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Efficacy of a Specialized Group Intervention for Compulsive Exercise in Inpatients with Anorexia Nervosa: A Randomized Controlled Trial

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Anorexia nervosa · Compulsive exercise · Treatment · Group intervention · Randomized controlled trial

Abstract
Introduction: Treatment of compulsive exercise is recognized as a key unmet challenge in the treatment of anorexia nervosa (AN). To address this challenge, we developed the manualized group intervention "healthy exercise behavior" (HEB). This study evaluates the efficacy of HEB for the reduction of compulsive exercise as add-on to routine inpatient treatment (treatment as usual [TAU]) in a randomized controlled trial. ***Methods:*** Two hundred and seven adolescent and adult female inpatients with (atypical) AN were randomly allocated to TAU or to additional participation in HEB (TAU + HEB). HEB integrates elements of exercise-based therapy into a cognitive-behavioral approach. Assessments took place at admission, pre-intervention, post-intervention, discharge, and 6 months follow-up. Primary outcome was the severity of compulsive exercise assessed by the Commitment to Exercise Scale between pre- and post-intervention; secondary outcomes were additional aspects of compulsive exercise, assessed by the Compulsive Exercise Test, weight gain, eating disorder and general psychopathology, and emotion regulation. ***Results:*** In intention-to-treat analysis for the primary outcome, the TAU + HEB group showed significantly stronger reductions in the severity of compulsive exercise compared to the TAU group ($z = -2.81$; $p = 0.005$; effect size [ES] = –0.3). We also found significantly stronger reductions from admission to discharge ($z = 2.62$; $p = 0.009$; ES = –0.43), and from admission to follow-up ($z = 2.1$; $p = 0.035$; ES = –0.39). Regarding secondary outcomes, we found significant group differences between pre- and post-intervention in additional aspects of compulsive exercise ($z = -2.55$; $p = 0.011$; ES = –0.27). We did not find significant differences regarding weight gain, eating disorder and general psychopathology, and emotion regulation. ***Conclusions:*** Our intervention proved efficacious in reducing compulsive exercise in inpatients with (atypical) AN.

Introduction

Anorexia nervosa (AN) is a serious psychiatric disorder associated with one of the highest mortality risks of all mental disorders [1, 2]. Besides well-known symptoms

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such as food restriction, intense fear of weight gain, and body image distortions, a common and distinctive symptom that has been described from the very beginning of AN research is compulsive exercise behavior despite severe emaciation [3]. Compulsive exercise is observed in 31–81% of adolescent and adult patients with AN depending on sample characteristics and on methodology used for assessment [3–6]. Several studies showed that compulsive exercise is associated with treatment dropout and longer hospital stays and represents a significant predictor for relapse and chronic course of the disorder [7–10].

Over the last decade, terminology, definition, assessment as well as underlying and maintaining factors of compulsive exercise have been an issue of debate. In studies examining underlying personality variables, trait anxiety, obsessive-compulsive personality traits, and perfectionism were found to be associated with compulsive exercise in AN [11–15]. Neurobiological research by Hebebrand and Holtkamp [3, 16–19] revealed that "elevated physical activity" and "restlessness" correlate with hypoleptinemia due to semi-starvation. However, a considerable proportion of AN patients shows persisting compulsive exercise even after weight restoration. This may be attributable to different psychological maintaining factors of compulsive exercise. Klein et al. [20] suggested the term "exercise addiction" and emphasized the positive effect of exercise on mood. Studies on "excessive exercise" focused more on quantitative features of the exercise behavior such as excessive frequency, intensity and duration that are maintained by eating disorder pathology like shape and weight concerns or dietary restraint [15, 21–27]. In comparison, studies [28–30] on "compulsive exercise" highlighted the importance of qualitative aspects as maintaining factors. They emphasized the psychological commitment to exercise to prevent or alleviate negative affects like guilt, anxiety, or depression when unable to exercise [26, 27, 31, 32] and the rigid, obligatory exertion of exercise. Taken together, these studies indicate that compulsive exercise is maintained by a complex interplay of mood improvement, compulsivity, difficulties in emotion regulation, weight and shape concerns, and rigid and perfectionistic personality traits [14, 15, 33, 34]. Agreement also exists that compulsive exercise is likely biologically mediated in AN patients [19]. A recent Delphi study by Noetel et al. [35] meant a leap forward towards development of a consensus framework: "Compulsive exercise" was found to be the preferred term for describing the phenomenon. Consensus was reached that definition and assessment of compulsive exercise should consider both quantitative and qualitative dimensions. Our work group developed a proposal for a transdiagnostic definition and a clinical assessment for compulsive exercise that closely matches the results of this Delphi study [36].

Evidence-based therapeutic approaches for compulsive exercise in AN have been scarce so far. Zipfel et al. [37] recognized treatment of compulsive exercise as one of the key unmet challenges in the treatment of AN. A literature review about existing intervention studies for compulsive exercise in eating disorders can be found in online supplementary Material 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000504583).

Most of these studies are characterized by methodological shortcomings like small sample size or lack of randomization. However, Hay et al. [38] recently conducted a multicenter randomized controlled trial (RCT) in an outpatient setting. They evaluated their new cognitive-behavioral therapy (CBT)-based treatment approach called compuLsive Exercise Activity theraPy (LEAP). Schlegel et al. [39] developed an exercise-based program for outpatients with AN and bulimia nervosa (BN) that is currently being evaluated in an RCT. Both treatment approaches focus either on CBT *or* exercise-based therapy. A therapeutic approach that comprises CBT-based *and* exercise-based elements was still missing. As outlined in detail elsewhere [40], we consider an integrative approach crucial to simultaneously challenge distorted cognitions about exercise, reduce compulsivity of the exercise behavior, teach emotion regulation skills, *and* practice healthy exercise behavior. Our team aimed to fill this gap to further improve treatment options for compulsive exercise in affected patients. We developed the new manualized group therapeutic approach "healthy exercise behavior (HEB)" [41] integrating exercise-based elements into a CBT approach. In a pilot study, the feasibility of the manualized group intervention for compulsive exercise was confirmed, effect sizes on most outcomes were promising, and the intervention was well accepted [40]. The aim of this study was to evaluate the efficacy of HEB as add-on module to routine inpatient treatment (treatment as usual [TAU]; TAU + HEB) compared with TAU in a randomized controlled dismantling trial [42].

