Affect Following First Exercise Session as a Predictor of Treatment Response in Depression

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ABSTRACT

Objective: Remission rates are low with first-step or even second-step antidepressant treatments. Furthermore, despite extensive investments from National Institutes of Health and from industry, novel treatments are not yet available in clinical care for depression. Predictors of treatment response very early in the course of treatment can avoid unnecessarily lengthy trials with ineffective treatments and reduce the trial and error process. This article examines the expression of positive affect immediately following an acute exercise session at the end of the first exercise session as a predictor of treatment response in the National Institute of Mental Health–funded TREAD (Treatment with Exercise Augmentation for Depression) study, which was conducted from April 2003 to August 2007.

Methods: 122 subjects with *DSM-IV*–diagnosed major depressive disorder were randomized to public health dose (16 kcal/kg/wk) or low dose (4 kcal/kg/wk) of exercise for 12 weeks. Affect following the first exercise session was assessed using the Positive and Negative Affect Scale (PANAS), and depressive symptoms were assessed weekly using the Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) (primary outcome measure).

Results: The PANAS composite affect score (positive-negative total) predicted change in IDS-C score ($P < .05$), as well as treatment response ($P < .02$) and remission ($P < .03$) for those in the high-dose group but not in the low-dose group.

Conclusions: These findings suggest that the composite positive affect following the first exercise session has clinical utility to predict treatment response to exercise in depression and match the "right patient" with the "right" treatment.

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Although numerous treatments are available for major depressive disorder (MDD), selecting among the options remains the biggest challenge facing clinicians. Remission rates are low with standard antidepressant treatments with the first-step[1] or even second-step treatments[2] in the short term, and remission rates are even lower in the long term.[2] Nonpharmacologic interventions like psychotherapy and aerobic exercise have also been shown to be efficacious for the treatment of MDD.[3–5] While treatment outcomes do improve with additional treatment steps, in the absence of reliable predictors and moderators,[6] the trial-and-error process required to identify appropriate treatment for a given individual prolongs the disease burden in these patients. Therefore, there is a clear need to identify behavioral or biological markers in order to determine who is most likely to respond to any given treatment. Identification of these markers will lead to early treatment matching, reducing the burden of multiple steps for the patient and ultimately reducing the burden of the illness.

The link between exercise and mental health is well documented. Exercise has long-term benefits for general health, and physically active people are at a lower risk of developing mood and anxiety disorders.[7–12] Research also supports the use of exercise in the treatment of MDD. Exercise has proven efficacious as a monotherapy[5,13,14] as well as an augmentation treatment[15,16] of MDD. As an intervention, exercise has the additional advantage of targeting residual symptoms such as insomnia, psychosocial functioning, and cognitive function.[17–19] Despite the benefits of exercise as a treatment, it is, like other antidepressant treatments, not universally effective. Determining clinically useful behavioral and biological markers as predictors of response to exercise can improve the process of treatment matching for exercise as an antidepressant.

Post hoc analyses of prior studies have attempted to identify predictors of response to exercise. Using this baseline model, our preliminary work has already shown that insomnia, tumor necrosis factor-α, and brain-derived neurotrophic factor are predictive of treatment response and suggests these as possible biological markers for exercise augmentation.[17,20,21] However, it is clear that identification of multiple predictors is necessary in order for these predictors to have clinical utility.[22]

Exercise is effective in reducing depressive symptoms and also produces acute improvements in affect following a single bout in patients with MDD.[23,24] However, no study has evaluated whether this acute affective response postexercise is predictive of long-term treatment outcome. Just as long-term reductions in depressive symptoms are heterogeneous, acute affective responses to exercise also vary across individuals. This variation has important implications for exercise treatment interventions, as positive affective response to an exercise session has been associated with long-term exercise adherence.[25] Furthermore, research[26,27] has identified genetic predictors of affective response, indicating this variation can be attributed to underlying biological mechanisms. It is therefore possible that these biological mechanisms underlying variations in affective response to

Clinical Points

- Optimal treatment of major depressive disorder requires identification of treatment outcome predictors.
- Postexercise affect appears to be a potential predictor of depression treatment outcome.
- However, predictive capability of this, or any other individual predictor, is limited. Future work should aim to synthesize multiple predictors.

acute exercise may be the same mechanisms underlying variations in treatment response to exercise.

