

# Affective Mediators of a Physical Activity Intervention for Depression in Multiple Sclerosis

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**Objective:** Previous analyses showed that a telephone-based intervention to increase physical activity in individuals with multiple sclerosis (MS) and depression resulted in significantly improved depressive symptoms compared to a wait-list control group. The aim of this study was to test positive affect and negative affect as mediators of the effect of the physical activity counseling on depressive symptoms. **Method:** Ninety-two adults with MS, who met diagnostic criteria for either major depression or dysthymia and who reported low levels of physical activity, were randomized 1:1 to a 12-week telephone-based motivational interviewing (MI) intervention to improve physical activity ( $n = 44$ ) or to a 12-week wait-list control group ( $n = 48$ ). Self-reported positive and negative affect, physical activity, and depressive symptoms were gathered at baseline and postintervention. Path-analysis was used to test whether positive affect and negative affect mediated the positive effects of the intervention on depressive symptoms. **Results:** Both positive and negative affect were significant mediators of the effects of the intervention on depressive symptoms; however, only positive affect mediated the association between changes in physical activity and improved depressive symptoms. **Conclusions:** Findings support physical activity and positive affect as key mediators of the MI treatment effect on improved mood. Decreases in negative affect were also evident in the treatment group, but were not related to improved physical activity. Findings may suggest the use of exercise-based interventions in conjunction with treatments that specifically target negative affective mechanisms for depression.

**Keywords:** motivational interviewing, physical activity, multiple sclerosis, positive affect, depression

## Impact

- Depression is a common problem for individuals with multiple sclerosis (MS). Although physical activity has been shown to improve depressive symptoms in MS, the mechanisms (mediators) of this treatment effect have not been examined. This is the first study to examine how changes in positive and negative affect may mediate improvements in mood in a randomized controlled trial of people with clinical depression.
- The findings from this study show that positive affect, but not negative affect, is a key mediator of the association between increased physical activity and improved mood. Future research is needed to determine whether combining interventions that target different affective processes have a synergistic effect on improving mood.
- The results suggest that physical activity interventions and other interventions that increase positive affect may play important roles in treating depression in people with MS. Rehabilitation professionals and organizations should consider integrating exercise interventions into depression treatment protocols in people with MS and depression.

## Introduction

Multiple sclerosis (MS) is a progressive neurological disease causing inflammation, myelin damage and axonal destruction in the central nervous system. Although the frequency of MS varies by geographical region, MS is a global disease with worldwide prevalence rates estimated at 30 per 100,000 individuals (Pugliatti, Sotgiu, & Rosati, 2002; Thompson et al., 2008). Prevalence of depression in MS is about twice the rate of that in the general population (15.7% vs. 7.4%; Patten, Beck, Williams, Barbui, & Metz, 2003) and depression is related to worse physical and social functioning, quality of life, and health in MS (Goldman Consensus Group, 2005). Unfortunately, it is estimated that two thirds of those with MS and major depression do not receive adequate treatment for their depression (Feinstein, 2002; Mohr, Hart, Fon-areva, & Tasch, 2006). A number of factors may be contributing to

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these low treatment rates. Antidepressants may be less effective and more poorly tolerated in those with MS compared with those without neurological conditions (Ehde et al., 2008; Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001). Although cognitive-behavioral therapy has been shown to be effective in treating depression in MS, about 50% do not respond to treatment (Mohr et al., 2001; Mohr et al., 2005). Consequently, the search is on for new treatments for depression in MS.

Exercise-based treatment for depression, which has shown antidepressant effects in healthy people, psychiatric patients, and the elderly (Brosse, Sheets, Lett, & Blumenthal, 2002) may be a promising alternative in MS, a clinical population in which physical activity levels tend to be low (White & Dressendorfer, 2004). Our research group designed and tested a telephone-based motivational interviewing (MI) intervention to increase physical activity and improve depressive symptoms in people with MS and Major Depressive Disorder or Dysthymia. We previously reported primary outcome findings that this intervention resulted in both significant increases in physical activity and statistically significant decreases in depressive symptoms, with 34% of those in the treatment condition showing a 50% or more reduction in depressive symptoms (Bombardier et al., 2013). In an effort to better understand how this intervention contributed to improvements in depressive symptoms, we turned to the consideration of positive affect and negative affect as potential mediators of the treatment effects that led to improved depressive symptoms for individuals with MS and clinical depression.

Although the terms affect and mood are sometimes used interchangeably, affect is a basic component of mood states. Affect reflects both the intensity (low vs. high activation) and valence (pleasant vs. unpleasant) of experiential responses to stimuli (Watson, Wiese, Vaidya, & Tellegen, 1999). Mood subsumes affect and also includes other components, such as attention and cognitive appraisals (Ekkekakis, 2003). Depression is characterized by increased negative affect and decreased positive affect (Clark & Watson, 1991), and effective treatments for depression can be conceptualized in terms of restoring the individual to a more balanced affective state (i.e., increasing positive affect and/or decreasing negative affect).

