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Effects of acute exercise on drug craving in adults with poly-substance use disorder. A randomized controlled trial

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ABSTRACT

Objectives: To examine the short-term effects of exercise on drug craving in poly-drug-dependent inpatients, duration of effects, differences between exercise types, explore the relationship between craving and mood, and possible moderators.
Design: Multicenter randomized control trial (RCT) with a crossover design.
Methods: 38 (25 completed) inpatients (37.3 ± 6.4 years; 84 % male) from three treatment centers participated in soccer, circuit training and control condition in random order for 45-min. Craving was assessed with a self-rated visual analog scale (VAS), mood with Feeling scale (FS), immediately before and after each condition and 1, 2, and 4 h post interventions. Ratings of perceived exertion (RPE) and heart rate were assessed. Intervention effects were assessed using linear mixed effects model, including moderator analyses.
Results: Exercise sessions were perceived as "somewhat hard" to "hard". Compared to control, there was an immediate reduction in craving after soccer and circuit training (β = −1.35, 95 %CI: 1.96, −0.75, p = 0.000; β = -1.44, 95 %CI: 2.06, −0.83, p = 0.000) that persisted for 4 h (β = −1.11, 95 %CI: 1.72, −0.49, p = 0.000; β = -0.85, 95 %CI: 1.49, −0.22, p = 0.008). Elevations in mood after soccer (β = 1.08, 95 %CI: 0.41, 1.76, p = 0.002) and circuit training (β = 0.99, 95 %CI: 0.32, 1.67, p = 0.004) were significantly larger than control. Depressive disorder and primary drug of use might moderate the effect.
Conclusion: Reduced drug cravings and elevated mood following soccer and circuit training were observed in people with poly-SUDs. Single exercise sessions can be an effective strategy to alleviate craving and potentially prevent relapse and treatment drop-out.

1. Introduction

Substance use disorders (SUD) contribute substantially to the global burden of disease with wide-reaching impacts on health and well-being. SUDs are associated with shorter life expectancy and comorbid medical conditions (Degenhardt et al., 2013; Walker & Druss, 2018). Current treatment options include medication assisted therapy, cognitive behavioral therapy, and motivational interviewing, with treatment delivery both in inpatient and outpatient settings. Although treatment is documented as effective, remission rates are low and medications have adverse side effects (Fleury et al., 2016; Lappan, Brown, & Hendricks, 2019; NIDA, 2012). A large number of people with SUDs never receive treatment, pointing to a need for alternative treatment options (Cunningham & Breslin, 2004; Kuramoto, Martins, Ko, & Chilcoat, 2011).

Physical activity and its sub-set exercise (that is planned, structured, repetitive, and purposive physical activity to improve or maintenance physical fitness) has been suggested as an alternative or adjunctive treatment. It is usually inexpensive, highly accessible, non-stigmatizing,

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and rarely associated with side effects (Brellenthin, Crombie, Hillard, Brown, & Koltyn, 2019; Caspersen, Powell, & Christenson, 1985; Giesen, Deimel, & Bloch, 2015; Manthou et al., 2016; Probst, Manthey, Martinez, & Rehm, 2015; Schuler, Puttaiah, Mojtabai, & Crum, 2015; Zschucke, Heinz, & Strohle, 2012). Studies suggest that physical activity and structured exercise can help prevent relapse, alleviate symptoms of comorbid disorders, and potentially reduce treatment costs (Abrantes & Blevins, 2019; Bernstein & McNally, 2017; Colledge, Gerber, Pühse, & Ludyga, 2018; Giménez-Meseguer, Tortosa-Martínez, & Cortell-Tormo, 2020; Pareja-Galeano & Sanchis-Gomar, 2013; Weinstock, Farney, Elrod, Henderson, & Weiss, 2017).

Craving is a common symptom of SUDs, thought to be a driving force for continued drug use, linked to drop-out from treatment and relapse after a period of abstinence (American Psychiatric Association, 2013; Rosenberg, 2013; Sayette et al., 2000; Weiss, 2005; WHO, 2004). Treatment interventions focused on attenuating craving are therefore important in treatment and rehabilitation of SUDs (Tiffany & Wray, 2012). Short bouts of exercise might be an effective strategy to decrease craving, prevent relapse to drugs, and promote retention in treatment (Brown, Prince, Minami, & Abrantes, 2016; Hallgren et al., 2021; A.H Taylor, Oh, & Cullen, 2013).

Available studies addressing the effects of single sessions of exercise on craving or urges to drink alcohol have found that craving is reduced during and after low-to-moderate intensity exercise (Hallgren et al., 2021; Ussher, Sampuran, Doshi, West, & Drummond, 2004). Reductions in craving for amphetamines and opioids following exercise have also been reported (D. Wang, Zhou, & Chang, 2015; D. Wang et al., 2020). Giménez-Meseguer et al. (Giménez-Meseguer et al., 2020) concluded in their meta-analysis that craving decreased after acute aerobic exercise for both alcohol and other SUDs.