Our primary hypothesis was that patients in the TAU + HEB group would show a significantly stronger reduction in compulsive exercise as assessed by the Commitment to Exercise Scale (CES) between pre- and post-intervention compared to patients in the TAU group.

Secondary hypotheses included significantly stronger decreases in the TAU + HEB group compared to the TAU group concerning additional aspects of compulsive exer-

cise, eating disorder and general psychopathology, emotion regulation, as well as a significantly higher weight gain.

Methods

Study Design and Study Population

Our study was a single-center, randomized controlled dismantling trial in adolescent and adult inpatients with AN.

Over a 1.75-year period, we screened all female patients for inclusion in our study who were referred for inpatient treatment to Schoen Clinic Roseneck, Prien am Chiemsee, Germany, with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of AN or atypical AN/Eating Disorder Not Otherwise Specified (EDNOS).

According to the German S3-guideline for diagnosis and treatment of eating disorders [43], qualifiers for inpatient treatment are as follows: rapid and persisting weight loss, a body mass index (BMI) <15 kg/m^2, medical complications, family or social factors impeding recovery, failure in an outpatient or day-patient therapeutic setting, pronounced purging or compulsive exercise, low insight, or marked psychiatric comorbidity. The average length of inpatient stay for AN treatment in Germany is 12 weeks [44].

Female patients were eligible if they met the following inclusion criteria during screening: (1) DSM-IV diagnosis of AN (DSM-IV 307.1) or atypical AN/EDNOS (DSM-IV 307.50), which was assessed by the diagnostically relevant questions of the Structured Expert Interview for Anorexic and Bulimic Syndromes according to DSM-IV and ICD-10 (SIAB-EX) [45]; (2) presence of compulsive exercise, which was assessed with a structured interview [36]. This interview asks about the following characteristics of the exercise behavior: A pathologically increased exercise pattern characterized by (1) excessive exercise that a patient feels driven to perform in response to an obsession or according to rules that must be applied rigidly, and (2) exercise that is aimed at preventing or reducing distress or at preventing some dreaded consequence. A second necessary criterion is the physical or psychological burden caused by compulsive exercise, that is, that it is time-consuming, significantly interferes with the patient's daily routine, occupational functioning, or social relationships or is continued despite medical injury, illness, or lack of enjoyment (see online suppl. Material 2 for the entire clinical interview for the assessment of compulsive exercise); (3) age: 13–45 years.

Exclusion criteria were: (1) BMI <13 kg/m^2 at pre-intervention. As a BMI below 13 kg/m^2 represents a life-threatening condition, we decided to exclude this subgroup of AN patients from our study due to medical safety reasons. It was considered medically irresponsible to include these patients in a therapeutic intervention that includes any elements of exercise; (2) current drug, alcohol or other substance abuse; (3) presence of additional severe psychiatric (i.e., psychotic and bipolar disorders) or neurological diseases (multiple sclerosis), and suicidality; (4) concurrent exposure-based treatment for obsessive-compulsive disorder (OCD). One very specific element of HEB represents exposure with response management. In treatment for OCD, CBT including exposure with response management represents the therapeutic gold standard [46]. To make sure that patients receive exposure as specific therapeutic element only as part of HEB, we excluded patients with concurrent treatment for OCD; (5) severe somatic complications prohibiting light to moderate supervised exercise; and (6) marked cognitive impairment due to underweight severe enough to preclude attending and following a 100-min group session. The clinical assessment of cognitive impairment was based on the Association for Methodology and Documentation in Psychiatry (AMDP) System [43]: Patients had to report moderate or severe deficits in comprehension, attention span and short- or long-term memory or these deficits had to be observable by the clinician during the screening procedure.

The trial is registered at http://isrctn.org, number ISRCTN14208852.

Due to a lack of data concerning treatment effects of inpatient compulsive exercise interventions, sample size estimation was calculated to detect differences of treatment effects between study groups with a medium effect size of $d = 0.5$. The two-sided significance level (type I error) was set to $p < 0.05$ and the power (1 – type II error) was set to 0.8. G * Power (version 3.1.9.2) [47] recommends a sample size of 64 patients per treatment arm, resulting in a total sample size of $n = 2 \times 64 = 128$. To compensate for an estimated dropout rate of 30% [48], we had to include a minimum of 184 patients in the study.

Procedures

Patients were regularly admitted to our hospital and participated in routine inpatient treatment from day 1 onwards. Within one week following hospital admission, all patients were screened for inclusion in the study by experienced clinicians: Patients participated in a diagnostic session with SIAB-EX interview and a structured interview for compulsive exercise. In this diagnostic session, we also approved inclusion/exclusion criteria. Eligible patients received detailed information on the study. All patients gave written informed consent to participate. For minors, an additional briefing of their legal guardians was provided via telephone, and informed consent forms were sent out to be signed. We medically assessed all patients at admission as part of routine inpatient treatment, which included taking weight and height.

Patients were randomized to 1 of 2 treatment arms: (1) Routine inpatient treatment (TAU), and (2) TAU and additional participation in the 4-week HEB intervention as add-on module to TAU (TAU + HEB). After randomization, patients of the TAU + HEB group had to wait until the next closed HEB group started.