Theory and previous empirical findings provide justification for considering affect, and positive affect in particular, as a potential mediator of the effects of an exercise intervention on depression. Affect is theoretically tied to motivational systems and approach and withdrawal behaviors. Specifically, theorists have proposed that positive and negative affect are linked to the *behavioral activation system* and the *behavioral inhibition system*, respectively (Carver & White, 1994). The goal of the behavioral inhibition system is self-protection enacted through withdrawal behaviors (Carver & White, 1994); in terms of psychopathology, the behavioral inhibition system has been broadly linked to psychological distress, including depression (Mineka, Watson, & Clark, 1998). The behavioral activation system, on the other hand, is related to approach, appetitive behaviors, and seeking reward and pleasure. As part of this motivational approach process, positive affect is thought to be a reward and reinforcement for the behavioral activation system goal-directed behaviors (Carver & White, 1994). In terms of psychopathology, low levels of positive affect and the behavioral activation system have been specifically linked to depression (Gable, Reis, & Elliot, 2000; Kasch, Rottenberg,

Arnou, & Gotlib, 2002; Mineka et al., 1998) and to the hallmark depressive symptom anhedonia.

Correlational, experimental, and clinical trial research provides evidence that physical activity is related to lower depression and greater positive affect. Inactivity is associated with higher rates of depression in able-bodied persons (Brosse et al., 2002) and people with MS (Sutherland & Andersen, 2001). Exercise is an effective form of treatment for depression among healthy adults, psychiatric patients, and the elderly (Brosse et al., 2002). Meta-analyses consistently conclude that exercise interventions significantly reduce depressive symptom severity in people with major depressive disorder (Krogh, Nordentoft, Sterne, & Lawlor, 2011; Mead et al., 2009), including those whom also have a comorbid chronic health condition (Herring, Puetz, O'Connor, & Dishman, 2012). Greater frequency (Watson, 1988) and longer duration of physical activity corresponded to greater positive affect (Dua & Hargreaves, 1992; Kelsey et al., 2006). A recent meta-analysis of 158 studies showed that exercise, even at low intensity and for short durations, resulted in moderate ( $ES d = .45$ ) increases in positive affect, and that these positive effects lasted about 30 min postexercise (Reed & Ones, 2006). In one randomized clinical trial with 154 mostly nondepressed seniors, group strength/balance or flexibility/relaxation exercise programs were associated with significant increases in positive affect relative to no treatment control group; notably, the exercise interventions did not result in significant changes in negative affect (Brown, Liu-Ambrose, Tate, & Lord, 2009). A randomized clinical trial of adults with MDD found that a single bout of 30 min of moderate intensity exercise (i.e., brisk walking) resulted in significant improvements in positive mood, well-being, and vigor relative to 30 min of rest (Bartholomew, Morrison, & Ciccolo, 2005). Although scientists have speculated that exercise influences affect via multiple neurological pathways, the mechanisms by which exercise changes affect are, unfortunately, not well understood (Ekkekakis, 2003).

Positive affect has recently been conceptualized as a *facilitator* of positive physical rehabilitation outcomes (Kortte, Gilbert, Gorman, & Wegener, 2010). Indeed, positive affect has been shown to function as a buffer or moderator of the negative effects of severe physical injury (Quale & Schanke, 2010), acute stress (Folkman & Moskowitz, 2000), and chronic pain (Kratz, Davis, & Zutra, 2007) and is related to greater quality of life in physical rehabilitation populations (Man et al., 2004; Powell et al., 2009). Examining the role of positive affect in the treatment of clinical depression fits well within the current emphasis in the field of psychology on bolstering positive psychological factors and individual assets, such as positive affect and hope, in addition to reducing symptoms (e.g., depressive symptoms) or barriers (e.g., physical limitations) to facilitate positive adjustment (Dunn & Brody, 2008; Dunn & Dougherty, 2005; White, Driver, & Warren, 2008, 2010).

This is the first study to our knowledge that has tested whether changes in positive affect and/or negative affect mediate the effects of an exercise intervention on depressive symptoms in people who are depressed. Efforts to identify mediators of successful interventions are important for a number of reasons. Identification of "core components" or "active ingredients" that are responsible for intervention effects can aid in the further development of more effective, targeted, and streamlined interventions and can bring clarity about how different interventions bring about change

through common mediators. Identification of mediators can also contribute to theories of how mental health issues are developed and maintained and detection of different avenues to successful treatment. Identification of mediators can also aid in the detection of moderators of a treatment response. Finally, a clearer understanding of *how* interventions work can be a powerful tool for clinicians who are tasked with both generalizing interventions to a patient population and tailoring interventions to specific clients (Kazdin, 2007, 2009).

Based on current theory and previous findings of affect, exercise, and mood, we predicted that increased physical activity in the treatment group would be related to greater positive affect, but not greater negative affect, and that the effects of the exercise intervention on depressive symptoms would be mediated by way of increased physical activity and positive affect. In contrast, we did not expect negative affect to mediate the association between the intervention and improvements in depressed mood.

## Method

This article is a follow-up to that of Bombardier et al. (2013). Essential information of the study is described here, and interested readers are directed to the earlier article for additional details on study design, methodology, and primary outcomes of the intervention.

## Design

The study was a two-group, parallel randomized controlled trial with blinded outcome assessment. Participants were assigned to either a telephone counseling-based physical activity promotion group or a wait-list control group. Outcomes were assessed at baseline (before randomization) and at 12-weeks postrandomization (primary outcome assessment point).

## Participants and Setting

Study participants consisted of community-dwelling individuals with clinically definite MS. They were identified from the following sources: (a) the Western Regional MS Center at the University of Washington; (b) advertisements in regional newspapers, MS newsletters, and MS Web sites; (c) flyers sent to local rehabilitation physician and neurologists offices; (d) MS support groups in the Puget Sound region; (e) a large mailing sent to those on the North American Research Consortium on MS and MS Association registries; and (f) two MS survey studies, the methods of which are described elsewhere (Bamer, Cetin, Johnson, Gibbons, & Ehde, 2008).

