Multiple Sclerosis and Related Disorders 91 (2024) 105897

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Lifestyle intervention improves cognition and quality of life in persons with early Multiple Sclerosis

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A R T I C L E I N F O

Keywords:
Early multiple sclerosis
Diet
Exercise
Cognition
Quality of life
Remote intervention

A B S T R A C T

Background: Lifestyle changes have been demonstrated to impact pathophysiology in Multiple Sclerosis (MS). Various diet and exercise protocols have been reported to improve symptoms and function in persons with MS. Evidence is accumulating that interventions as early as possible in the disease course are warranted. The objective of this study was to investigate the effect of a remotely delivered lifestyle program focusing on specific diet and exercise recommendations in persons with early MS.

Methods: MS patients, with disease diagnosis no more than 2 years prior, were recruited from the patient population of the MS clinic of the Pacific Neuroscience Institute. Participants followed recommendations for diet and exercise delivered via remote heath coaching. Each participant received 6 sessions with a health coach over a 12-week period. They were given parameters of a Mediterranean-type diet to follow, and specific and individualized recommendations about duration, intensity and type of exercise and physical activity. Outcome measures included Quality of Life (QOL), cognition (Symbol Digit Modalities Test, SDMT), fatigue (Multiple Sclerosis Fatigue Impact Scale, MFIS), fitness (estimated with Metabolic equivalents, METS) and other objective and patient reported outcomes (PRO). Changes in outcomes were analyzed using mixed effects general linear models and standardized pre-post differences.(Cohen's d)

Results: Fifteen persons with early ($\leq$ 2 years) MS enrolled in the study, 14 of whom completed the study. We observed significant improvements in QOL ($p = 0.02$), SDMT ($p = 0.006$), fatigue($p = 0.005$), fitness ($p = 0.04$), and other PRO and objective metrics at the end of the protocol compared to baseline. Adherence and patient satisfaction measures were high.

Conclusions: Specific and individualized lifestyle recommendations can be effectively delivered remotely, and may produce improvement in symptoms and function in persons with early MS. Larger controlled trials of these interventions are warranted.

1. Introduction

Multiple Sclerosis (MS) is the second most common cause of neurologic disability in young adults, with a current prevalence of over 900,000 people in the US. (Mc Ginley, et al 2021). As a result of white matter demyelination, axonal loss, grey matter atrophy and neurodegeneration, multiple central nervous system (CNS) impairments may occur, with impact on physical, cognitive, psychologic, and psychosocial functioning. Most people presenting with MS are young adults who are just starting careers and/or families. Studies show that over a third of newly diagnosed persons with MS have significant anxiety, depression, and decreased quality of life (QOL).(Jannssens et al. 2003). Decreased QOL is also a function of cognitive impairment in persons with MS. (Campbell et al 2017). Up to 45 % of persons with early (< 5 years) MS demonstrate cognitive impairment on formal testing (Oset et al. 2020, DiGiuseppe G et al 2018), Additionally, data suggest that exercise and physical activity may have a direct effect on function in persons with MS, by improving symptoms such as fatigue, depression, spasticity and

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https://doi.org/10.1016/j.msard.2024.105897
Received 8 April 2024; Received in revised form 11 September 2024; Accepted 15 September 2024
Available online 18 September 2024

cognition (Motl & Pilutti,2012). Preclinical and clinical studies indicate that physical exercise may have anti-inflammatory and neuroprotective actions in MS as well (Cotman et al 2007).

A robust literature supports the effects of exercise on improving quality of life (QOL) in persons with MS, with one review suggesting that aerobic exercise was effective in improving physical and mental QOL, although other modalities of exercise (such as resistance and neuromotor training) also are shown to be beneficial (Reina Gutierrez et al. 2022). Studies also have demonstrated the positive relationship between physical activity and QOL in persons with early MS (Huynh et al 2023). At least one study has examined the benefits of increasing physical activity via a remotely delivered intervention in persons with early MS and demonstrated increased QOL after a 12 week intervention Huynh, et al (2024).

