Am J of Geriatric Psychiatry 27:6 (2019) 611–616

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journal homepage: www.ajgponline.org

Brief Report

# Exercise for Depression: A Feasibility Trial Exploring Neural Mechanisms

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**ARTICLE INFO**

*Article history:*
Received November, 13 2018
Revised January, 9 2019
Accepted January, 16 2019

*Key Words:*
Exercise
depression
brain
MRI

**ABSTRACT**

***Objective:*** *The aim of this study was to test the feasibility of an exercise augmentation to pharmacotherapy in depressed younger and older adults while exploring neural mechanisms.* ***Methods:*** *A randomized, double-blind, controlled clinical trial was conducted in 15 inactive younger (20–39 years) and older (60–79 years) adults meeting* Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, *criteria for a major depressive episode (https://clinicaltrials.gov/ct2/show/NCT02407704). Participants were randomized to receive a 12-week regimen of venlafaxine XR or venlafaxine XR plus supervised exercise. Cardiorespiratory fitness was assessed using a submaximal* $Vo_2$ *test, and neuroimaging assessments were conducted using a Siemans MAGNETOM 7-Tesla magnetic resonance scanner at the University of Pittsburgh.* ***Results:*** *Attrition was 38% and 14% for the medication and exercise groups, respectively. Attendance was 91% for the exercise intervention. Exploratory analyses revealed an association between improvement in fitness and increased cortical thickness in the anterior cingulate cortex.* ***Conclusion:*** *Exercise augmentation to pharmacotherapy is feasible for depressed younger and older adults and may have neural benefits in a core brain region implicated in depression.* (Am J Geriatr Psychiatry 2019; 27:611–616)

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Published by Elsevier Inc. on behalf of American Association for Geriatric Psychiatry.
https://doi.org/10.1016/j.jagp.2019.01.012

## INTRODUCTION

Exercise has emerged as an effective nonpharmacologic treatment for depression in older and younger adults.[1] The neural benefits of exercise overlap with several regional structural brain abnormalities in depression (i.e., prefrontal cortex, anterior cingulate, and hippocampus).[2] Only one study (N = 41) has examined structural brain changes associated with exercise in depression, and it did not find changes in hippocampal volume; however, poor intervention adherence (mean: 30%) limits interpretation of these findings.[3]

The aim of this pilot trial was to establish the feasibility of conducting an exercise intervention in younger and older adults with major depression receiving antidepressant pharmacotherapy while exploring neural mechanisms. We explored patterns in efficacy of the exercise intervention and examined links between change in cardiorespiratory fitness (CRF) and cortical thickness in regions sensitive to depression.

## METHODS

### Participants

Participants included inactive adults aged 20−39 and 60−79 years who met criteria for a current major depressive episode as defined by the Primary Care Evaluation of Mental Disorders.[4] Exclusion criteria included contraindications for magnetic resonance imaging (MRI), self-reported active lifestyle (i.e., exercise >3 days per week >20 minutes per day), self-reported gait or balance difficulties, safety concerns for engaging in regular moderate-intensity aerobic exercise based on a physical exam conducted by the study nurse practitioner or disapproval by the participant's primary care provider (for older adult participants), uncontrolled hypertension, acute risk of a cardiovascular event (i.e., cardiovascular event within the past 12 months), Type 2 diabetes (later removed from exclusion criteria), substance use problems in the past 3 months, lifetime diagnosis of bipolar disorder or any psychotic disorder, and clinically significant cognitive impairment (e.g., diagnosis of dementia or Modified Mini-Mental State Exam score <84).[5] Please see Figure 1 for a summary of study recruitment and enrollment.

### Procedures

Eligible participants who provided informed consent completed mood, cognitive, CRF, physical activity (PA) monitoring, and neuroimaging baseline assessments. Participants were then randomized to the medication only (MED) or medication plus exercise (EX) group. Participants on a different antidepressant medication regimen were first tapered off any previous antidepressant medication over a period of 2 weeks before being administered the study medication (venlafaxine XR). Study clinicians provided biweekly medication management throughout the study without knowledge of participants' group assignments.

