Randomized controlled trial of yoga and exercise in multiple sclerosis

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Abstract—*Objective:* To determine the effect of yoga and of aerobic exercise on cognitive function, fatigue, mood, and quality of life in multiple sclerosis (MS). *Methods:* Subjects with clinically definite MS and Expanded Disability Status Score less than or equal to 6.0 were randomly assigned to one of three groups lasting 6 months: weekly Iyengar yoga class along with home practice, weekly exercise class using a stationary bicycle along with home exercise, or a waiting-list control group. Outcome assessments performed at baseline and at the end of the 6-month period included a battery of cognitive measures focused on attention, physiologic measures of alertness, Profile of Mood States, State-Trait Anxiety Inventory, Multi-Dimensional Fatigue Inventory (MFI), and Short Form (SF)-36 health-related quality of life. *Results:* Sixty-nine subjects were recruited and randomized. Twelve subjects did not finish the 6-month intervention. There were no adverse events related to the intervention. There were no effects from either of the active interventions on either of the primary outcome measures of attention or alertness. Both active interventions produced improvement in secondary measures of fatigue compared to the control group: Energy and Fatigue (Vitality) on the SF-36 and general fatigue on the MFI. There were no clear changes in mood related to yoga or exercise. *Conclusion:* Subjects with MS participating in either a 6-month yoga class or exercise class showed significant improvement in measures of fatigue compared to a waiting-list control group. There was no relative improvement of cognitive function in either of the intervention groups.

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Mind-body medicine encompasses a range of methodologies, such as yoga, tai-chi, and meditation, that may be beneficial to the health of their practitioners. Yoga is a commonly practiced mind-body approach that has components centering around meditation, breathing, and postures. Of the active or Hatha yoga techniques, Iyengar yoga is probably the most common type practiced in the United States. A person assumes a series of stationary positions that utilize isometric contraction and relaxation of different muscle groups to create specific body alignments. There is also a relaxation component. Many people with multiple sclerosis (MS) have taken yoga classes and report high satisfaction. Of 1,980 survey respondents with MS in Oregon and southwest Washington, 30% indicated they had taken yoga classes; of those having taken yoga classes, 57% reported yoga as being "very beneficial."[1] This compared favorably to "very beneficial" ratings for therapeutic drugs: 37% of Avonex users, 26% of Betaseron users, 25% of Copaxone users, and 43% of IV corticosteroid users. Small pilot studies of other mind-body therapies in MS have suggested some benefit in physical measures and quality of life.[2,3]

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the June 8 issue to find the title link for this article.

Physical activity by itself may be beneficial in MS. There have been several controlled trials of aerobic exercise in MS suggesting improvement in cardiovascular fitness.[4] There have also been reported improvements in quality of life, fatigue, and mood.[5,6] Thus, in designing this study we included an exercise intervention designed to accommodate and benefit a person with MS in addition to a wait-list control group to compare to the yoga intervention.

Besides quality of life, fatigue, and mood, there are a number of cognitive changes often associated in MS that may be impacted by yoga or physical activity. Deficits in attention, including speed of processing, are a common part of the cognitive disorder of MS.[7] Exercise or yoga may improve cognitive ability in MS by improving mood and reducing stress. Hatha yoga has been reported to produce improvements in mood comparable to aerobic exercise.[8,9] Additionally, yoga involves focusing one's attention on breathing or specific muscles or parts of body and it is unknown whether the attentional practice in yoga would generalize to conventionally assessed attentional function.

Despite yoga's wide popularity, there are few con-

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trolled yoga studies in any neurologic disorder using objective quantitative outcome measures and these studies often have small numbers of subjects.[10-12] Further, despite the widespread advocacy and use of yoga in MS, there have been no controlled clinical trials. To help address this issue, we performed a randomized 26-week trial of yoga in MS in comparison to exercise and wait-list control groups.

