Lower physical activity is associated with higher disease burden in pediatric multiple sclerosis

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ABSTRACT

Objective: To evaluate the association between physical activity (PA) and multiple sclerosis (MS) disease activity, depression, and fatigue in a cohort of children with MS and monophasic acquired demyelinating syndrome (mono-ADS).

Methods: In this cross-sectional study of consecutive patients attending a specialized pediatric MS clinic, we administered the PedsQL Multidimensional Fatigue Scale, Center for Epidemiological Studies Depression Scale, and Godin Leisure-Time Exercise Questionnaire. Quantitative MRI analysis was performed to obtain whole brain and T2 lesion volume in a subset of participants (n = 60).

Results: A total of 110 patients (79 mono-ADS; 31 MS; 5–18 years; M:F 1:1.2) were included. Patients with MS reported less strenuous (33.21 ± 31.88 metabolic equivalents [METs] vs 15.97 ± 22.73 METs, $p = 0.002$) and total (44.48 ± 39.35 METs vs 67.28 ± 59.65 METs; $p = 0.0291$) PA than those with mono-ADS. Patients with MS who reported greater amounts of moderate PA METs had fewer sleep/rest fatigue symptoms ($r = -0.4$). Participation in strenuous PA was associated with smaller T2 lesion volumes ($r = -0.66$) and lower annualized relapse rate ($r = -0.66$). No associations were found between total brain volume and participation in PA.

Conclusions: Children with MS are less physically active than children with mono-ADS. Reasons for this are unclear, but may be related to ongoing disease activity, perceived limitations, or symptoms such as depression or fatigue. Children with MS reporting higher levels of strenuous PA had lower T2 lesion volumes and lower relapse rates, suggesting a potential protective effect of strenuous PA in this population. Further longitudinal studies are needed to establish the relationship of PA to MS symptoms and disease activity in this population. ***Neurology*® 2015;85:1663–1669**

GLOSSARY

ARR = annualized relapse rate; **CES-DC** = Center for Epidemiological Studies Depression Scale for Children; **EDSS** = Expanded Disability Status Scale; **GLTEQ** = Godin Leisure-Time Exercise Questionnaire; **HCS** = health contribution score; **IQR** = interquartile range; **MET** = metabolic equivalent; **mono-ADS** = monophasic acquired demyelinating syndrome; **MS** = multiple sclerosis; **NIHPD** = NIH-funded MRI Study of Normal Brain Development; **PA** = physical activity; **PedsQL MFS** = PedsQL Multidimensional Fatigue Scale; **TBV** = total brain volume.

Up to three-quarters of children with multiple sclerosis (MS) have depression, fatigue, or cognitive impairment.[1,2] Children with MS experience more active disease than adults with MS, as demonstrated by increased lesion burden on MRI,[3] relapse frequency,[4] and irreversible motor disability occurring in young adulthood.[5] Little is known about behavioral approaches for managing these problems in pediatric MS, but multicomponent interventions involving physical activity (PA) have improved cognition, mathematics, and reading,[6,7] and exercise interventions have improved depression,[8] executive function, and cognition,[9] in healthy children and individuals with chronic illnesses.

Several studies support relationships between PA and outcomes in adult MS. Studies have documented lower PA levels in patients with MS than healthy controls[10,11]; the level of premorbid PA predicts the trajectory of disability scores[12]; and an association has been demonstrated between

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increased PA and health-related quality of life[13] and decreased relapse rate,[14] and aerobic training has improved fatigue and depression.[15,16] We are unaware of research on PA and symptomatic, clinical, and MRI pediatric MS outcomes.

Conditions stemming from sedentary lifestyles may lead to increased risk for pediatric MS. Adolescent obesity yields an odds ratio for MS or clinically isolated syndrome of 3.76 (1.54–9.16) in extremely obese as compared to healthy girls in California.[17] Thus, a complex relationship likely exists between lifestyle and multifactorial diseases like MS. Such evidence indirectly supports the examination of PA and outcomes in pediatric MS.

