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Research paper

Antidepressants or running therapy: Comparing effects on mental and physical health in patients with depression and anxiety disorders

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ABSTRACT

Background: Antidepressant medication and running therapy are both effective treatments for patients with depressive and anxiety disorders. However, they may work through different pathophysiological mechanisms and could differ in their impact on physical health. This study examined effects of antidepressants versus running therapy on both mental and physical health.

Methods: According to a partially randomized patient preference design, 141 patients with depression and/or anxiety disorder were randomized or offered preferred 16-week treatment: antidepressant medication (escitalopram or sertraline) or group-based running therapy ≥2 per week. Baseline (T0) and post-treatment assessment at week 16 (T16) included mental (diagnosis status and symptom severity) and physical health indicators (metabolic and immune indicators, heart rate (variability), weight, lung function, hand grip strength, fitness).

Results: Of the 141 participants (mean age 38.2 years; 58.2 % female), 45 participants received antidepressant medication and 96 underwent running therapy. Intention-to-treat analyses showed that remission rates at T16 were comparable (antidepressants: 44.8 %; running: 43.3 %; p = .881). However, the groups differed significantly on various changes in physical health: weight (d = 0.57; p = .001), waist circumference (d = 0.44; p = .011), systolic (d = 0.45; p = .011) and diastolic (d = 0.53; p = .002) blood pressure, heart rate (d = 0.36; p = .033) and heart rate variability (d = 0.48; p = .006).

Limitations: A minority of the participants was willing to be randomized; the running therapy was larger due to greater preference for this intervention.

Conclusions: While the interventions had comparable effects on mental health, running therapy outperformed antidepressants on physical health, due to both larger improvements in the running therapy group as well as larger deterioration in the antidepressant group.

Trial registration: Trialregister.nl Number of identification: NTR3460.

1. Introduction

Depressive and anxiety disorders cause immense suffering by compromising both mental and physical health (Cosci et al., 2015; Penninx et al., 2013), and the need for effective treatment strategies continues to be pressing. Antidepressant medication is, next to psychotherapy, considered a standard first-line treatment with moderate effectiveness and sufficient tolerability (Bandelow et al., 2015; Cuijpers et al., 2020). However, antidepressants are not effective for all and often associated with side effects (Hu et al., 2004). An interesting alternative treatment is exercise therapy. Meta-analyses showed that for mild to moderate depression the effect of exercise interventions is comparable to antidepressant medication and psychotherapy (with largest effects for aerobic exercise with at least moderate intensity, supervised by exercise professionals), while for severe depression exercise interventions seems to be a valuable complementary therapy (Knapen et al., 2015; Schuch et al., 2016). For persons with anxiety disorders, exercise interventions also showed similar effectiveness to established treatments, although the

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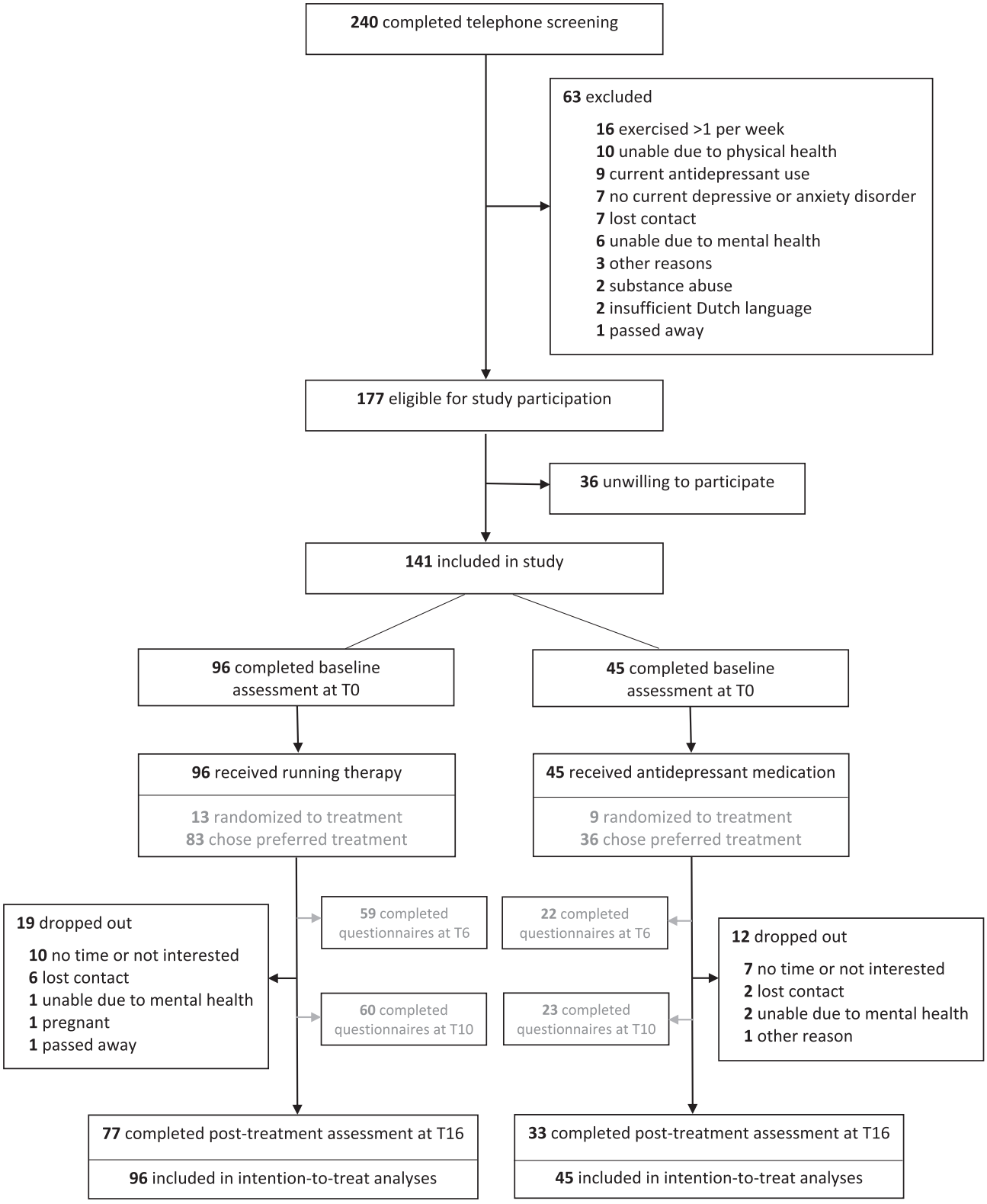

Fig. 1. Study flowchart.

number of studies are fewer and of varying quality (Stonerock et al., 2015; Wegner et al., 2014). While antidepressants and exercise interventions may have a comparable impact on mental health (Blumenthal et al., 2007), their impact on physical health is poorly examined in a psychiatric population.

Antidepressant and exercise therapies differ with respect to their underlying pathophysiological changes and may consequently differ in their impact on physical health. On psychosocial and behavioral levels, antidepressant medication and exercise are contrasting types of interventions. Treatment with antidepressants requires patients to adhere to their prescribed medication intake but this generally does not directly impact on daily behaviors. In contrast, exercise directly addresses the

sedentary lifestyle often found in patients with depressive and anxiety disorders by encouraging persons to go outside, set personal goals, improve their fitness and participate in a group activity (Knapen et al., 2015). On a biological level, antidepressant and exercise interventions have both shown to impact neurobiological and physiological pathways (Wegner et al., 2014). For instance, exercise has been shown to reduce oxidative stress (Nojima et al., 2008), inflammation (Fedewa et al., 2017), cortisol (Karacabey, 2009) and metabolic syndrome dysregulation (You and Nicklas, 2008). In contrast, some studies showed that selective serotonin re-uptake inhibitors (SSRIs) resulted in increased body weight (Serretti and Mandelli, 2010), parasympathetic tone (Licht et al., 2010) and inflammatory levels (Hernandez et al., 2008). A recent study comparing exercise with escitalopram in 128 patients with coronary heart disease (CHD) and anxiety disorder showed that exercise increased maximum oxygen uptake more but found no differences in heart rate variability and endothelial function (Blumenthal et al., 2021). While these studies are suggestive of differential physical health impacts, comparative evidence of the two different interventions in patients with depression and anxiety disorders is lacking.