In this study, we examine positive affect following the initial exercise intervention session as a predictor of final treatment outcomes. The Treatment with Exercise Augmentation for Depression (TREAD) study[15,28] concluded that exercise augmentation with a public health dose is an effective means to achieve remission in patients who are nonresponsive to initial selective serotonin reuptake inhibitor (SSRI) treatment, with a number needed to treat of 7.8 compared to the lower dose of exercise. This article examines (1) whether affect immediately following the first exercise session predicts treatment outcomes at the end of the 12-week exercise intervention, (2) whether this predictive effect is moderated by exercise dose, and (3) if the predictive effect is mediated by exercise adherence. We hypothesize that greater postexercise positive affect will be predictive of greater decreases in depressive symptoms at the end of the intervention. Furthermore, we hypothesize that this effect will be greater in the high-dose exercise treatment group. Finally, we hypothesize that the predictive effect of postexercise affect will be explained, at least partially, by differences in exercise adherence.

METHODS

The TREAD trial was a randomized trial comparing 2 doses of aerobic exercise as augmentation treatment for nonremitted MDD. Full study methodology has been previously published[15,29]; included below is a description of the study procedures relevant to the current analysis. The study was conducted from April 2003 to August 2007 and was registered on ClinicalTrials.gov (identifier: NCT00076258).

Participants

Participants were recruited through physician referrals and advertisements. Eligible participants signed an institutional review board–approved informed consent form before engaging in any study activities. Inclusion criteria were as follows: (1) men and women aged 18–70 years, (2) diagnosis of nonpsychotic MDD based on the Structured Clinical Interview for *DSM-IV* Axis I Disorders,[30] (3) completion of > 2 and < 6 months of treatment with an SSRI with at least 6 weeks of adequate dose, (4) moderate residual symptomatology from SSRI monotherapy defined by a score of ≥ 14 on the Hamilton Depression Rating Scale,[31] (5) not engaged in regular exercise, (6) capable of exercise, and (7) able and willing to provide informed consent.

Exclusion criteria included (1) significant medical condition; (2) depression due to a comorbid psychiatric disorder; (3) current pharmacologic or psychotherapeutic treatment other than SSRI; (4) treatment resistance, defined as failure of 2 or more pharmacologic treatments of adequate dose and duration; and (5) pregnancy or planned pregnancy.

Procedures

Participants were randomly allocated to 1 of 2 exercise groups for a 12-week exercise intervention. The dose of SSRI was kept constant during the exercise treatment. The low-dose group was prescribed a dose of exercise at 4 kcal/kg/wk, and the public health–dose group was prescribed a higher dose of exercise at 16 kcal/kg/wk, reflecting public health physical activity recommendations and standards.[32] The low dose is equivalent to approximately 45 minutes of moderate-to-vigorous exercise per week, and the public health dose is equivalent to approximately 180 minutes of moderate-to-vigorous exercise per week. Exercise intensity was self-selected and monitored with a Polar 610i heart rate monitor (Polar Electro, Inc). Participants completed the entire first week of exercise dose under supervision by trained personnel at the Cooper Institute (Dallas, Texas), and had 2 supervised sessions in the second week. In all subsequent weeks, participants had 1 supervised session per week and completed the remaining exercise dose in home-based sessions. All study procedures were approved by the local institutional review board.

Measures

The Positive and Negative Affect Scale (PANAS)[33,34] was administered following the first exercise session of week 1. The PANAS is a 20-item scale with two 10-item subscales designed to measure affect. The PANAS measures affect as both positive and negative. High positive affect reflects an individual's feelings using adjectives such as *enthusiastic*, *active*, and *alert*, and low positive affect is characterized by adjectives such as *sad* and *lethargic*. High negative affect is a general dimension of subjective distress characterized by anger, disgust, guilt, fear, and nervousness, and low negative affect is characterized by calmness and serenity. The PANAS has been widely used as a measure of acute affect with good psychometric properties,[33,34] with reliability for the immediate assessment at α of .89 for positive affect scores and .85 for negative affect scores, and has been further validated specifically within a psychiatric population.[35] In addition to the standard positive and negative affect scores, we also derived a composite affect score by combining the 2 measures in order to assess the overall general affect to the exercise session, accounting for both positive and negative aspects of affect. To evaluate the general affective state at the end of the exercise session, we combined the positive and negative PANAS scores. This was done by the subtraction of the negative PANAS total