In addition to the clinical trial data reported here, changes in accelerometry and biological parameters were investigated. Results of these parameters will be reported elsewhere.

Interventions

Routine Inpatient Treatment (TAU)

The specialized inpatient treatment for patients with AN consists of a multimodal cognitive-behavioral approach and intense psychiatric and general medical treatment. All patients receive individual treatment once to twice per week, take part in a manualized, symptom-oriented group intervention for eating disorder patients, and a nonspecific problem-solving group treatment 3 times per week. Furthermore, all AN patients participate in supervised meals 3 times per day, meal preparation classes, social skills training and art therapy. Patients also take part in graduated exercise therapy depending on their weight and physical condition. All underweight patients are required to gain 700–1,000 g per week, which is monitored by biweekly weight checks and visualized on individual weight charts. All patients were advised to elaborate an "exercise contract," i.e. a contingency plan, with their respective therapist.

HEB Intervention

The HEB intervention is manual-based [41], comprises 8 sessions (of 100 min), and is delivered by a clinical psychologist and a sports therapist twice per week. It is conceptualized as closed group for 8 patients with sequential sessions. The overarching goal of this intervention is threefold: First, to reduce the excessive quantity of the exercise behavior and reestablish a "healthy" exercise behavior, taking into account each patient's current weight and general health condition. Second, to reduce the compulsive quality of the exercise behavior and establish a more flexible exercise regimen. Third, to re-experience joy, social interaction, and relaxation when exercising. During each session, cognitive-behavioral as well as exercise-based treatment elements complement each other. Between the sessions, patients are required to complete homework tasks. Group sessions are supplemented by individually graded exposure and response prevention tasks concerning exercise behavior guided by one of the therapists. For further details concerning the intervention, see online supplementary Material 3.

Randomization and Masking

To minimize carry-over effects between treatment arms by patients on the same hospital wards and to increase feasibility of the study, we randomized hospital wards as a whole. Randomization to the TAU + HEB and TAU groups was conducted by a research associate at LMU Munich using randomizer.org [49]. The research associate was not involved in enrollment of patients, intervention delivery and data collection. The allocation ratio was 1:1. After 50% of the required number of patients had been included, we switched wards for the TAU + HEB and TAU treatment arms.

In psychotherapy outcome trials, it is impossible to blind patients to their respective treatment arm and the therapists delivering the intervention [50]. However, patients were blinded regarding purpose and hypotheses of the study. Patients were informed that they would be randomized to 1 of 2 treatment arms, and that we expected both to show effective treatment for compulsive exercise.

Regarding outcome measures, the nursing staff who measured weight/BMI was masked. Nursing staff was not informed about patients' participation in our study. Nursing staff regularly measures weight/BMI as part of routine inpatient treatment for all patients with eating disorders twice per week. We used these routine weight measurements for our study, so we did not ask nursing staff for any additional weight assessments of study participants.

All other outcomes were self-rating scales, which were completed by the patients themselves. Return of the questionnaires was organized by an inhouse postbox and took place without any involvement of nursing staff as well.

Primary Outcome Measure

The Commitment to Exercise Scale (CES; [51, 52][1]) total score between pre- and post-intervention served as primary outcome. The CES is a widely used self-rating scale for assessment of compulsive exercise in patients with eating disorders. It addresses 2 core aspects of compulsive exercise: Obligatory exercising and pathological exercising. Obligatory exercise implies the strict adherence to a regular and clearly structured exercise routine. Pathological exercise refers to the physical or psychological burden caused by the exercise.

Secondary Outcomes Measures

Secondary outcomes measures included additional aspects of compulsive exercise (assessed by Compulsive Exercise Test [CET] [55, 56]), BMI (calculated by weight in kg/height in m^2), eating disorder psychopathology (assessed by Eating Disorder Examination Questionnaire [EDE-Q] [57, 58]), general psychopathology (assessed by Brief Symptom Inventory 18 [BSI-18] [59, 60]), depression (assessed by Beck Depression Inventory-II [BDI-II] [61, 62]), and emotion regulation skills (assessed by Difficulties in Emotion Regulation Scale [DERS] [63, 64]).

Outcomes were assessed at 5 time points: admission (T0; within the first week after admission), pre-intervention (T1; within 3 days before the start of HEB), post-intervention (T2; within 3 days after the end of HEB), discharge (T3; within 1 week before discharge), and 6 months follow-up (T4; 6 months after discharge). For details concerning the applied outcome measures, see online supplementary Material 4.

Serious Adverse Events

We defined all life-threatening or fatal events as serious adverse events, which had to be reported to the principal investigator immediately.

Statistics

Baseline characteristics at admission and dropout rates were compared between the study groups using *t* tests for independent groups for metric variables and χ^2 tests for categorical variables. In case of significant differences between study groups, we conducted regression analyses to examine whether the respective variable contributed significantly to the prediction of the primary outcome measure to then include it as covariate. All these tests were carried out in SPSS, version 22 [65].

Statistical analyses of intervention effects on outcomes were carried out with STATA 15 [66] using linear mixed effects models for repeated measures with restricted maximum likelihood estimation. This approach has gained broad support for intention-to-treat (ITT) analyses in longitudinal clinical trials [67].

We conducted the primary analysis of the CES according to an ITT approach including all patients who underwent randomization. We did not impute missing values, as it was shown that mixed models analysis without any imputation yields more powerful tests than analyses with ad hoc imputation [68]. We tested the model with different covariance structures, and an unstructured within-subject covariance structure provided the best fit. The model was based on 5 assessment time points (admission [T0], pre-intervention [T1], post-intervention [T2], discharge [T3], 6 months follow-up [T4]). As treatment was nested within wards, we planned to additionally nest by ward. However, our model did not converge when including ward as second random effect, so we were not able to include this factor. Only in case of significant overall treatment effects (overall treatment group × time interaction) were post hoc contrasts calculated to specify these effects by testing group differences over time. We calculated effect sizes by dividing the difference of the model-estimated marginal means by the pooled pretest standard deviation (SD) [69]. SDs were derived from the standard errors of the estimated marginal means. All secondary outcome measures were analyzed equally.