We examine PA, fatigue, depression, relapse rate, and MRI metrics in children with MS and with monophasic acquired demyelinating syndrome (mono-ADS).

METHODS

Study design. The study had a cross-sectional design. We enrolled consecutive patients with demyelinating disorders followed at the Pediatric MS and Demyelinating Disorders Center at the Hospital for Sick Children, Toronto, Canada, from June through December 2013. The inclusion criteria were age between 5 and 18 years, ability to understand and complete the questionnaires, and diagnosis of a demyelinating disorder (mono-ADS or MS). International Pediatric MS Study Group consensus criteria for the definition of pediatric demyelinating disorders were followed.[18] Children with monophasic illnesses were chosen as a comparison group to establish differences between patients with relapsing-remitting MS and children without relapsing disease.

Clinical data were collected using a standardized case report form (SickKids Demyelinating Diseases Registry) on the same day as questionnaire administration. The questionnaires were completed by the participants with assistance from their parents or the study coordinator, as needed. Data collected included demographic information, Expanded Disability Status Scale (EDSS) score, disease duration, and annualized relapse rate (ARR). MRI scans were performed, as part of another research study,[19] on a subset of patients within 6 months of the PA questionnaire.

PA measure. The Godin Leisure-Time Exercise Questionnaire (GLTEQ) was used to evaluate PA.[20] The GLTEQ has been found to be reliable and valid for use in the pediatric population[21] and has also often been used in MS.[22] Individuals are asked to report the frequency of strenuous (i.e., running or jogging), moderate (i.e., fast walking), and mild (i.e., easy, leisurely walking) PA performed for periods of 15 minutes or more during leisure time over a usual week. Total leisure activity score was calculated by using the following formula: (frequency of strenuous PA × 9 metabolic equivalents [METs]) + (frequency of moderate PA × 5 METs) + (frequency of mild PA × 3 METs).

Following Godin,[23] a health contribution score (HCS) was calculated, as recently done in adults with MS.[22] This calculation is based on work that has shown the highest correlation between fitness level and subjective reporting to be related to reports of strenuous activity in addition to other work suggesting correlations between the volume of PA and health benefits; cutoff points are for 3 categories: active, moderately active, and insufficiently active. The HCS is calculated using the following formula: (frequency of strenuous PA × 9 METs) + (frequency of moderate PA × 5 METs). The HCS are then subdivided into 3 categories: ≥24 units (approximately 14 kcal/kg/wk or more), active; 14–23 units (between 7 and 13.9 kcal/kg/wk), moderately active; and <14 units (less than 7 kcal/kg/wk), insufficiently active.[23]

Fatigue and depression metrics. The Varni[24] PedsQL Multidimensional Fatigue Scale (PedsQL MFS), found to be reliable and valid in the pediatric population, was used to assess fatigue.[25] The 18-item, self-rated, symptom-oriented scale assesses 3 areas of fatigue (general, sleep/rest, and cognitive). It was scored as follows: general, sleep/rest, and cognitive fatigue = 12–17 (moderate), ≥18 (severe); total fatigue = 36–53 (moderate), ≥54 (severe).

Depression was evaluated using the Center for Epidemiological Studies Depression Scale for Children (CES-DC).[26,27] The CES-DC scale is a 20-item, self-rated, symptom-oriented pediatric depression scale that has been found to be valid, reliable, and predictive of depression in individuals aged 6–12 years. Higher scores have been found to correlate strongly with clinical depression (>15 considered significant).