Understanding the impact of antidepressants and exercise on physical health is clinically relevant for several reasons. Persons with depressive and anxiety disorders have an increased risk of a range of physical illnesses such as cardiovascular disease, diabetes and obesity (Cosci et al., 2015), thus detecting which treatment safeguards physical health might help prevent or reduce such morbidity. Furthermore, it might help uncover mechanisms through which interventions exert their antidepressant or anti-anxiolytic effects, and to identify patient subgroups with certain biological dysregulations that might respond better to antidepressants or exercise, which could ultimately benefit personalized treatment. This 16-week intervention study is the first to examine and compare the impact of antidepressant medication and exercise (running therapy) on mental (diagnosis status and symptom severity) and physical health (metabolic and immune indicators, heart rate (variability), weight, lung function, hand grip strength, fitness) variables in a sample of depressed and/or anxiety disorder patients. Based on earlier research we hypothesized that the interventions would not differ on mental health outcomes but might show differential physical health outcomes.

2. Methods

2.1. Study design

The MOod Treatment with Antidepressant or Running (MOTAR) study is a 16-week intervention study with two treatment arms: 1) antidepressant medication and 2) running therapy. Participants were recruited at depression and anxiety outpatient clinics of GGZ inGeest, a specialized mental health care organization in the Netherlands, affiliated to Amsterdam UMC. Inclusion criteria were having a current depressive disorder (major depressive disorder) or anxiety disorder (social phobia, generalized anxiety disorder, panic disorder, agoraphobia) as ascertained by the DSM-IV algorithms with the Composite International Diagnostic Interview (CIDI) (Wittchen, 1994) and being between 18 and 70 years old. Exclusion criteria were: 1) use of antidepressants in last 2 weeks; 2) current use of other psychotropic medication, except for the use of benzodiazepines with stable (not incidental) usage; 3) regular exercising more than once a week; 4) primary severe, clinically diagnosed psychiatric diagnosis other than a depressive or anxiety disorder; 5) evidence of acute suicidal risk; 6) somatic contraindications to running therapy or antidepressants (e.g. serious heart problems) as confirmed by the patient's physician; and 7) being pregnant.

Informed consent approved by the Medical Ethical Committee was signed before starting the baseline assessment. A 4-hour face-to-face assessment at baseline (T0) and 16-week post-treatment (T16) included a blood draw; the collection of demographic information, a diagnostic psychiatric interview, a somatic examination, and a cycle ergometer test. Further, participants were instructed to complete various self-reported clinical questionnaires. Additionally, at week 6 (T6) and week 10 (T10) depression and anxiety symptom severity was assessed by self-reported questionnaires. For each face-to-face assessment, patients received a gift voucher of €50. A complete overview of the data collection can be found in Van Milligen et al. (2019).

2.2. Treatment allocation

This study was designed as a pragmatic study, resembling a partially randomized preference patients design (Lambert and Wood, 2000). Those without strong preference for treatment allocation were randomly allocated (1:1) to either antidepressant medication or running therapy with the SPSS random generator (SPSS, version 20.0). Persons who were not willing to be randomized but willing to participate in the study, were allocated to their preferred intervention. Additional psychotherapy according to care-as-usual was allowed in both treatment conditions. This was defined as having received 5 or more sessions psychotherapy (including CBT, EMDR, IPT, CBASP or counseling) between the T0 and T16. After 16 weeks, further treatment was conducted following clinical guidelines by the responsible clinician.

2.3. Interventions

2.3.1. Antidepressant medication

Patients received standardized treatment with escitalopram, a SSRI which has documented efficacy and a rather favorable side effect profile. Escitalopram is recommended as a first-step treatment in depression and anxiety disorder treatment guidelines (Trimbos) and is a commonly prescribed antidepressant (Kennedy et al., 2009). An initial dosage of 10 mg per day was used. Medication management was provided by a psychiatrist who met each patient at study onset and at weeks 2, 6, 10 and 16. At these meetings, the psychiatrist evaluated treatment response, side effects and possibly increased the dosage (to a maximum of 20 mg) according to the Dutch evidence-based treatment guidelines in depressive and anxiety disorder, until a clinically effective dosage was achieved (Trimbos). Following the medication protocol, if escitalopram was ineffective or poorly tolerated, a second SSRI was prescribed: sertraline, with dosage of 50 mg to a maximum of 150 mg. Adherence to treatment was evaluated by a patient's diary and administration log by the psychiatrist. Being antidepressant adherent was defined as still using medication at the post-treatment assessment.

2.3.2. Running therapy

Running therapy consisted of supervised 45-min outdoor running sessions during 16 weeks. The target was to get persons to participate in these exercise sessions two to three times a week, because this is in line with the public health recommendations by CDC/American College of Sports Medicine (Department of Health and Human Services, 2018) and its established successful effects on depression and anxiety (Carek et al., 2011; Dunn et al., 2005). Patients were gradually assigned individual training ranges equivalent to 70–85 % of their heart rate reserve, calculated from the heart rate achieved during a baseline cycle ergometer test with the formula of Karvonen et al. (1957). This intensity level was confirmed to be effective in decreasing depressive symptoms (Rethorst et al., 2009). At the beginning of the running intervention, the running therapist discussed experience of exercise in the past, and provided information about food, moisture balance, fatigue, injuries, sleep and recovery. Running sessions were carried out and supervised by qualified staff, starting with a 10-minute warming-up exercise period, followed by 30 min of jogging at an intensity that maintained heart rate within the assigned training range (starting in the first 4 weeks at 50–70 % of heart rate reserve and in the subsequent 12 weeks at 70–85 % of heart rate reserve), and finishing with 5 min of cooling-down exercises. During the running sessions, all participants wore a heart rate monitor.

Heart rate was confirmed three times per session to ensure that patients were exercising within the prescribed exercise training ranges. Data of the heart rate monitor was uploaded after sessions and used to encourage study compliance. Patients were stimulated to participate in at least two of the organized exercise group sessions per week, but if not possible, home-based individual exercise was partly allowed. The trainer monitored training attendance, which was supplemented by the heart rate monitor data. Following evidence-based recommendations (Rethorst and Trivedi, 2013), being running therapy adherent was defined as exercising at least 70 % of the target of two times per week for 16 weeks (=0.70 * (2 * 16) = 22.4), so those with >22 sessions of running therapy within 16 weeks were considered compliant. Studies with lower compliance rates (of 1 time per week or lower) were often not able to show an antidepressant effect of exercise in MDD patients (e.g., Krogh et al., 2009).

2.4. Outcomes

2.4.1. Descriptive variables

Age, sex, obtained years of education, partner status, cigarette smoking, regular alcohol intake (assessed with the AUDIT questionnaire (Saunders et al., 1993)) and age at onset of psychiatric diagnosis were assessed at baseline.

2.4.2. Mental health outcomes

The presence of depressive disorders (major depressive disorder) and/or anxiety disorders (social phobia, generalized anxiety disorder, panic disorder and agoraphobia) was established at T0 and at T16 using the CIDI, which is a valid and reliable instrument to assess depressive and anxiety disorders (Wittchen, 1994) and was administered by specially trained research staff. Severity of depression was measured using the 30-item Inventory of Depressive Symptomatology – Self Report (IDS-SR) (Rush et al., 1996) and severity of anxiety was measured with

Table 1
Pre-treatment sample characteristics by treatment group (total n = 141).