Studies suggest that craving and mood are related. Higher levels of craving are observed when negative affects are high and positive affects are low, and changes in affective states have been proposed to mediate exercise effects on craving (Abrantes et al., 2017; Bernstein & McNally, 2017; Cheetman, Allen, Yücel, & Lubman, 2010; De Jesus & Prapavessis, 2018; Giménez-Meseguer et al., 2020; Haasova et al., 2014; Heckman et al., 2013; Perkins, Karelitz, Giedgowd, & Conklin, 2013; Schlauch, Gwynn-Shapiro, Stasiewicz, Molnar, & Lang, 2013; Weinstock et al., 2017). Potential moderators of exercise effects on craving have not been extensively studied, but some studies have suggested that participant characteristics such as SUD severity and comorbid disorders might moderate the effects of exercise (Haglund et al., 2015).

Although studies on the short term effects of exercise in SUDS show promising results, the evidence is limited. Most previous studies have been performed in laboratory settings using standardized exercise interventions studying participants with single drug SUD (Hallgren, Vancampfort, Giesen, Lundin, & Stubbs, 2017; Thompson et al., 2020; Zschucke et al., 2012). However, exercise is most commonly performed in naturalistic settings (settings that are readily available in everyday life such as a soccer field or gymnasium) and single substance misuse is exceptional in illicit SUDs (Hassana & Folla, 2019; Liu, Williamson, Setlow, Cottler, & Knackstedt, 2018; L.; Wang et al., 2017; Zambon et al., 2017). Whether exercise can benefit people with poly-SUDs in non-laboratory settings is unclear, and no previous RCT has examined the effects of single bouts of exercise in participants with poly-SUD in a naturalistic setting. Few studies have compared the benefits across different forms of exercise, and most studies have focused on pre- and post-assessments only.

In a feasibility study we compared the short-term effects of three different types of exercise (soccer, circuit training, and walking) on drug craving in nine adults with poly-SUD (Ellingsen, Johannesen, Martinsen, & Hallgren, 2018). Our results indicated that moderate intensive exercise (soccer and circuit training) attenuated drug cravings and improved mood. These results warranted replication in a controlled trial with an adequate sample size.

In the present study, we examined the short-term effects of 45-min of indoor soccer and circuit training on craving in poly-SUD inpatients, compared with a non-exercise control condition (lecture). The primary objective was to assess the short-term effects on craving, the duration of the effects (up to 4 h), and whether effects differed by exercise type. A secondary objective was to assess changes in mood and the relationship between craving and mood. Additionally, we performed exploratory analysis to examine potential moderators of exercise effects on craving.

2. Method

2.1. Design and setting

This study was a multi-center randomized controlled trial (RCT) with a cross-over design and random order condition allocation. Changes in craving before and after exercise were compared to a control condition (psychoeducation). The initial measurement (taken immediately before exercise) was compared with four follow-up assessments: immediately after, then at 1, 2 and 4-h post-intervention.

The main site for the trial was the Department of Substance Use Disorder Treatment, Inpatient Treatment Center for Adults, Oslo University Hospital. The two others were (1) Blue Cross Treatment Center, Slemdal, Oslo and (2) the Department of Substance Use Disorder Treatment, Inpatient Treatment Center for Young Adults, Oslo University Hospital. All treatment centers offer long-term inpatient treatment for individuals >18 years with SUDs. Most patients attending the clinics are males (aged 23–46 years) with poly-SUDs. Comorbid mental (e.g., depression/anxiety) and somatic health problems (e.g., hepatitis C, renal failure and lifestyle related disorders) are common. The study was conducted in the clinical setting where the participants were receiving ongoing inpatient treatment.

The study was registered on German Clinical Trials (drks.de: DRKS 00018869), and the protocol has been published (Ellingsen, Johannesen, Martinsen, Dahl, & Hallgren, 2020).

2.2. Participants

Participants were recruited between February and August 2019. All participants (n = 38) were aged ≥18 years and had two or more SUD diagnoses according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (WHO, 2004). Participants were in different stages of treatment, but all had completed detoxification before admission. Medical conditions contraindicated to physical exercise served as the only exclusion criterion, but no participants were excluded on this basis. Participants with comorbid mental disorders were considered eligible provided the participant was able to give informed consent.

The trial was approved by the Regional Committee for Medical and Health Research Ethics in South East Norway). All participants agreed to participate voluntarily, provided informed consent, and could withdraw from the study at any time.

2.3. Recruitment procedure

Patients were invited to join the study during an information-sharing meeting held by members of the research group and a local project coordinator at the treatment center. To minimize dropouts, recruitment took place no more than two weeks ahead of the intervention. Study conditions were randomized in order (determined by a random number generator).

2.4. Interventions

Intervention components are described in the published protocol (Ellingsen et al., 2020). Briefly, participants completed in random order two 45-min supervised group exercise sessions (soccer and circuit training) and one 45-min control condition (attending a lecture). The

exercises were deliberately chosen on the basis of participant feedback during the pilot study and because they include both aerobic and anaerobic training (Ellingsen et al., 2020). To control for possible carry-over effects, participants completed a one-day non-exercise 'washout' period between interventions, and were asked to refrain from doing other forms of structured exercise on the days when each intervention was completed. All interventions were undertaken on-site at the clinics between 9:30 a.m. and 11 a.m. on Monday, Wednesday, and Friday during one week between February and August 2019. Participants received treatment as usual between the sessions. Exercise sessions were supervised by a nurse with formal education in physical activity for people with mental health and addiction disorders.