MRI measures. Children (mono-ADS n = 47, MS n = 13) received MRI scans using a standardized research protocol on a single GE 1.5T Twin Speed Excite 12.0 scanner (GE Healthcare, Waukesha, WI).[28] MRI variables collected included total brain volume (TBV), TBV z score,[29] T1 lesion volume, and T2 lesion volume.[30] TBV was computed using the brain extraction based on nonlocal segmentation technique.[31] TBV z score was calculated using normative pediatric MRI brain volume data from the NIH-funded MRI Study of Normal Brain Development (NIHPD).[29] The following calculation was performed for each brain volume: z score = $(V-\mu)/\sigma$, where V is the participant brain volume, μ is the mean, and σ is the SD of the brain volumes of the subset of the NIHPD normal participants of same sex and age ± 6 months.[30]

Statistical analysis. Statistical analyses were conducted using GraphPad Prism 6 (GraphPad Software Inc., San Diego, CA). Between-group comparisons were performed using Mann-Whitney U tests, t tests, and χ^2/Fisher exact analyses, as appropriate. Spearman correlation analysis was performed on the variables in each sample. A cutoff of $p < 0.05$ was considered significant.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Research Ethics Board at the Hospital for Sick Children, Toronto, Canada.

RESULTS

A total of 110 children and adolescents were included in the study (mono-ADS n = 79, MS n = 31). Patient demographics are shown in table 1. No differences were seen between the EDSS scores of the mono-ADS and MS groups; however, 5 patients with mono-ADS had an EDSS greater than or equal to 4 (representing motor disability severe enough to limit walking), whereas all of the patients with MS had an EDSS score less than 4.

PA in pediatric MS. Pediatric patients with MS reported participating in less strenuous and total PA than those with mono-ADS (table 2). In addition, a lower proportion of the patients with MS reported participating in any strenuous PA (45.2%, 14/31)

Table 1 Demographics

Characteristics	Mono-ADS (n = 79)	Range	MS (n = 31)	Range	*p* Value	Cohen *d*
Age at visit, y, mean ± SD	13.91 ± 4.43	5–18	15.91 ± 2.36	11–18	0.019	−0.5635
M:F	36:43	—	6:25	—	0.016	—
EDSS	1.0 (1.0)	0–7.5	1.5 (1.0)	0–3	0.133	−0.0340
Time from first attack, y, median (IQR)	3.06 (5.03)	0–11.7	1.64 (4.22)	0–11.7	0.082	0.3360
Diagnosis, % (n)						
CIS						
ON	25.32 (20)	—	—	—	—	—
TM	35.44 (28)	—	—	—	—	—
ON + TM	2.53 (2)	—	—	—	—	—
CIS-other	15.19 (12)	—	—	—	—	—
ADEM	21.59 (17)	—	—	—	—	—
Relapses, mean ± SD	—	—	3.00 ± 2.81	1–13	—	—
ARR	—	—	1.00 (1.05)	—	—	—
Taking DMT, % (n)	—	—	74.2 (23)	—	—	—

Abbreviations: ADEM = acute disseminated encephalomyelitis; ARR = annualized relapse rate; CIS = clinically isolated syndrome; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IQR = interquartile range; mono-ADS = monophasic acquired demyelinating syndrome; MS = multiple sclerosis; ON = optic neuritis; TM = transverse myelitis.
The following were the statistical tests used for analysis: age, *t* test with Welch correction; sex, Fisher exact; time from 1st attack, Mann-Whitney.

compared to those with mono-ADS (82.3%, 65/79, $p = 0.0003$). There were no differences between the groups in moderate or mild PA. Patients with MS had lower HCSs than the patients with mono-ADS ($p = 0.01$). In addition, analysis of HCSs indicated that fewer patients with MS than patients with mono-ADS were considered active. Conversely, HCS analysis suggested that a higher proportion of patients with MS than patients with mono-ADS were insufficiently active ($p = 0.046$) (table 2). When excluding patients with mono-ADS who had an EDSS ≥4, the same differences were found in strenuous and total PA in the HCS (table e-1 on the *Neurology*® Web site at Neurology.org).