Currently, there are no definitive pharmacologic treatments for cognitive impairment in persons with MS (Chen et al. 2020). Systematic reviews of the literature have reported no benefit on cognitive function for the commonly used acetylcholinesterase inhibitors or stimulant medications (Cotter et al. 2018) and a very modest effect of some DMTs (Landmeyer et al. 2020). If lifestyle interventions can be reliably demonstrated to improve cognitive function in persons with MS, this would represent a significant therapeutic advance.

Several small studies of the effects of physical exercise on cognition in persons with MS suggest a beneficial impact (Sandroff et al. 2014, Sandroff et al. 2016, Sandroff et al. 2017, Sandroff et al. 2019, Briken et al. 2014, Feys et al. 2019, Ozkul et al. 2020). Some (Li et al. 2023), but not all (Gharanklou 2020), reviews of studies of multiple types of structured exercise interventions on cognitive function in persons with MS have concluded that there is a positive effect. Individual studies and literature reviews support an association between physical fitness levels and cognitive function in persons with MS (Beier et al. 2014, Tilsley et al. 2023) with specific emphasis on an association between physical fitness levels & cognitive processing speed (Sandroff et al. 2017, Sandroff et al. 2019). However, a recent RCT of aerobic exercise and cognitive rehabilitation vs. sham modalities did not show a significant improvement in processing speed in persons with progressive MS (Feinstein et al. 2023). Importantly, more recent investigations indicate that the effects of exercise on cognition may be greater in persons with MS who are cognitively impaired at baseline (Langeskov-Christiansen et al. 2021). This may account for the heterogeneity in the literature, as most studies did not enroll only participants who were screened/selected for cognitive impairment.

Olfactory dysfunction may serve as an index of cognitive function (Okada et al 2020) and occurs in up to 75 % of persons with MS (Goverover et al. 2020), including persons with early MS (Lutterotti et al. 2011). Olfactory dysfunction in persons with MS has been linked to decreased Quality of Life (QOL), and increased disability progression (Goverover et al. 2020,). Physical exercise has been reported to be associated with decreased risk of olfactory impairment in older adults (Shubert et al. 2013) and improvement in metabolic function in olfactory unsheathing cells in animal models of stroke (Li et al. 2019). An 8-week aerobic exercise program was reported to improve olfaction in Parkinson's disease, another neurodegenerative disease (Rosenfeldt et al. 2016). To date, there are no reports of lifestyle interventions improving olfactory function in persons with MS.

Diet and nutrients also affect MS pathophysiology. An extensive literature indicates that diet and gut microbiota composition directly affect immune function, blood brain barrier permeability, inflammation within the CNS and subsequent neurodegeneration (Fitzgerald et al. 2018,Katz Sand et al. 2018, Tremlett and Waubant, 2022). Persons with MS with greater adherence to the Mediterranean diet appear to have less objective disability (Katz Sand et al. 2023b), and a decreased risk of cognitive impairment (Katz Sand I et al 2023a). Other studies have also reported benefit of the Mediterranean diet in improving symptoms and QOL in persons with MS (Uygun et al 2024, Ertas et al, 2023).

Recently diagnosed persons with MS in general tend to be minimally impaired physically, and therefore usually not in need of rehabilitative services or equipment. However, they are invariably concerned about diet and other lifestyle behaviors, such as exercise. Studies suggest that they are unlikely to have received MS specific dietary advice, e.g. recommendations for a Mediterranean type diet or even general dietary information (Russell et al. 2020). However, up to 40 % of newly diagnosed MS patients make dietary modifications, without professional guidance (Wingo et al. 2020). As far as exercise, it has been reported that $<$ 20 % of persons with MS regularly engage in physical activity/exercise in amounts likely to confer benefit (Klaren et al. 2013), and that greater than 1/3 of newly diagnosed persons with MS are insufficiently active (Hyunh et al., 2023a Goverover et al 2020a). Additionally, they are unlikely to have received counselling about the importance of exercise in the management of MS or recommendations for specific exercise activities (such as aerobic exercise, resistance training, neuromotor exercise, and physical therapy) from their neurologist (Learmonth and Motl, 2016).

