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A Supervised Exercise Intervention for Youth at Risk for Psychosis: An Open-Label Pilot Study

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Abstract

Objective—A rapidly accumulating body of research suggests that exercise can improve symptoms and wellbeing in patients suffering from psychosis. Exercise may also promote neurogenesis in the hippocampus, a structure that plays an important role in the pathophysiology of psychosis. To date, there has not been an intervention focused on exercise prior to the onset of psychosis, a critical time for prevention of more serious illness.

Method—In this pilot study, 12 young adults at ultrahigh risk (UHR) for psychosis were enrolled in a 12-week open-label exercise intervention. Participants were randomized to exercise 2 or 3 times each week and exercised between 65–85% of maximal oxygen capacity (VO_2max) for 30 minutes each session under the supervision of an exercise physiologist. Positive and negative symptoms, social and role function, performance on neurocognitive tests, cardiovascular fitness, and hippocampal structure and functional connectivity were evaluated before and after the trial.

Results—A total of 9 participants completed the exercise intervention. Participants showed improved positive and negative symptoms and social and role functioning; improvement in multiple areas of cognition; and increased functional connectivity between the left hippocampus and occipital cortex after 12 weeks of exercise.

Conclusion—The results of this study suggest that exercise interventions are feasible in an UHR sample and may promote improvement in clinical, social, and cognitive domains as well as changes to brain function in regions impacted by the development of psychosis. These findings set the stage for an ongoing phase-II randomized controlled trial.

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CONFLICTS OF INTEREST

Dr. Mittal is a consultant with Takeda Pharmaceuticals. No other authors have conflicts to disclose.

Clinical Trials Registration—(https://clinicaltrials.gov/ct2/show/NCT02155699)

Keywords

Exercise; Hippocampus; Prodrome; Intervention; Open-Label

INTRODUCTION

Regular physical activity is an important component to maintaining physical and mental health.[1] A growing body of innovative research suggests that exercise could be an impactful supplement to traditional treatments for psychosis.[2, 3] Recent reviews illustrate a variety of aerobic, anaerobic and combined exercise interventions for patients with psychosis including running, walking, team sports, weight lifting, and yoga.[3–5] Indeed, there have been exciting developments in exercise interventions in schizophrenia populations, and findings suggest that exercise may improve symptom, cognitive, cardiovascular, social and role functioning, and neurobiological domains; potentially facilitating greater quality of life and well-being for people with debilitating mental illnesses.[3, 6–11] Given the demonstrated benefits of exercise interventions in those with a formal psychotic disorder, the current study aims to test the feasibility of an aerobic exercise intervention prior to the onset of the illness.

The period preceding the onset of psychosis is characterized by attenuated psychotic symptoms in both positive and negative domains and a decline in functioning.[12] Studying individuals at ultrahigh risk (UHR) for psychosis can be an important point of intervention, as the disorder typically develops in early adulthood and remains a chronic problem throughout life; intervening early in the course of the illness may help prevent or decrease the significant costs and distress caused by the illness.[13]

Previous work provides an impetus for exercise interventions prior to the onset of psychosis. Cross sectional and prospective studies show that UHR individuals on average spend more time being sedentary, engage in less intense exercise, and have poorer markers of cardiorespiratory fitness compared to those who did not develop the disorder or healthy controls.[14,15,16] In addition, UHR individuals report less motivation for getting exercise, and engage in exercise that requires little social interaction compared to healthy individuals.[17,18] Adolescents at risk for psychosis are less physically active and often engage in poor health behaviors compared to typically developing adolescents, including an increased rate of tobacco and alcohol use.[19] Taken together, individuals at risk for psychosis appear to be less physically active than typically developing young adults and this may have an impact on other markers of health and functioning.

One possible mechanism by which exercise improves cognition, as well as positive and negative symptoms, is by promoting neuroplasticity in the hippocampus.[20–22] The hippocampus has been widely cited as a major brain region impaired in psychosis.[23] This impairment has far ranging implications for the neurobiology underlying signs and symptoms of psychosis, as the brain region plays an important role in both modulating the biological stress response and higher order cognitive functions.[24] Furthermore, there is evidence that the structure and connections to the hippocampus are impaired prior to the onset of psychosis.[25, 26] Importantly, cross sectional research with UHR individuals suggests

that smaller temporal lobe volume is related to decreased physical activity.[16] Examining the structure and function of the hippocampus may provide important insight into neurobiological effects of exercise in UHR participants.