Subgroup analyses focusing on age and sex were performed, yielding differences between girls and boys. Boys in the mono-ADS group reported participating in more moderate PA (median [interquartile

Table 2 Physical activity

Characteristics	Mono-ADS (n = 79)	MS (n = 31)	*p* Value	Mann-Whitney *U*/χ^2	Cohen *d*
GLTEQ (METs), median (IQR)					
Strenuous	27.0 (36.0)	0.0 (27.0)	0.0012	752	0.7727
Moderate	15.0 (20.0)	15.0 (20.0)	0.4581	1,113	0.1159
Mild	6.0 (12.0)	9.0 (15.0)	0.7823	1,183	0.1729
Total	54.0 (49.0)	40.0 (46.0)	0.0284	895.5	0.4512
Health contribution score categories					
Score, median (IQR)	42.0 (45.0)	25.0 (47.0)	0.0098	838.5	0.4599
Active, % (n)	75.95 (60)	54.84 (17)			
Moderately active, % (n)	11.39 (9)	12.90 (4)	0.0459	6.164	—
Insufficiently active, % (n)	12.66 (10)	32.26 (10)			

Abbreviations: GLTEQ = Godin Leisure-Time Exercise Questionnaire; IQR = interquartile range; MET = metabolic equivalent; mono-ADS = monophasic acquired demyelinating syndrome; MS = multiple sclerosis.
The following were the statistical tests used for analysis: GLTEQ strenuous, moderate, mild, and total, and GLTEQ health contribution score, Mann-Whitney; GLTEQ health contribution score categories, χ^2 test.

range (IQR)]: 25 [25] METs) and total PA (66 [70] METs) than girls with mono-ADS (10 [20] METs, $p = 0.008$, and 46 [36] METs, $p = 0.047$, respectively). There were no differences between boys' and girls' participation in PA in the MS group. Analysis of the effect of age was performed. There were no patients with MS under 11 years of age. Girls who were 11 years old or older in the mono-ADS group (n = 34) reported participating in more strenuous PA (median [IQR]: 22.5 [27] METs) than the girls in the MS group (n = 25) (0 [27] METs, $p = 0.01$). No differences were seen between boys with MS and boys with mono-ADS 11 years old or older in strenuous ($p = 0.34$), moderate ($p = 0.31$), mild ($p = 0.42$), and total ($p = 0.18$) PA and HCS ($p = 0.19$). In the mono-ADS group, no differences were seen between preadolescents' (<11 years old) and adolescents' (≥11 years old) strenuous PA ($p = 0.29$).

Findings in the subgroup of patients with MRI scans were comparable to the larger group. Patients with MS in the MRI subgroup reported participating in less strenuous PA (median [IQR]: 0.0 METs [45.0 METs]) than those with mono-ADS (31.5 METs [36.0 METs], $p = 0.028$). There were no differences in moderate, mild, total, or HCS leisure activity scores between the groups in the MRI subpopulation.

Association of fatigue with PA and depression in patients with MS. Patients with MS reported higher levels of general and total fatigue on the PedsQL MFS compared with the patients with mono-ADS. Levels of cognitive fatigue followed the same trend. A higher proportion of patients with MS had moderate to severe levels of general, sleep rest, and total fatigue than the patients with mono-ADS. Patients with MS also had higher depression scores on the CES-DC than did the patients with mono-ADS (table e-2).

For all the patients with MS in the study, the lower the sleep/rest fatigue scores, the higher the moderate PA METs, and, conversely, the higher the sleep/rest fatigue scores, the lower the reported moderate PA METs ($r = -0.4$). Similar results were found for patients with MS with MRI assessments. The lower the general fatigue scores, the higher the moderate PA METs, total PA METs, and HCS. Conversely, the higher the general fatigue scores, the lower the moderate PA METs, total PA METs, and HCS ($r = -0.6$, $r = -0.5$, and $r = -0.6$, respectively).

Among the patients with MS, we performed bivariate correlation analysis on the different categories of fatigue and depression and found that the higher the depression scores, the higher the fatigue scores, and the lower the depression scores, the lower the fatigue scores. These same associations were found in the MS subpopulation with MRI assessments (table 3). An analysis of questionnaire results controlling for disease-modifying therapy use revealed no difference between the results of the 2 groups (data not shown).

