Designing a feasible exercise intervention in first-episode psychosis

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Designing a feasible exercise intervention in first-episode psychosis: exercise quality, engagement and effect

1. Introduction

First-episode psychosis (FEP) is a psychiatric illness characterised by positive and negative symptoms, cognitive difficulties and, for some, the onset of a poor physical health trajectory. FEP represents a crucial early intervention point to target symptoms of psychopathology, reduce the negative metabolic side-effects of antipsychotic medication and encourage a habitually active lifestyle. The transition from FEP to a functional psychosis like schizophrenia is often accompanied by a plethora of cardio-metabolic diseases.

1.1 Sedentary behaviour and metabolic perturbations in severe mental illness

Premature mortality is one of the principal issues associated with severe mental illness, including schizophrenia or related disorders. This is a result of co-morbid illness that is common across chronic mental ill health (Laursen et al., 2014). Sedentariness and physical inactivity are independent but modifiable risk factors that can contribute to all-cause mortality. In a meta-analysis comparing physical activity levels and sedentary lifestyles in schizophrenia, bipolar disorder and major depression, the average amount of sedentary time per day was 476 minutes during waking hours; significantly more than the age and gender matched healthy controls (Vancampfort et al., 2017). Compounding this, many psychotropic drugs, including antidepressants, mood stabilisers and antipsychotics are associated with long-term metabolic issues, such as significant weight gain (Allison et al., 1999), insulin resistance and an atherogenic lipid profile (Tschoner et al., 2007). NICE recommend that FEP be treated with an antipsychotic medication, alongside cognitive behavioural therapy (NICE, 2014), but do not address the cardiometabolic risk factors, or subsequent weight gain as a result of antipsychotic medication. One study demonstrated that at first-psychotic hospital admission, drug naive patients had an average BMI less than that of the general population (Wetterling et al., 2004). However, after 5 years of neuroleptic treatment, the proportion of overweight and obese patients greater than that of the general population. Aside from medication, there are a number of metabolic alterations that have been implicated in FEP, as a predisposition to illness. Dysglycaemia, a term that encapsulates insulin resistance, impaired glucose tolerance and fasting insulin, has been associated with FEP pathology independent of medication, and unbiased by sociological factors (Perry et al., 2019). In a meta-analysis assessing lipid and adipocytokine status in FEP (Pillinger et al., 2017), hypertriglyceridemia and resultant impaired glucose regulation were found to be intrinsic to psychosis, not a side-effect of antipsychotic medication. These underlying perturbed mechanisms are also cogent targets for exercise training, an enhancer of glucose control (Hawley and Lessard, 2008). Thus, the combination of a sedentary lifestyle with the poor metabolic profile associated with FEP pathogenesis and antipsychotic medication can lead to an exacerbated risk of type 2 diabetes, hypertension and cardiovascular disease (Glassman, 2005; Haslam and James, 2005) in FEP. Importantly, the recent Lancet Psychiatry Commission emphasized the importance of protecting physical health from the first presentation of mental illness, with the rationale of aiming to prevent physical comorbidities from arising, particularly in young people receiving antipsychotic treatment (Firth et al., 2019). Within this, exercise was recommended as a fundamental aspect of lifestyle interventions for improving health outcomes. Exercise is a key modulator of metabolic health, regulating chronic adaptions that not only improve physical fitness but also affect energy metabolism. Prescribing exercise as an adjunct treatment, and encouraging habitual activity in FEP is therefore important to counter the negative metabolic effects inherent in psychosis and precipitated by antipsychotic medication.

1.2 Exercise as an adjunctive therapy

It is well-established that exercise is beneficial to metabolic health measures, as well as the many known positive effects on psychological outcomes (Acil et al., 2008; Beebe et al., 2005; Carek et al., 2011; Dunn et al., 2005; Galper et al., 2006) in FEP and schizophrenia. However, most studies experience difficulties with drop-out or attendance, with many reporting less than 50% compliance with the intervention (Beebe et al., 2005) (Beebe et al., 2012). Supervised exercise training appears to be more successful in engaging participants. In our own comparison of FEP and schizophrenia studies that employed supervised training (Abdel-Baki et al., 2013; Battaglia et al., 2013; Beebe et al., 2005; Bredin et al., 2013; Curtis et al., 2016; Dodd et al., 2011; Firth et al., 2018a; Heggelund et al., 2012; Heggelund et al., 2011; Marzolini S., 2009; Pajonk et al., 2010; Scheewe et al., 2013) over non-supervised (Archie et al., 2003; Behere et al., 2011; Duraiswamy et al., 2007; Manjunath et al., 2013), the drop-out rates were 21.3% and 51% respectively. Average attendance for supervised sessions was 74.6%. The best attended interventions were those that included group sessions and structured activities, like football (Battaglia et al., 2013) or interval training (Heggelund et al., 2011), rather than a more general provision of gym access (Curtis et al., 2016), or jogging (Behere et al., 2011).