Methods. *Study design.* This was a 6-month parallel-group, randomized controlled trial performed in adults with MS that had the approval of the OHSU Institutional Review Board. All subjects provided written informed consent. After completion of the baseline evaluations, subjects were randomized to one of the three experimental groups lasting 6 months: yoga class, exercise class, or wait-list control group. To ensure acceptance of the protocol, wait-list subjects were told they could enroll in either a yoga or exercise class after the 6-month period at no cost.

Subjects were randomly assigned to treatment groups in this study using a modified minimization scheme in such a way as to maintain balance across multiple stratification variables with relatively small numbers of subjects. Cohorts were recruited and then treatment group assignments were made for the entire cohort at one time. A cohort is a group of subjects enrolled within a 1-month period that allowed for active intervention subjects to begin their exercise and yoga classes at the same time. The stratification variables were age group (less than 50 years old and 50 years or older), sex, and baseline Expanded Disability Status Scale (EDSS) (less than or equal to 2.5 and greater than 2.5). Treatment assignment was made by the project statistician who was otherwise uninvolved with the assessments. Initially, all the subjects in each of the cohorts were randomly ordered ensuring this assignment scheme is, in fact, random. Then, the minimization approach of Taves[13] was used as a starting point. This process minimizes the absolute differences between the groups for each possible assignment of the next patient to treatment groups. Where these absolute differences are equal in two or three groups, the subject was assigned randomly (with probability of being assigned to one group equal across groups). The minimization approach was modified to account for randomization within cohorts prior to treatment assignment.

Subjects. Subjects were recruited through the local newspaper, the OHSU newsletter Web site, the newsletter of the local MS Society, and through the OHSU MS Center. Recruitment began January 1999 and the last cohort of subjects had outcome assessments in June 2002. A neurologist reviewed medical records for diagnostic criteria for MS.[14] In order to create a consistent exercise and yoga intervention, we enrolled only subjects with an EDSS of 6.0 or less, i.e., able to walk 100 meters with at most unilateral support.[15]

Prospective participants were screened for other major medical problems with medical history, physical examination, and EKG to ensure the safety of the intervention and to exclude subjects with an underlying medical illness that may impair cognition. We excluded subjects with: insulin-dependent diabetes; uncontrolled hypertension; liver or kidney failure; symptomatic lung disease; alcoholism/drug abuse; symptoms or signs of congestive heart failure, ischemic heart disease, or symptomatic valvular disease; or corrected visual acuity worse than 20/50 binocularly. Color vision was intact to color dot perception on the Stroop with 100% accuracy. We excluded subjects if they had performed yoga or tai-chi in the last 6 months or were regularly performing aerobic exercise more than 30 minutes per day. Subjects spoke English as their primary language.

Initially, as for many studies with cognitive outcome measures, we planned to not include subjects taking any medications known to affect CNS function or subjects with significant psychiatric diseases including major affective disorder. However, these exclusions were immediately eliminated since we were unable to recruit subjects with these exclusions. This recruitment problem was not dissimilar to the mentioned difficulties of a recent multicenter trial of donepezil in MS.[16] We simply encouraged subjects to minimize changes in CNS-active medications (e.g., modafinil and antidepressants) during the course of the study. For CNS-active medications taken on an as needed basis, subjects were asked to not take the medications within 24 hours of the assessments. The original targeted enrollment was 150 subjects with a projected power of 0.8 for the Stroop test. This was based on an estimated moderate effect size and a reasonably low dropout rate. However, it was decided to stop the enrollment at the halfway point, prior to any analysis, because these drug and psychiatric issues would add significant variance to the primary outcome measures even with, at best incomplete, statistical correction. To maintain adequate power for the primary outcome measures once these exclusions were removed would have required randomizing significantly more subjects than feasible with the budget.