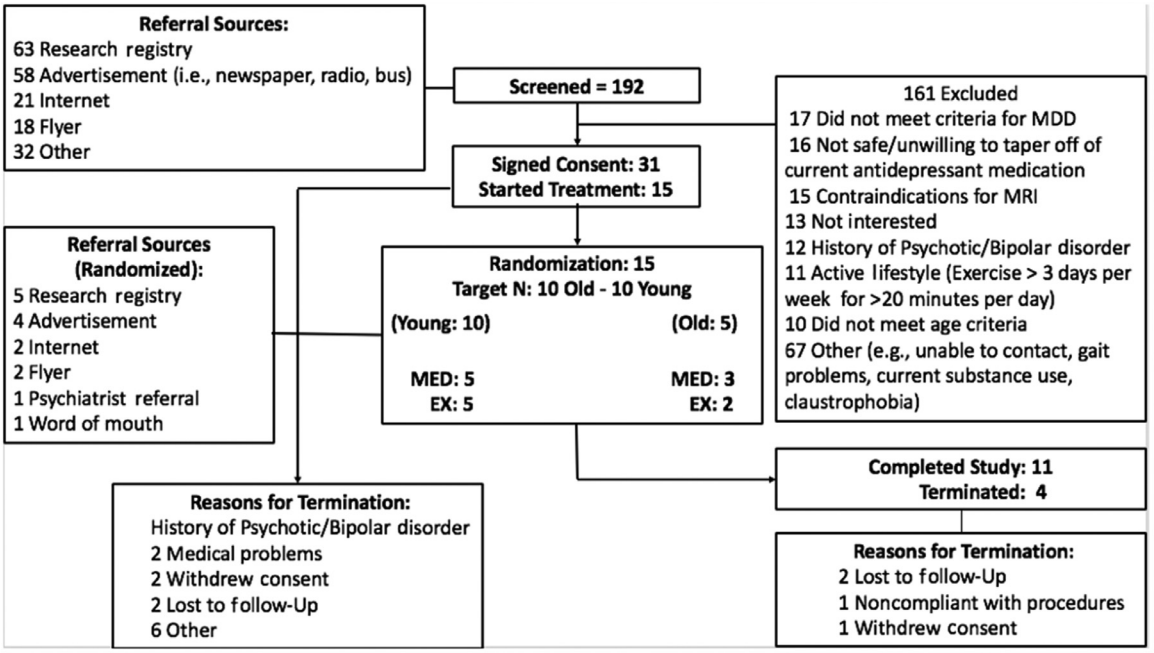
### Exercise Intervention

Participants randomized to the EX group participated in individualized, supervised exercise sessions at the University of Pittsburgh three times per week for 12 weeks. Exercise sessions included warm-up and cool-down periods, and participants exercised for 1 hour, including a gradual ramp-up period. Participants engaged in moderate-intensity aerobic exercise for approximately 45 minutes using a motor-driven treadmill or recumbent bike. Moderate intensity was defined by continuous heart rate monitoring and maintaining a range of 60%−75% of age-based maximum heart rate based on the Karvonen method (i.e., age-based maximum heart rate is calculated by subtracting an individual's age (in years) from 220). For participants on beta blockers, Rating of Perceived Exertion (RPE) (Borg 6−20) was used to measure intensity with a goal of 13−15 RPE. After completion of the intervention, all clinical, cognitive, CRF, and neuroimaging assessments were repeated for all participants.

### Screening Measures

Participants scoring greater than two on the Physical Activity Readiness Questionnaire required primary care provider approval before participation.[6] The Primary Care Evaluation of Mental Disorders was used to confirm diagnosis of major depression and to exclude other psychiatric diagnoses (i.e., bipolar disorder).[4] Scores less than 84 on the Modified Mini-Mental State Exam were used to exclude participants with possible dementia.[5]

**FIGURE 1. Summary of recruitment and enrollment in study. MDD: major depressive disorder.**




## Outcome Measures

### *Depression severity*

The Montgomery-Asberg Depression Rating Scale was used to assess severity of depressive symptoms.[7] A score cutoff of less than 10 was used to determine remission. Clinicians were instructed not to ask participants if they were in the EX group, and participants were instructed not to divulge this information.

### *Cardiorespiratory fitness*

A submaximal $V_{O_2}$ test assessed CRF. Participants underwent testing with a modified Balke protocol (i.e., speed remained constant, with 2% grade increments every 2 minutes). The test was terminated when a subject reached a heart rate of 85% of the age-based maximum (220-age), volitional fatigue, or RPE of 15 or greater.