In summary, almost half of persons with early MS demonstrate cognitive impairment which can adversely affect psychosocial functioning and quality of life. These patients are very interested in lifestyle recommendations and are likely to receive little information about this from their neurologist. Diet and exercise have been shown to have robust influences on MS pathophysiology and may improve some symptoms and function. Studies have indicated that recommendations about both diet or exercise can be effectively delivered via telehealth modalities (Wingo et al. 2020, Pilutti et al. 2014, Huynh et al 2024). Although reports of remotely delivered multi modality lifestyle interventions are few, one study has reported significant weight loss in persons with MS who participated in a 6 month protocol that provided remotely delivered behavioral strategies regarding diet and exercise (Bruce et al 2023). As persons with MS often face geographic and accessibility barriers to healthcare, effective remote interventions would be very valuable in increasing access to care for this population. Data indicate that early therapeutic intervention with disease modifying therapies in persons with early MS is warranted (Simpson et al. 2021) and some studies suggest that there may be an early therapeutic window for multi-modal exercise programming, as well (Remenschnieder et al. 2018, 2021). However, to date, most clinical trials of diet and/or exercise interventions have not focused on persons with early disease.

The purpose of this study was to investigate whether a combined lifestyle intervention focusing on specific diet and physical activity/exercise recommendations could be effectively delivered remotely, and demonstrate improvement in quality of life, cognition and other metrics in persons with early MS.

2. Materials and methods

2.1. Participants

Participants were recruited from the patient population of the MS clinic of the Pacific Neuroscience Institute between April and October 2022. The protocol was approved by the Providence St. John's Hospital IRB (Protocol #: SJCI-22–1001) and all subjects signed informed consent prior to entry into the protocol. This sample was a convenience sample. Patients attending the PNI MS clinic were screened by the PI for suitability, and then offered the opportunity to participate if all inclusion/exclusion criteria were met. It has been suggested that for a pilot study without preexisting data, a sample size of 10–12 participants is adequate (Julious 2005). We thus enrolled fifteen participants into the study, to allow for some attrition.

Inclusion criteria included diagnosis of MS meeting McDonald criteria (Thompson et al. 2017) of less than or equal to 2 years duration and no history of known olfactory impairment. Exclusion criteria were MS exacerbation within 3 months of entry into protocol, pregnancy or planned conception within next 6 months, and medical comorbidity that would exclude participation in diet and/or exercise protocol, e.g. brittle diabetes, unstable angina, severe musculoskeletal disease.

Our study, involving a minimal risk intervention, aimed primarily to provide preliminary evidence of the feasibility and efficacy of a lifestyle intervention. Consequently, we did not *a priori* establish go/no-go criteria.

2.2. Intervention

After screening and informed consent, participants underwent in-person neurologic examination (BG) and baseline assessment of outcome measures (CP, RG). Within 2 weeks of this initial assessment, they had an initial remote visit with the RDN health coach (MR) and continued these 30 min sessions every 2 weeks for 12 weeks. The participants were instructed in the parameters of the Mediterranean Diet and given general exercise recommendations, 150 min/week (2–5 days) of aerobic activity at a moderate intensity, 2 days per week of strength training, and 2–3 days/week of stretching and flexibility with some individual specificity based on their stated goals. Our recommendations were consistent with the Physical Activity Guidelines for Americans, 2nd Edition, and the American College of Sports Medicine (Garber et al 2011). These recommendations are also consistent with MS-specific exercise guidelines (Kalb et al 2020). Specific modifications to the general recommendations were overseen by a licensed physical therapist, including strategies for modifying duration, type, and intensity of exercise individually, as well as temperature management strategies