We recruited 12 UHR participants to complete 3 months of moderate-to-vigorous intensity aerobic exercise. The participants underwent structured clinical interviews, assessment of social and role function, cognitive testing, cardiovascular fitness testing, and structural and resting state functional neuroimaging of the hippocampus before and after the exercise intervention. The major objective of this pilot study was to establish the feasibility of an exercise intervention for UHR participants. Based on the noted results from patients with schizophrenia,[2, 3, 27] we conducted exploratory analysis of positive and negative symptoms, social and role function, cognition, and physical fitness. In addition, we examined change in hippocampal volume and anatomical seed based functional connectivity.

METHODS

About the participants

Adolescent and young adult UHR participants between 16 and 24 years of age (M = 19.42, SD = 1.16) were recruited to the University of Colorado Boulder's Adolescent Development and Preventive Treatment (ADAPT) research program. An inclusion criterion for the study was that the participant reported a predominantly sedentary lifestyle of no more than 60 minutes of at least moderate physical activity per week for the past six months. Exclusion criteria consisted of head injury, the presence of a neurological disorder, lifetime substance dependence, current antipsychotic medication use, and the presence of any contraindication to the magnetic resonance imaging (MRI) environment (e.g. pregnant or metal in the body). The presence or lifetime history of an Axis I psychotic disorder was also an exclusion criterion. The study was approved by the University of Colorado Boulder Institutional Review Board, written consent or assent was obtained, and the study was registered at ClinicalTrials.gov (identifier: NCT02155699).

Clinical Interviews

The Structured Interview for Prodromal Syndromes (SIPS)[28, 29] was administered before and after the exercise intervention to diagnose a prodromal syndrome and track positive and negative symptom changes. A total sum score for the positive and negative symptom domain is used as an indicator of the respective dimensions of symptomatology. The Structured Clinical Interview for Axis-I DSM-IV Disorders (SCID-IV)[30] was also administered to rule out a psychotic disorder diagnosis. Interviewers were kept blind to the prescribed exercise condition for each participant. See supplemental material for more information regarding UHR criteria and training of clinical interviewers.

Assessment of social/role functioning

Social and role functioning was assessed by trained graduate students using scales specifically designed for adolescents/young adults: the Global Functioning Scale: Social (GFS:S)[31] and the Global Functioning Scale: Role (GFS:R).[32,33] These scales provide

ratings on two separate 10-point Likert scales, which are scored independent of symptom severity and higher scores correspond to better functioning.

Cognitive Testing

Participants completed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery of cognitive tasks before and after the exercise intervention.[34] The MATRICS battery includes tests for speed of processing, verbal and visual learning, working memory, reasoning and problem solving, attention, and social cognition. The MATRICS was administered by trained graduate students in a quiet room. Raw scores were transformed to T scores using established standard scores, which were used in analyses concerning pre/post differences.

Physical Fitness Assessment

Baseline and follow-up cardiovascular fitness was measured with maximum oxygen uptake (VO_2max), which also served as the basis for individually tailored exercise prescriptions.[35] The participants ran on a treadmill and the speed remained the same throughout the test but the incline of the treadmill belt increased 2% every 2 min (or 2.5% for speeds 6 mph or greater). The treadmill speed was determined using participant heart rate and ratings of perceived exertion (RPE). The initial speed was set to 70% of age-predicted max heart rate and an RPE rating of around 13 (“somewhat hard”). Staying within these parameters generally yielded an 8–12 min test; the recommended target for VO_2max testing.[36] VO_2max was determined using a valid primary criterion of having achieved a plateau in VO_2 as well as secondary criteria outlined by Pimentel and colleagues[37] including respiratory exchange ratio (RER)max≥1.1, RPEmax≥18, and age predicted heart rate max ±10bpm.

Exercise Intervention

Participants were randomly assigned to one of two conditions: moderate or vigorous. The moderate condition required exercise 2 days a week at 65% of their VO_2max for a total of 24 sessions. The vigorous condition required exercise 3 days a week at 85% of the participant’s VO_2max for a total of 36 sessions. Participants wore a Polar FT1 heart rate monitor (https://www.polar.com/us-en) throughout each exercise session, and an exercise physiologist monitored the participant’s exercise in order to keep the participant’s heart rate at ± 5% of the prescribed target intensity. Initial exercise sessions lasted 15 minutes at 55% of VO2max intensity and were gradually increased to 30 minutes and target intensity within the first 3 weeks. The remaining exercise sessions lasted 30 minutes and were conducted at prescribed exercise intensity. Participants were given the choice to ride stationary bikes, run/walk on treadmills, or use elliptical machines at each session. At the end of each exercise session, participants were compensated.

