

# Exercise Reduces Dysphoria in Clinical High Risk for Psychosis: A Randomized Controlled Trial

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Individuals at clinical high risk for psychosis (CHR-p) are a heterogeneous behavioral endophenotype that includes attenuated positive symptoms and decreased function that predicts higher rates of psychosis, among other disorders.<sup>1</sup> Relatedly, early interventions for the CHR-p endophenotype with a narrow benefit to specific mechanisms of psychosis may not be appropriate.<sup>2</sup> Instead, early interventions for CHR-p should focus on benefits for general symptoms.<sup>3</sup> General symptoms are nonspecific neuropsychiatric symptoms that may result from CHR-p status, including sleep disturbance, dysphoric mood, motor disturbance, and stress tolerance.<sup>4–7</sup> Exercise has broad benefits for general symptoms, including improving sleep quality, elevating mood, improving motor control, and increasing stress tolerance, broadening the benefits of intervention

and suggesting potential transdiagnostic benefit.<sup>8–10</sup> Despite this potential, exercise interventions have focused on the engagement of a particular mechanistic pathway to target the distinguishing symptoms of psychosis, including neuroprotective hippocampal, cognitive, and core symptoms pathways.<sup>11–14</sup> It remains unknown if exercise benefits general symptoms or if general symptoms reduce as core symptoms abate.

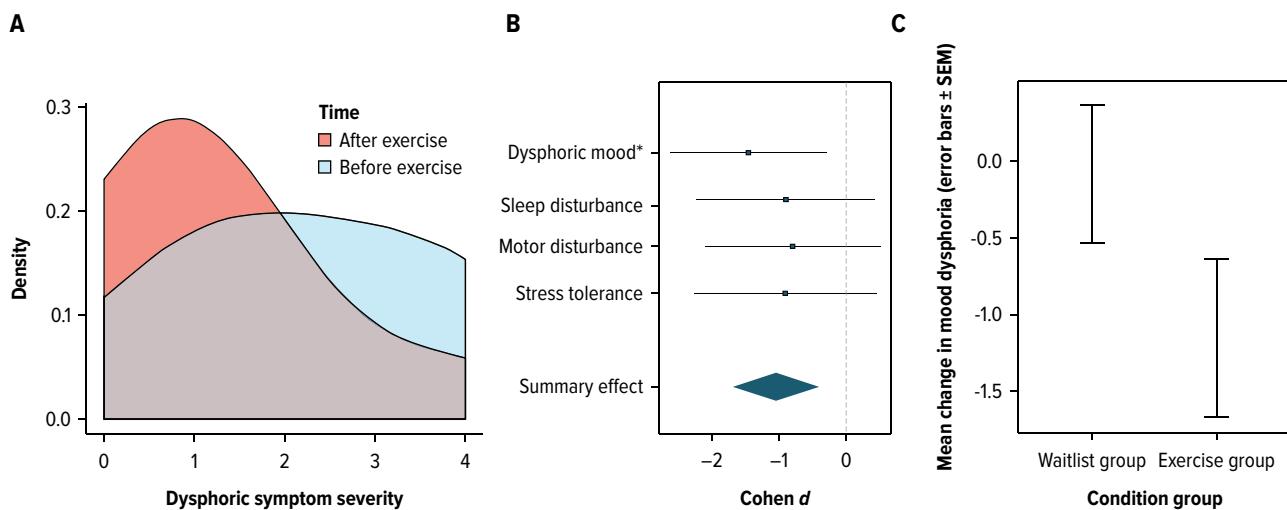
## Methods

The current analyses build on an exercise intervention (ClinicalTrials.gov identifier: NCT02155699; August 2018 to November 2021) that included high-impact treadmill interval training. This intervention consisted of participants beginning moderate progressing to intense aerobic exercise (twice weekly for 3 months) with

sessions designed to elicit 80%  $\text{VO}_{2\text{max}}$  for the majority of the time with 1-minute high-intensity intervals at 95% of  $\text{VO}_{2\text{max}}$  every 10 minutes for 3 repetitions, for a total of 30 minutes.<sup>11</sup> This study found that exercise improved hippocampal connectivity and working memory performance and attenuated positive symptoms of psychosis, and it added exploratory analyses of benefits for general symptoms.<sup>11</sup> All neuroimaging and clinical staff were independent of the intervention and remained blinded. Inclusion criteria included the presence of an attenuated psychosis syndrome<sup>15</sup> and a current sedentary lifestyle (<60-min exercise per week for 6 months). Exclusion criteria included current psychosis, antipsychotic prescription, or a substance use disorder. All participants were randomly assigned to intervention conditions with a balance for gender. They completed 2 assessments (before assignment and postintervention)<sup>11</sup> for a

Figure 1.

**Exercise Impact on General Symptoms: (A) Change in Distribution of Severity Scores, (B) Specificity of Decrease in Mood Dysphoria Among General Symptoms, and (C) Decrease in Mood Dysphoria by Treatment Condition**



\* $P = .0225$ .

full description of the protocol and subject demographics.<sup>14</sup> The final sample included 17 exercise and 13 waitlist subjects. Analyses first examine changes within individuals before and after exercise; significant changes will be related to changes in core symptoms to investigate whether the change is proportional to core symptom change or relatively independent.

## Results

A mixed-effects model approach was used that accounted for individual effects as random effects, and the fixed effects of age, sex, and body mass index were nested within time (pretrial, posttrial) to predict each general symptom (sleep disturbance, dysphoric mood, motor disturbance, stress tolerance as measured by the Structured Interview for Psychosis Risk Syndromes) in separate models with Satterthwaite correction. Dysphoric mood was significantly reduced after the exercise intervention ( $t_{17} = -2.43$ ,  $b = -0.588$  95% CI [-1.02, -0.156],  $P = .0225$ ,  $d = -0.76$  [-1.46, -0.06]) (Figure 1A). There were no other significant changes in other general symptoms ( $P > .5$ ) (Figure 1B). Waitlist individuals did not show a change in mood dysphoria in the same period ( $P = .82$ ) (Figure 1C). Follow-up analyses were conducted to examine a group-by-time interaction ( $t_{32} = 1.85$ ,  $P = .07$ ). Changes in mood dysphoria symptoms remained significant even when accounting for previously reported changes (positive symptoms, working memory, and hippocampal features) and were not significantly related to these variables ( $r$ 's  $< .02$ ,  $P$ 's  $> .93$ ).

## Discussion

Although caution is needed when interpreting this specificity, mood dysphoria may reflect a distinct benefit of exercise that may occur along distinct mechanistic pathways, eg, decreased inflammation, increased endorphins,<sup>16</sup> as there is no evidence of a relationship to change in core symptoms.

Limitations include that the current exercise protocol may not be optimized to elicit changes in sleep quality, motor

disturbance, or stress tolerance. Additionally, general symptom ranges may be limited because they are being assessed clinically rather than objectively,<sup>17</sup> and the sample was enriched for positive symptom severity rather than general symptom severity. Additionally, a small sample size may reduce power to detect a group-by-time interaction, warranting caution when generalizing these findings. Nevertheless, these findings encourage the consideration of early interventions that may benefit both core symptoms and general symptoms with the potential to also reduce alternative conversions, eg, depression.

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