### *PA*

PA was monitored for 1 week pre- and postintervention using BodyMedia Sensewear armband model MF-SW (BodyMedia, Pittsburgh). These devices were placed on the left arm and used a triaxial accelerometer to assess amount and intensity of PA.

### *Neuroimaging assessments*

Twelve participants underwent structural brain MRI scanning on a Siemens MAGNETOM 7-Tesla scanner at the University of Pittsburgh within 1 week prior to initiating and after completing the intervention. T1-weighted images were collected using a three-dimensional magnetization-prepared rapid gradient-echo imaging protocol. Scanning parameters included an echo time of 2.5 msec, repetition time of 3,000 msec, and field of view of 176 × 223 mm. The three remaining participants completed baseline and postintervention MRI scans on a 3-Tesla scanner. Similar scanning parameters were used for the Siemens 3-Tesla MAGNETOM TIM Trio scanner at the University of Pittsburgh.

### *Cortical thickness*

Given the small sample size, Spearman rank-order (rho) correlations were used to examine the association

between change in CRF and cortical thickness. Vertex-based estimates of regional gray matter thickness were generated using Freesurfer version 6.0, a software suite for brain MRI analysis developed by Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital .[8]

## RESULTS

### Feasibility

We screened 192 adults (Fig. 1). Thirty-one participants (16%) enrolled, of which 15 (48%) were randomized (MED = 8; EX = 7), and 11 participants (73%) completed the study (MED = 5; EX = 6). Two participants were lost to follow-up, one participant was nonadherent to study procedures (e.g., nonadherent to medication), and one participant withdrew consent. An initial recruitment challenge was to identify strategies for enrolling depressed older adults. Nonetheless, we identified several successful recruitment strategies, including the University of Pittsburgh Clinical and Translational Science Institute research registry (n = 5), paper-based and radio advertisements (n = 4), flyers (n = 2), online advertisements (n = 2), referral from a medical provider (n = 1), and self-referral through word of mouth (n = 1). All participants completing the study completed MRI, biomarker, cognitive, mood, fitness, and PA assessments without difficulty or endorsing burden related to the length of time required to complete study assessments.

### Participant Characteristics

Fifteen participants (10 younger adults and 5 older adults with major depression) were randomized to receive venlafaxine XR (MED) or venlafaxine XR and supervised aerobic exercise (EX). Randomization was performed by the study data manager using the permuted block randomization method. Study clinicians were blinded to group assignments. Eleven participants returned for follow-up assessments. Participants completing the study were adherent to the medication regimen, and those in the EX group attended 91% of the sessions on average. PA levels as assessed by accelerometers and self-report did not differ between treatment groups at baseline.

### Cardiorespiratory Fitness

Significant changes in fitness were not observed in the exercise group (paired samples *t*-test: $t = -0.96$; df = 5; p = 0.38). One out of six participants in the exercise group showed a decline in fitness (~2 standard deviations below the mean), whereas the other five participants showed an increase in fitness. Given the violation of normality in these data, an exploratory analysis was conducted using the nonparametric related-samples Wilcoxon matched-pair signed-rank test with and without exclusion of the participant showing a decline in fitness. Results indicated the exercise group overall did not show an increase in fitness (df = 5; p = 0.25), but an increase in fitness was observed in the exercise group after excluding the sole participant showing a decline in fitness (df = 4; p = 0.04).

### Depressive Symptoms

Participants in both treatment groups showed a significant reduction in depressive symptoms (mean [standard deviation] percent reduction in Montgomery-Asberg Depression Rating Scale score: MED = −63.85 [35.56]; EX = −74.34 [16.37]; paired samples *t*-test MED: $t = 8.36$; df = 4; p = 0.001; EX: $t = 6.46$; df = 5; p = 0.001). There was no group difference in trajectory of decline in depressive symptoms during the intervention when covarying for medication titration (repeated measures analysis of variance group × time interaction: F = 0.23; df = 6; p = 0.97); however, the EX group appeared to have a more efficient trajectory of decline in depressive symptoms (i.e., remitted after a shorter treatment duration relative to the MED group) based on visualization of the data; see supplemental data file.