Inclusion criteria were: (a) between the ages of 18 and 70 years; (b) physician confirmed diagnosis of MS; (c) Expanded Disability Severity Scale (EDSS; Kurtzke, 1983) of  $\leq 6.5$ ; (d) Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001) score  $\geq 10$  or a response of  $\geq 2$  on Questions 1 (anhedonia item) or 2 (depressed mood item); (e) diagnosis of major depressive disorder or dysthymia based on the Structured Clinical Interview for DSM-IV (SCID-IV; First, Gibbon, Spitzer, & Williams, 2001); and (f) currently exercising  $< 150$  min/week. Exclusion criteria were: (a) cardiovascular, balance, or bone/joint problem that render exercise unsafe based on the Physical Activity Readiness

Questionnaire (PAR-Q; Thomas, Reading, & Shephard, 1992); (b) extreme heat intolerance; (c) diagnosis of schizophrenia, paranoid disorder, or bipolar disorder; (d) current suicidal intent or plan; (e) current alcohol dependence based on the substance-dependence module of the SCID-IV; and (f) inability to independently complete study forms. In order to maximize generalizability of the findings, those on stable doses of antidepressant medications were not excluded from the study.

## Procedures

The University of Washington Institutional Review Board approved the research study protocol. A total of 634 individuals were assessed for eligibility for the study (see Figure 1). Of the 119 individuals who were enrolled in the study, 27 were excluded after a second round of screening, resulting in 92 individuals randomized to either the treatment condition ( $n = 44$ ) or the wait-list control condition ( $n = 48$ ). Potential participants eligible for the study at the initial telephone screening were invited to attend a baseline in-person visit at the medical center. During this baseline visit, informed consent was obtained, and participants completed the study self-report measures, and a trained research coordinator administered interview-based assessments, including: (a) the 7-Day Physical Activity Recall (7-Day PAR; Sallis et al., 1985); (b) the Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960); and (c) the SCID-IV major depression and dysthymia modules to confirm eligibility.

Each participant then met with a study counselor to undergo randomization. The study counselor opened the next sequentially numbered envelope (assignment was computer generated) to inform the participant of assignment to the intervention or control condition. Those randomized to the intervention condition then completed a 40 min–60 min motivational interview and goal setting session with the counselor. Those randomized to the wait-list control condition were sent home after being informed that they would be contacted for a reevaluation and to receive the intervention in 12 weeks. A trained research coordinator who was blind to group assignments conducted in-person outcome assessments with participants in both groups.

## Measures

**Demographic and clinical variables.** Demographic data (age, race, ethnicity, marital status, employment status, educational level), self-reported weight and height for Body Mass Index (BMI) calculation, date of MS diagnosis, and current medications (types and doses) were collected at baseline. Neurological status was assessed using a self-administered version of the Expanded Disability Status Scale (EDSS; Bowen, Gibbons, Gianas, & Kraft, 2001).

**Physical activity.** The 7-Day Physical Activity Recall Interview (PAR) was used to assess intensity and duration of physical activity at baseline and 12 weeks (Sallis et al., 1985). The PAR is a valid measure of physical activity in adults with MS (Motl, McAuley, Snook, & Scott, 2006). The number of minutes spent in light, moderate, hard, and very hard physical activities for the past 7 days were obtained and summed to produce the total number of minutes of exercise for the past week.