	N	Running therapy	Antidepressant use	p-value
Sociodemographics				
Age in years, mean (sd)	141	38.8 (11.5)	36.8 (11.8)	.351
Sex, no. (% female)	141	58 (60)	24 (53)	.427
Years of education, mean (sd)	138	11.5 (3.1)	11.5 (3.5)	.877
Partner status, no. (% married or partner)	141	65 (68)	25 (56)	.162
Lifestyle characteristics				
Smoking status, no. (%)	126			.729
Never smoked		42 (48)	16 (41)	
Former smoker		19 (22)	9 (23)	
Current smoker		26 (30)	14 (36)	
Alcohol (AUDIT sum score), mean (sd)	131	2.2 (3.4)	2.2 (3.4)	.961
Body mass index (kg/m^2), mean (sd)	141	25.6 (5.2)	25.5 (4.8)	.895
Mental health characteristics				
Diagnosis (past month), no. (% yes)	141			
Major depressive disorder		71 (74)	39 (87)	.089
Social phobia		41 (43)	17 (38)	.579
Panic disorder		35 (37)	20 (44)	.365
Agoraphobia		30 (31)	15 (33)	.805
Generalized anxiety disorder		30 (31)	11 (24)	.407
Number of diagnoses, mean (sd)	141	2.2 (1.1)	2.3 (1)	.585
Age at onset (years), mean (sd)	141	21.8 (13.0)	23.2 (14.2)	.566
Depressive severity symptoms (IDS-SR), mean (sd)	135	40.5 (13.5)	46.0 (13.2)	.028
Anxiety severity symptoms (BAI), mean (sd)	135	24.2 (13.0)	26.1 (13.4)	.437
Psychotherapy during study, No. (% yes)	123	40 (48)	22 (55)	.479
Physical health characteristics				
Lung function (l/min), mean (sd)	141	4.2 (1.2)	3.9 (1.4)	.174
Hand grip strength (kg), mean (sd)	141	36.0 (12.3)	39.8 (12.6)	.094
VO_{2max} (ml/kg/min), mean (sd)	136	32.8 (9.9)	34.3 (9.9)	.412
Diastolic blood pressure (mm Hg), mean (sd)	141	76.6 (9.0)	75.5 (9.0)	.509
Metabolic syndrome				
Waist (cm), mean (sd)	141	88.0 (15.6)	88.9 (13.7)	.734
Glucose (mmol/l), mean (sd)	130	5.5 (0.7)	5.4 (0.5)	.439
Triglycerides (mmol/l), mean (sd)	132	1.2 (0.8)	1.2 (0.7)	.706
HDL-cholesterol (mmol/l), mean (sd)	138	1.5 (0.4)	1.3 (0.4)	.728
Systolic blood pressure (mm Hg), mean (sd)	141	128.1 (13.4)	127.8 (16.8)	.890
Cardiac autonomic activity				
Heart rate (beats/min), mean (sd)	129	75.7 (9.3)	75.9 (10.9)	.896
Heart rate variability (ms), mean (sd)	128	69.0 (29.1)	78.4 (33.1)	.106
Pre-ejection period (ms), mean (sd)	129	106.8 (19.7)	110.4 (19.1)	.327
Inflammation				
Interferon-gamma (pg/ml), mean (sd)	137	12.3 (12.1)	11.5 (10.4)	.704
Interleukin-6 (pg/ml), mean (sd)	137	0.68 (0.42)	0.71 (0.46)	.744
Tumor necrosis factor-alpha (pg/ml), mean (sd)	137	1.44 (0.40)	1.47 (0.38)	.701
C-reactive protein (mg/l), mean (sd)	137	2.62 (3.51)	2.51 (3.01)	.857

Note. Means, standard deviations and p-values are raw results derived from unimputed data.
Abbreviations. BAI=Beck Anxiety Inventory; HDL = high-density lipoprotein; IDS-SR = Inventory of Depressive Symptoms-Self Report; VO_{2max} = maximal oxygen uptake; sd = standard deviation.

the 21-item Beck Anxiety Inventory (BAI) (Beck et al., 1988) at T0, T6, T10 and T16. Two primary mental health outcomes were 1) remission, which was defined as no longer meeting the criteria of a current (1-month recency) depressive disorder or an anxiety disorder at T16 as assessed with the CIDI; and 2) response, which was defined as symptom severity reduction of at least 50 % and was calculated separately for the IDS-SR and the BAI.

2.4.3. Physical health outcomes

All physical health outcomes were assessed at T0 and T16. Fasting blood was drawn from participants in the morning between 08:30 and 09:30 h. HDL-cholesterol, triglycerides, and glucose levels were determined using routine standardized laboratorial methods. Serum levels of Interferon-gamma (IFN-γ), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α) were measured using a multiplex sandwich immunoassay (V-PLEX Human Proinflammatory Panel I, Meso Scale Diagnostics, Rockville, MD, USA) with a lower detection limit of 0.21–0.62 pg/ml for IFN-γ, 0.05–0.09 pg/ml for IL-6, and 0.01–0.13 pg/ml for TNFα. Serum levels of C-Reactive Protein (CRP) were measured in duplicate by an in-house high-sensitivity enzyme linked immunosorbent assay (ELISA, CRPHS, Roche Diagnostics, Indianapolis, IN, USA) based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark) with a lower detection limit of 0.15 mg/l and a functional sensitivity of 0.3 mg/l.

Activity of the autonomic nervous system was measured using the VU-ambulatory monitoring system (VU-AMS) of which reliability and recording methodology have been described previously (de Geus et al., 1995). Also, blood pressure (mm Hg), waist circumference (cm), weight (kg) and height (cm) were assessed. Furthermore, hand grip strength (kg) was measured with the Jamar hand grip meter (Roberts et al., 2011) and lung function (peak expiratory flow (PEF), in l/min) using the Mini Wright peak flow meter (Quanjer et al., 1997). Physical fitness was determined as maximal oxygen uptake (VO_{2max} in ml/kg/min), estimated from the heart rate response using a 6-minute bicycle ergometer test with the Åstrand method (Vancampfort et al., 2014) on a Lode Corival indoor bike. Persons were wearing a Polar heart rate monitor, which first measured their resting heart rate on the bike, and at each consecutive minute their heart rate during activity. For each participant, the W1 (i.e., 33 % of estimated maximum resistance W_{max}) was calculated using different formulas for men ($W1 = height^2 \times 6.13 \times (4.66 - 0.02 \times age)$) and women ($W1 = height^2 \times 5.25 \times (4.35 - 0.02 \times age)$). Participants cycled 3 min at W1 at 60-70 rpm, and subsequently 6 min at W2 (i.e., 66 % of W_{max}). VO_{2max} scores for men and women were obtained from W2 and the final heart rate.

2.5. Statistical analyses

Baseline characteristics were presented per treatment condition and equality between groups was tested either using ANOVA or a Chi-square test. If differences existed, baseline characteristics were added as covariates in the main analyses comparing changes in both treatment groups. Effect modification of inclusion type (randomized versus preferential choice) was tested by adding the interaction term (inclusion type-by-treatment group) to the main analyses. If the interaction term was not statistically significant, analyses were further conducted with both types of inclusion combined within treatment group.

According to the intention-to-treat principle, participants were analyzed according to their treatment allocation group, regardless of whether they actually received the treatment or completed the study. Missing data were accounted for by using multiple imputation with 100 data sets, and results were pooled using the Rubin rules (Rubin, 2004). Imputation was carried out separately by treatment condition (Sullivan et al., 2018) and first transformed-then-imputed (Seaman et al., 2012). Subsequently, 16-week change scores (T16-T0) of all mental and physical health outcome variables were compared between treatment conditions with ANCOVA analyses that controlled for baseline values of the variables. Within-group differences were calculated with paired *t*-tests. For depressive and anxiety severity outcomes specifically, generalized

Table 2
Observed changes for all outcome measures in the intention-to-treatment sample stratified by treatment group (n = 141).