Soccer was played indoors at a local gym (20 × 40 m) with five participants on each team. Participants were asked to play a 'friendly match', where goals were counted. The match lasted for 45-min with a 2-min break after 15 and 30 min. Circuit training using bodyweight exercises was performed in groups (n = 5–9) at the same gymnasium as the soccer intervention. Participants completed four circuits consisting of eight individual exercise stations (air squats, inchworm, dips on bench, frog jumps, sit-ups, push-ups, walking lunges, and back hyperextensions). Participants performed 40-s exercises at each station followed by 20 s of rest before transitioning to the next station. Between each circuit, there was a 2-min rest. The first circuit was undertaken at lower intensity to function as a gradual warm up. Participants were asked to 'give their best' at each station and to perform as many repetitions as they could using proper form within 40 s. The average duration of training was 45 min (±3 min). The control condition consisted of a 45-min lecture on the benefits of physical activity and exercise with a focus on prevention of non-communicable diseases and mood disorders and the use of exercise in the treatment of somatic and mental disorders. A qualified nurse in the research group using a Power point presentation gave the lecture. The format and content of the lecture was similar to the psychoeducation that patients receive during usual treatment. All conditions were performed as group sessions; the same participants performed the three conditions together. Participants could converse during all conditions.

2.5. Measures

Socio-demographic characteristics (age, sex, education, employment, and socioeconomic status) and clinical data (diagnosis, comorbid disorders, medication, and primary drug use and drug use history) were collected through a survey filled out by therapists at the treatment centers based on an interview with the participants. Participants were asked about their past exercise experience (pleasurable, unpleasant, neutral) and whether they had exercised regularly prior to admission. Height and weight were also recorded.

Participants completed Borg's Rating of Perceived Exertion Scale (RPE) (Borg, Ljunggren, & Ceci, 1985) immediately after (within 5 min) each intervention to assess how strenuous they perceived the intervention to be. The single-item scale ranges from 6 (no exertion at all) to 20 (maximal exertion). During all conditions, participants also used a Polar Heart Rate Monitor to collect data on average and maximum heart rate (an objective measure of exercise intensity).

2.5.1. Primary and secondary study outcome, craving and mood

Subjective experience of drug craving was assessed using a single-item Visual Analogue Scale (VAS) ranging from 0 (no craving for drugs) to 10 (strong craving). Participants were instructed to indicate how strong their craving for drugs felt "*at this moment*". The instrument has been used in previous studies of acute exercise (Prapavessis et al., 2014) and was tested in our pilot study (Ellingsen et al., 2018) where it was shown to be sensitive to change. Changes in overall mood state were assessed with the Feeling Scale (Hardy & Rekeski, 1989), a single-item Likert scale ranging from −5 (very bad) to +5 (very good). Participants were instructed to indicate how they felt *"at this moment"*. Participants reported their experience of craving and mood immediately before the interventions, then four times after the interventions (immediately after, one-, two- and 4 h after). All surveys were completed under supervision of a staff nurse.

2.5.2. Potential moderator variables

Based on previous studies we tested whether mood or participant characteristics (primary drug of use, duration of SUDs, medication, and comorbid mental disorders) moderated the effects of the interventions over time (Abrantes & Blevins, 2019; Haasova et al., 2012, 2014).

2.6. Statistical analyses

Statistical power, based on results from our feasibility study (cross-over design) (Ellingsen et al., 2018) was estimated using G*Power (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf). Assuming an effect size of d = 0.28, power of 0.8, with three groups and five measurement points, we estimated needing at least 21 participants to test our hypothesis that moderate-to-vigorous intensity physical activity would be associated with positive psychological effects compared to a control condition. Allowing for drop-out of ~20 %, we aimed to recruit at least 30 participants (10 from each of the treatment centers).

Descriptive statistics (means and SDs for continuous variables, counts and percentages for categorical data) were calculated for each measure. Between intervention differences in RPE, maximum and average heart rate (HR) were tested with paired samples *t*-test.

Our main analyses were based on a linear mixed effects model (LMM) with a random intercept for each participant. With craving as the dependent variable, we first assessed within intervention differences over time (baseline/immediately before, immediately after, 1-hr, 2-hrs, and 4-hrs after) by stratified analyses. Next, between intervention differences were analyzed by including the interaction between the three interventions and time, with adjustment for baseline craving. The same analyses were performed with mood as the dependent variable. Estimated regression coefficients, which represent estimated mean differences in craving between the given conditions, 95 % CI and p-values, were reported. We checked for sequence effect and period effect by assessing main effects of the order of the trial days and the conditions. Potential moderating variables were assessed within the same model, testing for third order interactions between intervention, time, and the moderator variables. The moderating variables tested were mood (Feeling Scale), primary drug of use, duration of SUDs, comorbid mental disorders, and medical treatment. A likelihood ratio test with statistical significance level at $p < 0.05$ was used to assess the moderator effects. To assess whether baseline craving level was associated with the effect of exercise, Pearson's r correlation analyses were performed to check for correlations between baseline level and the change from baseline to immediately after exercise. Baseline correlations and correlations between changes in craving and mood from baseline to immediately after interventions were tested with partial correlation.

