.e., no intervention), the intervention group significantly reduced in global symptom severity with a moderate to large effect size ($d = 0.77$, $p = .007$) and increased in subjectively reported exercise behaviour ($d = 0.82$, $p < .001$) from baseline to post-treatment (Zeibig et al., 2021).

For this secondary analysis the following hypotheses were set:

1. The intervention group would increase more in resting vmHRV and reduce more in perceived stress compared with the control group.
2. The intervention effect on reductions in global symptom severity demonstrated in the original study (Zeibig et al., 2021) would be mediated by an increase in resting vmHRV and a reduction in perceived stress.

Methods

A detailed description of the study methods, particularly of study participants, the exercise intervention, the study procedure, and randomization, can be found in the original study (Zeibig et al., 2021) and in the study registration (see *Trial design*).

Trial Design

The study was preceded by registration on ClinicalTrials.gov (ID: NCT03542396, 25/04/2018) and an approval by the local ethics committee for self-reported research (Az_Wolf_2018_0108_99). The study was conducted as a randomized controlled trial with block-randomization, two treatment arms (intervention group, passive control group) and three assessment points (pre-treatment assessment (T1), post-treatment assessment (T2) and 1-year follow-up (T3)). This manuscript addresses mediators of the exercise-induced

intervention effects during the intervention period that were obtained in the ImPuls trial (Zeibig et al., 2021). Therefore, T1 and T2 were relevant to the current analyses. Reporting of the study followed the Consolidated Standards of Reporting Trials (CONSORT) statement (Schulz et al., 2011).

Measurements

Global symptom severity

The Global Severity Index (GSI) of the German version of the Symptom Checklist-90 (SCL-90-R; Derogatis, 1994) was used to measure participants' global symptom severity. The questionnaire consists of 90 items with nine domains: aggression/hostility, anxiety, depression, paranoid thinking, phobic anxiety, psychoticism, somatization, insecurity in social contact, and compulsivity. The average rating on all symptom scales is the GSI. The GSI can range from 0 to 4 with higher scores indicating higher distress. The GSI has demonstrated good internal consistency (α= .97) and construct validity (r= .77) among individuals with affective disorders (Prinz et al., 2013).

Vagally-mediated heart rate variability

The root mean square of successive differences between normal heartbeats (HRV-RMSSD) was chosen as an index of vagal tone because, unlike HRV-HF (Hill & Siebenbrock, 2009), it is free of respiratory influences and has higher validity in assessing vagal tone compared with pNN50 (Laborde et al., 2017; Mosley & Laborde, 2022). Furthermore, HRV-RMSSD is the most commonly reported parameter in studies of HRV and exercise (Mosley & Laborde, 2022). HRV-RMSSD "[…] is obtained by first calculating each successive time difference between heartbeats in milliseconds. Then, each of the values is squared and the result is averaged before the square root of the total is obtained" (Shaffer

et al., 2014, p. 13). Higher values on HRV-RMSSD are supposed to reflect increased vagal tone (Rajendra Acharya et al., 2006). To improve the generalizability and comparability of our results, we additionally performed all statistical analyses with HRV-HF (Appendix A).

Perceived stress

The Perceived Stress Scale (PSS; Cohen et al., 1983) is the most widely used and reliable and valid instrument to assess perceived stress in clinical and non-clinical populations (Klein et al., 2016; Schneider et al., 2020). The questionnaire is based on the psychological concept of stress (Lazarus & Folkman, 1984). 10 items measure the degree to which individuals have experienced their lives as unpredictable, uncontrollable, and overloading in the last month on a 5-point Likert-scale ranging from 0 = "never" to 4 = "very often". All items summed up build a total score of perceived stress. Scores can range from 0 to 40. Higher scores indicate higher perceived stress.

Procedure

Written informed consent was obtained prior to participation from all participants. Prior to randomization (T1) and within two weeks after the termination of the intervention (T2), participants completed online questionnaires and participated in an HRV assessment (see *HRV data recording and processing*).

Sample size calculation

The a priori power calculation was based on disorder-specific effects of exercise interventions among depressive disorders, anxiety disorders and insomnia (see Zeibig et al., 2021). An effect size of $d = 0.74$ was expected (i.e., differences between conditions on global symptom severity at T2). The significance level was $\alpha = .05$, Power: $1-\beta = .80$,

allocation ratio N2/N1: ε =1 resulting in a sample size of N = 60 (two-tailed independent t-test). Considering an expected attrition rate of 18% (Stubbs et al., 2017), the required sample size was N = 71.

HRV data recording and processing

HRV data recording, processing, and reporting were based on guidelines of Task Force from the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Malik et al., 1996) and current recommendations for HRV experiment planning, data analysis and data reporting (Laborde et al., 2017). To perform a reliable assessment of HRV, participants were instructed to follow a normal sleep routine, to not engage in intense exercise the day prior to HRV assessment and abstain from caffeine for two hours and from alcohol for 24 hours prior to HRV assessment (Laborde et al., 2017). HRV data were recorded using the Electrocardiogram (ECG) and Activity Sensor EcgMove 3 (Movisens GmbH, Karlsruhe, Germany) (Malik et al., 1996). The sensor was placed below the left anterior chest with an adhesive electrode, and ECG data were sampled continuously at 1024 Hz. The assessor left the room and data were recorded for a minimum of six minutes to obtain at least five minutes of analyzable HRV data, which is the recommended duration for short-term HRV recordings to ensure comparability with previous clinical studies (Laborde et al., 2017; Malik et al., 1996). A time interval between the start of recording and the analysis period was established to reduce the increased participant attention to breathing and heart rate that may be triggered by the knowledge that the recording will begin at this time (Quintana et al., 2016). Participants were instructed to remain relaxed, to sit without speaking or making any movements and to breathe spontaneously (Laborde et al., 2017; Malik et al., 1996). The raw ECG data were then visually inspected using the UnisensViewer

software (version 1.12.38.0). If the assessor noticed any artifact, the HRV assessment was repeated.

ECG data were imported into Kubios HRV 3.4 software (Tarvainen et al., 2014) to calculate HRV parameters. HRV-RMSSD was calculated automatically by the Kubios software. Five-minutes segments (Laborde et al., 2017; Malik et al., 1996) were selected for analyses with the starting point five minutes backwards from the time when the assessor re-entered the room. If artifact-free five-minute segments were not available, the start point was moved forward with the earliest start point 30 seconds after the assessor left the room. If this did not result in five-minute segments, HRV data were not included in the analyses (n = 4). HRV data before and after the selected sequence were marked as noise to avoid influence of the HRV segment being analyzed. The segment was then visually inspected and non-detected R-waves were corrected. In addition, technical and misaligned beats were carefully eliminated because they can lead to the largest HRV parameter errors after automatic artifact correction (Lipponen & Tarvainen, 2019). Evidence based automatic artifact correction was then used, which is based on time-varying thresholds and can detect ectopic, long, short, missed, and extra beats with nearly 100% accuracy, was used (Lipponen & Tarvainen, 2019). Detected artifacts were then visually inspected to verify accuracy (Laborde et al., 2017; Nunan et al., 2010).