Structural and Resting state functional connectivity MRI processing

Structural MRI scans were acquired on a Siemens 3-Tesla Magnetom TIM Trio MRI scanner (Siemens AG, Munich, Germany) with a 12-channel head coil. Left and right hippocampus and total intracranial volume were segmented using the FreeSurfer 5.3.0 suite of automated

tools.[38] Each structure was divided by the participant's TICV to control for whole brain volume.

A resting state functional connectivity MRI (fcMRI) scan was acquired. Data were preprocessed in FSL (v.5; http://fsl.fmrib.ox.ac.uk/fsl), and fcMRI analysis was performed in the Conn toolbox v.15b.[39] Connectivity between the left or right hippocampal seed ROI was calculated with all other voxels in the brain. For more detailed methods of the structural and fcMRI analysis see the supplemental material.

Data Analysis

Following a similar strategy to Nuechterlein and colleagues[7] for examining the magnitude of changes following exercise in a small sample only the effect size estimates (Cohen's d) were calculated for pre/post outcome variables.

RESULTS[1]

Participants

A total of 12 participants (6 male, 6 female) were recruited to the exercise study, which took place over a 24-month recruitment period. Of those participants, 9 (4 male, 5 female; 75% of sample) participants completed the exercise intervention and returned for follow-up assessment. There were 7 participants in the moderate condition that completed 24 sessions and 2 participants in the vigorous condition that completed 36 sessions. The 3 drop-outs were in the vigorous condition and completed 8, 18, and 31 sessions. Because there were few participants who completed the vigorous condition, subsequent analyses of the exercise intervention collapsed across conditions.

Social/Role functioning and symptom improvement post trial

There was a small to medium improvement in social functioning (d = .45) and role functioning (d = .33). Participants reported a medium to large decrease in positive symptoms post exercise, (d = −.61) as well as a small to medium decrease in negative symptoms, (d = −.47). See Table 1.

Cognitive improvement

Participants exhibited substantial post trial improvement in a number of cognitive domains including Working Memory (d = .92), Verbal Learning (d = .63), Visual Learning (d = .76), Speed of Processing (d = 1.3), Attention/Vigilance (d = .76), and Reasoning and Problem Solving (d = .47). There was no improvement in social cognition (d = −.31). Overall, the participants showed significant improvement on the MATRICS cognitive battery, with a large composite score improvement (d = 1.74).

[1]Previous Presentation: Poster presentation at the Society for Research in Psychopathology meeting, Baltimore, Maryland, September 29 – October 2, 2016.

Physical fitness

The participants did not show improvements to physical fitness as measured by VO_2max (d = −.28).

Structural imaging and resting state functional connectivity

There were no changes to hippocampal volume post exercise for either the left (d = .18) or right (d = .31) hippocampus. Using the left hippocampus seed, participants showed increased functional connectivity to bilateral occipital cortices after the exercise intervention. The right hippocampus seed did not show changes in connectivity. See Table 2 and Figure 1.

DISCUSSION

In the first open-label exercise intervention for youth at risk for psychosis, we showed that exercise led to a reduction in positive and negative symptoms, improved social and role function, and improved cognition. These results suggest that exercise interventions are feasible within UHR samples and may help to improve important domains that are affected during the development of psychosis. Unique to this study from others in psychosis is the examination of brain structure and functional connectivity, suggesting that exercise may lead to changes in the functional organization of cortico-hippocampal networks.