Interventions. Yoga classes were 90 minutes in duration once per week. The yoga class was set up following discussions among certified Iyengar yoga teachers and a neurologist. The details of the design of the yoga class have been previously reported.[17] Briefly, the modifications to a usual Iyengar yoga class had to take into account fatigue as well as spasticity and cerebellar dysfunction. Essentially all poses were supported, either with a chair or having the subject on the floor or against the wall. Within that framework, 19 poses were instructed, although not all each week. The sequence of poses minimized exertion in getting up or down. Each pose was held for approximately 10 to 30 seconds with rest periods between poses lasting 30 seconds to 1 minute. Participants were encouraged to honor individual limits and hold the pose for less time if necessary. All poses were adapted to suit individual needs and modifications of some of the poses were taught for periods of lowered ability, e.g., during an exacerbation. There was an emphasis on breathing for concentration and relaxation during the session. Each class ended with a 10-minute deep relaxation with the subject lying supine. Progressive relaxation, visualization, and meditation techniques were introduced during this time. Daily home practice was strongly encouraged. Subjects were given a booklet demonstrating the specific poses practiced to assist in their home practice.

The aerobic exercise intervention arm was directed by a physical therapist with extensive experience with the MS population. The intervention was analogous to the yoga intervention with one class per week along with home exercise. The aerobic exercise consisted of bicycling on recumbent or dual-action stationary bicycles. The weekly exercise class began and ended with about 5 minutes of stretching of cycling muscles. Participants were instructed to stretch to a gentle pull but not to the point of pain and hold it for 15 to 30 seconds while breathing. Subjects monitored cycling intensity using the modified Borg Rate of Perceived Exertion scale.[18] Subjects were instructed to exercise at the 2 to 3 or very light to moderate intensity on the scale, i.e., they were able to converse during the sessions. There was no monitoring of heart rate. Although cycling was the usual mode of exercise, periodically participants were given the option of exercising on a Swiss ball. Occasional variety was provided by batting a balloon among participants while cycling and adding some arm, trunk, and balance work. Subjects continued bicycling until they were ready to stop because of fatigue, onset of other MS symptoms, or they reached their personal goal (e.g., 1 hour for several subjects). Subjects were given an exercise bicycle for home use if they did not already have one. Subjects were encouraged to exercise regularly at home (on bicycles and any other modes of exercise of choice) in addition to the weekly class session.

Compliance with the interventions was assessed by study participants daily filling out 2-week log sheets that recorded whether they exercised or practiced yoga and for how long. Class attendance was also recorded.

Assessments. After screening medical history, physical examination, and routine EKG, baseline assessments of outcome measures were performed. Baseline assessments were performed before subjects were randomized and occurred 1 to 30 days before the classes started. The practical limitations on the rate of testing participants necessitated three separate cohorts of subjects. Each cohort contained 23 subjects, each of whom was allocated to one of the three intervention arms. Outcome assessments were done at baseline and 6 months. There was also a 3-month visit although not all outcome measures were obtained at this mid-study visit and these data were not included in the analysis. On the baseline visit, demographic data were recorded and the oral reading on the Wide Range Achievement Test (WRAT) 3rd edition[19] was administered to assess equality of educational achievement in the three intervention groups.

It was important to plan carefully to maintain blinding of the assessors generating the outcome measures, since the subjects were non-blinded. Only a single liaison person who was responsible for direct phone calls to subjects was unblinded, and this person did not participate in one on one testing after randomization, i.e., after the baseline assessment. The 3- and 6-month assessments were planned carefully to ensure continued blinding. Some of the outcome measures were done independently of any assessor (self-rating forms). For the in-person evaluations, the liaison person scheduling the appointment instructed the subjects to not tell the assessor what intervention group they were in. A reminder call the day prior to the assessment was made and subjects reminded to not speak about their intervention group. Even with these precautions there were rare instances of unblinding. However, the assessments were objective and many were computer based and scored. The blinded research staff maintained equipoise about potential results of the study. The data analysis was blinded to intervention group.

No assessments were performed within 50 days of an exacerbation, defined as new, recurrent, or worsening neurologic symptoms present for more than 24 hours, documented by neurologic examination and not associated with a febrile illness. Subjects with MS with a recent exacerbation were retested as soon as they were more than 50 days post exacerbation onset. During this time, they continued the intervention to which they were initially randomized to whatever degree they could.