### Cortical Thickness

Cross-sectional associations between depression severity and cortical thickness in regions commonly showing structural abnormalities in depression (i.e., prefrontal, anterior cingulate, hippocampal, and striatal regions) were explored at baseline. Depression severity was negatively associated with cortical thickness in the right rostral anterior cingulate cortex (ACC) (Spearman rho correlation: r = −0.75; df = 8; p = 0.01; $R^2 = 0.56$), right medial orbitofrontal cortex (OFC) (Spearman rho correlation: r = −0.78; df = 8;

$p = 0.008$; $R^2 = 0.61$), and right parahippocampal gyrus (Spearman rho correlation: $r = -0.93$; $df = 8$; $p < 0.001$; $R^2 = 0.86$). Change in depressive symptoms was not associated with change in cortical thickness in the OFC, ACC, or parahippocampal gyrus ($p > 0.10$). However, a pattern was observed such that improvement in CRF was associated with an increase in cortical thickness in the right rostral ACC (Spearman rho correlation: $r = 0.64$; $df = 8$; $p = 0.04$; $R^2 = 0.40$), a region in which greater depression severity was linked to reduced cortical thickness at baseline. Similar patterns (not statistically significant) were observed for the right medial OFC (Spearman rank-order correlation: $r = 0.60$; $df = 8$; $p = 0.06$; $R^2 = 0.40$); see supplemental data file for visualization of these results. These results suggest a link between improvement in CRF and an increase in cortical thickness in the rostral ACC, which was sensitive to greater depression severity in this sample and is a core brain region implicated in depression.

## DISCUSSION

Our pilot study showed that an exercise intervention as augmentation to pharmacotherapy in depressed younger and older adults was feasible and acceptable, without excessive or unacceptable participant burden. Notable strengths of this pilot study include the double-blind, randomized nature of the study design; exceptional exercise adherence (91% attendance); and exploration of neuroimaging outcomes. Exploratory analyses suggested improvement in CRF was associated with an increase in cortical thickness in the rostral ACC, a core brain region affected in depression.

Our findings are limited by the small sample size, disproportionate representation of depressed younger relative to older adults, exclusion of middle-aged adults, and group differences in sex and antidepressant medication use prior to the study. Further, technical difficulties related to the 7-Tesla Siemans MR scanner at the University of Pittsburgh resulted in a few participants being scanned on a 3-Tesla Siemens MR scanner at the University of Pittsburgh, which may have affected our ability to detect changes in regional brain morphology.

This pilot study demonstrated the feasibility of developing an exercise intervention in depressed older and younger adults taking antidepressant medication. Recruitment challenges were overcome, and intervention adherence was exceptional. Further, the association between exercise-related improvement in fitness and an increase in cortical thickness in a key region sensitive to depression is a promising avenue for future large-scale studies to explore.

*Swathi Gujral, Ph.D., was supported by the United States National Science Foundation Graduate Research Fellowship Program grant 2014192810 and is currently funded through the VA Mental Illness Research, Education, and Clinical Center Advanced Fellowship. Kirk I. Erickson, Ph.D., was supported by research grants R01 DK095172, P30 AG024827, P30 MH90333, R01 CA221882, R01 AG053952, and R01 CA196762. Partial support was also received from the University of Pittsburgh Medical Center Endowment in Geriatric Psychiatry (Charles F. Reynolds III, M.D., and Howard Aizenstein, M.D., Ph.D.). Meryl A. Butters, Ph.D., was supported by research grants P50 AG005133 and P30 MH090333. Jordan F. Karp, M.D., was supported by research grant P30 MH090333; he has also received medication supplies from Indivior and Pfizer for investigator-initiated trials. Financial support for the development of this article was supplied exclusively by the Advanced Center in Intervention and Services Research in Late-Life Depression Prevention (P30MH090333).*

*Swathi Gujral, Ph.D., Howard Aizenstein, M.D., Ph.D., Charles F. Reynolds III, M.D., Meryl A. Butters, Ph.D., and Kirk I. Erickson, Ph.D., were involved in study concept and design. Swathi Gujral, Ph.D., George Grove, M.S., Meryl A. Butters, Ph.D., Howard Aizenstein, M.D., Ph.D., and Kirk I. Erickson, Ph.D., were involved in analysis and interpretation of data. All authors (Swathi Gujral, Ph.D., Howard Aizenstein, M.D., Ph.D., Charles F. Reynolds III, M.D., Meryl A. Butters, Ph.D., Jordan F. Karp, M.D., George Grove, M.S., Kirk I. Erickson, Ph.D.) were involved in acquisition of subjects and data and preparation of the manuscript.*

## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2019.01.012.

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