**Depressive symptoms.** The primary outcome measure was the HAM-D (Hamilton, 1960), a widely used, semistructured in-

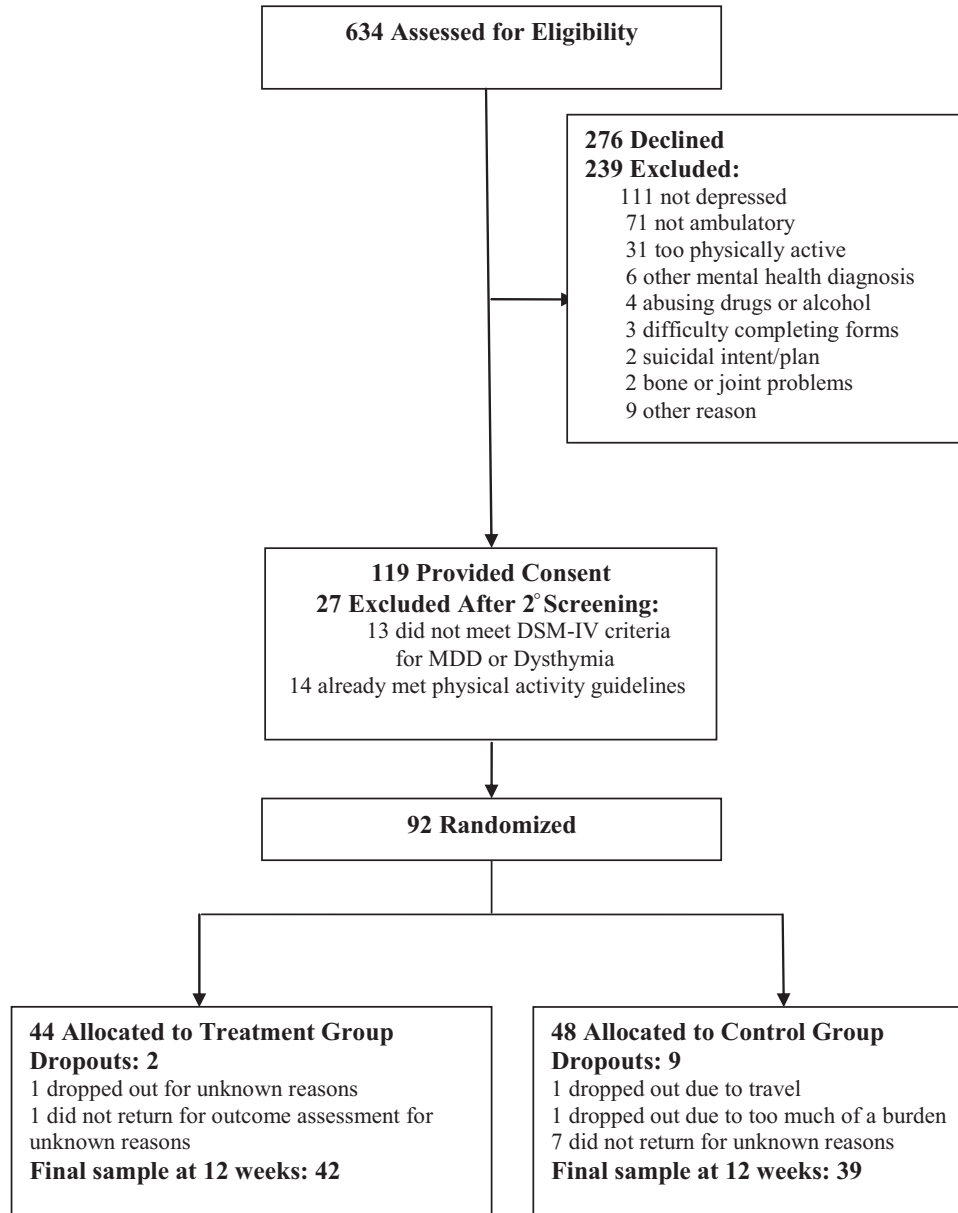


Figure 1. CONSORT table depicting participant flow through the study.

terview comprised of 17 items that assess depressive symptom severity. Eight of the items are scored on a 5-point scale, ranging from 0 = *not present* to 4 = *severe* and nine of the items are scored from 0–2. Scores are summed for a possible range of 0–50, with higher scores indicating greater depressive symptomatology.

**Affect.** The Positive and Negative Affect Schedule (PANAS) was used to measure affect. The PANAS is a 20-item measure with 10 positive and 10 negative affect descriptors, rated on the extent that the affect was experienced in the past week on a 5-point Likert scale from 1 = *very slightly or not at all* to 5 = *extremely* (Watson, Clark, & Tellegen, 1988). The 10 items from each subscale were summed to produce scores for positive affect and negative affect, each with a possible range of 10–50. Cronbach's alphas for positive affect in this sample were .83 at baseline and .98 post-

treatment; and for negative affect were .88 at baseline and .97 posttreatment.

### Study Conditions

**Motivational interviewing condition.** The intervention was based on MI, a client-centered and directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence (Miller & Rollnick, 2002). Counseling techniques include asking open questions to elicit motivation and commitment to change and reflective listening to foster rapport and understanding. Affirmations and summaries may be used to highlight successes and reiterate reasons and/or ability to change. There are two phases to the MI process: building motivation to change and then negotiating goals and



action planning (Miller & Rollnick, 2002). The goal of this intervention was to use MI to promote increased physical activity or exercise.

The initial in-person session was followed by seven scheduled telephone counseling calls at Weeks 1, 2, 3, 4, 6, 8, and 10, each lasting about 30 minutes. There was also a final in-person session lasting up to 60 minutes. Consistent with the MI framework, all sessions were intended to promote motivation and commitment to the activity plan, and to monitor progress toward goals, adjust goals, and resolve barriers, based on MI principles and techniques.

**Training and fidelity.** Three masters-level counselors, who had completed a 2–3 day MI training program and received ongoing supervision from a clinical psychologist and motivational interviewing trainer (CHB), delivered the intervention. To evaluate treatment fidelity, 20% of the intervention sessions ( $n = 65$ ) were randomly selected to be audio recorded and rated. Key indices of MI proficiency including percent open questions, reflections to questions ratio, frequency of MI-inconsistent behaviors, are reported elsewhere (Bombardier et al., 2013), and suggest an intervention with good fidelity and consistent with the spirit of MI.

**Control condition.** Participants in the wait-list group were not provided with any depression treatments and were not prevented from independently pursuing depression treatment. The study intervention was offered to control group participants at the end of the 12-week wait-list trial.

## Data Analysis

The test of the mediated effect of the intervention in this study was a test of the theorized process where the exercise intervention resulted in changes in physical activity, which related to changes in positive affect; these affective changes, in turn, were hypothesized to result in improvements in depressed mood. Mediation was tested via a path-analysis model (i.e., structural equation model) with MPlus statistical program software (Version 5.21; Muthen & Muthen, 1998–2009) using an analysis of covariance procedure where postintervention (i.e., 12 weeks) values for all endogenous variables were predicted with preintervention values of each variable (i.e., baseline positive affect, negative affect, physical activity, and depression) included as covariates. Within this model, depressive symptoms were predicted from study condition (treatment vs. control) with physical activity, positive affect and negative affect tested as mediators of this association. Path analysis procedures using maximum likelihood estimation were used to estimate complex relations between the multiple variables, including the multiple mediators. This single just-identified model predicting depressive symptoms provided significance tests for total indirect effects (i.e., total mediated effects from treatment to depressive symptoms variable) and specific indirect effects (i.e., precise mediational pathways via a portion of the mediators under consideration) within the model. Because our model tests two mediators, we followed current recommendations for examining multiple mediators by utilizing bootstrap resampling (bootstrap samples = 500), which has been shown to provide more accurate confidence interval estimates than those based on normal theory (Taylor, MacKinnon, & Tein, 2008). Negative affect and positive affect were specified as correlated in the model. Prior to conducting the path analyses, we examined the descriptive statistics for all variables under consideration and found them all to meet the minimum criteria for normality (i.e.,  $< 2$  skew and  $< 7$  kurtosis;