Two participants were identified as outliers. Their response styles deviated on both Feeling scale and craving, changing between extreme values (the highest/worst and the lowest/best) at the different assessment times. Re-running analysis with the two outliers included resulted in a marginally lower significance for circuit training, but interpretation of the results were unchanged. Participants who dropped out or did not complete all three interventions were included in the main analyses (intention to treat sample). To identify any unique characteristics of those who dropped out of the study, we conducted a Chi square Goodness of fit test of participant characteristics. All data was analyzed using SPSS version-25.

3. Results

3.1. Retention and adherence

Reasons for dropping out of the study (N = 8) or not participating in a given intervention (N = 5) were recorded (CONSORT Fig. 1). Dropout and non-adherence were largely due to factors unrelated to the trial or circumstances beyond the participant's control. Four participants dropped out of the study after the first intervention; two relapsed to drug abuse and were discharged from treatment, one acquired an injury on the day between the first and second intervention, and one reported lack of motivation to participate in the rest of the trial. Four participants dropped out after the second intervention, one due to infectious disease, one was unmotivated to participate and two had other treatment interventions that could not be rescheduled. For the participants who did not adhere in all three interventions, lack of motivation and medical advice not to participate in the given intervention were reported as the causes. Three participants did not receive their last intervention due to illness of the project coordinator. Of the 38 participants initially included in the study, 25 (65.8 %) completed all three interventions, eight (21.1 %) participated in two and five (13.2 %) participants completed only one intervention. The final analytic sample, without outliers, consisted of 36 participants (of these 24 completed all interventions). Participants who did not complete the study did not differ significantly in participant characteristics. No adverse events/effects were reported.

3.2. Participant characteristics

In total, mean age was 37.3 (±6.39), 83.3 % of the participants were male, 50 % reported opioids as their primary drug of use, and 63.9 % had a history of >15 years of problematic drug use (Table 1). 80.6 % had one or more co-morbid mental disorder.

3.3. Exercise variables

On the RPE participants reported soccer as "somewhat hard" (M = 13.2 ± 2.5) and circuit training as "somewhat hard" to "hard" (M = 14.4 ± 2.9). The control condition was perceived as "easy" (M = 9.78 ± 3.29), which was significantly lower than the exercise conditions ($p < 0.001$). Mean average HR was higher during soccer (122 ± 13.7), than during circuit training (115 ± 12.2 ($p < 0.014$). There was no significant difference in mean maximum HR (soccer: 154 ± 17.9, circuit training: 149 ± 16).