All of these approaches to design must be considered when developing an exercise intervention to enable effective exercise. Allowing choice of mode of exercise for the intervention is important in this population, together with supervised exercise training has the potential to promote attendance and reduce drop-out rates that are normally very high in this clinical group.

The cost-benefit of exercise provision in early intervention care may potentially outweigh the increasing cost of treatment of symptoms and long-term cardio-metabolic comorbidities. The 2014 NICE costing statement for psychosis and schizophrenia ((NICE), 2014) reported an annual cost of £2.2 billion predicted to rise to £3.7 billion by 2026. The guidelines also stated that "Savings are likely to arise in the future from avoiding adverse health events". It was also reported that 60% of schizophrenia patients have at least one cardiac co-morbidity, costing between $10606 and $15355 per year (Correll et al., 2017).

1.3 Targeting motivations and barriers to exercise participation

A meta-analysis assessed the motivations and barriers to exercise in severe mental illness (Firth et al., 2016), the most common barriers to participation being stress/ depression, lack of support, tiredness, disinterest and physical illness. These self-reported factors closely link to many of the negative symptoms that could be causally linked to the very high rates of exercise-study attrition seen in this clinical group (Vancampfort et al., 2016). However, a review by Firth (Firth et al., 2016) reported motivating factors for taking part in exercise, which were to improve physical health, reduce weight, manage mood, mental health benefits, reducing stress and tension and appearance. Stress was reported as both an important motivating factor as well as a barrier to exercise.

1.4 Standardising exercise bouts for use in an intervention

In order to successfully design an intervention of exercise that is replicable in the future, it is crucial to control for as many components of each training session as possible. It is necessary to employ a particular training intensity that will have a therapeutic benefit, whilst catering to the preferences of each individual patient, in terms of environment and activity type. The minimum training intensity for improvement in cardiovascular fitness, or VO_2max, is 55-65% heart rate (HR) max (Karvonen and Vuorimaa, 1988), so it would be logical to exceed this level in order to observe a meaningful and significant effect of exercise. A review by Roy et al (Roy and McCrory, 2015) described the most accurate equation for estimating HRmax, (*208-(0.7 x age)),* first proposed by Tanaka (Tanaka et al., 2001). The use of this equation, alongside 50-70% VO_2max, which corresponds to 60-80% HR max has the potential to elicit improvements in measures of cardiorespiratory fitness, a method that may be standardized for use during an intervention by setting a personalized ‘HR target zone’ that corresponds to this range. Standardising exercise bouts for the purpose of research is salient for controlling variables in order to maintain scientific integrity of a study. Translating these techniques into ‘real-life’, or clinical practice, is also useful for progressing with an exercise programme or habitual adoption of regular exercise training. Alongside these intensity measures, the World Health Organisation (WHO) recommend that people aged 18-64 should engage in 150 moderate intensity or 75 vigorous intensity minutes of physical activity per week; simple measures that can be accrued in variety of ways, and represent a motivating target for sedentary individuals initiating a more active lifestyle.

1.5 Aims

This study aimed to assess the feasibility of engaging people with FEP with a 12-week exercise training programme. The exercise intervention was designed to maximize participation and engagement by allowing choice of exercise mode and choice of environment in which to exercise.