West, Finch, & Curran, 1995). Model fit statistics were evaluated based on the criteria suggested by Hu and Bentler (1999), CFI and TLI  $> 0.90$  indicating good fit and RMSEA  $< 0.06$  indicating good model fit. Statistical tests of direct and indirect effects were conducted as part of the path analysis. A direct effect is, as it sounds, the effect of one variable on another with no intervening variables and is captured by a single-link pathway. An indirect effect is made up of pathways with two or more links between two variables of interest. The total effects of a given model is the sum of all direct and indirect effects. These tests provide a statistical test of various “mechanistic chains” between one variable and another, such as between treatment/control condition and the primary outcome of depressive symptoms. Because all mediators were assessed at the same time as the outcome, temporal order of change cannot be inferred. Therefore, focus should be on the factors within a given mechanistic chain and not on their particular order.

## Results

### Preliminary Analyses

Descriptive statistics of baseline demographic, clinical, and outcome variables for each group are depicted in Table 1. The groups were not different in terms of age, sex, education level, race, marital status, years since MS diagnosis, relapsing remitting MS, BMI, mobility, positive affect, or negative affect. The groups were significantly different in terms of physical activity and depressive symptoms levels at baseline. The control group, on average, reported about twice as many minutes per week of physical activity compared with the treatment group. Closer examination of the distribution of activity across the groups shows that the treatment group had more people reporting no (0) exercise in the past week ( $n = 30, 68.2\%$ ) compared with the control group ( $n = 22, 45.8\%$ ). The control group reported significantly lower levels of depressive symptoms, though in absolute terms, this difference was small and both of these average scores fall in the category of “moderate depression.”

The means and zero-order correlations between the presumed mediators and the outcome, depressive symptoms, at baseline and postintervention are shown in Table 2. At baseline, physical activity was not significantly correlated with any study variables, but was positively correlated with positive affect and negatively correlated with both negative affect and depressive symptoms postintervention. Positive affect and negative affect were not significantly correlated at baseline but showed a moderate negative correlation postintervention. As anticipated, positive affect showed negative correlations and negative affect positive correlations of moderate to large magnitude with depressive symptoms at both baseline and postintervention. In absolute terms, physical activity and positive affect means increased and depressive symptoms and negative affect means decreased from baseline to postintervention.

### Mediational Analyses Predicting Depressive Symptoms

The results of the path analysis are depicted in Figure 2. Examination of the fit statistics for this model (CFI = .96, TLI = .87, RMSEA = .05) indicated satisfactory fit of the data to the model. In terms of mechanistic pathways between group and depressive

Table 1  
Demographic and Clinic Characteristics at Baseline for Treatment and Control Groups

Baseline variable	Treatment (n = 44)		Control (n = 48)		Test results*
	N (%)	Mean (SD)	N (%)	Mean (SD)	
Age		47.1 (8.9)		49.7 (7.9)	$\chi^2(1) = 2.10; p = .15$
Female	39 (89)		40 (83)		$p = .56$
Education					$p = .61$
HS or less	10 (23)		9 (19)		
Community college	15 (34)		13 (27)		
Bachelor's degree or higher	19 (43)		26 (54)		
White (not Hispanic)	42 (95)		43 (90)		$p = .44$
Married or cohabitating	13 (30)		18 (38)		$p = .51$
Years since MS diagnosis		9.4 (7.1)		11.7 (8.3)	$\chi^2(1) = 1.75; p = .19$
Relapsing remitting MS	32 (76)		36 (75)		$p = 1.00$
BMI category					$p = .64$
<25	13 (31)		18 (38)		
25–<30	9 (21)		12 (25)		
30+	20 (48)		18 (38)		
Mobility (EDSS Score)†					$p = .68$
4.0	24 (54)		24 (50)		
4.5–6.5	20 (46)		24 (50)		
		<u>Mean (SD)</u>		<u>Mean (SD)</u>	
Positive affect		21.82 (7.08)		22.92 (6.28)	$\chi^2(1) = 1.44; p = .23$
Negative affect		27.64 (9.52)		24.96 (7.17)	$\chi^2(1) = 2.05; p = .15$
Physical activity		16.7 (31.7)		35.7 (43.8)	$\chi^2(1) = 5.7; p = .02$
HAM-D		17.7 (4.9)		15.5 (4.6)	$\chi^2(1) = 4.80; p = .03$

† self-reported. \* Fisher's exact test for categorical variables, Kruskal-Wallis for continuous variables.

symptoms, as can be seen in the figure, the pathway from group to physical activity was positive and significant, indicating that participation in the motivational interviewing intervention was associated with increased physical activity. The positive pathway from physical activity to positive affect indicates that physical activity was related to greater increases in positive affect. Notably, the small negative association between physical activity and negative affect was nonsignificant. The significant negative pathway indicates a moderately sized inverse relation between positive affect and depressive symptoms. Direct pathways between treatment group and both positive affect and negative affect were significant, indicating that the intervention was directly associated with increased positive affect and decreased negative affect, aside from

the association of changes in physical activity and changes in affect.