	Running therapy (n = 96)	Antidepressant use (n = 45)	Cohen's d	p-Value
Mental health outcomes				
Remission (% no diagnosis at T16)	43.3 (5.8)	44.8 (8.3)	0.02	.881
Response (50 % reduction on IDS-SR)	30.3 (5.1)	34.2 (8.9)	0.07	.730
Response (50 % reduction on BAI)	32.4 (6.4)	47.2 (9.8)	0.26	.196
Physical health outcomes (change score T16-T0)				
Lung function change	30.6 (10.7)	16.0 (12.7)	0.15	.378
Hand grip strength change	0.5 (1.0)	1.8 (1.2)	0.14	.399
VO_{2max} change	2.1 (1.1)	−0.3 (1.2)	0.25	.149
Weight change	−0.6 (0.7)	3.3 (1.0)	0.57	.001
Diastolic blood pressure change	−2.9 (1.0)	1.9 (1.2)	0.53	.002
Metabolic syndrome				
Waist change	−1.6 (0.8)	1.5 (0.9)	0.44	.011
Glucose change	0.05 (0.09)	0.10 (0.12)	0.06	.722
Triglycerides change	0.05 (0.10)	0.23 (0.12)	0.20	.231
HDL-cholesterol change	0.03 (0.06)	0.01 (0.07)	0.04	.763
Systolic blood pressure change	−2.5 (1.6)	3.8 (1.8)	0.45	.011
Cardiac autonomic activity				
Heart rate change	−3.4 (1.1)	−0.1 (1.1)	0.36	.033
Heart rate variability change[a]	1.2 (3.8)	−14.4 (3.9)	0.48	.006
Pre-ejection period change	−2.8 (3.0)	−2.4 (2.9)	0.02	.924
Inflammation				
Interferon-gamma change	1.85 (1.73)	−0.05 (1.86)	0.13	.463
Interleukin-6 change	0.10 (0.07)	0.11 (0.09)	0.02	.942
Tumor necrosis factor-alpha change	0.06 (0.06)	0.07 (0.08)	0.02	.940
C-reactive protein change	0.62 (0.45)	1.53 (0.48)	0.24	.167

Note. Results shown are pooled estimated marginal means and standard errors derived from multiple imputed data in univariate analyses. Models were adjusted for baseline levels of the variable and baseline IDS-SR score.
Abbreviations. BAI=Beck Anxiety Inventory; HDL = high-density lipoprotein; IDS-SR = Inventory of Depressive Symptoms-Self Report; VO_{2max} = maximal oxygen uptake.
[a] Heart rate variability was additionally corrected for respiration rate.

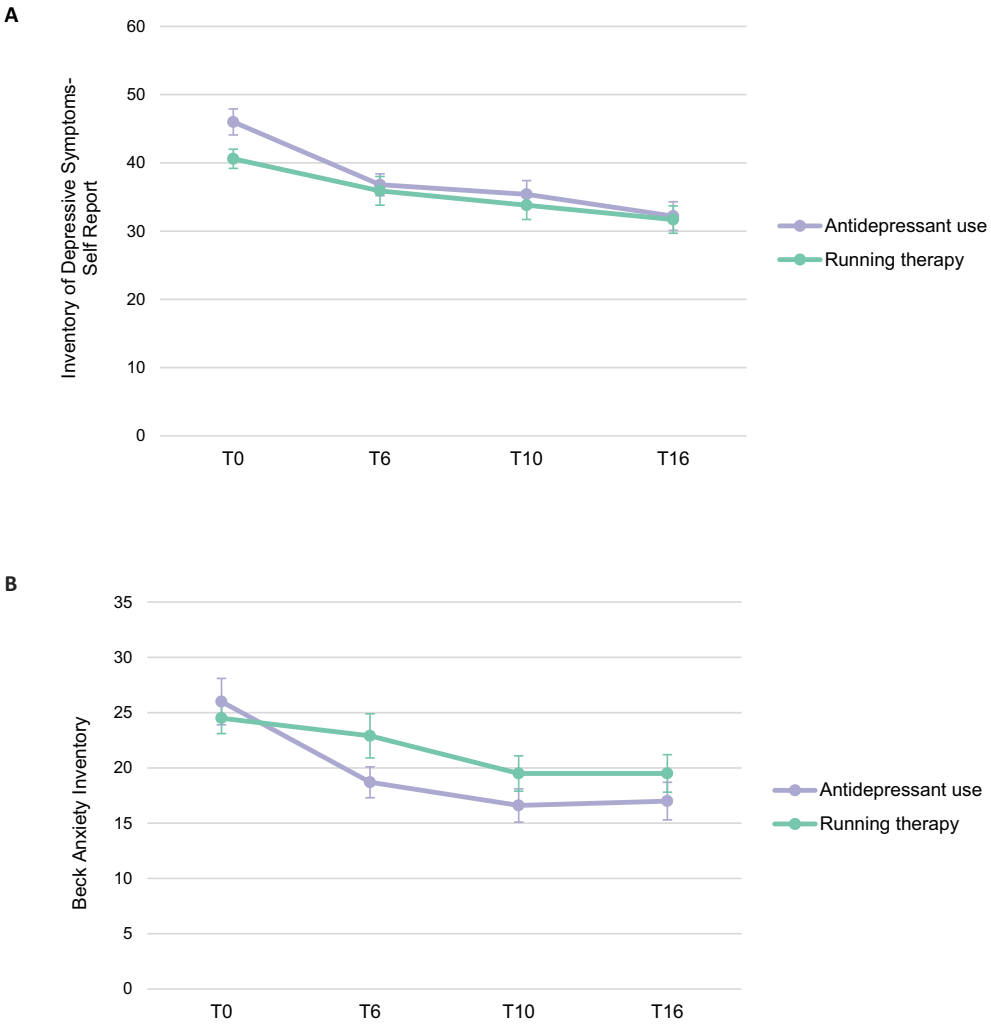

Fig. 2. Trajectories for the (A) depression (IDS-SR) and (B) anxiety (BAI) symptom severity over 16 weeks for the antidepressant use (n = 45) and running therapy (n = 96) groups.

estimating equations (GEE) longitudinal analyses of covariance (ANCOVA) with an exchangeable correlation structure were used to model scores at T0, T6, T10 and T16 both treatment conditions. Last, in per-protocol analyses ANCOVA analyses were repeated for participants that adhered to the treatment protocols.

3. Results

Between July 2012 and July 2019, 240 patients were approached by means of a telephone screening, of which 141 were willing to participate and eligible for the trial, see study flowchart in Fig. 1. Out of 141 participants, 22 were willing to be randomized into the antidepressant (n = 9) or the running therapy (n = 13) groups, while 119 participants chose the treatment of their preference: antidepressant (n = 36) or running therapy (n = 83).

Table 1 shows pre-treatment characteristics per treatment intervention group, where inclusion type (randomized versus preferential choice) was combined. Baseline characteristics were comparable between the groups except for the depression severity (IDS-SR) score which was higher for the antidepressant group (mean = 46.0; s.d. = 13.2) compared to the running therapy group (mean = 40.5; s.d. = 13.5; p = .028). Therefore, in all subsequent between-group analyses, baseline IDS-SR was included as a covariate. Approximately half of the participants received psychotherapy according to care-as-usual between T0 and T16. This did not differ between the intervention groups as shown in Table 1.

Of the 141 patients, 110 (78.0 %) completed the T16 assessment. The 31 participants who dropped-out were younger, more often current smokers, had a higher number of diagnoses and higher symptom severity. Drop-out rates did not significantly differ across the treatment groups (antidepressant use: n = 12, 26.7 %; running therapy: n = 19, 19.8 %; p = .24).

3.1. Treatment adherence

In the antidepressant group, 82.2 % (N = 37) of all participants adhered to the medication treatment protocol. In the running therapy group, 52.1 % (N = 50) of participants completed >22 sessions of exercise therapy. On average, participants attended 23.7 (SD = 19.0) exercise therapy sessions. It should be noted that 14 participants (15 %) did not start with the running therapy intervention at all and 16 participants (17 %) participated in <9 sessions. The treatment adherence was significantly higher in the antidepressant group compared to the running therapy group (p < .001). Average treatment adherence did not differ between those that were randomized (59.1 %) or chose the treatment of their preference (62.2 %; p = .79).