The baseline and outcome sets of cognitive assessments were performed at the same time of day for each subject, at their preferred time either in the morning or afternoon. The subjects were instructed to refrain from alcohol consumption for 24 hours prior to the testing. They were allowed to ingest their usual dose of morning caffeine.

Cognitive measures. The cognitive assessments focused on aspects of attention (focusing attention, shifting attention, dividing attention, and sustaining attention) that may be impaired in subjects with MS and were also thought to be most likely to be improved with the intervention. The Stroop Color and Word Test[20] color-word interference was used as a measure of ability to focus attention. The covert orienting of spatial attention task compares reaction time (RT) when targets are validly cued, neutrally cued, invalidly cued, or not cued.[21-23] Median RTs were calculated for the four cue conditions and the change in RT to validly cued circles from the beginning to last quartile was used as a measure of mental fatigue or vigilance. The attentional shifting task utilized was adapted from that used in the Cambridge Neuropsychological Test Automated Battery and is related to the Wisconsin Card Sorting Test. It allows attentional shifting to be broken down into three types: intradimensional, reversal, and extradimensional.[24] The outcome measure was the percentage of error trials and numbers of shifts correctly performed prior to completion. A modified Useful Field of View task was chosen as a divided attention test since it has been used in MS and has ecologic validity in relationship to driving ability[25,26] and has been previously shown to be changed in people with MS.[27] Our modification determined a precise temporal threshold. Simple visual RT was measured at the beginning and end of the test session. The difference in median RT between the end and beginning of the session was used as a measure of vigilance or mental fatigue. The Paced Auditory Serial Addition Test (PASAT) was also administered.[28,29] In case there were effects of the intervention on alertness and attention, we performed other cognitive tasks to determine the specificity of the effect: the Wechsler Memory Scales III Logical Memory[30] (delayed memory adjusted for immediate recall) and the Wechsler Adult Intelligence Scale III Similarities.[31]

Alertness, mood, fatigue, and quality of life. Alertness was measured with two subjective scales, the Stanford Sleepiness Scale (SSS)[32] and the Profile of Mood States (POMS)[33] subscales, and an objective measure based on EEG frequency analysis as we have previously done.[23] The only EEG frequency analysis measures used for this analysis were posterior median power frequency and relative alpha activity recorded from the eyes closed rest and eyes closed attentive state. We have previously shown these alertness measures to be sensitive to drug effects.[23,34] The SSS was administered at the beginning and end of the cognitive testing sessions. Subjects took the POMS once at the end of the session. We used the POMS mood subscales as well since it has been reported to show improvement with an exercise intervention in MS study[5] and with a Hatha yoga intervention in young adults.[8]

Mood, including measures of fatigue and vigor, was assessed using the POMS.[33] Fatigue was also assessed using the Multidimensional Fatigue Inventory (MFI).[35] Depression was assessed by the POMS and the CESD-10.[36] Stress was assessed using the State Trait Anxiety Inventory (STAI).[37] Health-related quality of life was assessed by the Short Form (SF)-36.[38] The MFI, POMS, STAI, and SF-36 were filled out by the subjects at home and reviewed by the research assistant at the time of the cognitive testing to help minimize the duration of the assessment session.

Physical measures. As part of the standard MSFC, 25-foot timed walk and the 9-Hole Peg Test were performed. Subjects performed a measure of forward bend flexibility: the chair sit and reach.[39] Subjects were asked to stand as long as they could on one leg with and without their eyes open. Data from subjects requiring an aid to stand were eliminated from this particular outcome analysis.

Data analysis. The analysis used all randomized subjects who completed the 6-month study and no attempt was made to impute missing variables.

Comparisons of the baseline factors age, MSFC, and EDSS among the three intervention groups were done using an analysis of variance. The outcome data were analyzed using an analysis of covariance (ANCOVA) approach with baseline value as the covariate, indicator variables for each of the two active groups (i.e., yoga and exercise), and the interactions of the indicators with baseline. In addition, three baseline factors (age, EDSS, and sex) were evaluated as potential confounding variables. The numeric values of age and of EDSS were included in these models rather than grouping the numeric values into categories.