Statistical analyses

The Statistical Package for Social Science (IBM SPSS, Inc., Chicago, IL, USA, version 26) were used for data preparation. R (version 4.0.3) and RStudio (version 1.1.453) were used for statistical analyses. Missing data were assessed at scale level/HRV index. To assess the mechanisms of missingness, we performed Little's test of missing completely at

random (MCAR). All analyses were performed on the intention-to-treat sample using the (full-information) maximum likelihood method that is offered in the R packages; *lme4* for linear mixed models (LMM; Bates et al., 2015) and *lavaan* for structural equation modeling (SEM; Rosseel, 2012). Since all obtained values were plausible, we did not exclude any observations as outliers for the main analyses reported here. However, as we found potential outliers (data points with greater than three time the average leverage, cook's distance greater than 1, and studentized residuals greater than 3 (Cook & Weisberg, 1982; Pituch & Stevens, 2016); $n = 1$ for HRV-RMSSD, $n = 5$ for PSS), we performed a sensitivity analysis to see if the inclusion and exclusion of the potential outliers affected the results (Appendix B). Furthermore, we reported the results of per-protocol analyses in Appendix C. Descriptive statistics were used to analyze sample characteristics and dropout rates. Baseline differences between groups were analyzed using two-tailed t-tests for independent samples (continuous variables), Chi-scared tests or Fisher's exact tests (categorical variables). Statistical significance was defined as a p-value < 0.05.

LMMs were used to test differences between groups on resting HRV-RMSSD and perceived stress. Models included condition, assessment point and their interaction (*assessment point x condition*) as predictors. A random effect was assumed only on the intercept. For the LMM predicting HRV-RMSSD, baseline variables of age, gender and smoking were used as covariates because these variables are known to influence HRV (Laborde et al., 2017). Assumptions of LMMs were visually inspected. If residuals of LMMs were not normally distributed, data were log-transformed. Post-hoc tests for differences between the two conditions at T2 were carried out using two-tailed t-test for independent samples. Effect sizes were calculated according to Cohen's d (Cohen, 1988) based on estimated marginal means.

To establish the mediational role of the ability to cope with stressors and perceived stress (Hypothesis 2), we used SEM with the group allocation as the predictor and with global symptom severity as the outcome. We selected the mediator based on the results of the LMM – a mediator was included in SEM if improved significantly by the intervention (Baron & Kenny, 1986). The mediators and outcome were specified as the simple changes, i.e., T1 being subtracted from T2 scores (Valente et al., 2021). We were interested in the following three effects: the direct effect (i.e., effect of the intervention on global symptom severity after controlling for the mediators), indirect effect (i.e., the product of the effect of the intervention on a mediator and that of the mediator on global symptom severity), and total effect (i.e., the sum of the direct and indirect effects). If normality was expectedly violated and potential outliers were present, a robust estimator (maximum likelihood estimation) was used, which has statistical advantages over bootstrapping (e.g., provides robust standard errors *and* robust model fit indices) (Rosseel, 2012). As sensitivity analysis, we computed bootstrapped standard errors for the three (direct, indirect, and total) effects with 5000 iterations (see Appendix D).

Results

Participants

The flow of participant recruitment and data collection is shown in Figure 1. At T2, n = 1 participant of the intervention group did not fill out questionnaires but participated in the HRV assessment.

[insert Figure 1]

Baseline characteristics of the studied sample are reported in Table 1. Among others, reported baseline characteristics include important variables that might influence HRV

measurement (Laborde et al., 2017). Participants of the control group dropped out more often than those of the intervention group. Neither the two conditions nor completers vs. dropouts differed with respect to baseline characteristics (Table 1 and Appendix E). No adverse events were reported by therapists or participants during the study.

[insert Table 1]

Missing values

We assumed missing data to be missing at random ($\chi^2(32) = 14.87$, $p = .996$). At T1, 6 (2.8%) and at T2, 67 (31.0%) values of all outcomes (vmHRV, perceived stress, GSI) were incomplete.

Data of vagally-mediated heart rate variability

Overall, 2.4% ($n = 3$) of the total HRV data ($N = 124$) could not be analyzed because 30-second artifact-free segments were not available, which are required to analyze segments with Kubios. In addition, 3.23% ($n = 4$) of HRV data could not be included in the analysis because the sum of artifact-free segments was shorter than five minutes. of the HRV data that could be analyzed, the software detected 0.9% ($SD = 3.18\%$) as artifacts after excluding misaligned beats or technical artifacts.

Intervention effects on vagally-mediated heart rate variability and perceived stress

Table 2 shows results of hypothesis 1. The interaction effect of group by time was statistically significant for resting HRV-RMSSD ($F(1, 57.67) = 11.35$, $p = .001$). The intervention group showed a significantly greater increase in resting HRV-RMSSD from T1 to T2 assessment compared with the control group with moderate to large effect size. The post-hoc analysis on the group differences at T2 revealed a moderate effect for resting HRV-

RMSSD reaching statistical significance, with higher scores in the intervention group. The interaction effect of group by time was not statistically significant for PSS ($F(1, 50.53) = 1.21$, $p = .277$).

[insert Table 2]

Mediation analysis

First, we tested whether resting HRV-RMSSD and perceived stress covaried through the intervention. Indeed, the changes from T1 to T2 were significantly correlated with each other: a Kendall rank correlation = -0.28, $p = .010$. That is, people who showed an increase in resting HRV-RMSSD experienced reduction in perceived stress and vice versa. Second, we ran SEM with resting HRV-RMSSD as the only mediator because the LMM results showed that perceived stress was not significantly responsive to the intervention (see *Statistical analyses*). Since the assumption of multivariate normality might not be met, a robust model estimation was used. The estimated model showed excellent fit to the data ($X^2(3) = 2.81$, $p = .423$; RMSEA = 0.00[0.00;0.19]; CFI = 1.00, NFI = 0.86; SRMR = 0.04). The results showed that the intervention group experienced a significant increase in vmHRV, which was predictive of significant reduction in global symptom severity (see Figure 2). The total effect of the intervention was statistically significant (ß = -0.38, $p = .003$); furthermore, we identified a significant indirect effect (ß = -0.06, $p = .005$) mediated by an increase in resting HRV-RMSSD. We also estimated bootstrapped standard errors for the direct and indirect effect, which showed overall similar results (see Appendix D).