Table 1. Baseline Demographic and Clinical Characteristics

Variable	All (N = 118)	Exercise, 16 kcal/kg/wk (n = 58)	Exercise, 4 kcal/kg/wk (n = 60)
Age, mean (SD), y	47.1 (10.0)	45.7 (10.4)	48.5 (9.4)
Women, n (%)	96 (81.4)	49 (84.5)	47 (78.3)
Race, n (%)			
White	103 (86.3)	49 (81.7)	54 (93.1)
Black	12 (10.2)	8 (13.3)	4 (6.9)
Hispanic	1 (0.8)	3 (5.0)	1 (1.7)
Other	2 (1.7)	1 (1.6)	3 (5.2)
Marital status, n (%)			
Single, never married	20 (17.0)	10 (17.2)	10 (16.7)
Cohabitating	5 (4.2)	3 (5.2)	2 (3.3)
Married, living together	62 (50.8)	31 (53.4)	30 (50.0)
Married, living apart	1 (0.8)	0 (0.0)	1 (1.7)
Separated	1 (0.8)	0 (0.0)	1 (1.7)
Divorced	27 (22.9)	12 (20.1)	15 (25.0)
Widowed	3 (2.5)	2 (3.5)	1 (1.7)
Weight, mean (SD), kg	86.8 (20.0)	87.0 (23.6)	87.8 (17.7)
BMI, mean (SD)	30.6 (6.09)	29.9 (6.3)	31.5 (5.5)
VO_2 max, mean (SD), L/min	1.7 (0.6)	1.7 (0.5)	1.8 (0.7)
Age at onset, mean (SD), y	27.1 (11.3)	27.4 (10.7)	26.8 (12.0)
Length of current episode, mean (SD), mo	82.1 (97.1)	73.4 (95.0)	90.5 (99.0)
Baseline symptom severity, mean (SD)			
$HRSD_{17}$	17.8 (3.7)	17.6 (3.6)	18.0 (3.8)
IDS-C	33.8 (7.5)	33.2 (7.1)	34.7 (7.8)
Function, mean (SD)			
Q-LES-Q GA[41]	41.9 (7.6)	41.3 (7.6)	42.4 (7.5)
WSAS[42]	20.2 (8.9)	19.2 (7.7)	21.0 (9.9)
SF-36 physical,[43] mean (SD)	80.1 (20.4)	80.2 (20.1)	80.1 (20.8)
SF-36 mental,[43] mean (SD)	49.4 (15.4)	49.8 (14.9)	49.0 (16.0)

Abbreviations: BMI = body mass index; $HRSD_{17}$ = 17-item Hamilton Depression Rating Scale; IDS-C = Inventory of Depressive Symptomatology, Clinician Rating; Q-LES-Q GA = Quality of Life Enjoyment and Satisfaction Questionnaire, general activities; SF-36 = 36-item Short-Form Health Survey, VO_2 max = maximal oxygen consumption; WSAS = Work and Social Adjustment Scale.

from the positive PANAS total to produce the composite affect score.

The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) version,[36] was used to measure depressive symptoms. The IDS-C is a 30-item rating scale with excellent psychometric properties and has been widely used in clinical trials.[36] The IDS-C was administered weekly by blinded raters. Change in IDS-C was calculated as the week 12 IDS-C total score minus the baseline IDS-C total score. If data were missing for the week 12 IDS-C score, the last assessed value was carried forward. Response and remission were also determined based on the IDS-C total score values. Response was defined as a 50% reduction in IDS-C score, while remission was defined as an IDS-C score of 12 or less at study completion.

Statistical Analyses

Primary analyses. Primary analyses were designed to evaluate the composite affect score following the first acute exercise session as a predictor of change in depressive symptoms from baseline to exit. The composite affect score at the conclusion of the first exercise session was used as a predictor of treatment response for the primary analysis. Change in depressive symptoms was calculated using the IDS-C total. A general linear model included main effects for both exercise group and composite affect score along with group-by–composite affect interaction as the predictors of IDS-C change (decrease from baseline to exit). The main effect of group provides a measure of differences in treatment response, the main effect of composite affect provides the measure of the ability of affect after an exercise session to predict treatment response, and the interaction tests whether the prediction is specific to 1 or the other of the 2 treatments. This model was repeated using both the positive affect and negative affect subscale scores.

Covariate analyses. To control for the effects of the influence of possible confounding variables, we conducted a series of covariate analyses. Gender and family history were included, as these covariates were associated with treatment outcome in the primary outcome article.[15] We also included fitness (maximal oxygen consumption [VO_2 max]) and exercise adherence (median percentage of kilocalories per kilogram per week dose). The covariate analysis was conducted as a 2-step process that would include all variables plus 2-way interaction as a first step. As a second step, all covariates with a P value $<.10$ were retained in the final covariate model.[37]

Prediction of response and remission analyses. We conducted logistic regression models to examine treatment response (50% reduction from baseline) and treatment remission (IDS-C total score ≤ 12). In these models, exercise group and composite affect score are the main effects and a group-by–composite affect interaction were predictors of response and remission. To examine the utility of the composite affect score to predict the likelihood of response and remission, we also conducted a receiver operating characteristic (ROC) analysis and report the area under the curve (AUC) for the ROC. Perfect prediction would have an AUC of 1.0, with an AUC above 0.90 still providing a clinically useful test; an AUC above 0.80 is considered meaningful but with modest clinical usefulness.[38,39] As an example, the AUC for the Patient Health Questionnaire self-report and a clinical diagnosis of MDD is about 0.88.[40] Finally, to test for any impact of exercise adherence over the course of the treatment trial, we ran a set of analyses that included adherence (as measured by the median number of sessions) added to the general linear models with interaction terms for both group and composite affect.