The following approach was used to determine the "best" ANCOVA model for each response. Backward variable elimination determined which among baseline, age, EDSS, and an indicator for age were significant predictors. Any predictor significant at 0.10 was included in the next stage of model fitting. Second, indicator variables for the two active groups and the interactions of these indicators with baseline were added to the best model above. Partial F-tests were used to test whether the two interaction terms were simultaneously equal to zero. If the interactions were not significant, partial F-tests were also used to simultaneously test whether the two group indicators were simultaneously equal to zero. If either hypothesis was rejected, backward elimination was used to eliminate any individual terms that were not significant (using a significance level of 0.05). Residuals from the best model were assessed to determine if normality was violated (in particular if there was substantial skewness). If so, one or more transformations (the natural logarithm, square root, or the rank transformation, in order) were evaluated by following this same approach.

The primary outcome measures were assessment of alertness based on EEG median power frequency and color-word interference on the Stroop Color and Word Test.[20] No Bonferroni adjustments were made for multiple outcome measures. The secondary measures were the rest of the cognitive assessments, self-rated scales (MFI, POMS, CESD-10, SF-36), and the physical measures.

Results. Following phone screening of 129 subjects, 69 eligible subjects gave informed consent and were randomized to one of three groups (figure). Forty potentially eligible subjects declined the study for various reasons including practical issues (could not attend a weekly class, too far a drive to the class site), not wanting to accept randomization (e.g., wanted to start a yoga class and would not accept randomization to a wait-list group), and religious reasons (one subject believed that the yoga class conflicted with religious beliefs). Characteristics of the enrolled subjects are shown in table 1. There were no significant differences in age, baseline EDSS, MSFC, or WRAT among the three groups (p values all greater than 0.1). Twelve subjects did not complete the 6-month intervention and the dropout rate was not significantly different across the groups as assessed by Pearson chi-square ($p = 0.23$). The 17% dropout rate was not related to adverse events

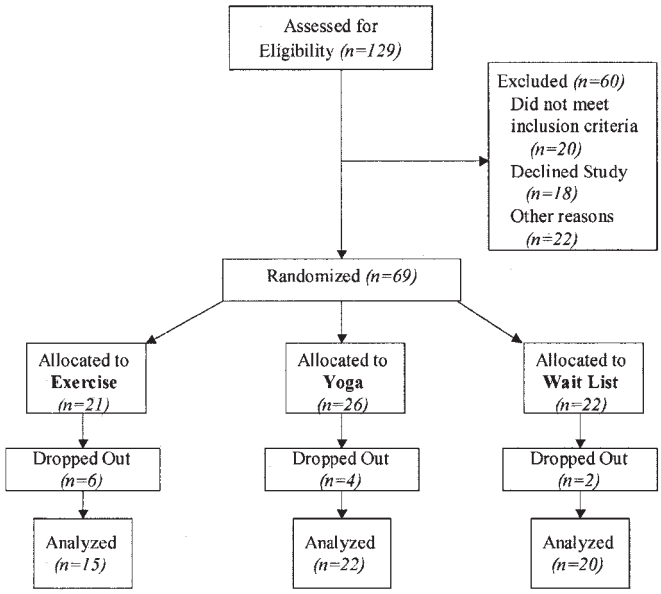

Figure. Numbers of subjects screened, enrolled in study, randomized, dropped out, and analyzed.

since there were no adverse events related to the intervention. There were six adverse events reported: three for unrelated surgeries; two MS exacerbations, one in the yoga and one in the exercise group; and one low back pain related to an auto accident. The most common cause for dropping out of the study was the inability to attend classes for various reasons (family health issues, time constraints, too far to get to class, and new personal health issues not related to the intervention). There were several dropouts related to dissatisfaction with the randomization group (wait-list and exercise) despite the subjects having been given a clear explanation of the randomization process and the subjects having to specifically verbally consent to accept the random assignment in addition to signing the consent form that contained this information as well.