Coaching sessions: The first coaching session focused on learning each participant's diet and exercise history, as well as reviewing relevant baseline information, including the Mediterranean Diet Adherence Scale (MEDAS) and the Perceived Stress Scale (PSS; Cohen et al. 1983). The health coach explored goals with the participants and discussed how these could be met with study recommendations. Positive feedback was given for lifestyle behaviors that met the study guidelines and participants were encouraged to set 2–4 action items that would help subjects reach their health goals while incorporating Mediterranean diet principles and a well-rounded exercise routine. The second coaching session focused primarily on exercise. To ensure participant safety, the health coach consulted the physical therapist who completed the baseline physical assessment, in addition to reviewing current activity level from the baseline International Physical Activity Questionnaire (IPAQ; Lee et al. 2011). Participants were encouraged to meet the general multi-modal exercise recommendations to the best of their ability and in a way that meets their health goals. The general exercise recommendations, which included trying to attain at least 150 min/week of moderate intensity exercise including stretching, resistance, neuromotor and aerobic exercise recommendations, were also individualized for each subject based upon a physical therapy evaluation and behavioral analysis. For example, one subject was provided balance exercise targeted to their specific deficit, while another was advised to engage in flexibility training to support their running routine. Participants were also provided exercise options including beginner level videos on YouTube, specific modifications to certain exercise modalities, and tailored exercises from the physical therapist. In addition, the health coach encouraged participants to take advantage of their current resources such as gym memberships, classes, and home exercise equipment. The health coach revisited health goals and compliance with study recommendations during follow-up sessions, adjusting action items based on participant's current circumstances and performance.

Type of exercise/Activity	Frequency	Examples
Aerobic (Cardiovascular)	2 or more days/ week	Brisk walking, Cycling, Swimming, Treadmill
Resistance (Weights)	2 or more days/ week	Dumbbells, Weight Machines, Bands
Neuromotor/Coordination (Skill based)	2 or more days/ week	Dance, Tai Chi, Badminton, Boxing, Yoga, Pilates
Flexibility (Stretching)	Daily	NMSS Stretching

Diet recommendations were organized around parameters of the Mediterranean diet. Participants were instructed in the "Healthy Plate Model": ½ plate non-starchy vegetables, ¼ plate lean protein or fatty fish, and ¼ plate complex carbohydrate. Foods following the Mediterranean Diet such as colorful fruits and vegetables, whole grains, seafood, legumes, poultry and dishes made with olive oil were encouraged, with accommodations made for individual preferences.

Outcome measures were collected at baseline, and within 2–4 weeks of completing the intervention. Participants also completed a satisfaction questionnaire at the end of the study (Table 3).

2.3. Outcome measures

Outcome measures were collected at in-person assessment visits, and administered according to standard published protocols. The primary outcome measure was QOL as assessed by the MS QOL-29 (Rosato et al. 2016). Secondary outcomes included cognition (Symbol Digit Modalities Test (SDMT); Strober et al. 2019), fatigue (Multiple Sclerosis Fatigue Impact Scale (MFIS); D'Souza 2016), and adherence to the Mediterranean diet (Mediterranean Diet Adherence Scale (MEDAS); Martinez-Gonzalez, et al. 2012), as well as physical performance metrics such as level of physical activity (IPAQ), mobility (TUG, Timed Up & Go), and dual-tasking (Timed Up & Go Cognitive and Manual), (Allali et al. 2012). The MSQOL-29 includes subscales for physical health, mental health, and cognition. Each subscale is scored from 0 to 100, with higher scores indicating better quality of life. The Symbol Digit Modalities Test (SDMT) is an index of cognitive processing speed, with the total score reflecting the number of correct responses made in 90 seconds. The Modified Fatigue Impact Scale (MFIS) has subscales assessing the impact of fatigue on physical, cognitive, and psychosocial functioning. Scores range from 0 to 84, with higher scores indicating greater fatigue impact. The Mediterranean Diet Adherence Scale (MEDAS) scores range from 0 to 14, with higher scores indicating greater adherence to the Mediterranean diet. The Timed Up & Go (TUG) and Dual-Task TUG assesses mobility, with the dual-task versions also assessing mobility under cognitive or manual task conditions. Lower scores indicate better performance. MET minutes for the IPAQ are scored by multiplying intensity of physical activity (rest=1 MET, walking=3.3 MET, moderate activity= 4 MET, vigorous activity=8 MET) by number of minutes engaged in activity times number of days that activity was performed (Lee et al 2011). Metabolic equivalents (METS) were calculated using the Jurca equation (Jurca 2005), and were used to estimate fitness. Olfaction was assessed by the University of Pennsylvania Smell Identification Test (UPSIT; Doty et al.1984) and was included as an exploratory measure.