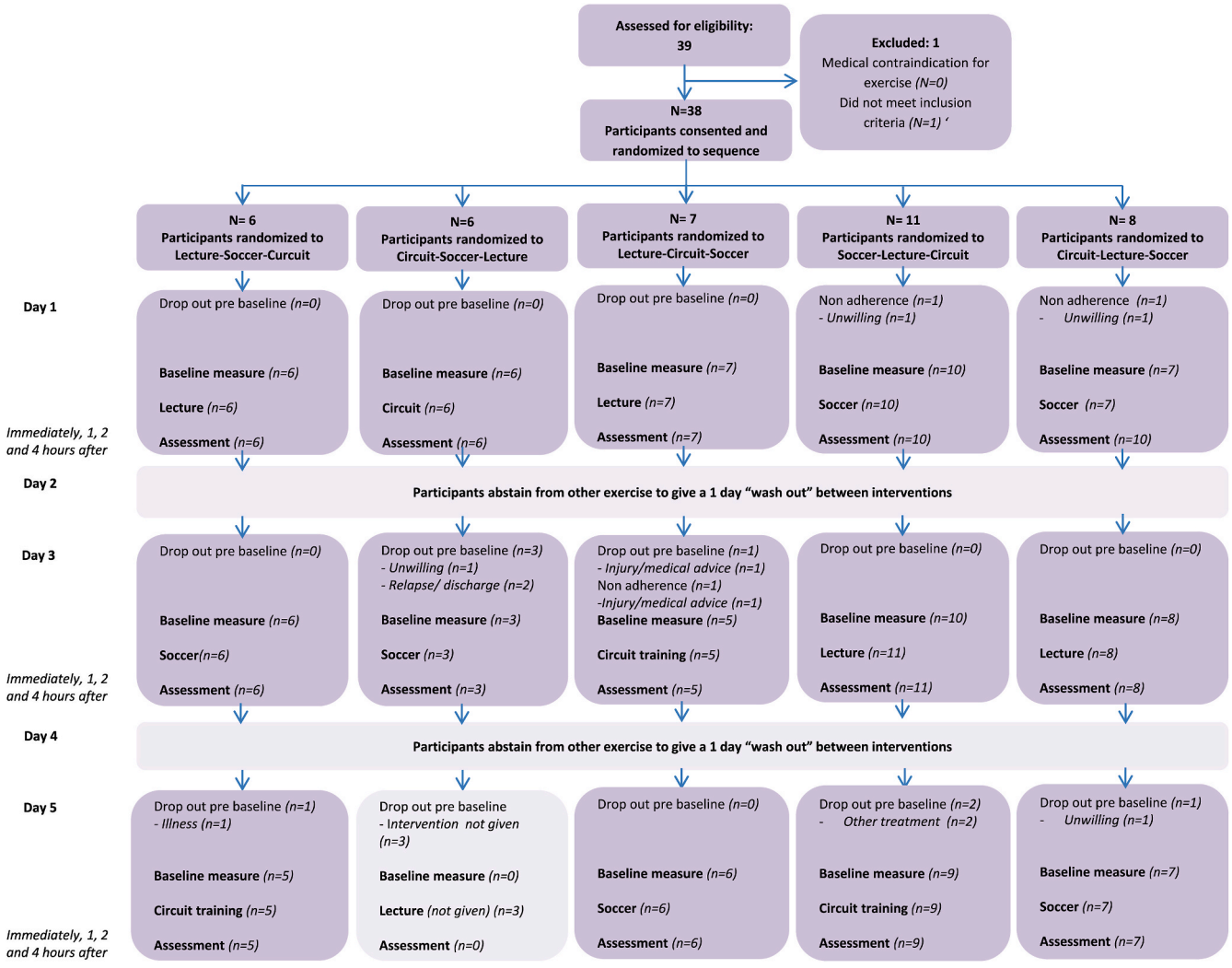

Fig. 1. CONSORT flow diagram.
* Non adherent participants were allowed to participate in following interventions.
** Detailed descriptions on drop-out and non-adherence is described in supplementary material.

Table 1
Participant characteristics.

Characteristics	Value ($N = 36$)	
Male, *n* (%)	30	(83,3)
Female, *n* (%)	6	(16.7)
Age, mean (SD)	37	(6.6)
Body mass index (kg/m2), median (25–75th percentile)	23.8	(20.2–26.9)
Education, *n* (%)		
Primary education	17	(47.2)
Secondary education	15	(41.7)
Tertiary education	4	(11.1)
Housing, *n* (%)		
Without housing	17	(43.6)
Other institution	2	(5.1)
Private	20	(51.3)
Marital status, *n* (%)		
Single	25	(69.4)
In a relationship	11	(30.6)
Primary drug of use, *n* (%)		
Opioids	18	(50)
Alcohol	7	(19.4)
Stimulants	5	(13.9)
Cannabinoids	2	(5.6)
Previously used Anabolic androgenic steroids, *n* (%)	3	(8.3)
Years of SUD, *n* (%)		
0–5 years	2	(5.6)
5-10	4	(8.3)
10-15	8	(22.2)
15 +	23	(63.9)
Medication assisted treatment for opioids, *n* (%)	14	(38.9)
Currently treated with benzodiazepines, *n* (%)	10	(27.8)
Comorbid mental disorder, *n* (%)	29	(80.6)
Psychosis	4	(11.1)
Depression	5	(13.9)
Anxiety	19	(52.8)
Eating disorder	1	(2.8)
Personality disorder	5	(13.9)
ADHD	5	(13.9)
Asperger	2	(5.6)
Anoxic brain damage	1	(2.8)
Previous experience with exercise, *n* (%)		
Neutral	2	(5.6)
Positive	34	(94.5)
Regular exercise pre admission, *n* (%)		
Yes	16	(44.4)
No	20	(55.6)

* ICD-10 diagnosis set by psychologist/doctor at the treatment centers.

3.4. Exercise effects on craving

Within the two exercise interventions there was a main effect of time on craving (soccer: $p < 0.001$; circuit training: $p = 0.006$) (Table 2). Soccer was associated with reduced craving at all four assessment times. The same pattern was observed for circuit training. However, the reduction was significant only immediately and 1 h after the exercise ended. In the control condition, there was a reduction in craving 1 h after the intervention. Fig. 2 displays changes in craving over time for the three conditions.

Comparing the exercise interventions to the control condition, craving was a significantly lower at baseline in the circuit condition ($p = 0.012$). Table 3 shows the difference in craving over time between soccer, circuit training and the control condition after adjusting for baseline level. There was no significant main effect of period (day of intervention) or the sequence of the interventions. Both exercise interventions significantly reduced craving compared to the control condition. Overall, the effect of exercise on craving was strong, with a predicted decrease at all assessment points for both soccer and circuit training. In soccer, there was an average reduction in participant's craving for drugs (baseline to immediately after exercise) of 1.54 points (i.e., 52 %) with an estimated mean difference of −1.35 compared to the control condition. In circuit training there was an average reduction of 0.95 points (i.e., 41.5 %) with an estimated mean differences of −1.44 compared to control. The exercise effects remained stable until 4 h after exercise. The reductions in craving associated with soccer and circuit training were similar, and there was no significant difference between the two exercise interventions after adjustment for baseline craving. There were no significant reductions in craving for the control condition.