[1] A German version of the CES was validated by Zeeck et al. [53]. In accordance with Thome and Espelage [54] we used a 4-point Likert scale instead of the original answering format (visual analogue scale) and a different German translation of "exercise." This alternative German version of the CES is currently validated by our work group.

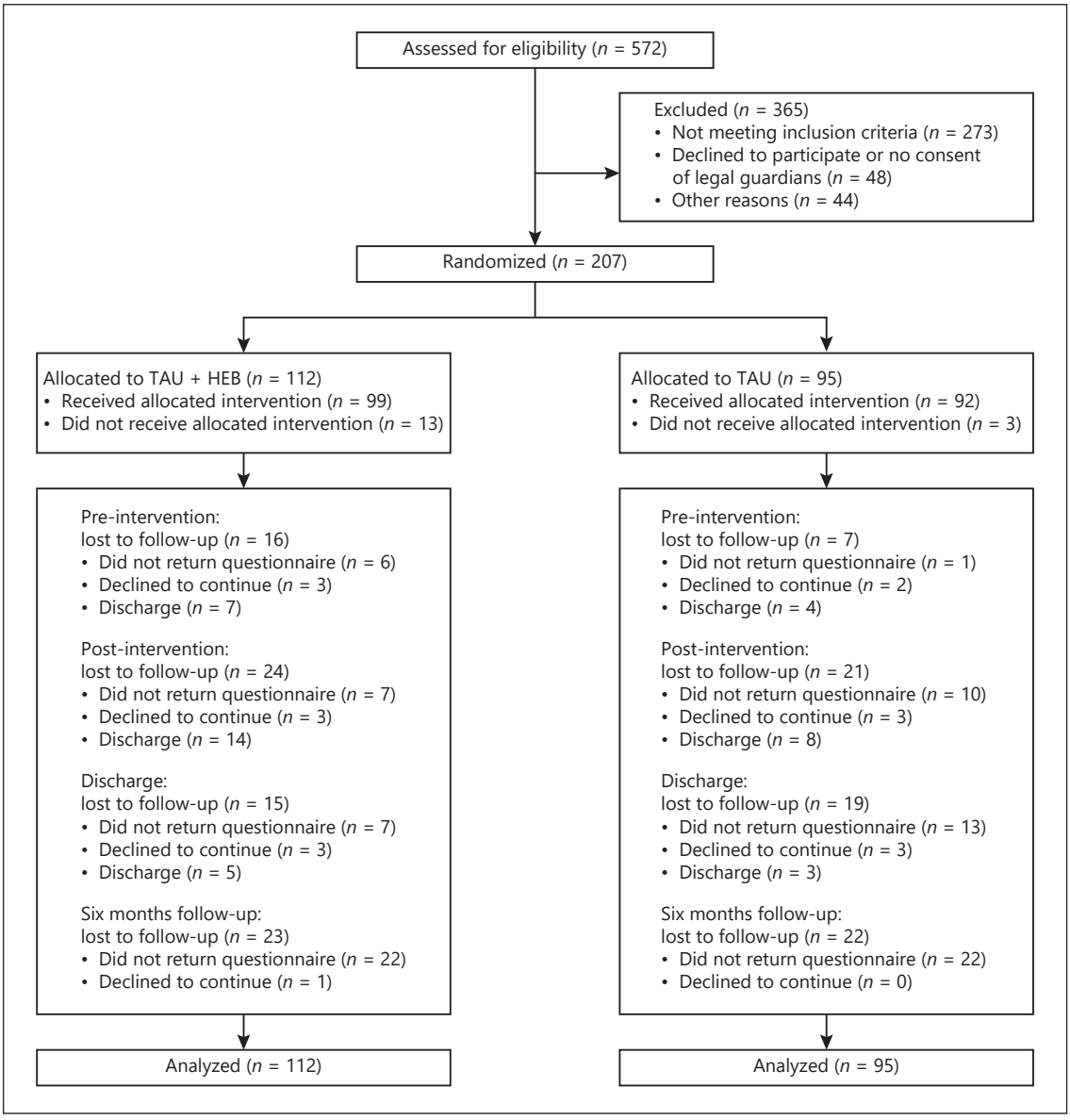

Fig. 1. CONSORT flow diagram of the study. HEB, "healthy exercise behavior" intervention; TAU, treatment as usual.

Results

Baseline Characteristics

Between October 1, 2013, and June 30, 2015, we screened 572 patients for eligibility. The prevalence rate of compulsive exercise in our clinical sample was 52.3%.

Two hundred and seven adolescent and adult female AN patients were included and randomized to the 2 treatment arms (adolescents: $n = 108$, adults: $n = 99$; see CONSORT flow, Fig. 1). At post-intervention, 24 (21.4%) patients of the TAU + HEB group and 21 (22.1%) patients of the TAU group were lost to follow-up.

At discharge, data of 15 (13.3%) patients of the TAU + HEB group and 19 (20.0%) patients of the TAU group were missing. By 6 months follow-up, 23 (20.5%) patients of the TAU + HEB group and 22 (23.2%) patients of the TAU group were lost to follow-up. At no assessment time, did loss-to-follow-up rates differ significantly between study groups (Table 1).