[insert Figure 2]

Discussion

This study was a secondary analysis of a randomized clinical trial (Zeibig et al., 2021) that found a moderate to large effect of the exercise intervention ImPuls on global symptom severity across depressive disorders, anxiety disorders, insomnia and ADHD compared with a passive control condition. We aimed to examine the effects of the intervention on the ability to adaptively respond to stressors (i.e., coping), as measured by resting vmHRV (HRV-RMSSD) and perceived stress It was of interest to determine whether changes in these parameters would mediate the previously reported effects of the intervention on global symptom severity (Zeibig et al., 2021). Compared with the passive control condition, the intervention increased resting vmHRV with a large significant effect and reduced perceived stress with a small but non-significant effect from T1 to T2. The difference between groups in resting vmHRV at T2 was significant with a moderate effect size. The increase in resting vmHRV partially mediated the intervention effect on global symptom severity.

As expected, the exercise intervention ImPuls was able to improve the ability to cope with stressors across diagnostically heterogenous stress-related mental disorders. However, the intervention did not result in a statistically significant reduction in the perception of stress. Both indicators showed a significant correlation, indicating that the increase in resting vmHRV and the reduction in perceived stress were related. The demonstrated relationship is in consistent with the psychological concept of stress, which proposes that the appraised ability to cope with stressors (indexed by resting vmHRV in this study) is a major contributor to the perception of stress (Lazarus & Folkman, 1984). Accordingly, the questionnaire includes items that capture this ability (Klein et al., 2016). The power might have been too small to detect significant intervention effects on perceived stress because a priori power calculation was based on the effects of exercise on disorder-specific symptoms

of mental disorders and not on intervention effects on resting vmHRV or perceived stress. Effects of exercise on subjective stress responses may be smaller (median of effect sizes: d = 0.27) (Jacquart et al., 2019) than on symptoms of depressive disorders, anxiety disorders and insomnia (median of effect sizes: d = 0.74) (Kelley & Kelley, 2017; Powers et al., 2015; Schuch et al., 2016). Effects on resting vmHRV were large in previous studies among clinical and non-clinical samples (median of effect sizes: d = 0.93) (Sandercock et al., 2005; Toni et al., 2016). Thus, the current results regarding the reduction in perceived stress and the increase in resting vmHRV are consistent with previous studies in clinical and non-clinical samples. The result of a meta-analysis including 13 studies about the effects of regular exercise on HRV in non-clinical samples (Sandercock et al., 2005) suggest a moderate within-group effect on resting vmHRV. Similarly, a large effect of an exercise intervention on resting vmHRV was found among individuals with depressive disorders (Toni et al., 2016). Therefore, it could be suggested that results about the exercise-induced increase in resting vmHRV among non-clinical and disorder-specific samples might be transferable to samples with diagnostically heterogenous stress-related mental disorders.

As expected, the increase in resting vmHRV through the exercise intervention partially mediated the intervention effect on global symptom severity found in the original randomized controlled trial (Zeibig et al., 2021). This finding suggests that an improved ability to cope with stressors might be a transdiagnostic mechanism of action through which exercise achieves its beneficial effects on symptoms across stress-related mental disorders. The finding of a *partial* mediation indicates that there might be additional factors of the intervention that led to improved symptom outcomes (e.g., increase in self-efficacy) (Chatoor & Krupnick, 2001; Jacquart et al., 2019). Toni et al. (2016) tested the impact of resting rvmHRV on depression status using a correlation analysis. The increase in resting

rvmHRV and remission of depression were not significantly associated. Although based on an exploratory analysis, the results suggest that the increase in resting-state rvmHRV was not due to treatment effects. The opposite results in our study may have been caused by a different outcome. While the authors used a cut-off score of the Hamilton Depression Rating Scale to define remission (yes/no), we used a continuous variable as the study outcome. Continuous variables contain more information than dichotomous ones. This suggests that our results may provide more valid evidence for the mediating role of resting vmHRV on treatment effects of exercise interventions. Similar to the cited study (Toni et al., 2016), it is common to make assumptions about transdiagnostic mechanisms of action based on correlation analyses and/or disorder-specific samples (e.g., Jacquart et al., 2019). Therefore, the study results extend the current body of research on transdiagnostic mechanisms of exercise interventions by demonstrating that the increase in resting vmHRV partially mediated the effect of global symptom severity across a diagnostically heterogenous clinical sample.

Practical implications

Study results suggest that exercise interventions can increase the ability to cope with stressors, which is considered to be an underlying mechanism across common and debilitating stress-related mental disorders (e.g., Smoller, 2016). Increasing this ability, in turn, seems to be partially responsible for the efficacy of exercise interventions across diagnostically heterogenous stress-related mental disorders. Therefore, a major goal in developing efficacious exercise interventions for individuals with stress-related mental disorders may be to create optimal conditions to increase resting vmHRV. In agreement with previous studies (Melanson & Freedson, 2001; Toni et al., 2016), the optimal criteria for

efficaciously increasing resting vmHRV are aerobic training of at least moderate intensity (optionally in conjunction with strength training), a duration of 12 weeks, and at least two training sessions of 30 minutes each per week, performed by trained exercise specialists and in group format. To additionally strengthen the efficacy of exercise interventions for stress-related mental disorders, the intentional use of exercise to cope with stressors could be promoted. For instance, knowledge of the potential of exercise to reduce stress could be improved. Similarly, participants' awareness of immediate effects on stress perception after exercise could be raised (e.g., through visualization of changes in stress perception before and after training).

Due to their transdiagnostic efficacy, exercise interventions can address the clinical reality in which heterogeneous diagnoses and psychiatric comorbidity are rather common (Kessler & Üstün, 2008). Compared with treatments tailored to a single diagnosis (i.e., disorder-specific interventions), exercise could simultaneously treat diagnostically heterogenous samples or individuals with comorbid stress-related mental disorders. In addition, clinicians need to learn a single treatment protocol for a broad range of patients, which may fasten dissemination (Dalgleish et al., 2020). Consequently, exercise interventions seem to be very efficient in the treatment of stress-related mental disorders and to meet the needs of clinical reality better than the prevailing disorder-specific interventions (Dalgleish et al., 2020).

Strengths and limitations

The study has several strengths. First, the inclusion of HRV-RMSSD as a physiological measure of the ability to cope with stressors may have reduced potential bias from retrospective self-report measures. Second, the inclusion of a diagnostically

heterogeneous clinical sample allowed for the evaluation of transdiagnostic mechanisms mediating the treatment effects of exercise interventions across a broad spectrum of stress-related mental disorders. This was important to support the assumption that exercise improves *transdiagnostic* treatment targets, which has usually been studied in non-clinical or disorder-specific samples (Jacquart et al., 2019). Third, the mediation analysis using SEM allows valid and reliable assumptions about mechanisms of exercise effects, which are largely unknown. Therefore, the current results may provide novel insights into how exercise intervention achieve their beneficial effects on symptoms across stress-related mental disorders.