3.2. Intention-to-treat analyses

We first checked on the potential impact of inclusion type

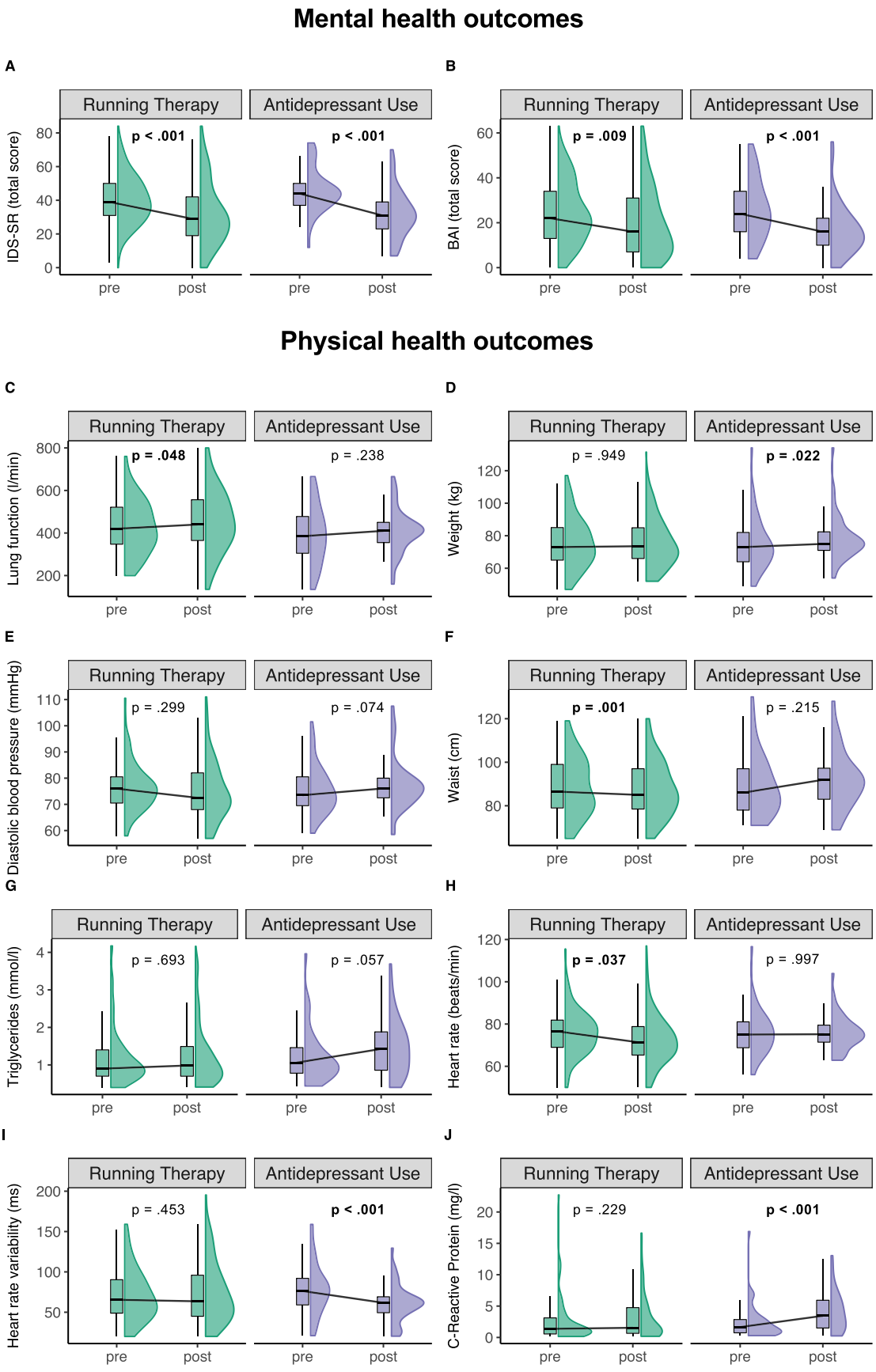

Fig. 3. Plots showing the within-group pre-post intervention changes by treatment group (n = 141).

(randomization versus preference) by adding an "inclusion type-by-treatment" interaction term to all main ANCOVA analyses. However, none of the interaction effects were statistically significant, showing that inclusion type did not impact the results. Consequently, we subsequently combined groups within treatment arm, resulting in a total of 45 participants in the antidepressant group and 96 participants in the running therapy group.

3.2.1. Mental health outcomes

Remission rates did not significantly differ between the two groups and were 43.3 % for the running therapy group and 44.8 % in the antidepressant group (Cohen's d = 0.02; p = .88), as shown in Table 2. Furthermore, response rates on the IDS-SR were 30.3 % for the running group and 34.2 % for the antidepressants group (Cohen's d = 0.07; p = .73); and on the BAI were 32.4 % and 47.2 % for running and antidepressants groups, respectively (Cohen's d = 0.26; p = .20). Fig. 2 shows the longitudinal GEE analyses of the IDS-SR and BAI trajectories over T0, T6, T10 and T16. Estimated means depicted in Fig. 2A show no statistically significant group-by-time interaction effect ($F_{(3,4288)=}1.16$, p = .33), illustrating that the decline in IDS-SR score did not statistically differ between treatment groups. Similarly, there was no significant overall group-by-time interaction effect for the BAI trajectory ($F_{(3,3561)}$ = 1.66; p = .17) over 16 weeks, as shown in Fig. 2B. When considering the specific time points separately, however, there was a significant group-by time interaction at week 6 (B = 5.7; p = .039), showing that the drop in BAI score was 5.7 points larger in the antidepressant group (mean = −7.3) compared to the running group (mean = −1.6), indicating a slightly faster improvement but no overall difference over the entire treatment period.

Within-group analyses showed significant pre-post intervention decreases on the IDS-SR and BAI in both groups, see Fig. 3A and B. It must be noted that despite reaching remission, remitted participants still had considerable depressive and anxiety symptomatology.

3.2.2. Physical health outcomes

Participants in the two treatment groups showed significantly different changes in several physical health outcomes, namely weight (Cohen's d = 0.57; p = .001), waist circumference (Cohen's d = 0.44; p = .011), systolic (Cohen's d = 0.45; p = .011) and diastolic (Cohen's d = 0.53; p = .002) blood pressure, heart rate (Cohen's d = 0.36; p = .033) and heart rate variability (Cohen's d = 0.48; p = .006), see Table 2. Generally, physical health changes were more favorable in the running therapy group, both due to larger improvements in the running therapy group but also due to larger deterioration in the antidepressant group (i.e., opposite effects). Within-group pre-post intervention analyses in the running therapy group showed a significant decrease in heart rate (mean = −3.2; p = .037), waist circumference (mean = −1.0; p = .001) and an increase in lung function (mean = +29.4; p = .048). Further, the antidepressant group showed a significant within-group decrease in heart rate variability (mean = −17.0; p < .001), an increase in weight (mean = +3.2; p = .022) and CRP (mean = +1.59; p < .001), and borderline significant increases in diastolic blood pressure (mean = +2.1; p = .074) and triglycerides (mean = +0.24; p = .057), see Fig. 3C–3J. See Online Supplementary Fig. S1 for an overview of all within-group changes.

3.3. Per-protocol analyses

Per-protocol analyses for 50 patients in the running therapy group and 37 in the antidepressant group that were treatment compliant were presented in online Supplementary Table S1. Here, again, no group differences were found on remission or response outcomes. Further, Supplementary Table 1 showed that in those that adhered to treatment protocol, the treatment groups differed in changes in weight, waist, systolic and diastolic blood pressure, triglycerides, heart rate, heart rate variability and CRP. Within-group analyses in the running therapy group showed a significant increase in lung function (mean = +30.6; p = .002) and VO_{2max} (mean = +2.9; p = .012) and significant decreases in waist circumference (mean = −1.6; p = .015), diastolic blood pressure (mean = −2.9; p = .011) and heart rate (mean = −4.3; p < .001). Within-group analyses in the antidepressant group showed a significant increase in weight (mean = +3.0; p = .024), CRP (mean = +1.5; p < .001) and grip strength (mean = +2.2; p = .042) and a decrease in heart rate variability (mean = −16.4; p < .001). Again, physical health changes were more favorable in the running therapy group.