Of the subjects who completed the 6-month exercise intervention arm, attendance rate at the weekly classes was 65%. Home exercise occurred on an average of 45% of the days other than the class day and lasted an average of 32 minutes (range 15 to 57 minutes). For the group completing the 6-month yoga intervention, attendance rate was 68%; home practice occurred on 51% of the non-class days and averaged 39 minutes (range 14 to 80). None of these active group differences were significant.

There was no effect of assignment group on any of the cognitive function or alertness measures, which included the primary outcome measures for this study (table 2 and supplementary data, available at www.neurology.org).

The active intervention groups were significantly better than the wait-list control group on several self-rated measures. The SF-36 quality of life measure demonstrated an assignment group effect on Vitality ($p < 0.001$), which has been also named Energy and Fatigue[40] (see table 2 and supplementary data, available at www.neurology.org). Both treatment groups demonstrated similar improvements compared to the wait-list control group. The Health Transitions subscore on the SF-36 was slightly different in the yoga group ($p < 0.01$) but there was an interaction with baseline score such that only people who self-rated themselves at baseline worse than they were a year ago may have improved. On the MFI there was an effect on general fatigue with either intervention ($p < 0.01$) but no clear effect on the other domains of the MFI (see table 2). The POMS subscales including Fatigue and Depression, the CESD-10, and the State Trait Anxiety measure demonstrated no significant changes from the interventions (see supplementary data, available at www.neurology.org).

Several measures that were included because they were thought to be potentially sensitive to the physical aspects of the intervention (chair sit and reach and one-legged standing) did not demonstrate any significant changes from the interventions.

Baseline SF-36 Energy and Fatigue and MFI General Fatigue were not correlated with EDSS, and there was only a borderline significant correlation between SF-36 Energy and Fatigue and MSFC (see supplementary data, available at www.neurology.org). There were more significant correlations between these two fatigue measures and the two depression measures, the CESD-10 and POMS Depression subscore. However, the improvements in fatigue based on the changes in the SF-36 Energy and Fatigue score and MFI General Fatigue score were not correlated to baseline CESD-10 or EDSS scores and covarying for CESD-10 scores produced no significant change in the effect of the interventions on the fatigue measures.

Discussion. This is the first randomized controlled trial of yoga in MS. The trial demonstrated that a 6-month yoga program improved fatigue to the same degree as a traditional exercise program and was adhered to at a level comparable to that of a traditional exercise program. More specifically, the interventions produced improvements in fatigue as assessed by the MFI (General Fatigue) and the SF-36 Energy and Fatigue (Vitality) dimension of the SF-36. The yoga and aerobic exercise program produced no significant changes compared with the

Table 1 *Subject demographics by group for all subjects whose baseline and 6-month data were available*

Groups	Total	Women	Men	Age, y	EDSS	MSFC	WRAT-R
Exercise	15	13	2	48.8 ± 10.4	2.9 ± 1.7	0.18 ± 0.6	50.5 ± 3.1
Yoga	22	20	2	49.8 ± 7.4	3.2 ± 1.7	0.13 ± 0.8	49.0 ± 4.3
Waiting list	20	20	0	48.4 ± 9.8	3.1 ± 2.1	0.04 ± 0.7	48.7 ± 6.4

Means ± SD are shown. The EDSS range was 1.5–6.0 in all groups.

EDSS = Expanded Disability Status Scale; MSFC = Multiple Sclerosis Functional Composite; WRAT = Wide Range Achievement Test.

Table 2 *Baseline and 6-month outcomes data on all subjects for whom both data points were available*