Table 1. Demographic and clinical characteristics of the sample at admission

Items	TAU + HEB (*n* = 112)	TAU (*n* = 95)
Demographic characteristics		
Age at admission, years	20.04 (5.7)	18.32 (5.19)
Marital status, *n* (%)		
Single, never married	21 (18.8)	10 (10.5)
Married or committed relationship	91 (81.2)	85 (89.5)
Clinical characteristics		
Subtype of AN, *n* (%)		
AN	72 (64.3)	48 (50.5)
AN binge/purge	18 (16.1)	17 (17.9)
EDNOS (atypical AN)	22 (19.6)	30 (31.5)
BMI at admission, mean (SD), kg/m^2	14.98 (1.96)	15.35 (1.86)
CES at admission	3.00 (0.65)	2.85 (0.71)
Comorbidity[1], *n* (%)		
Affective disorder	80 (71.4)	72 (75.8)
OCD	15 (13.4)	6 (6.3)
Illness duration, mean (SD), years	4.07 (4.53)	3.31 (4.41)
Previous inpatient treatment, mean (SD), *n*	1.54 (1.67)	1.68 (4.37)
Outpatient psychotherapy before admission, *n* (%)	84 (76.4)	78 (82.1)
Length of inpatient stay, mean (SD), days	101.46 (42.77)	99.82 (42.29)
Aftercare following discharge[2], *n* (%)		
Regular outpatient psychotherapy	64 (83.1)	53 (82.8)
Readmission to hospital due to AN or related issues	12 (10.7)	16 (16.8)
Day-hospital treatment	3 (3.9)	1 (1.6)
Specialized living communities for ED patients	8 (10.4)	2 (3.1)

n, number; AN, anorexia nervosa; EDNOS, eating disorder not otherwise specified; BMI, body mass index; SD, standard deviation; CES, Commitment to Exercise Scale; OCD, obsessive compulsive disorder; ED, eating disorder; TAU, treatment as usual; HEB, "healthy exercise behavior" intervention.

[1] Affective and obsessive-compulsive disorders were assumed to be the most relevant comorbid diagnoses.

[2] Information on aftercare was collected at 6 months follow-up; due to loss to follow-up, results are based on data of 141 patients.

Concerning demographic and clinical characteristics at admission, both study groups only differed significantly in age ($p = 0.025$). Data inspection revealed that this result was mainly attributable to an outlier in the TAU + HEB group (1 patient at age 44). As regression analyses showed that age did not contribute significantly to the prediction of the primary outcome measure, it was not included as covariate in further analyses.

The mean time between admission and start of HEB in patients of the TAU + HEB group was 30.06 days (range 0–113 days). On average, 7 patients participated in each HEB group.

Primary Outcome CES

Supporting our hypothesis, we found a significant overall interaction between treatment group × assessment time (Table 2; Fig. 2) in the CES. Post hoc contrasts (Table 3) revealed that patients of the TAU + HEB group showed significantly stronger decreases in the severity of compulsive exercise than patients of the TAU group between pre- and post-intervention, from admission to discharge, and from admission to follow-up. These treatment effects were small between pre- and post-intervention ($d = -0.30$), small to moderate from admission to discharge ($d = -0.43$), and again small to moderate from admission to follow-up ($d = -0.39$). Additionally, we found a significant main effect of time (Table 2). Post hoc contrasts showed that severity of compulsive exercise scores decreased significantly between each assessment time during inpatient treatment, from admission to discharge and from admission to follow-up (relevant post hoc contrasts are shown in Table 3).

Secondary Outcome Variables

Concerning CET, we also found a significant overall interaction between treatment group × assessment time for the CET total score (i.e., overall severity of compulsive exercise) and the following 3 subscales: Avoidance and Rule-driven Behavior (i.e., maintenance of a strict exercise pattern to avoid negative affect), Weight Control Exercise (i.e., exercise to control weight and shape), and Mood Improvement (i.e., positive effect of exercise on mood; Table 2). Post hoc contrasts (Table 3) revealed that patients of the TAU + HEB group demonstrated greater reductions in these 3 aspects of compulsive exercise between pre- and post-intervention than patients of the TAU group with a small effect size (ES = –0.3 for each scale). Concerning the overall severity of compulsive exercise, patients of the TAU + HEB group also showed a stronger decrease from admission to follow-up than patients of the TAU group with a small to moderate effect size (ES = –0.39). We also found a significant main effect of time for the CET total score and all 5 subscales (Table 2; Table 3 for relevant post hoc contrasts). Patients of both study groups showed significant reductions in all aspects of compulsive exercise during inpatient treatment.

We found a significant main effect of time for weight gain/BMI increase (Table 2). Patients of both groups showed a significant weight gain over the course of inpatient treatment. We did not find a significant overall interaction between treatment group × assessment time (Fig. 3).

Analyses concerning EDE-Q, BDI-II, Global Severity Index (GSI) of the BSI-18, and DERS total score showed main effects of time (Table 2). Patients of both groups showed significant reductions in eating disorder and general psychopathology and significant improvements in emotion regulation skills during inpatient treatment. No significant differences concerning symptom reduction or improvements between study groups were found.

For means and SDs of all outcome measures for both study groups at admission, pre-intervention, post-intervention, at discharge and at follow-up, see online supplementary Material 5.

The lack of control for multiple comparisons implies that the statistical significance of all these findings should be interpreted with caution.

Serious Adverse Events

No serious events were reported in either study group during our clinical trial.