However, the study has several limitations that must be considered when interpreting the results. First, despite the high standardization of the HRV assessment, we did not control for some factors that might have influenced HRV parameters (e.g., time of assessment or participants' posture) (Laborde et al., 2017; van Eekelen et al., 2004). Furthermore, we did not objectively measure potentially confounding variables (e.g., normal sleep routine) as recommended (Laborde et al., 2017). Second, the a priori power calculation was based on the effects of exercise on disorder-specific symptoms of depressive disorders, anxiety disorders and insomnia. Therefore, the power to detect significant effects on perceived stress might have been diminished. Third, the mean baseline levels of resting vmHRV and perceived stress were not lower in participants compared with non-clinical samples (Nunan et al., 2010; Schneider et al., 2020). Therefore, it could be assumed that the included sample might not have been representative with respect to these parameters (e.g., Koch et al., 2019; Schneider et al., 2020). Fourth, more dropouts were recorded in the control group in in the intervention group, and overall, there was a high number of missing values at T2 (see *Missing values*). Nevertheless, no difference was found between study completers and

dropouts, and missing values were missing at random. The additional use of statistical analyses that can validly handle missing data (LLM and SEM) might have reduced the bias that could have resulted from differential dropouts and a high number of missing values. Fifth, the diagnosis of ADHD was poorly represented in the current sample, which was expected given a point prevalence of 0.24% in the adult population in Germany (Global Burden of Disease Collaborative Network, 2020). Nevertheless, this might limit the generalizability of the results to individuals with ADHD.

Future directions

Future research should conduct a similar study with higher standardization of HRV assessment (e.g., controlling for participants' sitting position) to assess the ability to cope with stressors even more reliably. The inclusion of a larger sample size, determined a priori on effects of exercise on potential mediators of treatment effects, would increase the power to detect potential significant intervention effects. A larger sample size would also allow subgroup analyses assessing differences in intervention effects on resting vmHRV and perceived stress between participants with initial high vs. low levels of resting vmHRV and perceived stress, respectively. It would be of interest to assess whether ImPuls improved not only the ability to cope with stressors but also physiological stress levels. Although we measured an important part of the physiological (i.e., withdraw of parasympathetic activity) and psychological stress response (i.e., increased perceived stress), it would be important to also measure sympathetic activity (e.g., via pre-ejection period) and the activity of the hypothalamus-pituitary-adrenal (HPA) axis (e.g., via cortisol or alpha amylase) to make valid assumptions about changes of physiological stress levels (Charmandari et al., 2005). Furthermore, investigating different potential transdiagnostic mechanisms, such as anxiety

sensitivity or self-efficacy (Jacquart et al., 2019), would allow to assess the largest contribution to intervention effects of exercise across mental disorders. This knowledge could be used to further improve the efficacy of exercise interventions for diagnostically heterogenous mental disorders and may allow the inclusion of other mental disorders with similar transdiagnostic mechanisms. A follow-up project is currently being conducted to investigate this research question (see Wolf et al., 2021).

Conclusion

This study demonstrated large effects of an exercise intervention on resting vmHRV across outpatients with depressive disorders, anxiety disorders, insomnia, and ADHD. Results suggest that the increase in resting vmHRV may be a transdiagnostic mechanism of action through which exercise interventions achieve their beneficial effects on symptoms across diagnostically heterogenous stress-related mental disorders. These findings highlight that exercise interventions aimed at improving the ability to cope with stressors may represent an evidence-based transdiagnostic treatment for diagnostically heterogenous stress-related mental disorders. The improved ability to cope with stressors as a transdiagnostic mechanism of exercise interventions warrants further investigation with a larger sample and alternative assessments.

References

Arnsten, A. F., & Goldman-Rakic, P. S. (1998). Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. *Archives Of General Psychiatry, 55*(4), 362-368. https://doi.org/10.1001/archpsyc.55.4.362

Ashdown-Franks, G., Firth, J., Carney, R., Carvalho, A. F., Hallgren, M., Koyanagi, A., et al. (2020). Exercise as medicine for mental and substance use disorders: a meta-review of the benefits for neuropsychiatric and cognitive outcomes. *Sports Medicine, 50*(1), 151-170. https://doi.org/10.1007/s40279-019-01187-6

Aubert, A. E., Seps, B., & Beckers, F. (2003). Heart rate variability in athletes. *Sports Medicine, 33*(12), 889-919. https://doi.org/10.2165/00007256-200333120-00003

Banno, M., Harada, Y., Taniguchi, M., Tobita, R., Tsujimoto, H., Tsujimoto, Y., et al. (2018). Exercise can improve sleep quality: a systematic review and meta-analysis. *PeerJ, 6*, e5172. https://doi.org/10.7717/peerj.5172

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51*(6), 1173-1182. https://doi.org/10.1037/0022-3514.51.6.1173

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *J Stat Softw, 67*(1), 1-48. https://doi.org/10.18637/jss.v067.i01

Beauchaine, T. P., & Thayer, J. F. (2015). Heart rate variability as a transdiagnostic biomarker of psychopathology. *Int J Psychophysiol, 98*(2 Pt 2), 338-350. https://doi.org/10.1016/j.ijpsycho.2015.08.004

Berntson, G. G., Bigger, J. T., Jr., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., et al. (1997). Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology, 34*(6), 623-648. https://doi.org/10.1111/j.1469-8986.1997.tb02140.x

Carver, C. S. (2011). Coping. In *The handbook of stress science: Biology, psychology, and health.* (pp. 221-229). Springer Publishing Company.

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep, 100*(2), 126-131.

Chalmers, J. A., Quintana, D. S., Abbott, M. J., & Kemp, A. H. (2014). Anxiety Disorders are Associated with Reduced Heart Rate Variability: A Meta-Analysis. *Front Psychiatry, 5*, 80. https://doi.org/10.3389/fpsyt.2014.00080

Charmandari, E., Tsigos, C., & Chrousos, G. (2005). Endocrinology of the stress response. *Annual Review of Physiology, 67*, 259-284. https://doi.org/10.1146/annurev.physiol.67.040403.120816

Chatoor, I., & Krupnick, J. (2001). The role of non-specific factors in treatment outcome of psychotherapy studies. *European Child & Adolescent Psychiatry, 10 Suppl 1*, I19-25. https://doi.org/10.1007/s007870170004

Chihaoui Mamlouk, A., Younes, M., Zarrouk, F., Shephard, R., & Bouhlel, E. (2021). Heart rate variability and stress perception: The influence of physical fitness. *Science & Sports, 36*(4), 276-283. https://doi.org/10.1016/j.scispo.2021.02.001

Christiansen, H., Hirsch, O., Albrecht, B., & Chavanon, M.-L. (2019). Attention-Deficit/Hyperactivity Disorder (ADHD) and Emotion Regulation Over the Life Span. *Current Psychiatry Reports, 21*(3), 17. https://doi.org/10.1007/s11920-019-1003-6

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Erlbaum. http://www.utstat.toronto.edu/~brunner/oldclass/378f16/readings/CohenPower.pdf

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *J Health Soc Behav*, 385-396.