As noted, we recruited a total of 12 participants to the exercise intervention. Of the 9 participants who completed the study, each attended 100% of the exercise sessions. It is important to note that the retention of participants and adherence to the aerobic exercise guidelines was in line with and in some cases better than other exercise interventions in adolescent and adult samples.[40–42] While the sample size in this study is small, it is similar to other aerobic exercise interventions in schizophrenia that have reported sample sizes between 8 and 16 participants.[2] Anecdotally, many of the participants were interested in being in the study to become more physically active and to improve their overall health. This may have been an important motivational tool to seeking help initially, as exercise has positive social benefits and does not carry the same stigma as psychotherapy or pharmacological treatment.[43, 44] Social factors regarding the high value of exercise in the community in which the study was conducted (Boulder, CO) as well as monetary and other incentives may have also played a role in motivating participants to complete the intervention. For those who did not complete the exercise intervention, low motivation and loss of contact during the exercise intervention remained a substantial barrier. Innovative efforts to address adherence to exercise regimens in patients with psychosis have suggested that initial sessions of an exercise intervention include psychoeducation around exercise and goal setting.[45–47]

An important outcome of this study is the improvement of positive and negative symptoms, as well as social and role functioning. One mechanism by which exercise may improve symptoms and increase social and role function is through behavioral activation.[48, 49] Another explanation from exercise interventions in schizophrenia patients suggests that exercise may promote self-esteem and confidence, leading to further engagement in the

world and better well-being.[50] It is also possible that regression to the mean accounted for these results, and it will be important to conduct a controlled trial to ensure the changes are related to the intervention. The UHR period is heterogeneous in terms of symptom presentation and course; fluctuations in the intensity and distress of symptoms are common in this population.[51] Importantly, we have begun recruitment for a follow-up randomized controlled trial (RCT) study incorporating a wait-listed group of UHR and healthy matched controls, which may provide further understanding of the mechanisms by which exercise can help ameliorate features of psychosis development.

Cognitive function improvement is consistent with a large body of work in human and non-human exercise studies.[6, 8, 52–54] However, there remains some controversy about whether aerobic or anaerobic exercise produces improved cognition in patients with psychosis.[48] A promising avenue of research combines high intensity exercise and cognitive remediation training.[7] Future work examining aerobic and anaerobic exercise to improve cognition in UHR youth would be helpful for developing personalized medicine and exercise prescriptions for those at risk for psychosis.

The exercise intervention was calibrated to each individual's physical fitness level using VO_2max. We were surprised to see that VO_2max did not improve after the exercise intervention. However, individual differences in genetic heritability for cardiovascular performance, response to training, body composition of lipids, and glucose metabolism could potentially affect these results.[55, 56] Although the finding that VO_2max didn't change is consistent with a number of other aerobic exercise interventions in schizophrenia patients, these results also encourage future interventions to consider including higher intensity exercise. A wealth of evidence now indicates that higher intensity aerobic exercise – particularly high intensity interval (HIIT) training – improves cardiovascular fitness and related metabolic measures.[57] The current sample included cardiovascularly healthy but sedentary participants who exercised at two different intensities (i.e., 65% and 85% of VO_2max), and most exercised at the lower intensity, thus it is not terribly surprising that we did not see large improvements in cardiovascular fitness. However, even without notable improvements in cardiovascular fitness in the UHR group, the results suggest that there are substantial benefits to this exercise intervention in other functional domains critical to quality of life in this population. This study thus represents an important starting point for exercise prescriptions for UHR individuals.

Consistent with other UHR studies we did not find changes to hippocampus volume for either the left or right hippocampus.[9, 58] Importantly, we used a multimodal neuroimaging approach and the finding that increased hippocampal functional connectivity of the hippocampus is an innovative development to understanding the role of the hippocampus in the neurodevelopment of psychosis. The direction and magnitude of the change in hippocampal connectivity is difficult to interpret given the lack of comparison subjects. However, it has been suggested in other studies that increased occipital-hippocampal connectivity is associated with the task positive network and spatial memory performance.[59, 60]

A diathesis stress model of psychosis suggests that neurodevelopmental abnormalities begin early in adulthood, and then brain maturational factors and stress from the environment interact with these vulnerabilities to promote the emergence of psychosis.[61–63] As noted, exercise may target brain regions thought to be a part of the abnormal neurodevelopment in psychosis. One brain region that is central to the neural diathesis stress model of psychosis – the hippocampus – is susceptible to neurogenesis and improved synaptic plasticity through regular exercise.[6, 64] The current results support this model of exercise intervening on both neurodevelopmental and behavioral levels of risk for psychosis. Importantly, we found that the exercise intervention attenuated psychotic symptoms, improved social and role function, and improved cognition. In addition, we saw increased functional connectivity between the hippocampus and the occipital cortex. Replication of these results and further examination of the links between these results in larger samples of UHR participants using a higher intensity exercise stimulus may produce a helpful treatment prescription for those at risk for psychosis.