Results of statistical tests of direct and indirect effects are depicted in Table 3. The direct effect from the intervention to depressive symptoms was not significant, indicating that in this model, the intervention did not directly impact depressive symptoms. The simpler specific indirect effects, from the intervention through positive affect and negative affect to depressive symptoms (bypassing physical activity) indicate that that intervention resulted in significant improvements in both positive affect and negative affect, that, in turn, resulted in decreased depressed mood. These findings indicate that the intervention was related to increased positive affect and decreased negative affect by way of an

Table 2  
Means, Standard Deviations, and Zero-Order Correlations of Physical Activity, Positive Affect, Negative Affect, and Depression Scores at Baseline (T1) and Postintervention (T2)

Variable	Physical activity		Positive affect		Negative affect		HAM-D score	
	T1	T2	T1	T2	T1	T2	T1	T2
T1 Physical activity	—							
T2 Physical activity	.14	—						
T1 Positive affect	.15	.03	—					
T2 Positive affect	.11	.39**	.39**	—				
T1 Negative affect	-.16	-.05	-.09	-.05	—			
T2 Negative affect	-.03	-.25*	.12	-.42**	.50**	—		
T1 HAM-D score	-.19	.17	-.32**	-.07	.46**	.34**	—	
T2 HAM-D score	-.06	-.23*	-.13	-.68**	.24*	.65**	.29**	—
Mean	26.63	112.50	22.39	27.05	26.24	21.79	16.59	12.14
SD	39.46	78.70	6.66	8.26	8.44	7.97	4.84	6.27

Note. HAM-D Score = total score on Hamilton Depression Scale; T2 (postintervention) is 12 weeks after T1 (baseline).

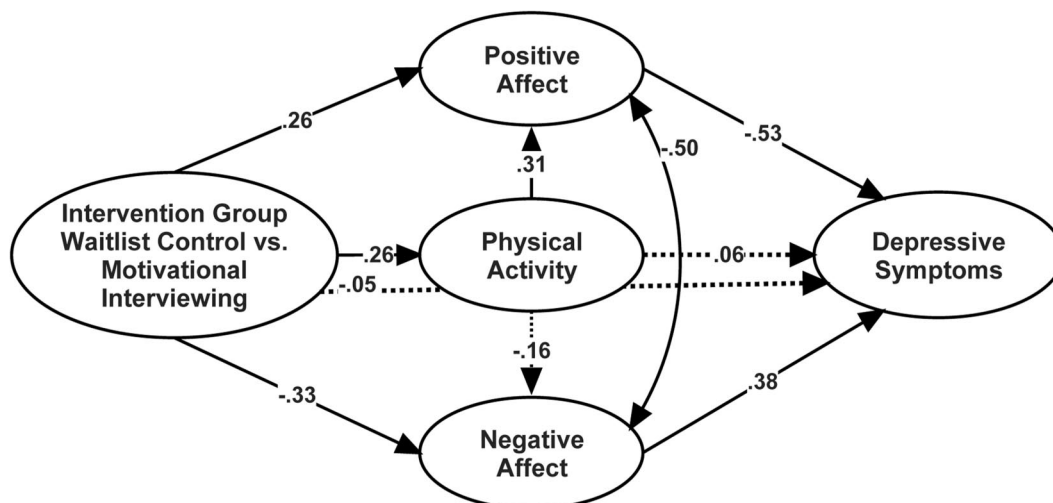


Figure 2. Path analysis results showing the association of intervention group, depression symptoms, physical activity, positive affect, and negative affect. Wait-list control = 0 and Motivational interviewing condition = 1; Coefficients are standardized path coefficients. All solid lines are significant at  $p < .01$ ; all dashed lines are nonsignificant at  $p > .10$ .

unexamined mechanism other than changes in physical activity. The indirect pathway of primary interest in this study, group  $\rightarrow$  physical activity  $\rightarrow$  positive affect  $\rightarrow$  depressive symptoms was statistically significant. This finding is especially notable in context of the fact that indirect pathway group  $\rightarrow$  physical activity  $\rightarrow$  negative affect  $\rightarrow$  depressive symptoms was not significant. Essentially, these findings indicate that increased positive affect is related to increased physical activity and decreased depressive symptoms in a way that negative affect is not.

### Discussion

Efforts to identify the mediators, or “mechanisms,” of a successful intervention are an essential part of the process of understanding, developing, refining, and effectively applying the intervention. The purpose of this study was to examine positive affect and negative affect as potential mediators of a physical activity counseling intervention aimed at improving depression in people with MS. Taken as a whole, the path analyses indicate that the

motivational interviewing intervention was related to decreased depressive symptoms by way of changes in a number of specific mechanistic pathways. The role of change in physical activity is a key mediator under consideration because a primary aim of the intervention was to increase participants’ physical activity. We found that the intervention did result in increased physical activity compared with the waitlist control. As expected, physical activity was related to increased positive affect, which in turn, was related to lower depressive symptoms. Also as anticipated, physical activity was unrelated to negative affect. These findings are consistent with the literature that has consistently demonstrated linkages between physical activity and positive affect, with less consistent linkages to negative affect (Dua & Hargreaves, 1992; Watson, 1988; Wichers et al., 2012).