MRI and other metrics: Associations of PA with disease activity in MS. In the subpopulation of patients with MS and patients with mono-ADS with MRI assessment, age at the time of scan and sex were not different between groups. Patients were clinically stable between the clinical and MRI assessment. Consistent with previous studies, comparison of the mono-ADS and MS MRI total brain volume z scores with the expected 0.0 mean and 1.0 SD of the NIHPD population revealed lower z scores for both groups than the NIHPD population (t test: mono-ADS z score $= -0.78 \pm 1.27$, $p = 0.0001$; MS z score $= -0.78 \pm 0.84$, $p = 0.0058$). Thus, mean brain volumes were within the normal range for both patient groups, but the z scores of the patients were centered around lower means than the NIHPD group of healthy individuals. The total brain volumes and total brain volume z scores were normally distributed in both patient groups and there were no differences between the patients with MS and patients with mono-ADS (table 4). Patients with MS had greater T1 and T2 lesion volumes vs patients with mono-ADS (table 4).

We performed bivariate correlations on data from the MS population and found that higher strenuous PA METs were associated with lower T2 ($r = -0.66$, $p = 0.006$) lesion volume and lower ARR ($r = -0.66$, $p = 0.006$). In order to validate the association between strenuous PA and T2 lesion volume and ARR, the MS patient sample was dichotomized by whether or not they participated in strenuous activity. In keeping with the associations found, the groups were different in their T2 lesion volume and ARR (table 5).

Table 3 Depression and fatigue Spearman correlations in patients with multiple sclerosis

	Depression			
	Total (n = 31)		MRI (n = 13)	
	r Value	*p* Value	*r* Value	*p* Value
General fatigue	0.70	1.43×10^{-5}	0.70	0.01
Sleep/rest fatigue	0.58	0.001	0.67	0.01
Cognitive fatigue	0.48	0.006	0.66	0.02
Total fatigue	0.68	3.12×10^{-5}	0.77	0.003

DISCUSSION

We found lower levels of self-reported strenuous PA and overall activity in children with MS in comparison to children with mono-ADS.

Similar to other studies,[32,33] we found higher levels of fatigue and depression in patients with MS than in children with monophasic demyelinating conditions.

Table 4 Demographics and MRI measures: Comparison between groups

Measure	Mono-ADS (n = 47)	MS (n = 13)	*p* Value	Cohen *d*
Age at visit, y, mean ± SD	14.09 ± 3.89	15.88 ± 2.72	0.068	−0.5333
M:F	22:25	3:10	0.204	—
ARR, median (IQR)	—	0.66 (0.54)	—	—
TBV, cm^3, mean ± SD	1,307.79 ± 133.39	1,277.05 ± 62.75	0.246	0.2066
TBV *z* score, mean ± SD	−0.78 ± 1.27	−0.78 ± 0.84	0.980	0.0000
T1 lesion volume, cm^3, median (IQR)	0.00 (0.00)	0.44 (0.99)	<0.0001	−1.0149
T2 lesion volume, cm^3, median (IQR)	0.00 (0.01)	2.00 (3.81)	<0.0001	−1.0857

Abbreviations: ARR = annualized relapse rate; IQR = interquartile range; mono-ADS = monophasic acquired demyelinating syndrome; MS = multiple sclerosis; TBV = total brain volume.
The following were the statistical tests used for analysis: age, TBV, and TBV *z* score, *t* test with Welch correction; sex, Fisher exact; ARR and T1 and T2 lesion volume, Mann-Whitney.

In the patients with MS, correlations were found between higher self-reported levels of PA and lower levels of sleep/rest and general fatigue. Lower levels of self-reported PA correlated with higher fatigue scores. This is in keeping with studies of adult MS, in which associations between both PA and exercise and fatigue and depression[15,16] have been described. The cross-sectional nature of the study limits our ability to draw conclusions regarding the causal relationship between PA and fatigue in our population. Future studies should be oriented toward understanding factors that may influence the complex relationships between PA, depression, and fatigue. Certainly, multiple factors, such as sleep, pain, and disease activity, and psychological factors, such as self-efficacy,[34] among others, may influence these outcomes.[35,36]

Within the MS cohort, sleep/rest fatigue levels were higher in patients who reported lower moderate PA participation. The same association held for general fatigue and moderate and overall PA, thus suggesting the potential for improvements in fatigue with increased levels of PA. Given the high correlation between fatigue and depression in our study, and high levels of depression in our patient population (approximately 1/5 of all patients), future studies should examine whether depression decreases through time in children who experience increases in PA. The robustness of these associations will be explored in the future in longitudinal and interventional studies.