RESULTS

Baseline characteristics of the study sample are provided in Table 1. One hundred twenty-six subjects completed the baseline assessments and were randomized to an exercise condition. Four subjects did not provide postbaseline data and were excluded from the analyses. Mean changes in IDS-C, response and remission for the total sample and by group, and in PANAS scores following the initial exercise session are presented in Table 2. t Tests conducted to determine if there were differences in week 1 PANAS scores (positive affect, negative affect, and composite affect) yielded no significant differences.

Composite Affect Score as a Predictor of Change in Depressive Symptoms

The primary analysis for week 1 included 118 of the 122 subjects, as 4 subjects did not provide PANAS ratings. There was a significant main effect for group ($F_{1,114} = 4.87$, $P < .03$: $\eta^2 = 0.041$), a marginal effect for composite affect ($F_{1,115} = 3.36$, $P < .07$: $\eta^2 = 0.029$), and a significant group-by–composite affect interaction ($F_{1,115} = 4.13$, $P < .05$: $\eta^2 = 0.035$). As seen in Figure 1, higher composite affect scores predicted better outcomes (as measured by reduction in total IDS-C scores) for subjects in the public health–dose group but not in the low-dose group.

Covariate Analysis

The first step of the covariate analyses included gender, family history of mental illness, fitness, and exercise adherence and 2-way interactions in the model with group and composite affect. Only the exercise adherence ($F_{1,106} = 5.98$, $P < .02$: $\eta^2 = 0.04$) and the family history of mental illness–by-group interaction ($F_{1,106} = 3.43$, $P < .07$: $\eta^2 = 0.03$) produced P values < .10. The final model included just these 2 covariates with group, composite affect, and the group-by–composite affect interaction. There were significant main effects for median percent KKW of dose ($F_{1,106} = 5.98$, $P < .02$: $\eta^2 = 0.04$), family history of mental illness ($F_{1,106} = 4.76$, $P < .04$: $\eta^2 = 0.03$), family history of mental illness–by-group interaction ($F_{1,106} = 4.66$, $P < .01$: $\eta^2 = 0.03$), and the group-by–composite affect interaction dose ($F_{1,106} = 5.01$, $P < .03$: $\eta^2 = 0.04$). The group-by–composite affect interaction remained significant and was not moderated by either exercise adherence or family history. Note the family history results were previously reported in the primary outcome article.[15]

Table 2. IDS-C Decrease From Baseline and PANAS Scores at End of First Exercise Session

Variable, Mean (SD)	All (N = 118)	Exercise, 16 kcal/kg/wk (n = 58)	Exercise, 4 kcal/kg/wk (n = 60)
IDS-C change	12.2 (11.7)	11.0 (11.6)	13.3 (9.6)
PANAS positive	29.3 (9.1)	28.7 (8.6)	29.9 (9.6)
PANAS negative	13.2 (4.4)	13.5 (4.6)	13.0 (4.2)
PANAS composite	16.1 (11.0)	15.2 (11.0)	16.9 (11.0)

Abbreviations: IDS-C = Inventory of Depressive Symptomatology, Clinician Rating; PANAS = Positive and Negative Affect Scale.

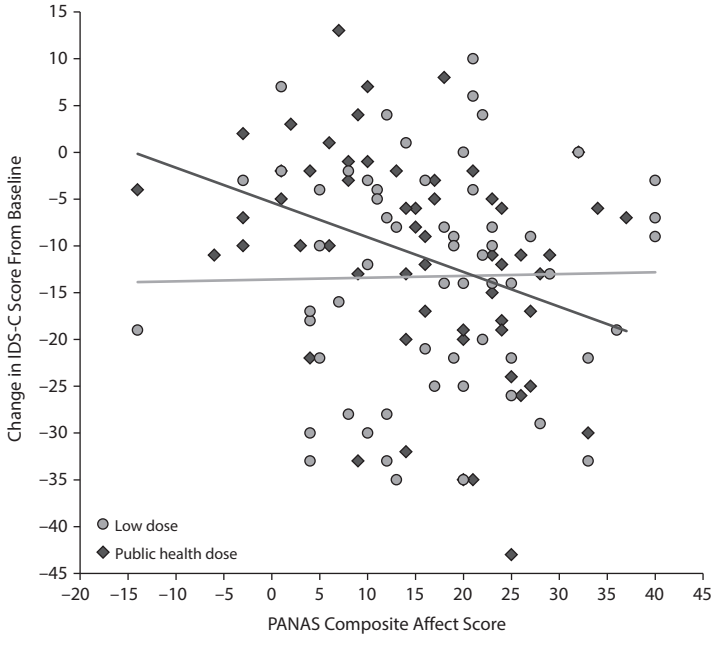
Composite Affect Score as a Predictor of Response and Remission