4. Discussion

This 16-week intervention study compared the impact of antidepressant medication and running therapy on mental and physical health in a sample of depressed and/or anxiety disorder patients in a partially randomized patient preference design. Several important conclusions can be drawn. First, both interventions did not differ significantly on mental health outcomes. After 16 weeks, 45 % of patients in the antidepressant group vs. 43 % in the running group no longer had a DSM-IV based depression or anxiety disorder. Also, 50 % response rates did not differ between the treatment groups. Second, intention-to-treat analyses showed that the groups significantly differed on changes in physical health, namely in weight, waist circumference, systolic and diastolic blood pressure, heart rate and heart rate variability, with medium effect sizes (Cohen's d = 0.36–0.57), with more favorable outcomes for the running therapy group. These group differences were even more pronounced in per-protocol analyses, where also change scores of triglycerides and CRP differed between the groups, showing medium to large effect sizes (Cohen's d = 0.28–0.89). Third, type of inclusion did not impact the results, showing that treatments effects were similar if participants were randomized or when they chose the treatment of their preference. Fourth, treatment adherence differed substantially between the two interventions, with 82 % for those that used antidepressants and 52 % for those in the running therapy group, which may have important implications for implementation.

Our findings regarding mental health are in line with earlier studies (Blumenthal et al., 2007, 1999; J.A. Blumenthal et al., 2021; James A. Blumenthal et al., 2021) concluding that antidepressant medication and exercise have similar remission percentages (40–45 %) and effects on self-reported depression and anxiety levels (Blumenthal et al., 2007). Interestingly, our study did show a larger decrease in anxiety symptoms after six weeks in the antidepressant group, which suggests faster improvement on especially anxiety-related symptoms. Similarly, an earlier study in CHD and anxiety disorder patients showed a larger decrease in anxiety for escitalopram compared to exercise (Blumenthal et al., 2021). Another important clinical finding was the difference in treatment adherence to the interventions, and particularly the compliance in the running therapy group of 52 % (despite the high patient preference for this intervention). It should be noted that in this trial 14 participants (15 %) did not start with the running therapy intervention at all, showing that it is important (but also challenging) to stimulate adherence from the start. In a meta-analysis reviewing 39 studies with a total of 2326 participants an important observation was that attendance rates for exercise treatments varied greatly (Cooney et al., 2013). It is conceivable that higher levels of compliance may lead to stronger effect sizes, highlighting the importance to build motivation, sustainability, and adherence to exercise therapy, possibly aided by web-based support intervention (Haller et al., 2018). Strategies for improving implementation are well summarized by Knapen et al. (2015).

Physical health consequences of psychiatric treatment are much less studied. This study showed worsening of several physical health variables after antidepressant use, partly in line with commonly reported side effects of SSRIs. First, weight gain is often reported as a side effect (Serretti and Mandelli, 2010) and here too we showed that persons on antidepressants gained on average 3 kg during 16 weeks. We further showed a significant difference in waist circumference change, with an

increase of 1.5 cm. In addition, our results are greatly in line with the bulk of evidence that antidepressant use decreases heart rate variability (Kemp et al., 2010; Noordam et al., 2016; O'Regan et al., 2015). For instance, the Netherlands Study of Depression and Anxiety (NESDA) showed antidepressant use to be robustly associated with cardiac autonomic dysregulation across nine-year longitudinal data (Hu et al., 2019, 2017; Licht et al., 2010). Also, and to be expected when autonomic tone changes, we showed parallel increased blood pressure levels in antidepressant users, again in line with earlier research (Licht et al., 2009; Niazi et al., 2021). Within-group analyses also showed an increase in CRP after antidepressant treatment, and no statistical differences in levels of IFN-γ, IL-6 or TNF-α. These are contrasting to earlier studies that suggested a reduction in anti-inflammatory cytokine profile after treatment with SSRIs in depressed individuals (Hernandez et al., 2008), although such findings are inconsistent across studies and potentially depending on type of medication (Więdłocha et al., 2018).

This study showed various beneficial changes in physical health after a 16-week exercise intervention. Within-group analyses in the intention-to-treat sample showed a significant mean decrease in heart rate of 3.4 bpm and a mean increase in lung function of 30.6 l/min. Per-protocol analyses showed that those that sufficiently adhered to the treatment protocol additionally increased their maximal oxygen uptake (VO_{2max}) and showed decreases in waist circumference and blood pressure. These results suggest that part of the beneficial effects of regular exercise in persons with depression and anxiety disorders might be related to impact on the autonomic nervous system and lung capacity (Fu and Levine, 2013). The degree to which each of these variables can improve, in turn, determines a person's maximal oxygen uptake. Further, the decrease in waist circumference, in the absence of a significant within-group weight change, is indicative of a decrease in abdominal fat. The changes in waist circumference and blood pressure are indicative of a lower incidence of metabolic syndrome after exercise and replicate an earlier study in 42 in-patients with moderate to severe depression (Kerling et al., 2015). This study did not show any changes in inflammatory markers after exercise, which is in line earlier research in healthy adults (Sloan et al., 2018). Within the depressed population, however, exercise might have particularly anti-inflammatory effects in patients with high baseline inflammation levels (Rethorst et al., 2012), which asks for future analyses in specific subgroups.

This study had several strengths and limitations. The major strengths are the relatively large sample size, the wide range of both mental and physical health variables resulting in well-characterized individuals and the representative study sample with different levels of depression and/or anxiety disorder severity. These strengths allowed us to thoroughly examine and compare both mental and physical health effects of antidepressant medication versus running therapy. Further, this study was designed as a partially randomized patients preference design (Lambert and Wood, 2000) which had benefits but also several limitations. Only 15 % of the participants in this study were willing to be randomized, causing this group to be too small for separate analyses. Also, due to greater preference for running therapy, this group was larger (n = 96) than the relatively small antidepressant group (n = 45). However, despite the sample size difference and large preference arm, both treatment groups were comparable and only differed on baseline depression severity, which was controlled for in all main analyses. A notable advantage of the preference arms in our design though, is that it allowed studying participants with a strong preference for treatment to participate, who otherwise might have refused randomization and not entered the trial, thereby optimizing generalization and ecological validity of the results (Torgerson and Sibbald, 1998; Wasmann et al., 2019). An interesting lead for future research is examining patient subgroups with certain biological dysregulations who may respond better to antidepressants or exercise, which was beyond the scope of this paper. First examples of such clinical implications show that exercise interventions might work better for patients with high inflammation levels (Rethorst et al., 2012) and indicate that patients with physical comorbidities and immuno-metabolic dysregulations (Milaneschi et al., 2020), in turn, show lower antidepressant treatment response (Eller et al., 2008; Kim et al., 2011).

In conclusion, we showed that while antidepressant medication and running therapy did not statistically significantly differ on mental health outcomes in a sample of depression and anxiety disorder patients, the interventions had a significantly different and often contrasting impact on several physical health outcomes, with more favorable outcomes for those in the exercise intervention. Taken together, antidepressant users showed a decrease in heart rate variability and increases in waist circumference, blood pressure and triglyceride levels, suggestive of an increasing incidence of metabolic syndrome (Taylor, 2010), and higher cardiovascular risk (Wegner et al., 2014). The running group showed a decrease in both metabolic syndrome components and heart rate which indicated, in turn, protective effects on cardiovascular incidents. Overall, this study showed the importance of exercise in the depressed and anxious population and caution of antidepressant use in physically unhealthy patients. Exercise therapy is therefore a valuable option in mental health care with respect to both mental and physical health and should be considered standard practice for those with depression and/or anxiety disorders.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.02.064.

Statement of ethics

This study is in accordance with the ethical standard of relevant national and international committees on human experimentation and with the declaration of Helsinki. All participants provided written informed consent, and the study protocol was approved by the Medical Ethics Committee of the VU University Medical Centre (NL38203.029.12) and registered with the Netherlands Trial Register (NTR3460).

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Credit authorship contribution statement

B.P. is the principal investigator of this trial. B.L-v.M., J.V., D.R. and L.H. coordinated the trial, contributed to the implementation of the trial, and collected the data. B.P., N.B., D.v.S., A.v.B. and P.v.O supervised the implementation of the trial. J.V. and A.H. performed the statistical analyses. J.V. and B.P. interpreted the results and drafted the manuscript. J.V. and L.H. created the figures. All authors reviewed and approved the manuscript.