2. Methods

2.1 Participants

Male patients, aged 16-35, with a diagnosis of first-episode psychosis (as identified by a psychiatrist in keeping with ICD-10 F 20-29, F31.2, 32.3), were recruited from the community-based Birmingham Early Intervention service. Male patients only were recruited, to negate the need to control for the menstrual cycle in female participants. The oestrogen cycle has a significant effect on antioxidant concentration, which was one of the primary outcomes in another arm of this study (Fisher et al., 2020)(in submission). Patients were within 3-years of first presentation of illness. Eligibility criteria were assessed initially by the primary care coordinators for each patient, followed by assessment of habitual activity, via Garmin activity monitoring device, to ensure a sedentary lifestyle. A general health questionnaire was provided to ensure the patient was free from medical conditions that would have prevented participation in moderate intensity aerobic exercise. Exclusion criteria included failure to adhere to pre-testing requirements e.g. refusal to be scanned, provide a blood sample, or significant risk to self or others as identified by the clinical team. Height and weight were assessed at baseline, mid and post-intervention and BMI was calculated at each stage. This study was commenced following approval from the NIHR HRA ethics committee (West Midlands- Edgbaston REC 17/WM/04120).

2.2 Randomisation

Following consent, participants were randomised to either the exercise intervention arm or the control arm (treatment as usual; in terms of clinical care, medication, psychotherapy) of the study. A block randomisation method (http://www.randomization.com) was utilised to allow for equal group distribution in the event of poor or slow recruitment.

2.3 Exercise intervention

Exercise sessions were delivered by an exercise scientist from the School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham. Exercise was undertaken 2-3 times per week, for 40-60 minutes, for 12 weeks. To maximise attendance and participation, participants were given a choice of different activities. Modes of exercise included were running; cycling; swimming; tennis; squash; badminton; circuit training and football. Each training session was supervised and accompanied by a researcher in a 1-to-1 manner. Researchers participated in each activity alongside subjects. Each training session was standardised by use of a HR target zone, based on 60-80% HRmax for each participant. Attendance, drop-out and tracking of HR was measured throughout the intervention period.

2.4 Activity tracking

Habitual activity was assessed for one week at baseline, mid-intervention and post-intervention for both intervention groups via a Garmin VivoSmart® HR (Garmin Ltd., Kansas, USA) activity monitoring watch. Measures of steps, floors climbed, active calories and intensity minutes were taken. ‘Intensity minutes’ refers to the number of minutes per week that a participant achieves a HR above a threshold for ‘moderate intensity’, for periods of 10 minutes or more. Garmin watches were also worn by participants during every exercise session of the intervention. Average HR during the bout, calories burned and time participating in exercise were measured during exercise bouts. Exercising participants were also asked to fill in the International Physical Activity Questionnaire (IPAQ) at each time-point. This questionnaire was employed as a subjective measure to assess habitual activity, including non-leisure time activities (Duncan et al., 2017).

2.5 Analysis of activity data

The quality of the exercise undertaken in training sessions was explored based on heart rate during the activity and by activity type. Each HR zone is defined by a predicted lactate threshold (LT). Zone 1 <68% LT or ‘active recovery’, zone 2 69-82% LT or ‘endurance’, zone 3 83-92% LT or ‘tempo’, zone 4 94-104% LT or ‘threshold and zone 5 105 to max LT or ‘VO2max’. Zone 2 represented the average activity distribution (43%), which was equivalent to 110-130 bpm. The aim of the present study was to exercise participants at 50-70% VO_2max, which would be represented by 115-150 bpm average HR during a session.

2.6 Psychiatric outcomes and functional disability

At each assessment time-point, participants completed the Positive and Negative Symptom Score (PANSS) (Kay et al., 1987), via a structured clinical interview designed to monitor symptoms of psychosis. The PANSS interview assesses positive and negative symptoms and is widely considered the 'gold-standard' method of scoring psychotic behaviour. Interviewers were trained in the completion of PANSS. Quality of life and functional disability were also assessed via the World Health Organisation Quality of Life (WHOQOL) (Group, 1998) and World Health Organisation Disability Assessment (WHODAS) (Andrews et al., 2009) questionnaires. The PANSS interviews and questionnaires alike were delivered by the same researcher delivering the exercise intervention (EF).

2.7 Data analysis

Data analysis was performed using GraphPad Prism 8 software (version 8.0.1, 2018). For baseline and post-intervention measures, relationships between markers were determined using linear regression, and to assess any difference at baseline between the two groups, two-sample t-tests were used. To assess changes between different time points in the study, paired t-tests were used. To compare relationships between marker pre-intervention/ control period vs mid or post, Pearson's correlation coefficient was employed. Outlying values were identified using the ROUT method (Q=1%). Shapiro-Wilk tests for normality were also performed. Fisher's exact test of qualitative measures (smoking status) was employed. An alpha significance value of 0.05 was used throughout.