A supplementary analysis of within and between intervention changes was performed with a sub-sample of participants who completed all three interventions (N = 24). The results were materially comparable with the results from the complete sample. We also repeated the analysis with male participants only (N = 30), and the results were virtually identical.

Participants with higher baseline craving had a larger decrease in craving immediately after exercise. The positive correlation between baseline level of craving and level of decrease for soccer ($r = 0.698$, $p <$

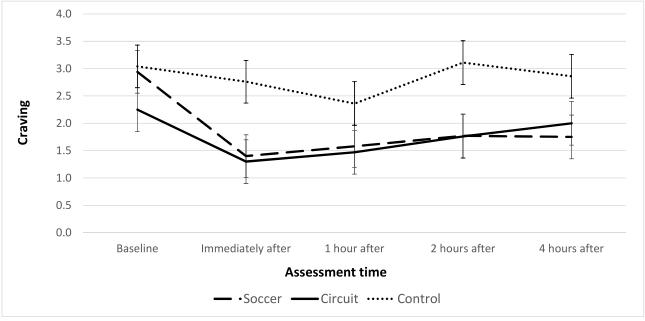

Fig. 2. Changes in craving over time within soccer, circuit training, and control condition.
* Estimated marginal means of craving and standard error.

Table 2
Craving level and associated changes over time within the control, soccer, and circuit-training intervention.

				Within-intervention changes from baseline								
	Control	Soccer	Circuit	Control			Soccer			Circuit		
	EMM (95 %CI)	EMM (95 %CI)	EMM (95 %CI)	B	(95 % CI)	*p*	β	(95 % CI)	*p*	β	(95 % CI)	*p*
Baseline	2.73 (1.91–3.56)	2.91 (2.1–3.72)	2.29 (1.49–3.1)									
Immediately after	2.46 (1.63–3.28)	1.37 (0.56–2.18)	1.34 (0.54–2.13)	−0.28	(-0.87 - 0.32)	0.357	−1.54	(-2–1.07)	0.000	−0.95	(-1.5–0.41)	0.001
1 h after	2.03 (1.2–2.86)	1.56 (0.75–2.36)	1.49 (0.69–2.29)	−0.7	(-1.3 - - 0.1)	0.022	−1.35	(-1.82–0.89)	0.000	−0.8	(-1.35–0.25)	0.005
2 h after	2.83 (1.99–3.66)	1.73 (0.92–2.54)	1.79 (0.98–2.59)	0.09	(-0.51- 0.69)	0.759	−1.18	(-1.66–0.71)	0.000	−0.51	(-1.06 - 0.05)	0.072
4 h after	2.58 (1.75–3.4)	1.72 (0.92–2.53)	1.99 (1.19–2.8)	−0.15	(-0.75 - 0.45)	0.619	−1.19	(-1.65–0.72)	0.000	−0.3	(-0.86 - 0.26)	0.29

* EMM: estimated marginal mean.

Table 3
Changes in craving associated with exercise exposure compared to the control condition.

	Control			Interventions compared with the control condition					
				Soccer			Circuit training		
	β	(95 %CI)	*p*	B	(95 % CI)	*p*	β	(95 % CI)	*p*
Baseline/intercept	2.75	(2.04–3.45)							
Immediately after	0.00	(-0.49–0.5)	0.99	−1.35	(-1.96–0.75)	0.000	−1.44	(-2.06–0.83)	0.000
1 h after	−0.4	(-0.9–0.1)	0.12	−0.76	(-1.38–0.15)	0.015	−0.87	(-1.5–0.24)	0.007
2 h after	0.35	(-0.15–0.86)	0.17	−1.33	(-1.96–0.71)	0.000	−1.33	(-1.95–0.7)	0.000
4 h after	0.11	(-0.39–0.61)	0.67	−1.11	(-1.72–0.49)	0.000	−0.85	(-1.49–0.22)	0.008

* Note: analyses were adjusted for baseline craving.

0.001) was larger than that for circuit training (r = 0.58, p = 0.001). There was no significant correlation between baseline craving and the change in craving for the control condition.

3.5. Exercise effects on mood

There was a significant increase (improvement) in mood after soccer and circuit training compared to the control condition. The improvement was significant on all measurement times for soccer, and up to 2 h after circuit training, after adjusting for baseline level (Table 4). There was no significant difference between soccer and circuit training.

Craving and mood were negatively correlated at baseline (r = *-0.37, p < 0.001*); participants with higher perceived craving reported lower mood. There was also a significant negative correlation between changes in craving and mood from baseline to immediately after conditions (r = −0.31, p = 0.003); a larger decrease in craving was associated with a larger increase in mood. Comparing the intervention effects on craving over time, mood had a significant main effect on craving (p < 0.001), but it did not moderate the interaction.