Table 2. Results for primary and secondary outcomes from intention-to-treat analyses using linear mixed effect models: main and interaction effects

Outcome measure	χ^2 (df)	*p* value
CES		
Group	0.06 (1)	0.801
Time	213.22 (4)	<0.001
Group × time	13.57 (4)	**0.009**
CET total		
Group	0.33 (1)	0.568
Time	222.88 (4)	<0.001
Group × time	12.80 (4)	**0.012**
Avoidance and Rule-Driven Behavior		
Group	0.05 (1)	0.818
Time	189.52 (4)	<0.001
Group × time	17.23 (4)	**0.002**
Weight Control Exercise		
Group	0.37 (1)	0.545
Time	159.05 (4)	<0.001
Group × time	13.85 (4)	**0.008**
Mood Improvement		
Group	0.6 (1)	0.438
Time	83.1 (4)	<0.001
Group × time	9.8 (4)	**0.044**
Lack of Exercise Enjoyment		
Group	0.05 (1)	0.831
Time	36.11 (4)	<0.001
Group × time	7.84 (4)	0.098
Exercise Rigidity		
Group	0.15 (1)	0.7
Time	176.98 (4)	<0.001
Group × time	6.72 (4)	0.152
BMI		
Group	0.55 (1)	0.457
Time	768.1 (4)	<0.001
Group × time	4.43 (4)	0.351
EDE-Q total		
Group	1.01 (1)	0.315
Time	408.46 (4)	<0.001
Group × time	4.23 (4)	0.376
BDI-II		
Group	0.49 (1)	0.485
Time	305.38 (4)	<0.001
Group × time	6.96 (4)	0.138
BSI-18 GSI		
Group	0.34 (1)	0.561
Time	204.85 (4)	<0.001
Group × time	7.86 (4)	0.097
DERS total		
Group	0.36 (1)	0.551
Time	86.89 (4)	<0.001
Group × time	6.42 (4)	0.17

CES, Commitment to Exercise Scale; CET, Compulsive Exercise Test; BMI, body mass index; EDE-Q, Eating Disorder Examination-Questionnaire; BDI-II, Beck Depression Inventory-II; BSI-18, Brief Symptom Inventory-18; GSI, Global Severity Index; DERS, Difficulties in Emotion Regulation Scale.

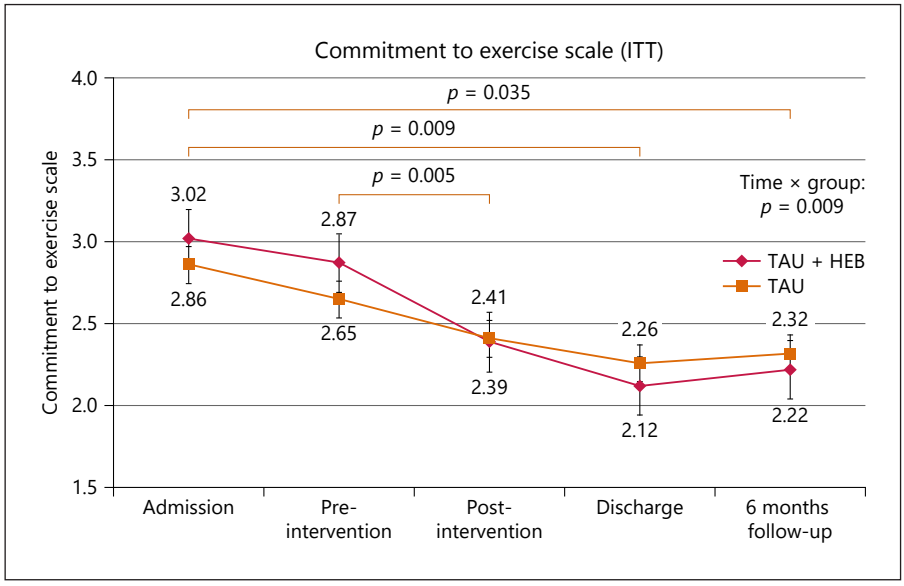

Fig. 2. Severity of compulsive exercise assessed by the Commitment to Exercise Scale from admission to pre-intervention, to post-intervention, to discharge, and to 6 months follow-up by treatment group. Values are estimated marginal means (with standard error of the mean) from intention-to-treat analyses using linear mixed effect models. Post hoc contrasts for TAU + HEB vs. TAU. ITT, intention-to-treat analysis; HEB, "healthy exercise behavior" intervention; TAU, treatment as usual.

Table 3. Results for primary and secondary outcomes from intention-to-treat analyses using linear mixed effect models: post-hoc contrasts

Measure	Time effects					Group × time effects					
	contrast	*z*	*p* value	CI lower limit	CI upper limit	contrast	*z*	*p* value	CI lower limit	CI upper limit	effect size
CES											
Pre- to post-intervention	−0.372	−8.75	<0.001	−0.455	−0.289	−0.239	−2.81	**0.005**	−0.406	−0.073	−0.30
Admission to discharge	−0.759	−13.83	<0.001	−0.867	−0.652	0.290	2.62	**0.009**	0.073	0.506	−0.43
Admission to follow-up	−0.680	−10.9	<0.001	−0.802	−0.557	0.264	2.10	**0.035**	0.018	0.510	−0.39
CET total											
Pre- to post-intervention	−1.971	−8.62	<0.001	−2.419	−1.523	−1.167	−2.55	**0.011**	−2.065	−0.269	−0.27
Admission to discharge	−4.788	−14.69	<0.001	−5.427	−4.149	0.887	1.35	0.175	−0.396	2.171	−0.24
Admission to follow-up	−4.344	−12.39	<0.001	−5.031	−3.657	1.433	2.03	**0.042**	0.052	2.813	−0.39
Avoidance and Rule-Driven Behavior											
Pre- to post-intervention	−0.552	−8.35	<0.001	−0.681	−0.422	−0.404	−3.05	**0.002**	−0.664	−0.145	−0.32
Admission to discharge	−1.294	−12.91	<0.001	−1.490	−1.097	0.193	0.96	0.338	−0.201	0.587	−0.16
Admission to follow-up	−1.236	−11.77	<0.001	−1.441	−1.030	0.349	1.66	0.098	−0.064	0.762	−0.29
Weight Control Exercise											
Pre- to post-intervention	−0.361	−6.20	<0.001	−0.475	−0.247	−0.347	−2.97	**0.003**	−0.576	−0.118	−0.28
Admission to discharge	−1.145	−12.54	<0.001	−1.324	−0.966	0.126	0.69	0.493	−0.234	0.486	−0.11
Admission to follow-up	−1.003	−9.50	<0.001	−1.210	−0.796	0.400	1.89	0.059	−0.015	0.816	−0.35
Mood Improvement											
Pre- to post-intervention	−0.272	−5.03	<0.001	−0.378	−0.166	−0.267	−2.46	**0.014**	−0.480	−0.054	−0.29
Admission to discharge	−0.648	−8.72	<0.001	−0.794	−0.502	0.068	0.46	0.648	−0.224	0.361	−0.08
Admission to follow-up	−0.591	−7.37	<0.001	−0.748	−0.434	0.128	0.79	0.427	−0.188	0.443	−0.15