Cook, R. D., & Weisberg, S. (1982). *Residuals and influence in regression*. Chapman & Hall.

Dalgleish, T., Black, M., Johnston, D., & Bevan, A. (2020). Transdiagnostic approaches to mental health problems: Current status and future directions. *J Consult Clin Psychol, 88*(3), 179-195. https://doi.org/10.1037/ccp0000482

Derogatis, L. R. (1994). *SCL-90-R: Administration, scoring and procedures manual* (3rd ed.). NCS Pearson.

Francis, J. L., Moitra, E., Dyck, I., & Keller, M. B. (2012). The impact of stressful life events on relapse of generalized anxiety disorder. *Depress Anxiety, 29*(5), 386-391. https://doi.org/10.1002/da.20919

Gaul-Alácová, P., Boucek, J., Stejskal, P., Kryl, M., Pastucha, P., & Pavlík, F. (2005). Assessment of the influence of exercise on heart rate variability in anxiety patients. *Neuro Enocrinology Letters, 26*(6), 713-718.

Gerber, M., Brand, S., Herrmann, C., Colledge, F., Holsboer-Trachsler, E., & Pühse, U. (2014). Increased objectively assessed vigorous-intensity exercise is associated with reduced stress, increased mental health and good objective and subjective sleep in young adults. *Physiology & behavior, 135*, 17-24. https://doi.org/10.1016/j.physbeh.2014.05.047

Global Burden of Disease Collaborative Network. (2020). *Global Burden of Disease Study 2019 (GBD 2019) Results* Institute for Health Metrics and Evaluation (IHME). http://ghdx.healthdata.org/gbd-results-tool

Hartmann, R., Schmidt, F. M., Sander, C., & Hegerl, U. (2018). Heart Rate Variability as Indicator of Clinical State in Depression. *Front Psychiatry, 9*, 735. https://doi.org/10.3389/fpsyt.2018.00735

Healey, E. S., Kales, A., Monroe, L. J., Bixler, E. O., Chamberlin, K., & Soldatos, C. R. (1981). Onset of insomnia: role of life-stress events. *Psychosomatic Medicine, 43*(5), 439-451. https://doi.org/10.1097/00006842-198110000-00007

Hill, L. K., & Siebenbrock, A. (2009). Are all measures created equal? Heart rate variability and respiration - biomed 2009. *Biomed Sci Instrum, 45*, 71-76.

Jacquart, J., Dutcher, C. D., Freeman, S. Z., Stein, A. T., Dinh, M., Carl, E., et al. (2019). The effects of exercise on transdiagnostic treatment targets: A meta-analytic review. *Behav Res Ther, 115*, 19-37. https://doi.org/10.1016/j.brat.2018.11.007

Kelley, G. A., & Kelley, K. S. (2017). Exercise and sleep: a systematic review of previous meta-analyses. *J Evid Based Med, 10*(1), 26-36. https://doi.org/10.1111/jebm.12236

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. https://doi.org/10.1371/journal.pone.0030777

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry, 156*(6), 837-841. https://doi.org/10.1176/ajp.156.6.837

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annu Rev Psychol, 48*, 191-214. https://doi.org/10.1146/annurev.psych.48.1.191

Kessler, R. C., & Üstün, T. B. (2008). *The WHO World Mental Health Surveys: Global Perspectives on the Epidemiology of Mental Disorders* (R. C. Kessler & T. B. Üstün, Eds.). Cambridge University Press.

Klaperski, S. (2018). Exercise, stress and health: The stress-buffering effect of exercise. In *Stress regulation and exercise [Handbuch Stressregulation und Sport]* (pp. 227-249). Springer.

Klein, E. M., Brähler, E., Dreier, M., Reinecke, L., Müller, K. W., Schmutzer, G., et al. (2016). The German version of the Perceived Stress Scale–psychometric

characteristics in a representative German community sample. *BMC Psychiatry, 16*(1), 159. https://doi.org/10.1186/s12888-016-0875-9

Koch, C., Wilhelm, M., Salzmann, S., Rief, W., & Euteneuer, F. (2019). A meta-analysis of heart rate variability in major depression. *Psychological Medicine, 49*(12), 1948-1957. https://doi.org/10.1017/S0033291719001351

Laborde, S., Mosley, E., & Thayer, J. F. (2017). Heart Rate Variability and Cardiac Vagal Tone in Psychophysiological Research - Recommendations for Experiment Planning, Data Analysis, and Data Reporting. *Front Psychol, 8*, 213. https://doi.org/10.3389/fpsyg.2017.00213

Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal, and coping*. Springer publishing company.

Lipponen, J. A., & Tarvainen, M. P. (2019). A robust algorithm for heart rate variability time series artefact correction using novel beat classification. *Journal of Medical Engineering & Technology, 43*(3), 173-181. https://doi.org/10.1080/03091902.2019.1640306

Malik, M. (1996). *Heart rate variability: Standards of measurement, physiological interpretation, and clinical use* (Vol. 93).

Malik, M., Bigger, J. T., Camm, A. J., Kleiger, R. E., Malliani, A., Moss, A. J., et al. (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *European Heart Journal, 17*(3), 354-381. https://doi.org/10.1093/oxfordjournals.eurheartj.a014868

McEvoy, P. M., Nathan, P., & Norton, P. J. (2009). Efficacy of Transdiagnostic Treatments: A Review of Published Outcome Studies and Future Research Directions. *J Cogn Psychother*(1), 20-33. https://doi.org/10.1891/0889-8391.23.1.20

McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences, 840*, 33-44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x

Melanson, E. L., & Freedson, P. S. (2001). The effect of endurance training on resting heart rate variability in sedentary adult males. *Eur J Appl Physiol, 85*(5), 442-449. https://doi.org/10.1007/s004210100479

Moreno-Peral, P., Conejo-Ceron, S., Motrico, E., Rodriguez-Morejon, A., Fernandez, A., Garcia-Campayo, J., et al. (2014). Risk factors for the onset of panic and generalised anxiety disorders in the general adult population: a systematic review of cohort studies. *J Affect Disord, 168*, 337-348. https://doi.org/10.1016/j.jad.2014.06.021

Morres, I. D., Hatzigeorgiadis, A., Stathi, A., Comoutos, N., Arpin-Cribbie, C., Krommidas, C., et al. (2019). Aerobic exercise for adult patients with major depressive disorder in mental health services: A systematic review and meta-analysis. *Depress Anxiety, 36*(1), 39-53. https://doi.org/10.1002/da.22842

Mosley, E., & Laborde, S. (2022). A scoping review of heart rate variability in sport and exercise psychology. *International Review of Sport and Exercise Psychology*. https://doi.org/10.1080/1750984X.2022.2092884

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 and clinical electrophysiology : PACE, 33*(11), 1407-1417. https://doi.org/10.1111/j.1540-8159.2010.02841.x

Pituch, K. A., & Stevens, J. P. (2016). Multiple Regression of Prediction. In *Applied multivariate statistics for the social sciences* (6 ed.). Erlbaum.