3.6. Potential moderators

Comparing the exercise intervention's effect on craving over time with that of the control condition, being diagnosed with a depressive disorder (N = 5) had a significant moderating effect (p = 0.003). Depressive disorder was associated with higher estimated craving at baseline (p < 0.001) and a larger effect of exercise immediately and 1 h after both soccer and circuit training (β = -1.93, 95 %CI: 3.59, −0.28; β = -1.67, 95 %CI: 3.33, −0.02 and β = - 1.94, 95 %CI: 3.69, −0.2; β = -2.32, 95 %CI: 4.18, −0.47). Primary use of opioids (N = 18) moderated the interaction (p = 0.008) with a larger effect 4 h after soccer (1.21, 95 %CI -2.41, −0.2) and one and 4 h after circuit training (β = –1.96, 95 % sCI −3.17, 0.76; β = −1.52, 95 %CI: 2.72, 0.31) compared to the control condition. Primary use of cannabinoids (N = 2) had a moderating effect (p = 0.04) with less effect of circuit training one and 4 h after the session (β = 2.77, 95 %CI: 0.36, 5.18; β = 3.03, 95 %CI: 0.62, 5.44), compared to control. Medical treatment and duration of SUDs did not moderate the effects. None of the variables had a moderating effect on mood.

4. Discussion

In this RCT, single bouts of moderate to vigorous-intensity exercise performed in a naturalistic setting were associated with reduced cravings in participants with poly-SUDs. Reductions in craving following exercise were significantly larger than the control condition (lecture). Our findings extend previous knowledge, showing effects on craving lasting 4 h post-exercise. There were no significant differences between the effects of soccer and circuit training. Mood was improved up to 4 h after exercise, and in line with previous studies, lower levels of mood were associated with higher levels of craving.

Our finding that reduction in craving remained stable (low) through to the last assessment (4-h) contrasts somewhat with our feasibility study (n = 9) (Ellingsen et al., 2018). That study found steady reductions in craving up to 1 h after exercise, before an increase above baseline levels two and 4 h post-exercise. This was not observed in the present study. The difference is likely due to the low number of participants in the feasibility study, which included four participants who reported high craving levels two and 4 h, respectively, compared to five who did not.

Overall, baseline craving was substantially lower than those reported in previous studies using VAS (D. Wang et al., 2015; D. Wang, Zhou, Zhao, Wu, & Chang, 2016). We did not expose participants to drug-related stimuli before the intervention, as has been done in other studies, which might explain this difference. Furthermore, being admitted to an inpatient clinic after detoxification and with strong stimulus control probably contribute to reduced baseline cravings. Lower baseline craving might have affected the results, making it more difficult to observe post-exercise reductions; thus, our findings could underestimate exercise effects on craving. The observed association between higher baseline craving (sub-group analysis) and a larger initial decrease supports this possibility and suggests that exercise interventions may be particularly relevant when cravings are high such as during stress or negative affect. While the clinical meaning of the exercise-related reductions in craving are unclear and warrant investigation in future validation studies, the magnitude of reductions are in line with other acute exercise studies for SUDs using comparable single-item visual analogue scales. These report average reductions of 1.4–4.1 points (Daniel, Cropley, & Fife-Schaw, 2007; Everson, Daley, & Ussher, 2008; Janse Van Rensburg, Taylor, Benattayallah, & Tim Hodgson, 2012; Prapavessis et al., 2014; A. H Taylor, Katomeri, &

Table 4
Changes in mood associated with exercise exposure compared to the control condition.

	Control			Interventions compared with the control condition					
				Soccer			Circuit training		
	β	(95 %CI)	*p*	β	(95 % CI)	*p*	β	(95 % CI)	*p*
Baseline/intercept	0.69	(0.04–1.35)							
Immediately after	0.52	(-0.02–1.07)	0.061	1.08	(0.41–1.76)	0.002	0.99	(0.32–1.67)	0.004
1 h after	0.46	(-0.09–1.02)	0.100	1.03	(0.36–1.71)	0.003	1.63	(0.94–2.32)	0.000
2 h after	0.14	(-0.42–0.69)	0.629	1.19	(0.51–1.87)	0.001	1.24	(0.55–1.93)	0.000
4 h after	0.65	(0.1–1.2)	0.021	0.65	(0.01–1.36)	0.047	0.64	(-0.06 - 1.34)	0.071

* Note: analyses were adjusted for baseline craving.

Ussher, 2005).

We found no difference between soccer and circuit training on craving, which suggests that effects of exercise are not dependent on the type of exercise. However, the exercises chosen did not differ in intensity (perceived exertion), and an impact of exercise intensity on craving or mood cannot be excluded on the basis of this study. Social bonding and peer support have been suggested as possible explanations for the positive effects of exercise in SUDs (Colledge et al., 2018; Muller & Clausen, 2015). Activities such as soccer, which is often perceived as enjoyable and requiring co-operation, might have more positive psychological effects than individual types of exercise. In this study circuit training was also performed within a group setting, which might have given the participants a feeling of social support and team effort, although the specific exercises were performed individually. Future studies should assess the effects of social integration in exercise interventions.