Only variables that achieved a nominal *p* value of <0.05 for the overall treatment group × assessment time interaction are presented. CI, confidence interval; CES, Commitment to Exercise Scale; CET, Compulsive Exercise Test.

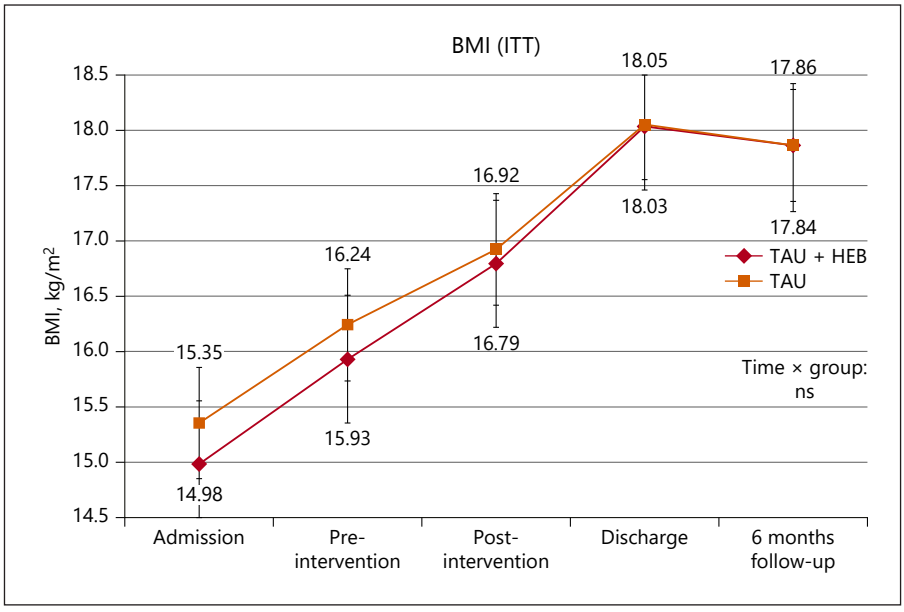

Fig. 3. Body mass index (BMI) increase from admission to pre-intervention, to post-intervention, to discharge, and to 6 months follow-up by treatment group. Values are estimated marginal means (with standard error of the mean) from intention-to-treat analyses using linear mixed effect models. ITT, intention-to-treat analysis; HEB, "healthy exercise behavior" intervention; TAU, treatment as usual.

Discussion and Conclusions

To our knowledge, the present study is the largest RCT to date evaluating the efficacy of a new specialized group intervention for compulsive exercise in patients with AN or atypical AN. The findings of our dismantling trial show that our HEB intervention proved efficacious in an inpatient setting with acutely ill AN patients. In ITT analyses, we found that additionally participating in HEB as add-on module to routine inpatient treatment leads to significantly stronger reductions in compulsive exercise symptomatology between pre- and post-intervention and between admission and discharge compared to receiving routine inpatient treatment only. These differences between study groups were stable at 6 months follow-up. Patients additionally receiving HEB maintained to show a significantly stronger improvement concerning compulsive exercise.

We found significant reductions in eating disorder and general psychopathology and significant weight gain over the course of inpatient stay for all patients but did not find significant differences between groups. However, given that both treatment groups received specialized multimodal inpatient treatment for eating disorders, no significant differences between groups with respect to these parameters was not unexpected.

In further analyses of our data, we will conduct per-protocol analyses including all patients who attended at least 6 out of 8 HEB sessions to investigate whether complete participation in HEB affected outcome concerning severity of compulsive exercise and weight gain. Additionally, we will explore "sudden gains" [70] in terms of weight gain during participation in HEB.

For clinicians treating severely ill AN patients on a daily basis, the contribution to a positive long-term outcome is decisive when evaluating the clinical significance of new treatment approaches like HEB. Compulsive exercise represents a key factor in this regard. Insufficient management of compulsive exercise has repeatedly been shown to be associated with a poor long-term outcome of AN patients and therefore was classified as one of the key unmet challenges for treatment of AN [7, 9, 10, 71, 72]. Participating in HEB positively contributed to clinically relevant improvements in this factor, which confirms the clinical significance of our intervention. In HEB participants, we observed a reduction in key aspects of compulsive exercise like obligatory, rule-driven exercising or exercising despite injury or illness.

The effect of HEB could eventually be pushed by "booster-sessions" after the end of HEB, which was regularly asked for by study patients, but could not be implemented while our trial was ongoing. Given the high ambivalence about "giving up" compulsive exercise on patients' side and HEB being primarily designed for patients who are "ready to change" their compulsive exercise, it might also prove useful to extend HEB by 1–2 sessions at the beginning to focus on increasing motivation. In these sessions, motivational interviewing adopted to eating dis-

orders [73] might be employed. Our approach, integrating exercise-based therapy into a CBT approach, is strongly supported by a recent Delphi study about compulsive exercise conducted by Noetel et al. [35]. An international group of experts in the treatment of eating disorders recommended to gradually reintroduce healthy exercise under supervision rather than to completely prohibit exercise. Additionally, psychoeducation about exercise, learning emotion regulation strategies, identifying risk situations, and conducting behavioral analyses for compulsive exercise – all of which are core elements of HEB – have been accepted as important treatment strategies. Integrating exposure with response management did not reach consensus level. However, integrating this element into our new group therapeutic approach was strongly supported by patients of our pilot study [40] and was suggested in early studies on treatment of compulsive exercise as well [74].