The logistic regression at week 1, using composite affect and group to predict response, produced significant main effects for group ($\chi^2_3 = 3.88$, $P < .05$) and composite affect ($\chi^2_3 = 5.45$, $P < .02$) and a significant group-by–composite affect interaction ($\chi^2_3 = 5.46$, $P < .02$: low dose, odds ratio [OR] = 1.00; public health dose, OR = 1.10). Similarly, the logistic regression predicting remission produced a marginal main effect for group ($\chi^2_3 = 3.07$, $P < .08$), a significant main effect for composite affect ($\chi^2_3 = 8.56$, $P < .004$), and a significant group-by–composite affect interaction ($\chi^2_3 = 4.55$, $P < .03$: low dose, OR = 1.02; public health dose, OR = 1.13). These results indicate that higher composite affect scores predicted a higher likelihood of response and remission within the public health–dose group.

In order to better understand the extent to which acute affect following the first exercise session can be used to predict treatment response and remission, ROC analyses were also conducted. Since the models for both response and remission produced a significant interaction with group, separate ROC curves were produced for each group. For the low-dose group, composite affect did not predict response ($\chi^2_1 = 0.00$, $P < .99$: ROC curve AUC = 0.51), but composite affect did predict response for the public health–dose group ($\chi^2_1 = 8.4$, $P < .004$: ROC curve AUC = 0.76). The same pattern appeared for remission, with composite affect not predicting remission for the low-dose group ($\chi^2_1 = 0.51$, $P < .48$: ROC curve AUC = 0.57), but predicting remission for the public health–dose group ($\chi^2_1 = 9.2$, $P < .003$: ROC AUC = 0.81). The ROC curves are presented in Figure 2.

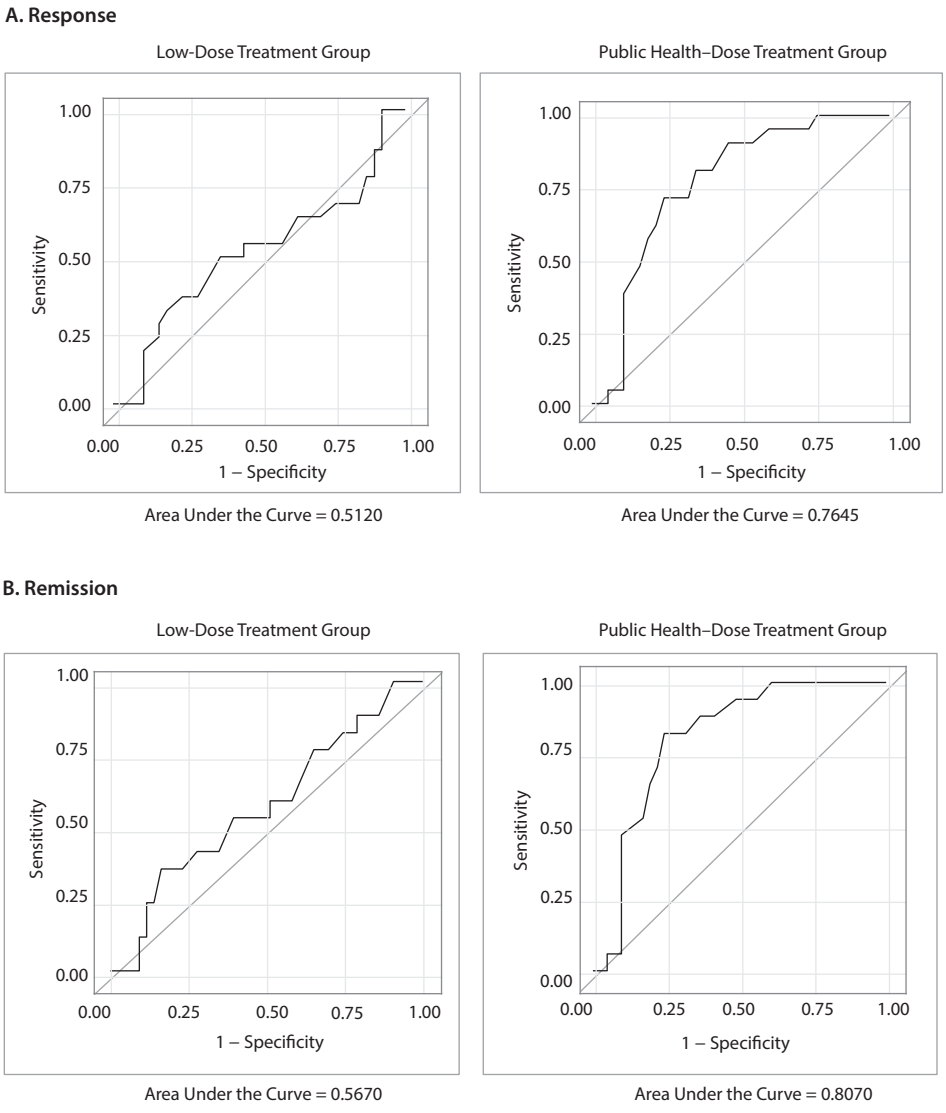
To better understand these results, we conducted analyses using the positive affect and negative affect subscales of the PANAS. The model included a significant main effect for group ($F_{1,114} = 4.09$, $P < .05$: $\eta^2 = 0.02$), a significant main effect for positive affect ($F_{1,114} = 6.14$,