The exercise habits of poly-substance dependent adults are diverse. While many have a sedentary lifestyle, which detrimentally affects cardiometabolic and mental health, others report a highly active lifestyle that includes regular vigorous exercise. It is therefore important to assess the feasibility and effects of diverse exercise interventions in long-term trials, and to include exercises that may appeal to a broad spectrum of patients. As their motivation to exercise is often low, and some patients have mild cognitive impairments due to drug use, flexibility and supported exercise interventions that combine behavioral activation with physical activity promotion (BAcPAc) are recommended (Horrell et al., 2020; Pentecost et al., 2015). In practice, this could mean integrating social-cognitive and practical behavior change elements (e.g., self-monitoring, SMART goal setting) to support exercise adherence.

Improvement in mood after exercise is well documented; exercise is a highly effective method to improve mood states and reduce symptoms of depression, also within SUD populations (Ashdown-Franks et al., 2019; Basso & Suzuki, 2017; Hallgren et al., 2016, 2017; Stubbs et al., 2018). In line with previous studies, we found that lower mood was associated with higher craving (Perkins et al., 2013; Schlauch et al., 2013). Changes in craving were associated with changes in mood, which could indicate a possible mechanism underlying the effects of acute exercise (via improvements in mood). However, the relationship between mood and craving should be examined further in future studies.

Moderator analyses were exploratory, and sample sizes were too small for conclusions to be drawn. The results, however, indicate that exercise might be especially appropriate for some subgroups of SUD patients, such as patients with comorbid depressive disorder and certain primary SUDs. This is in line with previous studies showing effects of acute exercise with reduced symptoms in people with major depression and reductions in craving for opioids in people with opioid dependence (Bailey, Hall, & Fareed, 2011; Bartholomew, Morrison, & Ciccolo, 2005; Meyer, Koltyn, Stegner, Kim, & Cook, 2016). We found that primary opioid SUD might be associated with a larger effect of exercise. One hypothesis for the efficacy of exercise in SUDs is that the release of endogenous opioids might function as a "substitute" for drugs in similar ways as opioid agonist treatments. Because of the chemical similarities of endogenous opioids to heroin and morphine, it is possible that people with opioid SUD might especially benefit from exercise interventions with reduced craving (Bailey et al., 2011; Pareja-Galeano & Sanchis-Gomar, 2013).

The study has several strengths. This is a cross-over RCT where participants act as their own controls, which increases statistical power by eliminating individual subject differences from the overall treatment effect. Although participants were inpatients at the time and they would not be exposed to the environmental cues when not admitted for treatment, exercise was performed in normal naturalistic exercise settings (indoor soccer field and gymnasium) and the generalizability of our finding is expected to be large. Unlike previous studies, which mainly examine pre-post changes, we assessed effects of exercise on craving up to 4 h post exercise, and demonstrated that effects were maintained beyond the initial exercise stimulus. Repeated exercise sessions might give prolonged and possibly accumulated effects on craving, promote longer periods of abstinence and reduce drop out from treatment. Poly-SUDs have been associated with greater psychopathology, increased mortality and poorer treatment outcomes (Gjersing & Bretteville-Jensen, 2017; Medina & Shear, 2007; Williamson, Darke, Ross, & Teesson, 2006). Our findings suggest that exercise-based interventions are a valuable supplementary treatment for this population.

Some limitations are also acknowledged. Single item measures of craving are limited to one definition or aspect of craving, and participants were not asked to specify to which drug they reported craving. Some participants could have misinterpreted psychological or physical sensations associated with acute exercise as 'the urge to use', potentially misclassifying the primary outcome. The participants identified as outliers also lend support to the limitations of using a single item scale. Feasibility and a need to minimize participant burden influenced our decision to use this single-item measure. Although sub-optimal, single item measures of craving have been used in previous acute exercise studies (e.g. (Prapavessis et al., 2014)).

Most of the participants were male, which limits generalizability of the findings. Several participants failed to complete all three interventions, and some participants only participated in one. Dropout and non-adherence rates were higher than expected and at the high end of previous exercise studies for SUDs (7–54 %) (Hallgren et al., 2017). Drop-out rates from SUD treatment is in general high, and might be particularly high for patients with illicit SUDs (Deane, Wootton, Hsu, & Kelly, 2012). In a study of poly-SUDs a higher dropout rate might therefore be expected. Although reasons for not completing the study were in large part due to factors outside the participants' control, factors contributing to participation in exercise interventions over time should be explored further. Analyses performed with completers only indicated a stronger association between exercise and reduced craving. Future studies should explore characteristics related to non-adherence and drop out to assess further possible differences in effect and ways to promote exercise participation.

5. Conclusion

During acute bouts of moderate-intensity exercise cravings were reduced and mood improved among inpatients with poly-SUDs. The effects of exercise were larger than those of psychoeducation. There were no difference in effects of the two types of exercise studied, soccer and circuit training. The exercises we studied are easily accessible and can readily be integrated in clinical settings. Our findings suggest that exercise can be especially useful when craving levels are high and for patients with comorbid depression or opioid use disorder. This suggests that exercise may be useful for a large array of SUD populations and treatment stages.

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