Powers, M. B., Medina, J. L., Burns, S., Kauffman, B. Y., Monfils, M., Asmundson, G. J., et al. (2015). Exercise Augmentation of Exposure Therapy for PTSD: Rationale and Pilot Efficacy Data. *Cogn Behav Ther, 44*(4), 314-327. https://doi.org/10.1080/16506073.2015.1012740

Prinz, U., Nutzinger, D., Schulz, H., Petermann, F., Braukhaus, C., & Andreas, S. (2013). Comparative Psychometric Analyses of the SCL-90-R and its Short Versions in Patients with Affective Disorders. *BMC Psychiatry, 13*, 104. https://doi.org/10.1186/1471-244X-13-104

Quintana, D. S., Alvares, G. A., & Heathers, J. A. J. (2016). Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH): recommendations to advance research communication. *Translational psychiatry, 6*(5), e803-e803. https://doi.org/10.1038/tp.2016.73

Rajendra Acharya, U., Paul Joseph, K., Kannathal, N., Lim, C. M., & Suri, J. S. (2006). Heart rate variability: a review. *Medical and Biological Engineering and Computing, 44*(12), 1031-1051. https://doi.org/10.1007/s11517-006-0119-0

Ramos-Sanchez, C. P., Schuch, F. B., Seedat, S., Louw, Q. A., Stubbs, B., Rosenbaum, S., et al. (2021). The anxiolytic effects of exercise for people with anxiety and related disorders: An update of the available meta-analytic evidence. *Psychiatry Research, 302*, 114046. https://doi.org/10.1016/j.psychres.2021.114046

Rosseel, Y. (2012). lavaan: An R Package for Structural Equation Modeling. *J Stat Softw, 48*(2), 1 - 36. https://doi.org/10.18637/jss.v048.i02

Saccaro, L. F., Schilliger, Z., Perroud, N., & Piguet, C. (2021). Inflammation, Anxiety, and Stress in Attention-Deficit/Hyperactivity Disorder. *Biomedicines, 9*(10). https://doi.org/10.3390/biomedicines9101313

Sandercock, G. R., Bromley, P. D., & Brodie, D. A. (2005). Effects of exercise on heart rate variability: inferences from meta-analysis. *Med Sci Sports Exerc, 37*(3), 433-439. https://doi.org/10.1249/01.mss.0000155388.39002.9d

Schneider, E. E., Schönfelder, S., Domke-Wolf, M., & Wessa, M. (2020). Measuring stress in clinical and nonclinical subjects using a German adaptation of the Perceived Stress Scale. *International Journal of Clinical and Health Psychology*. https://doi.org/10.1016/j.ijchp.2020.03.004

Schuch, F. B., Vancampfort, D., Richards, J., Rosenbaum, S., Ward, P. B., & Stubbs, B. (2016). Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. *J Psychiatr Res, 77*, 42-51. https://doi.org/10.1016/j.jpsychires.2016.02.023

Schulz, K., Altman, D., & Moher, D. (2011). *CONSORT 2010: Aktualisierte Leitlinie für Berichte randomisierter Studien im Parallelgruppen-Design* (Vol. 136). https://doi.org/10.1055/s-0031-1272983

Seiffer, B., Hautzinger, M., Ulrich, R., & Wolf, S. (2021). The Efficacy of Physical Activity for Children with Attention Deficit Hyperactivity Disorder: A Meta-Analysis of Randomized Controlled Trials. *J Affect Disord*, 10870547211017982. https://doi.org/10.1177/10870547211017982

Shaffer, F., eMcCraty, R., & Zerr, C. (2014). A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. -1. https://doi.org/10.3389/fpsyg.2014.01040/full

Sin, N. L., Sloan, R. P., McKinley, P. S., & Almeida, D. M. (2016). Linking Daily Stress Processes and Laboratory-Based Heart Rate Variability in a National Sample of

Midlife and Older Adults. *Psychosomatic Medicine, 78*(5), 573-582. https://doi.org/10.1097/psy.0000000000000306

Smoller, J. W. (2016). The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 41*(1), 297-319. https://doi.org/10.1038/npp.2015.266

Spiegelhalder, K., Fuchs, L., Ladwig, J., Kyle, S. D., Nissen, C., Voderholzer, U., et al. (2011). Heart rate and heart rate variability in subjectively reported insomnia. *J Sleep Res, 20*(1 Pt 2), 137-145. https://doi.org/10.1111/j.1365-2869.2010.00863.x

Stubbs, B., Vancampfort, D., Rosenbaum, S., Firth, J., Cosco, T., Veronese, N., et al. (2017). An examination of the anxiolytic effects of exercise for people with anxiety and stress-related disorders: A meta-analysis. *Psychiatry Research, 249*, 102-108. https://doi.org/10.1016/j.psychres.2016.12.020

Tarvainen, M. P., Niskanen, J.-P., Lipponen, J. A., Ranta-aho, P. O., & Karjalainen, P. A. (2014). Kubios HRV – Heart rate variability analysis software. *Computer Methods and Programs in Biomedicine, 113*(1), 210-220. https://doi.org/10.1016/j.cmpb.2013.07.024

Thayer, J. F., Ahs, F., Fredrikson, M., Sollers, J. J., 3rd, & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neuroscience and biobehavioral reviews, 36*(2), 747-756. https://doi.org/10.1016/j.neubiorev.2011.11.009

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Annals of Behavioral Medicine, 37*(2), 141-153. https://doi.org/10.1007/s12160-009-9101-z

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord, 61*(3), 201-216. https://doi.org/10.1016/s0165-0327(00)00338-4

Toni, G., Belvederi Murri, M., Piepoli, M., Zanetidou, S., Cabassi, A., Squatrito, S., et al. (2016). Physical Exercise for Late-Life Depression: Effects on Heart Rate Variability. *Am J Geriatr Psychiatry, 24*(11), 989-997. https://doi.org/10.1016/j.jagp.2016.08.005