In contrast to the LEAP approach [38], our new intervention integrates elements of exercise-based therapy in a CBT approach. Exercise-based interventions may induce faster behavioral changes than CBT alone through their experiential and emotion-activating nature [75, 76]. By establishing alternative behavior in difficult situations and integrating playful movement experiences in the sessions, healthy exercise behavior is practiced directly. In our pilot study, 85% of the patients were satisfied or very satisfied with the integrated exercise-based elements [36]. We postulate that exercise-based elements as specific, integrative aspect of our new treatment approach contribute strikingly to the positive outcome in the TAU + HEB group.

Identifying disorder-related features that can serve as targets for special treatment was recently listed as one of the top 10 research priorities for eating disorders by van Furth et al. [77]. Compulsive exercise might represent one of these features to target, as our results underline that significant improvement can be achieved in inpatient treatment for AN by providing targeted treatment for this symptom. However, as our approach primarily focuses on psychological maintaining factors of compulsive exercise, new treatment options for severely underweight AN patients, in whom a primarily neurobiological base for compulsive exercise due to hypoleptinemia is assumed, should urgently be investigated [3, 16, 18, 19, 78]. These patients would most probably only marginally benefit from psychotherapeutic interventions, but would rather need an appropriate pharmacological treatment (and weight gain). The recent approval of metreleptin might offer the possibility to treat severely ill patients with AN and extreme hyperactivity off-label [79].

Our study has considerable strengths. First, we used an RCT design and included a large and representative sample of inpatients with AN or atypical AN with sufficient power to test the hypotheses of interest. Second, we achieved high participant retention and treatment completion rates. Third, we used a manualized treatment as well as standardized interviews and outcome measures.

Our study has the following limitations: First, we conducted the study in a specialized inpatient setting in Germany, which inhibits the generalization of the findings to less-severely ill outpatients and patients in treatment settings of other countries. However, HEB can easily be administered in an outpatient setting as well, so a similar trial in an outpatient setting is highly recommended. As nonspecific treatment components that are affecting treatment outcome have been given increasing attention [80], an outpatient study of HEB should compare participation in HEB with participation in an "attention placebo" group [42] that receives psychological support and relaxation training from a professional within a comparable time frame. Applying the concept of "clinical management," this attention placebo group should offer psychological support, provide opportunities for disclosure and identify current difficulties of the patients without applying any specific CBT interventions of HEB. Additionally, relaxation techniques like autogenic training, breathing exercises or progressive muscle relaxation should be taught. In our clinical experience, these "passive relaxation" techniques will hardly work for AN patients with compulsive exercise as sitting still usually leads to heightened tension and anxiety instead of relaxation. As HEB only lasts over 4 weeks (HEB comprises 8 sessions and should be facilitated twice per week), it is applicable in other countries where inpatient and/or residential stays are much shorter as well. As treatment setting is known to be an important variable affecting effectiveness of an intervention [80], studies in other countries and treatment settings are urgently needed to further evaluate the efficacy of our intervention. Second, inherent in psychotherapy studies, therapists delivering HEB were not blinded. This lack of blindness may have biased the results towards showing a treatment effect even in the absence of a true effect due to nonspecific expectation ("placebo") effects. Third, to increase homogeneity of our study sample, we applied strict inclusion and exclusion criteria and only included AN or atypical AN patients. It therefore remains unclear whether our new treatment approach also works for patients with BN. As compulsive exercise also represents a common symptom in BN patients [15, 81, 82], efficient treatment approach-

es targeting these symptoms are urgently needed as well. Fourth, as primary outcome, we chose the CES as self-rating scale. Additional clinical interviews would have further strengthened the interpretability. Fifth, we carried out the intervention at a single site, and the intervention was mainly led by the investigators who developed the intervention, so a certain allegiance effect should be taken into consideration. Sixth, loss to follow-up rates of 20.5% in the TAU + HEB group and 23.2% in the TAU group at follow-up limit generalizability of our results concerning long-term effectiveness of our intervention. Last, despite the nested design it proved to be statistically unfeasible to nest by ward, so this factor remains unexamined. Given these limitations, the results of our clinical trial must be interpreted with caution.

In conclusion, findings from this dismantling trial yield important scientific and clinical implications for improving treatment outcome for AN. Our study demonstrates the efficacy of a new treatment approach for inpatients with AN suffering from compulsive exercise, which has been considered one of the big unmet challenges in the treatment of AN so far. Patients participating in HEB showed a stronger reduction in compulsive exercise during inpatient treatment. Our results must be considered preliminary and may not apply to AN patients in other countries and treatment settings. Future studies may want to further examine the efficacy of our intervention in other countries and treatment settings and validate the effects against different control conditions.

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Statement of Ethics

Participants received detailed information on the study and gave written informed consent to participate. For minors, an additional briefing of their legal guardians was provided via telephone. Following that, informed consent forms were sent out to the legal guardians and had to be signed and returned. The study protocol was approved by the Ethics Committee of the Ludwig Maximilian University Munich (project number: 060-13).

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Author Contributions

Study design was by developed by N.D., U.V., U.C., C.J., and S.S. C.M. and N.D were responsible for patient recruitment and data collection. Data analysis was completed by N.D., U.V., C.J., and S.S. N.D. wrote the manuscript draft. U.V., C.M., U.C., C.J., and S.S. revised the manuscript draft. All authors read and approved the final manuscript.

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