Questionnaire assessments were conducted using paper formats. Questionnaire, cognitive & olfaction assessments were conducted in a quiet comfortable well lit room. Administration of the SDMT(oral version) was preceded by a standard short practice run to familiarize the participants with the testing procedure. Physical function tests were conducted in a quiet monitored environment to ensure participant safety and consistency in testing conditions. Each physical assessment was preceded by one practice trial to familiarize participants with the procedure and reduce variability in performance. All physical assessments were conducted with at least two trials and the best score was recorded as the final measure for analysis..

2.4. Statistical analysis

Data were entered at the time of collection and analyzed after completion of the trial. All data were inspected for outliers, homogeneity of variance and other assumptions to ensure their appropriateness for parametric statistical tests. All outcomes were analyzed using a mixed effects general linear model, as implemented in SAS PROC MIXED, with time as the within-subject factor. We present test scores and statistics as well as standardized pre-post mean differences (Cohen's

d) for within-group changes. We used the Benjamini-Hochberg procedure (with a false discovery rate of 10 %) to correct for multiple comparisons (Yoav and Hochberg 1995). We also examined associations between changes in cognitive scores and changes in MEDAS, fitness and UPSIT scores using non-parametric Spearman correlations. Given the novel and preliminary nature of the study, we present results of analyses conducted on a range of outcome measures and set the level of significance at the alpha level of $p \leq 0.05$, two-tailed, without accounting for multiple comparisons.

3. Results

3.1. Descriptive characteristics

Baseline demographic and clinical characteristics of the study sample ($n = 15$) are summarized in Table 1. Average age of participants at baseline was 35.2 (ranging from 23 to 50) years, and the mean EDSS was 1.1 (range 0 to 2.5). Of the fifteen enrolled participants, fourteen completed the study.

3.2. Outcomes

Table 2 presents baseline and post intervention scores for participants. At the end of the intervention, participants showed significant improvement in Overall QOL ($p = 0.02$; pre-post mean differences $d = 0.65$) as well as on the Physical Health Composite ($p < 0.05$; $d = 0.59$). Significant improvements were noted in cognitive performance as assessed by the SDMT ($p = 0.006$; $d = 1.22$), as well as the cognitive portion of the TUG ($p = 0.01$; $d = 0.93$) and the cognitive subscale of the MSQOL-29 ($p = 0.03$; d = 0.61). There were also significant improvements in the total MFIS score ($p = 0.005$, d=0.94) as well as the cognitive subscale ($p = 0.005$; $d = 0.94$).

Adherence to the Mediterranean Diet ($p = 0.002$; $d = 1.09$) and fitness (METS; $p = 0.04$; $d = 0.57$) were also significantly improved. Although there was increase in physical activity as assessed by the IPAQ at the end of the intervention compared to baseline, this difference was not significant ($p = 0.2$). Decrease in number of subjects with abnormal UPSIT score at the end of the study did not reach significance ($p = 0.07$). There were no significant associations between changes in cognitive scores and MEDAS, fitness, or UPSIT scores.

3.3. Participant satisfaction

Participant satisfaction scores were high, and there was no negative feedback. In particular, participants reported that the recommendations were easy to follow, and also endorsed high levels of confidence in knowledge about MS, and being less anxious about managing their disease (Table 3).