Figure 1. Prediction of Treatment Outcomes Using the Positive and Negative Affect Scale (PANAS) Composite Affect Score at End of First Exercise Session (week 1)[a]



[a]Low-dose intervention was 4 kcal/kg/wk; public health–dose intervention was 16 kcal/kg/wk.
Abbreviation: IDS-C = Inventory of Depressive Symptomatology.

Figure 2. Receiver Operating Characteristic Analysis of the Positive and Negative Affect Scale Composite Affect Scores for Prediction of Response and Remission



$P < .02$: $\eta^2 = 0.05$), and a marginal group-by–positive affect interaction ($F_{1,114} = 3.34$, $P < .08$: $\eta^2 = 0.03$). The results for the negative affect analysis indicated there is no main effect for group ($F_{1,115} = 1.19$, $P < .36$), no main effect for negative affect ($F_{1,115} = 0.10$, $P < .76$: $\eta^2 = 0.00008$), and a marginal group-by–negative affect interaction ($F_{1,115} = 3.37$, $P < .07$: $\eta^2 = 0.03$). These findings are worth noting only because they provide some insight as to why composite affect findings are more robust than the positive findings alone. For the public health–dose group, higher negative affect scores predict less symptom reduction, but for the low-dose groups, the contrary is true, with higher negative affect scores predicting greater symptom reduction.

DISCUSSION

The primary goal of this study was to examine affect following the first exercise session as a predictor of treatment response for patients with nonremitted MDD. Our results specifically indicate that greater positive affect following the first exercise session was predictive of greater improvements in depressive symptoms, response, and remission at the end of the 12-week exercise intervention. Most interestingly, this effect was moderated by treatment group, such that the predictive value of positive affect was significant only in the high-dose exercise group but not in the low-dose group.

Previous research[26,27,35,36] has shown variation in affective responses to acute exercise sessions. Our results suggest that variations in postexercise affect might be predictive of antidepressant response. In light of these results, it is of interest to determine the underlying mechanism of this effect. Potential explanations for the association of postexercise affect with the longer term acute phase antidepressant effect of exercise could be a result of enhanced self-efficacy, improved adherence to the exercise intervention, the patient's perception of early antidepressant effect, or the capacity

of the underlying neural circuitry to respond. Previous work[25] has linked positive acute affect following a single exercise session with improved exercise adherence over an extended period of time. However, including adherence in the regression model did not diminish the observed effect of postexercise affect.

Variations in affective response to an acute exercise session can also be due to the characteristics of exercise itself. For example, high exercise intensity, specifically intensity above the ventilator threshold, results in more negative postexercise affect.[44,45] A unique feature of our exercise intervention in the current study was that participants self-selected their exercise intensity, which has been associated with positive postexercise affect. The fact that the affective response to exercise is modulated by characteristics of the exercise might also explain the moderating effect of treatment group observed in our analysis. Due to the higher exercise dose, exercise sessions among individuals in the public health–dose group were of a greater duration (mean duration of 45 minutes for the public health dose vs 25 minutes for the low-dose exercise), and perhaps the longer sessions may elicit an affective response that is more predictive of treatment outcome. Given that characteristics of the exercise session can alter postexercise affect, it is possible that tailoring an exercise intervention to elicit positive affect could result in a more effective exercise intervention.

Finally, the predictive relationship between postexercise affect and long-term antidepressant outcomes may be indicative of common underlying biology. Research has identified genetic associations with variations in postexercise affect[26,27] as well as to antidepressant response to an exercise intervention.[46] It is possible that common genetic polymorphisms may predict both acute affective response and treatment outcomes in response to exercise.