Conflict of interest

All authors declare no conflict of interest.

Data availability statement

The data that support the findings of this study are available from Dr. Penninx, upon reasonable request.

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References

Bandelow, B., Reitt, M., Röver, C., Michaelis, S., Görlich, Y., Wedekind, D., 2015. Efficacy of treatments for anxiety disorders. Int. Clin. Psychopharmacol. 30, 183–192. https://doi.org/10.1097/YIC.0000000000000078.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. J. Consult. Clin. Psychol. 56, 893–897.

Blumenthal, J.A., Babyak, M.A., Craighead, W.E., Davidson, J., Hinderliter, A., Hoffman, B., Doraiswamy, P.M., Sherwood, A., 2021. The role of comorbid anxiety in exercise and depression trials: secondary analysis of the SMILE-II randomized clinical trial. Depress. Anxiety 38, 124–133. https://doi.org/10.1002/DA.23088.

Blumenthal, J.A., Babyak, M.A., Doraiswamy, P.M., Watkins, L., Hoffman, B.M., Barbour, K.A., Herman, S., Craighead, W.E., Brosse, A.L., Waugh, R., Hinderliter, A., Sherwood, A., 2007. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom. Med. 69, 587–596.

Blumenthal, J.A., Babyak, M.A., Moore, K.A., Craighead, W.E., Herman, S., Khatri, P., Waugh, R., Napolitano, M.A., Forman, L.M., Appelbaum, M., Doraiswamy, P.M., Krishnan, K.R., 1999. Effects of exercise training on older patients with major depression. Arch. Intern. Med. 159, 2349–2356.

Blumenthal, James A., Smith, P.J., Jiang, W., Hinderliter, A., Watkins, L.L., Hoffman, B. M., Kraus, W.E., Liao, L., Davidson, J., Sherwood, A., 2021. Effect of exercise, escitalopram, or placebo on anxiety in patients with coronary heart disease: the understanding the benefits of exercise and escitalopram in anxious patients with coronary heart disease (UNWIND) randomized clinical trial. JAMA Psychiatry 78, 1270–1278. https://doi.org/10.1001/JAMAPSYCHIATRY.2021.2236.

Carek, P.J., Laibstain, S.E., Carek, S.M., 2011. Exercise for the treatment of depression and anxiety. Int. J. Psychiatry Med. 41, 15–28. https://doi.org/10.2190/PM.41.1.c.

Cooney, G., Dwan, K., Greig, C., Lawlor, D., Rimer, J., Waugh, F., McMurdo, M., Mead, G., 2013. Exercise for depression. Cochrane Database Syst. Rev. 34, 1203. https://doi.org/10.1002/14651858.CD004366.PUB6.

Cosci, F., Fava, G.A., Sonino, N., 2015. Mood and anxiety disorders as early manifestations of medical illness: a systematic review. Psychother. Psychosom. 84, 22–29.

Cuijpers, P., Noma, H., Karyotaki, E., Vinkers, C.H., Cipriani, Andrea, Furukawa, T.A., 2020. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry 19, 92–107. https://doi.org/10.1002/wps.20701.

de Geus, E.J., Willemsen, G.H., Klaver, C.H., van Doornen, L.J., 1995. Ambulatory measurement of respiratory sinus arrhythmia and respiration rate. Biol. Psychol. 41, 205–227.

Department of Health and Human Services, 2018. Physical Activity Guidelines for Americans, 2nd edition.

Dunn, A.L., Trivedi, M.H., Kampert, J.B., Clark, C.G., Chambliss, H.O., 2005. Exercise treatment for depression: efficacy and dose response. Am. J. Prev. Med. 28, 1–8.

Eller, T., Vasar, V., Shlik, J., Maron, E., 2008. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. Prog. Neuro-Psychopharmacol.Biol. Psychiatry 32, 445–450.

Fedewa, M.V., Hathaway, E.D., Ward-Ritacco, C.L., 2017. Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. Br. J. Sports Med. https://doi.org/10.1136/bjsports-2016-095999.

Fu, Q., Levine, B., 2013. Exercise and the autonomic nervous system. Handb. Clin. Neurol. 117, 147–160. https://doi.org/10.1016/B978-0-444-53491-0.00013-4.

Haller, N., Lorenz, S., Pfirrmann, D., Koch, C., Lieb, K., Dettweiler, U., Simon, P., Jung, P., 2018. Individualized web-based exercise for the treatment of depression: randomized controlled trial. J. Med. Internet Res. https://doi.org/10.2196/10698.

Hernandez, M.E., Mendieta, D., Martinez-Fong, D., Loria, F., Moreno, J., Estrada, I., Bojalil, R., Pavon, L., 2008. Variations in circulating cytokine levels during 52 week course of treatment with SSRI for major depressive disorder. Eur. Neuropsychopharmacol. 18, 917–924.

Hu, M.X., Lamers, F., Penninx, B.W.J.H., de Geus, E.J.C., 2017. Temporal stability and drivers of change in cardiac autonomic nervous system activity. Auton. Neurosci. 208, 117–125. https://doi.org/10.1016/J.AUTNEU.2017.07.005.

Hu, M.X., Milaneschi, Y., Lamers, F., Nolte, I.M., Snieder, H., Dolan, C.V., Penninx, B.W. J.H., de Geus, E.J.C., 2019. The association of depression and anxiety with cardiac autonomic activity: the role of confounding effects of antidepressants. Depress. Anxiety 36, 1163. https://doi.org/10.1002/DA.22966.

Hu, X., Bull, S., Hunkeler, E., Ming, E., Lee, J., Fireman, B., Markson, L., 2004. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. J. Clin. Psychiatry 65, 959–965. https://doi.org/10.4088/JCP.V65N0712.

Karacabey, K., 2009. The effect of exercise on leptin, insulin, cortisol and lipid profiles in obese children. J. Int. Med. Res. 37, 1472–1478.

Karvonen, M.J., Kentala, E., Mustala, O., 1957. The effects of training on heart rate; a longitudinal study. Ann. Med. Exp. Biol. Fenn. 35, 307–315.

Kemp, A.H., Quintana, D.S., Gray, M.A., Felmingham, K.L., Brown, K., Gatt, J.M., 2010. Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. Biol. Psychiatry 67, 1067–1074.

Kennedy, S.H., Andersen, H.F., Thase, M.E., 2009. Escitalopram in the treatment of major depressive disorder: a meta-analysis. Curr. Med. Res. Opin. 25, 161–175.

Kerling, A., Tegtbur, U., Gützlaff, E., Kück, M., Borchert, L., Ates, Z., Von Bohlen, A., Frieling, H., Hüper, K., Hartung, D., Schweiger, U., Kahl, K.G., 2015. Effects of adjunctive exercise on physiological and psychological parameters in depression: a randomized pilot trial. J. Affect. Disord. 177, 1–6. https://doi.org/10.1016/j.jad.2015.01.006.

Kim, J.M., Stewart, R., Bae, K.Y., Yang, S.J., Yoon, J.S., Jung, S.W., Lee, M.S., Yim, H.W., Jun, T.Y., 2011. Physical comorbidity and 12-week treatment outcomes in Korean patients with depressive disorders: the CRESCEND study. J. Psychosom. Res. 71, 311–318. https://doi.org/10.1016/j.jpsychores.2011.05.001.

Knapen, J., Vancampfort, D., Moriën, Y., Marchal, Y., 2015. Exercise therapy improves both mental and physical health in patients with major depression. Disabil. Rehabil. https://doi.org/10.3109/09638288.2014.972579.

Krogh, J., Saltin, B., Gluud, C., Nordentoft, M., 2009. The DEMO trial: a randomized, parallel-group, observer-blinded clinical trial of strength versus aerobic versus relaxation training for patients with mild to moderate depression. J. Clin. Psychiatry 70, 790–800.

Lambert, M.F., Wood, J., 2000. Incorporating patient preferences into randomized trials. J. Clin. Epidemiol. 53, 163–166. https://doi.org/10.1016/S0895-4356(99)00146-8.