3. Results

3.1 Baseline

Twenty-two service users with psychosis were recruited and randomised into the study, aged between 17 and 34 (24.8 years ± 4.8 years) (average length of service use was 19 months). The exercise group (n=11) experienced 4 cases of drop-out, one immediately after baseline assessment, two during the first week of exercise, and one after 10 weeks of intervention duration. In the control group 3 participants dropped out immediately before the 13-week post assessment. At baseline, there were no significant differences between participants in the two groups with respect to physical health markers, symptomology and habitual activity (table 1). Antipsychotic, anti-depressant and anti-anxiety medication prescription are expressed in the table. Recruitment and drop-out patterns are detailed in the consort diagram below (figure 1).

3.2 Attendance and retention

Following consent, retention was 76% overall, 64% in the exercise group and 88% in the control group. For exercise group compliance, there was 83% attendance of 2 out of 3 sessions per week, and 41% attendance of 3 out of 3 sessions per week.

3.3 Quality of exercise sessions

As shown by figure 2, participants in the exercise group did not achieve the same intensity measure as the target HR, on average. Each activity type resulted in a different average HR, with running and football the achieving the highest average HR. All activities except for circuit training (which required greater rest periods) were within the target HR zone (50-70% VO_2max), and the distribution of HR zones for the average session was 43% for the target zone 2.

3.4 Concordance with WHO activity recommendations

Using data collected from the Garmin devices at baseline, mid- and post- intervention, it was possible to compare the activity levels of the participants with the WHO recommended level, expressed below as median (figure 3). In the exercise group, intensity minutes per week increased by 73.6% between pre- and mid-intervention, from 215 (±206.9) minutes to 358.9 (±225.8) minutes. However, at the post-intervention assessment the intensity minutes per week had reduced to 151 (±158.3) minutes. The activity in the control group declined between pre-and post-intervention, from 178.9 (±224.9) minutes to 124.1 (±217.7) minutes.

3.5 Comparison of self-report activity versus Garmin-measured activity

At baseline, the control group self-reported (via IPAQ) activity was 744 MET minutes per week, which was similar to the number of minutes measured objectively (via Garmin device). Step-count (*r=0.77 p=0.024*)) and intensity minutes (*r=0.86, p=0.006*) recorded by the Garmin activity monitors were significantly correlated with the self-reported IPAQ MET minutes. The exercise group over-reported their own volume of physical activity. Figure 4 shows Garmin measured moderate intensity exercise per week (bars) alongside self-reported IPAQ measured MET minutes per week (dots). There was no mid-point measure of IPAQ score for the control group. At mid-intervention assessment (6 weeks), self-reported activity recorded as step count (*r=0.53*) and intensity minutes (*r= 0.78*) were concordant, however, by end-point assessment the self-reported activity was far greater than actual recorded activity by the Garmin devices; IPAQ versus steps (r=-0.93, p=0.0021) and intensity minutes (*r=-0.011, p=0.98*). At post-intervention, the control group self-reported activity versus Garmin measures was significantly correlated for intensity minutes (*r=0.94, p=0.0005*) and positively correlated for steps (*r=0.48, p=0.22*). There was a significant decline in Garmin-recorded intensity minutes between mid and post intervention for the exercise group (p=0.05), which was not reflected by the self-reported measure of activity.

3.6 PANSS scores and symptomology

In each of the three scores exercise either conferred protection against declining scores observed in the control group or resulted in an improvement between baseline and post-intervention measurement, expressed as mean (±s.d.). There was a 1.44% increase in negative score in participants in the exercise group (a score of 19.43 (±2.1) to 19.71 (±4.11)), and a 13.89% increase in participants in the control group (18.88 (±6.66) to 21.5 (±4.45)) (*d= 0.76*). There was a 17.31% decrease in positive symptoms of PANSS in participants in the exercise group (18.14 (±5.55) to 15 (±4.97)), and a 7.83% decrease in the non-exercising controls (17.63 (±5.88) to 16.25 (±4.68)). Participants in the exercise group reported a 10.98% decrease in PANSS general score (40.43 (±9.81) to 36.43 (±5.86)) (*d= -0.59*), compared to a 2.82% decrease observed in participants in the control group (39.88 (±11.37) to 38.75 (±8.97)) (*d= -0.21*) (figure 5).