The results also show that the intervention was related to affective benefits (e.g., increased positive affect and decreased negative affect) that were not related to changes in physical activity but, regardless, were related to improved depressive symptoms. The

Table 3

Total Effects, Direct Effects, and Specific Indirect Effects From Group (Intervention) to Depression Post-intervention

	Est.	SE	p value	95% CI*	
				Lower	Upper
Total direct effects (Group $\rightarrow$ depression)	-.05	.08	.68	-.18	.12
Total effects (Direct + indirect)	-.30	.08	<.001	-.47	-.14
Total indirect effects	-.27	.07	<.001	-.40	-.14
Specific indirect					
Group $\rightarrow$ positive affect $\rightarrow$ Depression	-.12	.04	.006	-.21	-.04
Group $\rightarrow$ negative affect $\rightarrow$ depression	-.12	.04	.005	-.20	-.03
Group $\rightarrow$ physical activity $\rightarrow$ depression	.02	.01	.14	-.007	.05
Group $\rightarrow$ physical activity $\rightarrow$ positive affect $\rightarrow$ depression	-.04	.02	.04	-.08	-.001
Group $\rightarrow$ physical activity $\rightarrow$ negative affect $\rightarrow$ depression	-.02	.01	.08	-.03	.002

\* Bootstrap confidence intervals.

mechanisms of this direct association between the intervention and improved affect, which bypasses changes in physical activity, have yet to be identified or tested. Possible mechanisms could ostensibly include a number of nonspecific factors (e.g., therapeutic relationship, treatment expectancy), increased involvement in activities that are not physical in nature (e.g., socializing, quiet recreational activities, vocational activities, improved community integration), and/or cognitive changes (e.g., increased motivation, optimism, or self-efficacy, decreased “negative thinking”).

These lingering questions regarding other mechanisms beyond affect point to our inability to explore potential mediators because they were not assessed and suggests that clinical researchers who are involved in developing, implementing, and disseminating treatment programs should consider meditation at the point of study development. This would allow for inclusion of measures of hypothesized mediators and a thorough analysis of mediation at the conclusion of the clinical trial. Identification of mediators is an essential and often neglected step in clinical program development. Kazdin pointed out the potential for meditational studies to be used to understand and refine interventions as well as provide practical guidance to clinicians who are tasked with generalizing interventions to populations and tailoring treatment programs to individual patients (Kazdin, 2007, 2009). Identifying the mechanisms of change in an intervention can point to the core elements that are essential and should be focused on and practiced with high fidelity for the treatment to be effective (Price & Lorion, 1989). In the same way, meditational analyses can identify elements of an intervention that are not major contributors to positive change and therefore compromise the intervention’s efficiency and effectiveness. Although this study focused solely on positive and negative affect as potential mediators, it represents an important step in and model for identifying factors to develop theories of change and effective interventions for the treatment of depression in MS.

This study examined treatment effects immediately upon conclusion of the treatment. Duration of the effects of exercise on mood is central to determining the helpfulness of exercise-based interventions for depression. Indeed, it has previously been demonstrated that greater frequency (Watson, 1988) and longer duration of physical activity corresponded to greater positive affect (Dua & Hargreaves, 1992; Kelsey et al., 2006) and a diagnosis of depression influences the ability to maintain over time the benefits of physical activity on positive affect (Wichers et al., 2012). However, if physical activity is sustained, the benefits could be long lasting, a notion that is supported by studies that showed improved mood 10 (DiLorenzo et al., 1999) and 12 months (Babyak et al., 2000) following exercise-based intervention for clinical depression. Future research should examine the role of affective mediators in depression treatment outcomes over time (e.g., through longitudinal mediation models). This type of research is particularly important to determine whether physical activity can help to prevent depression relapse in MS.

One of the chief promises of studies that examine meditational effects is that they can help us identify the “active ingredients” of an intervention, thereby shedding light onto how a treatment works (Kazdin, 2007). In this way, mediation studies can help to refine and further develop our current interventions, resulting in treatment approaches that are more effective, targeted, and streamlined. The finding that the effect of the physical activity intervention on depression was mediated by increased positive affect suggests

more effective depression outcomes might be achieved by combining treatments with complementary mechanisms of action. For example, selective serotonin reuptake inhibitors have been hypothesized to have a greater impact on negative affect than positive affect (Dichter, Tomarken, Freid, Addington, & Shelton, 2005). Indeed, recent research indicates that exercise is an effective augmentation strategy for patients with major depression who do not respond fully to antidepressant treatment (Trivedi et al., 2011). Future research should examine whether other forms of depression treatment such as cognitive therapy or problem-solving therapy improve depression via positive or negative affect and whether combined treatments that address complementary mechanisms (e.g., negative affect *and* positive affect) are more effective than treatments that target similar mechanisms. Such an intervention, that includes efforts to bolster positive affect as well as reduce negative affect, would fit well within a current positive psychology movement (Dunn & Dougherty, 2005; Seligman & Csikszentmihalyi, 2000; Seligman, Rashid, & Parks, 2006) that emphasizes bolstering personal assets and positive experiences in addition to treating suffering, challenges, and barriers.