Exercise has been shown to be efficacious in the treatment of MDD, but many patients do not improve following an exercise intervention. Given the heterogeneity in treatment response, it is necessary to identify predictors of treatment response in order to optimally treat MDD. Our results suggest that postexercise affect may be a potential predictor of long-term antidepressant outcomes. This analysis continues a line of research examining predictors of treatment response to exercise in patients with MDD.[17,20,47,48] Despite these encouraging findings as a predictor of treatment response following the first exercise session, the current analysis does have limitations. This analysis represents a secondary data analysis, as the TREAD trial was not specifically designed to identify predictors of treatment response. Instead, our results should be viewed as "hypothesis generating," and future trials should be designed to specifically identify predictors of treatment response. Second, the PANAS was collected only at postexercise and therefore we were unable to examine changes in affect preexercise and postexercise. Finally, it is clear that a single predictor will not suffice to guide treatment selection and that a metric composed of several markers is very likely needed to enhance the accuracy of prediction.[22,49] As work in the field continues to identify predictors of treatment response, these individual predictors must be integrated into comprehensive algorithms to improve predictive abilities. Ultimately, this work will lead to matching patients with treatments most likely to elicit a treatment response for them.

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Potential conflicts of interest: **Dr Rethorst** has received grant/research support from the National Institute of Mental Health (NIMH) and the American Cancer Society. In the past 12 months, **Dr Greer** has received honoraria and consultant fees from and has served on speakers or advisory boards to H. Lundbeck A/S. In the past 12 months, **Dr Trivedi** has been an advisor/consultant to and received fees from Alkermes, AstraZeneca, Cerecor, Eli Lilly, Lundbeck, Naurex, Neuronetics, Otsuka, Pamlab, Pfizer, Shire Development, and Takeda; and has received grants/research support from NIMH and National Institute on Drug Abuse. **Drs Carmody** and **Jha**, **Ms Suterwala**, and **Mr Grannemann** have no conflict of interests to disclose.

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REFERENCES

1. Trivedi MH, Rush AJ, Wisniewski SR, et al; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163(1):28–40.
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905–1917.
3. Dobson KS. A meta-analysis of the efficacy of cognitive therapy for depression. *J Consult Clin Psychol*. 1989;57(3):414–419.
4. Gloaguen V, Cottraux J, Cucherat M, et al. A meta-analysis of the effects of cognitive therapy in depressed patients. *J Affect Disord*. 1998;49(1):59–72.
5. Rethorst CD, Wipfli BM, Landers DM. The antidepressive effects of exercise: a meta-analysis of randomized trials. *Sports Med*. 2009;39(6):491–511.
6. Trivedi MH. Modeling predictors, moderators and mediators of treatment outcome and resistance in depression. *Biol Psychiatry*. 2013;74(1):2–4.
7. Deslandes AC. Exercise and mental health: what did we learn in the last 20 years? *Front Psychiatry*. 2014;5:66.
8. Galper DI, Trivedi MH, Barlow CE, et al. Inverse association between physical inactivity and mental health in men and women. *Med Sci Sports Exerc*. 2006;38(1):173–178.
9. Camacho TC, Roberts RE, Lazarus NB, et al. Physical activity and depression: evidence from the Alameda County Study. *Am J Epidemiol*. 1991;134(2):220–231.
10. Farmer ME, Locke BZ, Mościcki EK, et al. Physical activity and depressive symptoms: the NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol*. 1988;128(6):1340–1351.
11. Dishman RK, Buckworth J. Increasing physical activity: a quantitative synthesis. *Med Sci Sports Exerc*. 1996;28(6):706–719.
12. Dishman RK, Berthoud HR, Booth FW, et al. Neurobiology of exercise. *Obesity (Silver Spring)*. 2006;14(3):345–356.
13. Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. 2007;69(7):587–596.
14. Dunn AL, Trivedi MH, Kampert JB, et al. Exercise treatment for depression: efficacy and dose response. *Am J Prev Med*. 2005;28(1):1–8.
15. Trivedi MH, Greer TL, Church TS, et al. Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. *J Clin Psychiatry*. 2011;72(5):677–684.
16. Mather AS, Rodriguez C, Guthrie MF, et al. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder: randomised controlled