4. Discussion

The results of this single arm pilot study suggest that remotely delivered lifestyle coaching improves quality of life and cognition in newly diagnosed persons with MS. The intervention was effectively delivered remotely, and with high patient satisfaction and adherence (93 % retention rate). This adds to the existing literature that it is feasible to implement lifestyle coaching to persons with MS via telehealth modalities, which has also been reported for other populations with early stage memory loss (Glatt et al., 2024). Our study was similar in design to that of Huynh *et al* (2024) who delivered a remote physical activity coaching intervention to 14 newly diagnosed persons with MS over 12 weeks and who also observed improvement in QOL after the intervention

The high patient satisfaction scores indicate that the coaching and specific lifestyle information was useful and reduced disease related anxiety, which would be expected to improve QOL. Cognitive performance, as assessed by both subjective and objective metrics, also showed significant improvement. While there are inherent limitations in the interpretation of improved cognitive scores in the absence of a randomized clinical trial, making it difficult to disentangle from placebo and practice effects, we note that three different tests showed

Table 1
Demographic & clinical characteristics.

Age (years)	35.2 (SD = 8.0)
Sex	12 F, 3 M
Race	2 Black, 12 White, 1 unknown
Education (years)	16.2 (SD = 1.5)
EDSS	1.1 (SD = 0.6)
MS course*	14 RR, 1 PP

[*] RR = Relapsing-Remitting; Pp = Primary Progressive

Table 2
Baseline and post-intervention scores as well as standardized mean differences.

Measure*	Baseline *N* = 15	Post-intervention		p value^	Cohen's d**
QOL	**Mean (SD)**	**Mean (SD)**	**N**		
MSQOL-29					
Overall QOL	80.3 (10.4)	87.5 (9.5)	14	***p* = 0.02**^	0.65
PHC	70.0 (11.5)	77.6 (13.8)	13	***p* = 0.05**	0.59
MHC	71.5 (12.8)	76.2 (16.0)	11	*p* = 0.2	0.41
COGNITION					
SDMT (oral)					
Number correct	56.4 (11.2)	63.1 (8.7)	9	***p* = 0.006**	1.22
Modified fatigue impact Scale (MFIS-5)					
Cognitive score	14.9 (8.4)	9.5 (6.5)	13	***p* = 0.005**	-0.94
Total score	32.5 (16.8)	21.9 (14.6)	13	***p* = 0.005**	-0.94
TUG (Cognitive)	10.1 (2.1)	9.3 (1.6)	13	*p* = **0.01**	-0.93
MSQOL (Cognitive)	70.0 (20.4)	78.5 (13.5)	14	*p* = **0.03**	0.61
PHYSICAL ACTIVITY					
IPAQ (MET min/ week)*	2595.2 (2445.6)	2874.3 (1732.2)	13	*p* = 0.2	0.49
Physical Function					
TUG (total)	8.0(1.3)	7.9 (1.1)	13	*p* = 0.2	0.41
FITNESS					
METS (Jurca)^^	10.2(2.2)	11.7(2.2)	11	**p-0.04**	0.57
OTHER					
UPSIT&					
# abnormal	11 (73.3 %)	5 (35.7 %)	14	***p* =** 0.07	
MEDAS					
Total score	6.6 (2.6)	8.6 (2.5)	14	***p* = 0.002**	1.09

[^] Significant findings, after correcting for multiple comparisons with the Benjamini-Hochberg procedure, are bolded.
[*] Mean (SD) for all measures except UPSIT (N (%)
[**] Standardized pre-post mean differences are Cohen's d estimates. For those measures (MSQOL, SDMT, UPSIT, MEDAS, METS etc), where a higher score represents better symptoms, a positive value of Cohen's d indicates improvement. For those measures (MFIS-5, Timed Up and Go), where a higher score represents worse symptoms, a negative value of Cohen's d indicates improvement.
[***] MET minutes: the amount of energy expended carrying out physical activity.
[^^] METS (via Jurca equation): Estimate of fitness
[&] UPSIT Total Score categorized as abnormal if ≤ 33 for males and ≤ 34 for females

Table 3
Patient satisfaction questionnaire ratings ($N = 14$).