Despite the positive effects of the intervention, the MI-based counseling resulted in modest improvements in physical activity. In fact, none of the participants met physical activity levels that met minimum public health guidelines by the end of the trial. However, previous studies have indicated that even mild physical activity, (e.g., 30 min of moderate exercise three times a week), is a robust and effective treatment for depression (Babyak et al., 2000) and there is movement toward focusing more on reduction of sedentary behavior to improve depressed mood rather than on increased physical activity. Indeed, findings suggest that small reductions of sedentary behavior can result in significantly improved mood (Teychenne, Ball, & Salmon, 2010a, 2010b). In terms of the meditational effects of affect, dose may have only affected the role of positive and negative affect at extremely high levels of physical activity. Affective benefits that are typical at mild and moderate levels of physical activity have been found to degrade with extreme intensity or duration of exercise, such as completing a marathon or an elite athletic training regimen (Berger & Owen, 1992a, 1992b; Douchamps-Riboux, Heinz, & Douchamps, 1989). Considering that this trial did not put people in danger of such extreme levels of exercising, this may not be a legitimate concern. However, these speculations need to be examined in future research to determine whether dose affects mechanistic pathways.

People with MS were historically counseled against physical exertion in order to avoid pain, fatigue, and/or thermosensitivity. Currently, there is evidence that exercise holds benefits, including improved muscle strength, mobility, balance, fatigue, depression, pain, self-efficacy, and quality of life that outweigh the risks for those with MS (Motl & Gosney, 2008; Motl, McAuley, Snook, & Gliottoni, 2009; Rietberg, Brooks, Uitdehaag, & Kwakkel, 2005; Sutherland & Andersen, 2001; White & Dressendorfer, 2004). Astute clinicians will assess and incorporate the unique challenges and risks related to exercise for people with MS. Effective collaboration between patient and clinician is necessary to account for baseline physical activity and fitness, physical and social limitations (including access-related barriers) that may prevent some types of physical activity, and personal preferences and motivations of the person with MS, in developing an individualized



exercise program. Timing and progression of exercise are especially important in MS. If activity is too frequent or intense at the start, the person with MS may experience excessive fatigue, pain, immobility, and so forth, precipitating discontinuation of the exercise program. Instead, physical activity should be increased gradually (Fordyce, 1976). MS is a progressive disease that may be punctuated by periods of disease exacerbation; consequently, adjustments to an exercise plan may be needed in the context of fluctuating symptoms and physical limitations. Rehabilitation clinicians should not be dissuaded from encouraging those with MS to progress in their physical activity and fitness in the context of challenges to regular exercise that are common to the general population and those added challenges that are specific to MS. We highlight the need for interdisciplinary collaboration that may incorporate input from rehabilitation physicians, physical therapists, psychologists, and others in formulating exercise interventions in people with MS.

This study has a number of notable strengths. It is the first known study to consider affective mediators in order to explore how an MI intervention works to improve depressive symptoms. As such, this work provides novel information that can be used to advance both theory and treatment approaches for depression. This study also considered the effects of an MI intervention in MS, a clinical population that is particularly vulnerable to depression and in great need of effective interventions. Use of structural equation modeling to examine mediational effects has a number of advantages over an approach that uses a series of linear regression. For example, path analysis allows for the simultaneous examination of multiple mediators and significance testing of specific mediational pathways (Mackinnon, 2008).

There are also several study limitations that need to be recognized. The study sample included individuals with MS who were primarily female, White, well-educated, able to ambulate, met criteria for mild to moderate major depression, did not have current alcohol dependence or diagnosis of schizophrenia, paranoid disorder, or bipolar disorder, did not have any number of common medical conditions (e.g., cardiovascular, balance, or bone/joint problems), and did not have suicidal intent or plan. Our inclusion/exclusion criteria and sampling procedures have resulted in sample characteristics that limit our ability to generalize the findings to a broader demographic or to those with greater MS-related disability or more severe depression. Our study sample may differ from many individuals who present to health care providers with more complex physical, social, and psychological challenges that may stymie efforts to initiate an exercise intervention such as the one used in this study. Findings may also not translate to those who are depressed but do not have MS. Physical activity was assessed via one self-report measure. Although self-report measures, including the study's measure, are valid in assessing activity in people with MS (Motl et al., 2006), objective measures, such as accelerometers, would likely provide a more reliable indicator of physical activity and should be considered in future research. The HAM-D includes a number of items that overlap with common MS symptoms, such as sleep disturbance, fatigue, cognitive problems, and psychomotor slowing. Future studies in MS should utilize measures, such as the Center for Epidemiologic Studies Depression Scale (CES-D) Scale (Radloff, 1977), that provide an assessment of depressed mood with less overlap

with MS symptoms. Because all variables were assessed simultaneously, it is not possible to determine the exact temporal order of changes in the mediating variables under consideration. For example, it is possible that changes in physical activity, positive affect, and depressive symptoms occurred simultaneously, or that changes in positive affect preceded changes in physical activity. The interplay between changes and physical activity, affect, and mood may be so dynamic and temporal intervals over which change could be identified so small that disentangling the precise order of change in mediating variables may be, in reality, extremely difficult. Although the methodology of this study does not allow us to infer temporal precedence of any given variable, our research question and approach is grounded in theory and previous empirical evidence; regardless of this specific limitation, the findings suggest that positive affect has an association with physical activity and depressive symptoms that negative affect does not have.

Despite these limitations, this study represents an important first step in understanding potential mechanisms of change in an exercise intervention for depression in MS and has demonstrated the benefits of using structural equation modeling for understanding such relationships. This study's results also point to the need for future research examining models inclusive of multiple potential mechanisms of change, including unique mechanisms (those factors specific to a therapy such as increased motivation in a MI intervention) and common factors (therapeutic alliance, treatment expectancy).

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