Outcome measures	Time point	Exercise	Yoga	Wait list
Stroop Color-Word Interference	Baseline	10.1 ± 3.7	10.8 ± 6.0	11.0 ± 7.1
	End of study	9.9 ± 6.2	8.5 ± 4.5	8.1 ± 4.4
EEG Median Power Frequency	Baseline	9.7 ± 1.1	9.7 ± 0.8	9.7 ± 0.9
	End of study	9.2 ± 1.2	9.2 ± 1.1	9.4 ± 1.1
SF-36 Health Survey				
Physical Functioning	Baseline	62.0 ± 25.9	58.6 ± 31.6	58.1 ± 19.0
	End of study	60.0 ± 27.9	61.0 ± 31.6	58.1 ± 23.3
Physical Health Impact	Baseline	76.7 ± 25.8	50.0 ± 44.0	40.3 ± 37.5
	End of study	61.7 ± 41.0	48.8 ± 39.1	52.8 ± 43.6
Bodily Pain	Baseline	55.1 ± 13.3	71.0 ± 19.8	65.1 ± 26.0
	End of study	70.8 ± 17.4	69.6 ± 17.3	68.9 ± 25.3
General Health	Baseline	62.7 ± 15.6	60.7 ± 24.8	49.9 ± 19.1
	End of study	61.0 ± 16.0	60.3 ± 18.4	55.4 ± 16.5
Energy and Fatigue	Baseline	45.7 ± 22.7	43.1 ± 17.7	39.7 ± 18.1
	End of study	52.8 ± 18.8*	51.2 ± 16.7*	36.7 ± 18.1
Social Functioning	Baseline	83.3 ± 16.8	72.0 ± 24.0	66.0 ± 27.1
	End of study	81.7 ± 24.0	64.9 ± 17.9	70.8 ± 23.5
Emotional Health Impact	Baseline	82.2 ± 27.8	72.4 ± 32.4	72.2 ± 43.2
	End of study	88.9 ± 30.0	87.3 ± 24.7	72.2 ± 36.6
Mental Health	Baseline	79.2 ± 16.4	73.7 ± 12.9	75.6 ± 18.8
	End of study	83.7 ± 10.5†	73.5 ± 14.3	75.6 ± 14.3
Health Transition	Baseline	43.3 ± 22.1	42.9 ± 25.2	58.3 ± 22.7
	End of study	36.7 ± 28.1	35.7 ± 20.8*	48.6 ± 20.1
MFI				
General Fatigue	Baseline	13.2 ± 4.0	14.7 ± 3.3	15.1 ± 3.4
	End of study	12.1 ± 2.8‡	13.0 ± 2.9‡	14.9 ± 3.0
Physical Fatigue	Baseline	13.2 ± 4.6	13.9 ± 3.5	14.4 ± 4.0
	End of study	10.8 ± 4.0	12.1 ± 4.4	13.9 ± 4.5
Reduced Activity	Baseline	10.5 ± 3.8	12.2 ± 4.7	12.9 ± 4.2
	End of study	9.9 ± 3.9	11.2 ± 4.1	11.5 ± 4.5
Reduced Motivation	Baseline	7.9 ± 2.7	10.1 ± 3.4	10.4 ± 3.2
	End of study	7.7 ± 3.4	9.2 ± 3.0	9.8 ± 3.0
Mental Fatigue	Baseline	8.3 ± 4.8	11.4 ± 4.7	11.7 ± 3.5
	End of study	7.8 ± 4.4	10.7 ± 4.0	11.2 ± 3.9

* $p < 0.001$.
† $p < 0.05$.
‡ $p < 0.01$.

Results are for the primary outcome measures, MFI and SF-36. Additional data on other outcome measures are available as supplemental data on the *Neurology* Web site.

SF-36 = Short Form-36; MFI = Multidimensional Fatigue Inventory.

wait-list control group on the primary outcome measures of alertness and attention, or on other secondary measures of cognitive function. While there are claims that yoga may affect the underlying disease process in MS, this 6-month intervention study was not designed to determine whether there would be any impact on the underlying disease.

Fatigue is a common and potentially disabling symptom in MS.[41-43] Some aspect of fatigue in MS relates to depression as we found in our study and others have found, but there are aspects of fatigue in MS that are not clearly related to depression.[41,44,45] In addition to our observation, others have also observed that the fatigue symptom in MS is relatively independent of disease severity as assessed by EDSS or MRI.[41,44,46] However, fatigue still contributes to

impairments in health-related quality of life.[47,48] The improvement in fatigue from the interventions in this study was partially independent of depression since there was not as significant an effect of the intervention on the depression measures as on fatigue. Also, the improvement in fatigue was not related to baseline levels of depression.