There are a number of strengths and limitations to this study. The final sample size was small, did not include enough participants to compare exercise conditions, and the participants did not show changes in cardiovascular fitness. The planned RCT will improve on these limitations by including a wait list clinical and healthy control group, require two weekly sessions (as 3 sessions was less tolerable), and incorporate HIIT training, which should be a more powerful exercise stimulus for improving $V0_2$max.[65] We assessed the participants directly after they finished the exercise intervention, and importantly, none of the participants transitioned to psychosis during the intervention. Current research suggests that as many as 35% of UHR individuals will transition to psychosis and others may experience problems with mood, anxiety, and other mental health issues. [51, 66] Thus, longitudinal studies incorporating multiple domains of physical and mental health assessment are needed to see if the benefits of exercise interventions continue to improve the health and well-being of people at risk for psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Points

- There are few interventions that can help with all of the early signs of psychosis; aerobic exercise may be a powerful treatment option with holistic benefits.
- Consider exercise in the treatment planning for young adults showing early signs of psychosis.

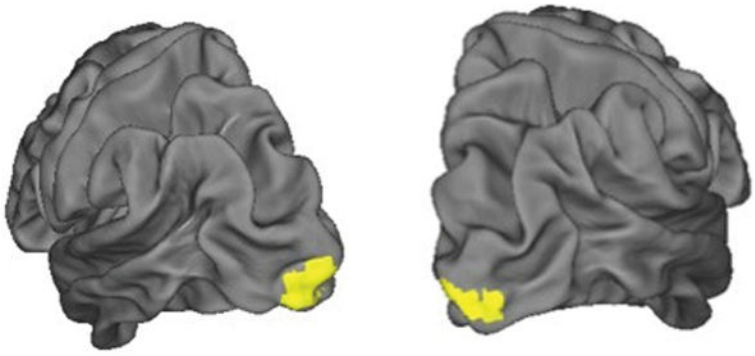

Figure 1.
Occipital regions showing increased connectivity to the left hippocampal anatomical seed after the exercise intervention.

Table 1

Behavioral outcome measures for the exercise intervention. Mean (SD) of outcome variables to the exercise study. Cohen's d is used to measure the change in outcome variable pre to post exercise intervention.

Variable	Pre - Exercise Mean (SD)	Post - Exercise Mean (SD)	d
Symptoms			
Positive Symptoms	12.33 (4.91)	9.89 (4.04)	−.61
Negative Symptoms	12.75 (9.29)	9 (6.16)	−.47
Social and Role Functioning			
Global Functioning: Social	6.83 (1.19)	7.33 (1.5)	.45
Global Functioning Role	6.83 (1.4)	7.22 (1.09)	.33
Cognition			
Speed of Processing	52.22 (9.3)	58.22 (13.38)	1.3
Attention	46.38 (7.84)	51 (6.08)	.76
Working Memory	49 (8.22)	51.78 (8.76)	.92
Verbal Learning	48.22 (9.4)	51.11 (9.61)	.63
Visual Learning	44.56 (8.43)	51.56 (5.96)	.76
Reasoning and Problem Solving	51.56 (4.85)	55 (5.81)	.47
Social Cognition	47.22 (7.31)	44.22 (12.83)	−.31
Composite	48.25 (8.41)	52.89 (9.21)	1.74
Hippocampus Volume			
Left Hippocampus	.0025 (.00024)	.0025 (.00019)	.18
Right Hippocampus	.0026 (.00025)	.0026 (.00019)	.31
Physical health			
VO2-max	41.16 (8.27)	39.52 (8.58)	−.28

Table 2

Results of the left hippocampal seed based connectivity analysis. MNI coordinates for the peak cluster location, the peak cluster size (in voxels) are included.

Direction of Connectivity	Region	Cluster Size	MNI Coordinates			t-value
			X	Y	Z	
Baseline < Post Exercise	Left Occipital Pole	526	−16	−104	4	9.71***
	Right Occipital Pole	256	32	−98	0	10.79***
	Lateral Occipital Cortex	63	52	−76	−6	10.96***

FDR corrected, cluster level *p*-values are noted for all t-values as

* $p \leq .05$,

** $p \leq .01$,

*** $p \leq .001$.