Question	MEAN (SD)	MEDIAN	RANGE
Q1. How Challenging were the Health Lifestyle recommendations to follow? (1, Very Difficult | 2, Difficult | 3, Neutral | 4, Easy | 5, Very Easy)	3.9 (1.0)	4	2–5
Q2. On a scale of 1 (not at all helpful) to 10 (extremely helpful) how helpful was the Health Lifestyle coaching to you?	9.0 (1.3)	10	7–10
Q3. On a scale of 1(not at all helpful) to 10 (extremely helpful) what was the quality of the information you received in the Health Lifestyle program?	9.1 (1.0)	9.5	7–10
Q4. Please rate this statement on a scale of 1(not at all) to 10 (very much so): "The Health Lifestyle coaching has made me more confident about my knowledge of lifestyle choices that can affect MS"	8.7 (1.7)	10	6–10
Q5. Please rate this statement on a scale of 1 (not at all) to 10 (very much so); "The Health Lifestyle coaching has made me less anxious about managing my MS"	8.8 (1.4)	9.5	6–10

improvement in cognitive function, with large pre-post mean differences seen for each metric. Cognitive performance was significantly higher following the intervention, suggesting *possible* cognitive improvement. However, in the absence of a control group, it is not possible to fully disentangle the extent to which changes in scores post interventions are above and beyond other factors known to be relevant (e.g., placebo, practice effects). Practice effects are typically expected when cognitive testing is repeated, and these effects are more pronounced when the same version of the SDMT is administered, such as in the current study. In light of the above inherent limitations, while the absence of a control group precludes inferring cognitive improvement, the current results are promising when considered in tandem that the change on the SDMT seen in our study was higher than practice effects seen in a longitudinal study administering the same SDMT written version monthly for an extended period of time among individuals with MS treated with natalizumab (Roar et al 2016).

The current results also parallel findings of a randomized control trial assessing the impact of a remotely delivered 16-week exercise intervention on cognition among individuals with MS who were relatively older (mean age=49.6 (9.0) years), and had longer disease duration (mean duration =14.9 (7.1) years) than our sample but were also fully ambulatory. That study found a 4.8-point increase in SDMT following exercise intervention compared to a 1-point increase in the control group (Sandroff et al 2023). Because our study utilized a combined intervention, it is not possible to ascertain if the improvement in cognitive scores was due to the diet or exercise portion of the intervention, or if there is a synergistic effect. Future studies might include a diet only arm, an exercise only arm, the combined intervention arm and a "usual care" or active control arm to address this. Further studies are also needed to elucidate the underlying mechanisms of the improvements noted. Feasibility and safety should be further assessed in future trials with " go/no go" criteria for participants.

In contrast to other literature reports of the beneficial effects of exercise and diet on cognition, (Sandroff et al. 2017, Sandroff et al. 2019, Katz Sand et al. 2023a) we were not able to demonstrate any correlation between change in cognitive scores and an approximate measure of fitness or adherence to the Mediterranean Diet, despite significant improvement in both METS and MEDAS. This may have primarily been due to the small sample size and variability in individual responses to exercise. Despite a non-significant change in self reported physical activity as assessed by the IPAQ ($p = 0.2$), there was a significant improvement in cardiorespiratory fitness as measured by METS ($p = 0.04$) estimated by the Jurca equation. This discrepancy may suggest that while self-reported physical activity levels in and of themselves did not show a significant increase, the intervention may have improved physiologic fitness levels as estimated by an equation. The Jurca equation does incorporate self reported physical activity, and also uses objective items such as age, BMI & heart rate. While the Jurca Equation has been shown to significantly correlate with MET values derived from maximal graded exercise testing ($r = 0.66$) and with cardiorespiratory fitness estimated from submaximal exercise testing ($r = 0.67$) in different populations, (Clasey et al 2020, Mailey et al 2010, Mc Auley et al 2011) it has not been validated in persons with MS. Future studies should use VO2max testing or other forms of validated/standardized sub maximal or maximal exercise testing to more accurately assess fitness. The increase in METS may also indicate that even modest increases in physical activity may lead to significant improvements in fitness. It has been suggested that > 1 point change in METS is clinically meaningful in cardiac rehabilitation (Franklin et al 2013). We observed a mean 1.7 change in METS post intervention. While the clinical significance of a 1.7 METS change in fitness is not definitively established for persons with MS, this increase may still suggest improved cardiorespiratory fitness, which is crucial for managing MS symptoms and function such as fatigue and mobility.