Valente, M. J., Georgeson, A. R., & Gonzalez, O. (2021). Clarifying the Implicit Assumptions of Two-Wave Mediation Models via the Latent Change Score Specification: An Evaluation of Model Fit Indices [Original Research]. *Front Psychol, 12*. https://doi.org/10.3389/fpsyg.2021.709198

van Eekelen, A. P., Houtveen, J. H., & Kerkhof, G. A. (2004). Circadian variation in cardiac autonomic activity: reactivity measurements to different types of stressors. *Chronobiology International, 21*(1), 107-129. https://doi.org/10.1081/cbi-120027983

Wolf, S., Seiffer, B., Zeibig, J. M., Welkerling, J., Bauer, L. L., Frei, A. K., et al. (2021). Efficacy and cost-effectiveness of a Transdiagnostic group-based exercise intervention: study protocol for a pragmatic multi-site randomized controlled trial. *BMC Psychiatry, 21*(1), 540. https://doi.org/10.1186/s12888-021-03541-3

Wolf, S., Zeibig, J.-M., Giel, K., Granz, H., Sudeck, G., & Thiel, A. (2020). Sportliche Aktivität und psychische Erkrankungen [Exercise and mental disorders]. *PSYCH up2date, 14*(Georg Thieme Verlag KG Stuttgart · New York), 1–17. https://doi.org/10.1055/a-0973-1982

Wolf, S., Zeibig, J.-M., Hautzinger, M., & Sudeck, G. (2020). *Psychische Gesundheit durch Bewegung. ImPuls: Ein sport- und bewegungstherapeutisches Programm für Menschen mit psychischen Erkrankungen* [Mental health through exercise. ImPuls: An exercise intervention for people with mental disorders]. Julius Beltz GmbH & Co. KG.

Wunsch, K., Wurst, R., von Dawans, B., Strahler, J., Kasten, N., & Fuchs, R. (2019). Habitual and acute exercise effects on salivary biomarkers in response to psychosocial stress. *Psychoneuroendocrinology, 106*, 216-225. https://doi.org/10.1016/j.psyneuen.2019.03.015

Zeibig, J.-M., Seiffer, B., Sudeck, G., Rosel, I., Hautzinger, M., & Wolf, S. (2021). Transdiagnostic efficacy of a group exercise intervention for outpatients with heterogenous psychiatric disorders: a randomized controlled trial. *BMC Psychiatry, 21*(1), 313. https://doi.org/10.1186/s12888-021-03307-x

Table 1. Baseline demographic and clinical characteristics of participants

Measure	Intervention group (*N* = 36)		Control Group (*N* = 36)		Intervention Group vs. Control Group (N = 72)		
	N	%	*N*	%	χ^2	*df*	*p*
Female	25	69.4	27	75.0	0.28	1.00	.599
Married or partnered	25	69.4	24	66.7	0.06	1.00	.801
High school[a]	31	86.1	25	71.4	2.89	1.00	.089
Employment[a,b]	33	94.3	31	88.6			.673[g]
Diagnosis							.866[g]
Depression[c]	13	36.1	11	30.6			
Depression + Anxiety disorder(s)[d]	10	27.8	13	36.1			
Anxiety disorder(s)	9	25.0	9	25.0			
Primary insomnia	3	8.3	3	8.3			
Attention deficit hyperactivity disorder	1	2.8	0	0.0			
smoking	8	22.2	9	25.0	0.08	1.00	.781
psychopharmaceuticals[a]	18	50.0	20	57.1	0.36	1.00	.546
Dropout	6	16.7	14	38.9	4.43	1.00	.035
	Mean	*SD*	*Mean*	*SD*	*t*	*df*	*p*
Age (years)	37.33	14.23	34.33	12.39	0.95	68.69	.343
Global Severity Index (SCL-90-R)	1.06	0.63	1.02	0.61	0.27	69.91	.790
HRV-RMSSD[e]	36.25	19.17	39.82	19.95	-0.75	65.89	.455
HRV-HF[f]	635.85	766.42	1002.77	976.96	-1.66	56.89	.102
perceived stress (PSS)[a,b]	23.80	5.18	24.71	5.67	-0.70	67.46	.484

Note. SCL-90-R = Symptom Checklist-90, HRV-RMSSD = root mean square of successive differences between normal heartbeats, PSS = perceived stress scale; [a]The number of participants was n = 35 for the control group because of incomplete data at pre-treatment assessment; [b]The number of participants was n = 35 for the intervention group because of incomplete/non-analyzable data at pre-treatment assessment; [c]participants diagnosed with a single depressive disorder; [d]participants diagnosed with depressive disorder and comorbid anxiety disorder(s). Anxiety disorders include panic disorder, specific anxiety disorder, generalized anxitey disorder, agoraphobia, post-traumatic stress disorder, obsessive compulsive disorder, social phobia; [e]The number of participants was n = 34 for the control group and n = 34 for the intervention group because of incomplete/non-analyzable data at pre-treatment assessment; [f]The number of participants was n = 31 for the control group and n = 33 for the intervention group because of incomplete/non-analyzable data at pre-treatment assessment; [g]Fisher's exact test was used as a replacement for the chi-square test because the frequency of one or more cells was less than 5.

Table 2. Marginal means, confidence intervals, effect sizes, and results of linear mixed model analyses

	Intervention Group (*N* = 36)			**Control Group (*N* = 36)**					**Change from T1 to T2 in Intervention Group Compared With Control Group (*N* = 72)**			
Measure and Assessment Point	***Mean***	***SD***	***95%CI***	***Mean***	***SD***	***95%CI***	***d*[a]**	***p***	***B*[b]**	***95%CI***	***d*[b]**	***p***
HRV-RMSSD[c]									0.49	0.20;0.78	0.89	.001
T1	3.47	0.56	3.28;3.66	3.61	0.56	3.42;3.80						
T2	3.67	0.54	3.47;3.88	3.32	0.53	3.10;3.55	-0.65	.047				
Perceived Stress scale									-1.64	-4.60;1.39	-0.31	.277
T1	23.80	5.52	22.00;25.60	24.70	5.50	22.90;26.60						
T2	19.90	5.39	17.80;21.90	22.40	4.78	20.20;24.70	0.49	.093				

Note. HRV-RMSSD = root mean square of successive differences between normal heartbeats; T1 = pre-treatment assessment; T2 = post-treatment assessment; [a]Cohen's d for post-treatment effect between the intervention and control group; [b]B = interaction effect of time x treatment, d = Cohen's d for the interaction effect; [c]Marginal means are reported in and post-hoc tests were performed on the log scale; controlled for age, gender and smoking