Licht, C.M., de Geus, E.J., Seldenrijk, A., van Hout, H.P., Zitman, F.G., van, D.R., Penninx, B.W., 2009. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. Hypertension 53, 631–638.

Licht, C.M.M., de Geus, E.J.C., van Dyck, R., Penninx, B.W.J.H., 2010. Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. Biol. Psychiatry 68, 861–868.

Milaneschi, Y., Lamers, F., Berk, M., Penninx, B.W., 2020. Depression heterogeneity and its biological underpinnings: towards immuno-metabolic depression. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2020.01.014.

Milligen, B.A.L.Van, Verhoeven, J.E., Schmaal, L., Van Velzen, L.S., Révész, D., Black, C. N., Han, L.K.M., Horsfall, M., Batelaan, N.M., Van Balkom, A.J.L.M., Van Schaik, D.J. F., Van Oppen, P., Penninx, B.W.J.H., 2019. The impact of depression and anxiety treatment on biological aging and metabolic stress: study protocol of the MOod treatment with antidepressants or running (MOTAR) study. BMC Psychiatry 19, 1–11. https://doi.org/10.1186/s12888-019-2404-0.

Niazi, S.K., Memon, S.H., Lesser, E.R., Brennan, E., Aslam, N., 2021. Assessment of psychiatric comorbidities and serotonergic or noradrenergic medication use on blood pressure using 24-hour ambulatory blood pressure monitoring. J. Clin. Hypertens. 23, 1599–1607. https://doi.org/10.1111/JCH.14311.

Nojima, H., Watanabe, H., Yamane, K., Kitahara, Y., Sekikawa, K., Yamamoto, H., Yokoyama, A., Inamizu, T., Asahara, T., Kohno, N., 2008. Effect of aerobic exercise training on oxidative stress in patients with type 2 diabetes mellitus. Metabolism 57, 170–176.

Noordam, R., Van Den Berg, M.E., Niemeijer, M.N., Aarts, N., Hofman, A., Tiemeier, H., Kors, J.A., Stricker, B.H., Eijgelsheim, M., Visser, L.E., Rijnbeek, P.R., 2016. Antidepressants and heart-rate variability in older adults: a population-based study. Psychol. Med. 46, 1239–1247. https://doi.org/10.1017/S0033291715002779.

O'Regan, C., Kenny, R.A., Cronin, H., Finucane, C., Kearney, P.M., 2015. Antidepressants strongly influence the relationship between depression and heart rate variability: findings from the Irish longitudinal study on ageing (TILDA). Psychol. Med. 45, 623–636. https://doi.org/10.1017/S0033291714001767.

Penninx, B.W.J.H., Milaneschi, Y., Lamers, F., Vogelzangs, N., 2013. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med. 11, 1–14.

Quanjer, P.H., Lebowitz, M.D., Gregg, I., Miller, M.R., Pedersen, O.F., 1997. Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society. Eur. Respir. J. Suppl. 24, 2S–8S.

Rethorst, C.D., Toups, M.S., Greer, T.L., Nakonezny, P.A., Carmody, T.J., Grannemann, B. D., Huebinger, R.M., Barber, R.C., Trivedi, M.H., 2012. Pro-inflammatory cytokines as predictors of antidepressant effects of exercise in major depressive disorder. Mol. Psychiatry 18 (10), 1119–1124.

Rethorst, C.D., Trivedi, M.H., 2013. Evidence-based recommendations for the prescription of exercise for major depressive disorder. J. Psychiatr. Pract. 19, 204–212.

Rethorst, C.D., Wipfli, B.M., Landers, D.M., 2009. The antidepressive effects of exercise: a meta-analysis of randomized trials. Sport. Med. 39, 491–511.

Roberts, H.C., Denison, H.J., Martin, H.J., Patel, H.P., Syddall, H., Cooper, C., Sayer, A. A., 2011. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing 40, 423–429. https://doi.org/10.1093/ageing/afr051.

Rubin, D.B., 2004. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons Inc., New York.

Rush, A., Gullion, C., Basco, M., Jarrett, R., Trivedi, M., 1996. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol. Med. 26, 477–486.

Saunders, J.B., Aasland, O.G., Babor, T.F., De La Fuente, J.R., Grant, M., 1993. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction 88, 791–804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x.

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.

Seaman, S.R., Bartlett, J.W., White, I.R., 2012. Multiple imputation of missing covariates with non-linear effects and interactions: an evaluation of statistical methods. BMC Med. Res. Methodol. 12 https://doi.org/10.1186/1471-2288-12-46.

Serretti, A., Mandelli, L., 2010. Antidepressants and body weight: a comprehensive review and meta-analysis. J. Clin. Psychiatry. https://doi.org/10.4088/JCP.09r05346blu.

Sloan, R.P., Shapiro, P.A., McKinley, P.S., Bartels, M., Shimbo, D., Lauriola, V., Karmally, W., Pavlicova, M., Choi, C.J., Choo, T., Scodes, J.M., Flood, P., Tracey, K. J., 2018. Aerobic exercise training and inducible inflammation: results of a randomized controlled trial in healthy,young adults. J. Am. Heart Assoc. 7 https://doi.org/10.1161/JAHA.118.010201.

Stonerock, G.L., Hoffman, B.M., Smith, P.J., Blumenthal, J.A., 2015. Exercise as treatment for anxiety: systematic review and analysis. Ann. Behav. Med. 49, 542–556. https://doi.org/10.1007/s12160-014-9685-9.

Sullivan, T.R., White, I.R., Salter, A.B., Ryan, P., Lee, K.J., 2018. Should multiple imputation be the method of choice for handling missing data in randomized trials? Stat. Methods Med. Res. 27, 2610–2626. https://doi.org/10.1177/0962280216683570.

Taylor, C.B., 2010. Depression, heart rate related variables and cardiovascular disease. Int. J. Psychophysiol. 78, 80–88. https://doi.org/10.1016/j.ijpsycho.2010.04.006.

Trimbos.nl | Richtlijnen voor behandeling depressie en angst [WWW Document], URL https://www.trimbos.nl/kennis/richtlijnen-depressie (accessed 12.14.20).

Torgerson, D., Sibbald, B., 1998. Understanding controlled trials: what is a patient preference trial? BMJ 316, 360. https://doi.org/10.1136/BMJ.316.7128.360.

Vancampfort, D., Guelinckx, H., De Hert, M., Stubbs, B., Soundy, A., Rosenbaum, S., De Schepper, E., Probst, M., 2014. Reliability and clinical correlates of the astrand-rhyming sub-maximal exercise test in patients with schizophrenia or schizoaffective disorder. Psychiatry Res. 220, 778–783. https://doi.org/10.1016/j.psychres.2014.08.049.

Wasmann, K.A., Wijsman, P., van Dieren, S., Bemelman, W., Buskens, C., 2019. Partially randomised patient preference trials as an alternative design to randomised controlled trials: systematic review and meta-analyses. BMJ Open 9, e031151. https://doi.org/10.1136/BMJOPEN-2019-031151.

Wegner, M., Helmich, I., Machado, S., Nardi, A., Arias-Carrion, O., Budde, H., 2014. Effects of exercise on anxiety and depression disorders: review of meta- analyses and neurobiological mechanisms. CNS Neurol. Disord. - Drug Targets 13, 1002–1014. https://doi.org/10.2174/1871527313666140612102841.

Więdłocha, M., Marcinowicz, P., Krupa, R., Janoska-Jaździk, M., Janus, M., Dębowska, W., Mosiołek, A., Waszkiewicz, N., Szulc, A., 2018. Effect of antidepressant treatment on peripheral inflammation markers - a meta-analysis. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 80, 217–226. https://doi.org/10.1016/J.PNPBP.2017.04.026.

Wittchen, H.U., 1994. Reliability and validity studies of the WHO–Composite International Diagnostic Interview (CIDI): a critical review. J. Psychiatr. Res. 28, 57–84.

You, T., Nicklas, B.J., 2008. Effects of exercise on adipokines and the metabolic syndrome. Curr. Diab. Rep. 8, 7–11.