Reports indicate that olfactory function is impaired in persons with early MS and may serve as a marker of cognition. (Groverover et al 2020, Okada et al 2020, Lutterotti et al 2011).The proportion of participants with abnormal UPSIT scores at baseline in our study is consistent with what has been reported in the literature (Groverover et al. 2020). Although we were not able to demonstrate a correlation between change in cognitive scores and UPSIT scores, the number of subjects with UPSIT scores in the abnormal range was fewer at the end of the study compared to the beginning (73 % abnormal at baseline, 35.7 % at end of study), although only 2 participants had clinically meaningful improvement of 4 or more points (Mahadev et al 2024). Olfactory measures should be included in future studies of cognitive function in persons with MS.

Although this pilot study has shown promising results, there are several limitations that must be acknowledged. First, this pilot study featured a small sample size and a within-subject design that did not include a comparison or control group, thus limiting the generalizability of the findings. As such, we cannot conclude that the benefits found in this study are replicable and due to the intervention alone. It is possible that practice effect (especially for the cognitive measures), the improved social connection created with the coach as well as the empowerment that comes with learning, may have contributed to the observed outcomes and exaggerated pre-post differences. Given our lack of control group, it is also possible that improvements were an effect of time. The apparent improvement in cognition may also have been a function of improved fatigue as indexed by MFIS score. Additionally, the effect of the intervention was assessed using several outcomes, thus increasing the possibility of a Type 1 error; as such all findings should be interpreted with caution. We did not screen for cognitive performance or diet & exercise behaviors as part of the inclusion/exclusion criteria; and so the results may have been influenced by "floor & ceiling" effects in some of the participants, although pre-post changes in SDMT and MEDAS were still significant. Future studies should include screening/cut-offs for baseline cognitive performance and lifestyle behaviors. Another limitation of our study is that we did not collect MRI data, so it is unknown if the lifestyle intervention produced any structural changes,. Previous studies have indicated positive effects of diet and exercise/ physical activity on MRI metrics such as brain volume (Katz Sand et al. 2021) and hippocampus size (Leavitt et al. 2014, Kalron et al. 2020, Sandroff et al 2021), including trials with only a 12 week intervention (Sandroff et al 2021, Wender et al 2021, Rahmani et al 2023), suggesting that it may have been possible to see MRI effects with a 12 week protocol. Also, the participants in our study were a selected population with early MS, and low disability. Larger and controlled studies are needed to ascertain not only if these results are reproducible in a larger population of persons with early MS, but also if this treatment strategy may be generalizable to persons with MS at later disease stages. Finally, although most of the participants were assessed within 2 weeks of the end of the intervention, several participants were not assessed until 4 weeks after the end of the study, which may have introduced some additional variability into the results.

5. Conclusions

Our single arm pilot study of remotely delivered lifestyle intervention had high patient adherence and satisfaction, and produced significant improvement in metrics of QOL, cognitive performance, and other objective and patient reported outcome measures. This study was done in a small sample of persons with very early MS. Larger randomized controlled trials with longer follow up are indicated to assess both short and long term efficacy and effectiveness.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the Providence St. Johns' Institutional Review Board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

All participants in the study signed informed consent.

CRediT authorship contribution statement

Barbara S. Giesser: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Molly Rapozo:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Ryan Glatt:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Corwin Patis:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Stella Panos:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation. **David A. Merrill:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Prabha Siddarth:** Writing – review & editing, Writing – original draft, Formal analysis.

Declaration of competing interest

NONE

Acknowledgement

This study was funded by the Pacific Neuroscience Institute Foundation and Will & Cary Singleton. Funding sources were not involved in any aspect of the study.

The technical assistance of Jenna Mattison and Fatima Iqbal is gratefully acknowledged.

These data were presented in part at the 9th triennial ECTRIMS-ACTRIMS meeting in Milan, October 2023.

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