It is important to at least distinguish between physical and mental fatigue which some scales such as the Fatigue Severity Scale[49] do not. There are other fatigue scales that distinguish physical and mental fatigue.[45,50] We chose to use the MFI because it has been used in a number of neurologic disorders[51,52] and has these two distinct fatigue subscales. The fact that MFI General Fatigue subscale was more significantly improved than other MFI subscales and that the Energy and Fatigue subscale on the SF-36 was the most significant suggests that the improvement is not in the realm of mental fatigue. This is further supported by the absence of any effects of the interventions on mentally fatiguing tasks and vigilance measures. Also, this observation is consistent with a prior study in MS that concluded mental fatigue did not correlate with the overall sense of fatigue as captured on the Fatigue Severity Scale.[53] However, it is possible that improvement in physical function is contributing to the observed improvements in fatigue given the types of questions on the MFI General Fatigue and SF-36 Energy and Fatigue subscales as well as the tendency to greater changes in MFI Physical than Mental subscales.

Most prior research on exercise in MS has focused on physiologic measurements (see review[4]). One study attained a 97% supervised exercise class attendance rate[5] but it seems unlikely that attendance rate would be sustainable for MS subjects outside a research study. That study observed improvements in the POMS on depression and anger at weeks 5 and 10 but not at week 15. They noted no change in the Fatigue Severity Scale throughout the study but did find improvements on POMS fatigue at week 10 only and thought this difference may be related to the Fatigue Severity Scale's lack of sensitivity to changes over time. Another study randomized 26 subjects with MS to either a stationary bicycle exercise program with five 30-minute supervised training sessions per week over 3 to 4 weeks or a no-intervention control group.[6] The exercise group did better than their baseline in Vitality and Social Interaction on the SF-36, as well as a trend toward improvement on fatigue as assessed on the Fatigue Severity Scale with no change in these measures noted in the control group.

While we showed that both interventions produced beneficial effects on measures of fatigue, the mechanism of action of these improvements is unclear and may not relate directly to the yoga or exercise. Socialization, placebo, and self-efficacy effects are other potential mechanisms. Both interventions had an element of socialization that, by itself, may have contributed to some benefits. Prior investigators have also commented on the lack of an adequate social control group for their exercise intervention study.[5] There is likely some placebo effect related to the interventions. One group has already shown that psychological benefits of an aerobic exercise intervention in a group of healthy young adults could be increased simply by telling subjects that the exercise program was specifically designed to improve psychological well-being.[54] The issues of placebo effect and self-efficacy, both of which may have a significant impact,[55,56] are difficult to adequately control for in behavioral interventions that are necessarily non-blinded.

Although there were many secondary outcome measures, we do not believe the findings are simply random results from multiple comparisons. The p value for the intervention effect on the SF-36 Energy and Fatigue measure was sufficiently low that it would have been significant even with a very conservative Bonferroni adjustment. The fact that the Energy and Fatigue measure on the SF-36 and the General Fatigue measure on the MFI showed similar results also represents independent confirmation of the finding. Given the decision to end the study after 69 subjects were enrolled, the study is underpowered for medium effect sizes, approximately only 0.50 power in the ANCOVA for medium effect sizes ($F = 0.25$). The 20 subjects per group powers the study to 0.80 only for a moderate to large effect size ($F = 0.35$), e.g., a 3.5 point difference on the CESD-10. Thus, the absence of statistically significant effects on the mood and cognitive measures needs to be interpreted cautiously and is still open to investigation. There is a possibility that mood improvements contributed to these improvements in quality of life and fatigue.

The yoga and exercise classes were significantly modified from the usual community classes to take into account some of the limitations subjects with MS may have. Thus, the results of this study many not be directly generalizable to a typical community yoga or exercise class. The other potential issue related to generalizability is that our subjects were almost all women but we do not believe the results of this study would not generalize to men.

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