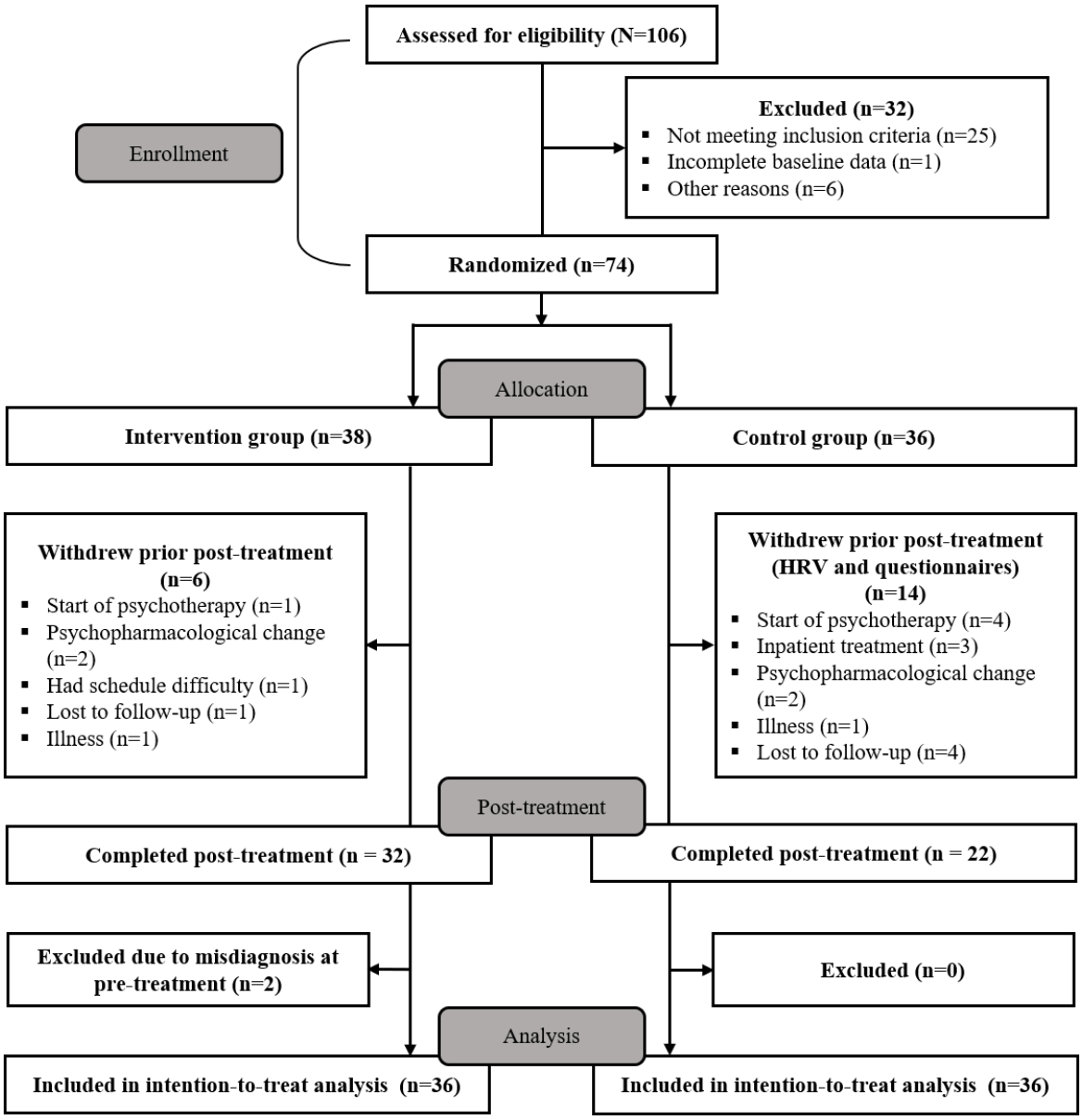

Figure 1. CONSORT flow diagram: profile and enrolment and flow through the randomized controlled trial of group exercise intervention versus a passive control group for individuals with diagnostically heterogenous mental disorders.

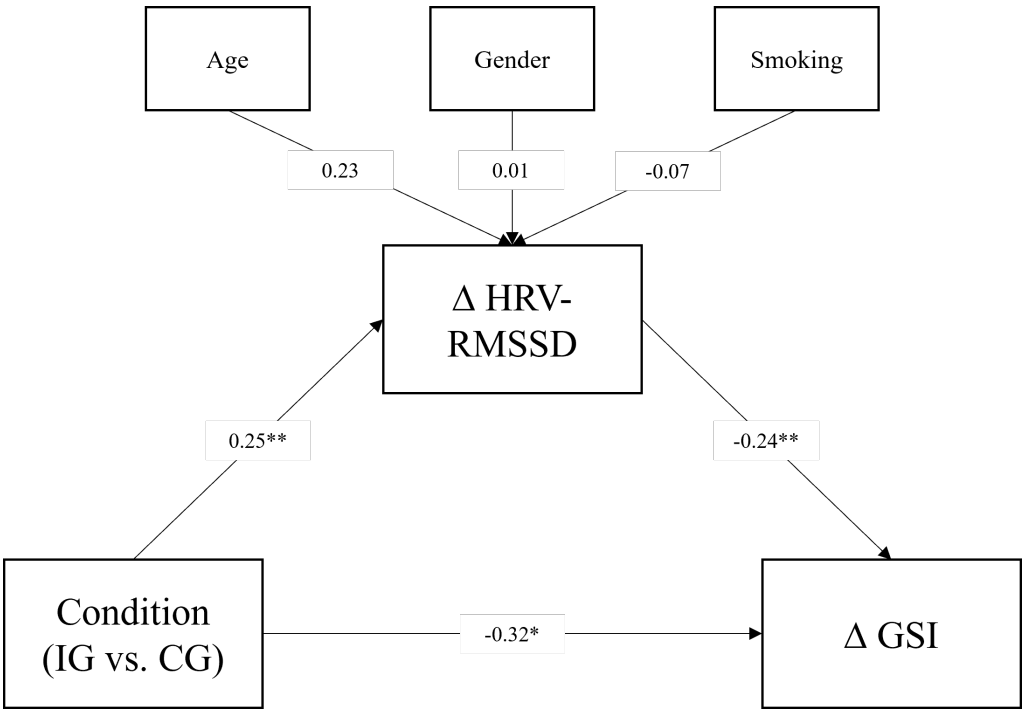

Figure 2. Results of the structural equation model with change of HRV-RMSSD mediator of the intervention effect on GSI. ΔHRV-RMSSD = change of the root mean square of successive differences between normal heartbeats, ΔGSI = change in the global severity index, IG = intervention group, CG = control group. Indicated are standardized regression coefficients.
*p<0.05. **p<0.01. ***p<0.001

Appendix C: Manuscript III

Zeibig, J.-M., Seiffer, B., Frei, A. K., Takano, K., Sudeck, G., Rösel, I., Hautzinger, M., & Wolf, S. (2022). Long-term efficacy of exercise across diagnostically heterogenous mental disorders and the mediating role of affect regulation skills. *Psychol Sport Exerc*, 102340. https://doi.org/https://doi.org/10.1016/j.psychsport.2022.102340