3.8 Patient measures of quality of life and disability

In an assessment of the WHODAS questionnaire, expressed as mean (±s.d.), there was an observed decrease of 12.65% in the exercise group (45.93 (±19.8) to 40.12 (±19.09)), and an increase of 20.78% in the control group (27.48 (±20.29) to 33.19 (±20.99)). For the WHOQOL, score increased in both groups with an 11.21% increase observed in participants in the exercise group (45.41 (±16.18) to 50.5 (±15.78)) and a 5.32% increase observed in the control group (48.13 (±18.77) to 50.69 (±16.78)) (figure 6).

3.7 Metabolic changes

No significant change in weight or BMI was observed in either group. A 2.27% increase in body weight was observed in participants in the exercise group, but this was not statistically significant. The control group demonstrated a 1.45% increase in body weight. A 7% weight gain is defined as clinically meaningful, particularly in the context of antipsychotic medication prescription (Dayabandara et al., 2017).

4. Discussion

This study has shown that it is feasible to engage an FEP population in a 12-week intervention of exercise training. The present study achieved 83% compliance in exercise twice per week, and 41% compliance in exercise three times per week. This level of engagement in regular exercise resulted in reductions in positive and general psychopathology scores, and the patient group reported a reduced disability score. 13% of eligible cases for this intervention refused as a result of disinterest, suggesting that study design promoted recruitment and participation. The choice of exercise modality offered to patients did not have an effect on reaching the pre-standardised target intensity for exercise bouts. Designing an intervention to maximise participation and retention prioritised exercise session quality, alongside a choice element for the participant. This choice provided the intervention cohort with novel experiences, and the opportunity for skill acquisition whilst maintaining intensity.

4.1 Facilitating a lifestyle change

As well as the barriers to participation and motivating factors described above, there are a number of common co-morbid conditions and symptoms associated with psychosis that may also impact the ability of FEP patients to initiate exercise. Anergia, anhedonia, tardive dyskinesia, depression, anxiety and poor concentration are all characteristic of FEP, and are contributing factors to the sedentary lifestyle that is often reported in this population. Facilitating behaviour change in a healthy group is challenging, and when transferred to an FEP group the feasibility of exercise alone is difficult, but to encourage a lifestyle change is especially challenging. This study demonstrated the sustainability of regular exercise in an FEP population, when accompanied by another leading the session.

Participants in the current study recorded physical activity via the IPAQ questionnaire, a well-validated self-report measure, in addition to wearing a Garmin activity monitor, which measured habitual activity objectively. The results from the Garmin activity device suggest that both the exercise and control groups met the WHO recommendations for moderate intensity physical activity per week, at baseline. This was unexpected, but this observation is likely to be an effect of being enrolled into an ‘exercise study’, without knowledge of which group they will be part of (Orne, 2002). In the UK biobank study (Firth et al., 2018b), people with schizophrenia were significantly less active than the general population, however self-report measures failed to identify this. In that study, schizophrenia patients and healthy controls both reported the same activity levels, but accelerometer data showed that 95% of schizophrenia patients fell within the bottom 15-35% of the general population. In the current study, the post-intervention measure of habitual activity was decreased compared to that of the mid-intervention measure (figure 4), in spite of the perceived high level of activity (IPAQ measure). These data indicate that in order for activity levels to be sustained, the support provided throughout the intervention also needs to be sustained, providing an argument for provision of regular exercise as part of day-to-day care. Alongside the positive psychological and functional outcomes demonstrated by this study, exercise provides a low cost, low side-effect adjunctive therapy to the traditional antipsychotic medications prescribed in FEP.

4.2 Functional measures, body weight and psychopathology

Exercise has the potential to protect against emerging functional decline in the early phases of psychosis. This study observed clinically meaningful changes in the PANSS positive and general psychopathology subscales, as well as the self-assessment of disability in those participants engaged in exercise training. The control group demonstrated an increase in the negative subscale, indicating that exercise was protective of this disease-related worsening of symptoms.