trial. *Br J Psychiatry*. 2002;180(5):411–415.
17. Rethorst CD, Sunderajan P, Greer TL, et al. Does exercise improve self-reported sleep quality in non-remitted major depressive disorder? *Psychol Med*. 2013;43(4):699–709.
18. Mota-Pereira J, Carvalho S, Silverio J, et al. Moderate physical exercise and quality of life in patients with treatment-resistant major depressive disorder. *J Psychiatr Res*. 2011;45(12):1657–1659.
19. Greer TL, Grannemann BD, Chansard M, et al. Dose-dependent changes in cognitive function with exercise augmentation for major depression: results from the TREAD study. *Eur Neuropsychopharmacol*. 2015;25(2):248–256.
20. Toups MS, Greer TL, Kurian BT, et al. Effects of serum Brain Derived Neurotrophic Factor on exercise augmentation treatment of depression. *J Psychiatr Res*. 2011;45(10):1301–1306.
21. Rethorst CD, Toups MS, Greer TL, et al. Pro-inflammatory cytokines as predictors of antidepressant effects of exercise in major depressive disorder. *Mol Psychiatry*. 2013;18(10):1119–1124.
22. Trivedi MH, McGrath PJ, Fava M, et al. Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): rationale and design. *J Psychiatr Res*. 2016;78:11–23.
23. Bartholomew JB, Morrison D, Ciccolo JT. Effects of acute exercise on mood and well-being in patients with major depressive disorder. *Med Sci Sports Exerc*. 2005;37(12):2032–2037.
24. Weinstein AA, Deuster PA, Francis JL, et al. The role of depression in short-term mood and fatigue responses to acute exercise. *Int J Behav Med*. 2010;17(1):51–57.
25. Williams DM. Exercise, affect, and adherence: an integrated model and a case for self-paced exercise. *J Sport Exerc Psychol*. 2008;30(5):471–496.
26. de Geus EJ, Bartels M, Kaprio J, et al. Genetics of regular exercise and sedentary behaviors. *Twin Res Hum Genet*. 2014;17(4):262–271.
27. Karoly HC, Stevens CJ, Magnan RE, et al. Genetic influences on physiological and subjective responses to an aerobic exercise session among sedentary adults. *J Cancer Epidemiol*. 2012;2012:540563.
28. Trivedi MH, Greer TL, Grannemann BD, et al. Exercise as an augmentation strategy for treatment of major depression. *J Psychiatr Pract*. 2006;12(4):205–213.
29. Trivedi MH, Greer TL, Grannemann BD, et al. TREAD: TReatment with Exercise Augmentation for Depression: study rationale and design. *Clin Trials*. 2006;3(3):291–305.
30. First MB, Spitzer RL, Gibbon M, et al. *User's guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version*. American Psychiatric Pub; 1997.
31. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
32. Haskell WL, Lee IM, Pate RR, et al; American Heart Association. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116(9):1081–1093.
33. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol*. 1988;54(6):1063–1070.
34. Crawford JR, Henry JD. The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. *Br J Clin Psychol*. 2004;43(pt 3):245–265.
35. Dyck MJ, Jolly JB, Kramer T. An evaluation of positive affectivity, negative affectivity, and hyperarousal as markers for assessing between syndrome relationships. *Pers Individ Dif*. 1994;17(5):637–646.
36. Trivedi MH, Rush AJ, Ibrahim HM, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. *Psychol Med*. 2004;34(1):73–82.
37. Bursac Z, Gauss CH, Williams DK, et al. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. 2008;3(1):17.
38. Fan J, Upadhye S, Worster A. Understanding receiver operating characteristic (ROC) curves. *CJEM*. 2006;8(1):19–20.
39. Fan J, Worster A, Fernandes CM. Predictive validity of the triage risk screening tool for elderly patients in a Canadian emergency department. *Am J Emerg Med*. 2006;24(5):540–544.
40. Kiely KM, Butterworth P. Validation of four measures of mental health against depression and generalized anxiety in a community based sample. *Psychiatry Res*. 2015;225(3):291–298.
41. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull*. 1993;29(2):321–326.
42. Mundt JC, Marks IM, Shear MK, et al. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *Br J Psychiatry*. 2002;180(5):461–464.
43. Garratt AM, Ruta DA, Abdalla MI, et al. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *BMJ*. 1993;306(6890):1440–1444.
44. Ekkekakis P, Lind E, Vazou S. Affective responses to increasing levels of exercise intensity in normal-weight, overweight, and obese middle-aged women. *Obesity (Silver Spring)*. 2010;18(1):79–85.
45. Ekkekakis P, Parfitt G, Petruzzello SJ. The pleasure and displeasure people feel when they exercise at different intensities: decennial update and progress towards a tripartite rationale for exercise intensity prescription. *Sports Med*. 2011;41(8):641–671.
46. Rethorst CD, Landers DM, Nagoshi CT, et al. Efficacy of exercise in reducing depressive symptoms across 5-HTTLPR genotypes. *Med Sci Sports Exerc*. 2010;42(11):2141–2147.
47. Rethorst CD, Moynihan J, Lyness JM, et al. Moderating effects of moderate-intensity physical activity in the relationship between depressive symptoms and interleukin-6 in primary care patients. *Psychosom Med*. 2011;73(3):265–269.
48. Rethorst CD, Trivedi MH. Evidence-based recommendations for the prescription of exercise for major depressive disorder. *J Psychiatr Pract*. 2013;19(3):204–212.
49. Wallace ML, Frank E, Kraemer HC. A novel approach for developing and interpreting treatment moderator profiles in randomized clinical trials. *JAMA Psychiatry*. 2013;70(11):1241–1247.