Antipsychotic medications are reported to be most effective in reducing the positive symptoms of psychosis (Mueser et al., 2013), whilst having minimal effect on negative symptoms and cognitive function. Positive symptoms represent a therapeutic target of exercise training, shown by this study, which may ultimately reduce the reliance on psychotropic medication. Conversely, since all participants in this study were treated with at least one antipsychotic, exercise may enhance the effect of medication. A recent 18-month study in a severe long-term schizophrenia population compared treatment as usual and a multidisciplinary lifestyle treatment (MULTI) that focussed on decreasing sedentary behaviour, increasing physical activity levels and improving dietary habits (Deenik et al., 2018). The MULTI group displayed significant reductions in daily dose of medication, indicating a lesser need for drug treatment as a result of lifestyle changes.

Physiologically, one of the greatest problems associated with psychosis and subsequent antipsychotic prescription is weight gain and related metabolic illnesses. Adaption to exercise training, as an adjunctive therapy, has a number of metabolic benefits, including cardiovascular fitness, reduced blood pressure and BMI and improved lean muscle mass (Wong et al., 2008). Exercise is often used as a means to lose weight in a healthy population. However, body weight was maintained in the participants of the present study, with neither a reduction nor an increase in weight observed, which was expected in this FEP population (Abdel-Baki et al., 2013; Ball et al., 2001; Daumit et al., 2011). An absence of reduction in body weight could be a result of continued poor diet alongside the intervention, or may be attributable to an increase in muscle mass often seen alongside a reduction in fat mass (Egan and Zierath, 2013); a positive metabolic change, but often not reflected in body weight assessment. However, as antipsychotic medication often causes weight gain, exercise as an adjunct alongside this treatment alongside antipsychotic treatment has the potential to negate this weight-gain, before it arises (Maayan and Correll, 2010) (Firth et al., 2019).

The quality of life score improved in both intervention groups across the 12-weeks of intervention, but a greater increase was recorded in the exercise group. Although the current study was not powered to detect this, further trials should focus on the physical health and functional outcomes measured here. Measures of quality of life and disability are informative markers of a patients' well-being, with 'recovery-orientated' outcomes being the most important measure from the view of a care team, and the patient themselves (Dixon et al., 2016). Other research has described exercise as a "robust add-on treatment in psychosis that improves quality of life, global functioning and depressive symptoms" (Dauwan et al., 2016). The WHODAS questionnaire represents a subjective measure of disability and questions the patients' own perception of incapacity in many daily tasks. This acuity is one of the salient barriers to recovery. Exercise may affect this notion as even the process of regular physical activity may interact with the self-perceived notion of inability and disability. The observed reduction in WHODAS score post-exercise versus the increased score in the non-exercising group may therefore represent a change in this perception.

4.3 Limitations and strengths

The strength of this study was that it demonstrated the feasibility of undertaking supervised exercise in a FEP group, at least twice per week. However, if considering this study as a trial based on symptom improvement then the main limitation of this study was participant number. The sample size was small, rendering many of the time-point and inter-marker comparisons statistically insignificant, despite the argued clinical importance of patient-orientated changes observed in the exercise group. However, as a proof-of-concept trial, it was successful in terms of intervention design and compliance. Football, the only team-based activity offered, was very popular, and was an easy way to facilitate target energy expenditure. Based on this experience, provision of group-sports is an aspect of the intervention that could be increased, in a definitive study across a variety of exercise modes.

Despite the provision of many indoor-based activities, poor and unpredictable weather in the UK was certainly a factor for participant engagement. There was a greater incidence of 'no-shows' during wet and cold days. This effect was particularly salient during the winter months of the year-long trial period. All time-point measures and activity accompaniment were conducted by the same researcher (EF). In the future, the processes of time-point data collection and exercise delivery should be separate, since interview answers may be somewhat different in the presence of a familiar member of the study team.

4.4 Conclusions

This study demonstrated the feasibility of a supervised exercise intervention in a cohort of males with a diagnosis of first-episode psychosis. Exercise was able to elicit a change in symptomology, quality of life and disability. By employing a study design that prioritised variety in exercise, but ensured the quality and intensity of each training bout this study recorded compliance to the intervention that was much greater than most other exercise studies in this clinical group.

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