An association was found between strenuous PA and lower T2 lesion volumes on MRI and lower ARR in patients with MS. Furthermore, we found a correlation between participation in strenuous PA had higher T2 lesion volumes and higher ARR. Although we could not determine the causal nature of this association in this cross-sectional study, others have shown associations between preservation of gray matter volumes and white matter integrity in patients with MS with high aerobic fitness, suggesting a beneficial effect of higher levels of PA on brain integrity.[37]

We acknowledge several limitations to our work. First, while consecutive children were recruited, the clinic itself is a specialized clinic at a tertiary care center, suggesting the possibility of patient selection bias. However, because the catchment area of the Hospital for Sick Children covers the entirety of the greater Toronto area, and most patients in the region with these disorders are captured by this clinic, the potential for selection bias is relatively small. Second, we did not have MRI scans available for volumetric analysis on all participants, suggesting the potential for selection bias with this subgroup. However, our analysis suggests that those with research scans did not differ substantially from those who did not have research scans (table e-3). Third, there are limitations to the use of 7-day recall questionnaires for documenting PA, although strong correlations have been found by others between an objective measure of PA (accelerometry) and the GLTEQ.[38] Finally, our study is limited by its cross-sectional nature. The directionality of the association of decreased activity with higher lesion volume cannot be concluded from

Table 5 Patients with multiple sclerosis dichotomized by strenuous activity participation

Measure	No strenuous PA (n = 7)	Strenuous PA (n = 6)	*p* Value	Cohen *d*
T2 lesion volume, median (IQR)	3.40 (6.08)	0.46 (1.82)	0.022	1.3200
ARR, median (IQR)	1.00 (0.38)	0.50 (0.22)	0.035	1.2800

Abbreviations: ARR = annualized relapse rate; IQR = interquartile range; PA = physical activity.
The Mann-Whitney test was used for the analyses of T2 lesion volume and ARR.

our study. Future studies should address these limitations by correlating questionnaire data with objective evaluations of fitness and PA and assessing patients longitudinally.

While we found an association between strenuous PA and lower brain T2 lesion volumes in this population, we were unable to explore gray matter volumes in this study as the analysis of gray matter volumes was outside the scope of the present work. Higher fitness in children has been associated with greater brain volumes, both overall and in the hippocampus and deep gray structures, including the putamen, caudate nucleus, and globus pallidus, as well as with higher performance on measures of cognitive control that involve working memory, inhibition, and cognitive flexibility.[39,40] Future studies focusing on the association of PA with gray matter volume and deep gray structures in children with MS are needed.

Thus, our data suggest low levels of overall and strenuous PA in children with MS, and a possible link between PA and fatigue and MRI lesion volume and ARR in the pediatric MS population. Future studies should focus on establishing the causal nature of this relationship by investigating interventions to improve PA and examining associated consequences in this population. These future interventions have the potential to improve quality of life by attenuating symptoms such as depression and fatigue and potentially reducing the rate of disease progression.

AUTHOR CONTRIBUTIONS

S.A. Grover helped to design and conceptualize the study, performed analysis and interpretation of the data, and drafted the manuscript. B. Aubert-Broche helped with the analysis/interpretation of the MRI data and revision of the manuscript for intellectual content. D. Fetco helped with the analysis/interpretation of the MRI data. D.L. Collins, D.L. Arnold, M. Finlayson, B.L. Banwell, and R.W. Motl helped revise the manuscript for intellectual content. R.W. Motl also helped to design the study. E.A. Yeh helped to design and conceptualize the study, interpret the data, and drafted and revised the manuscript.

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S. Grover, B. Aubert-Broche, and D. Fetco report no disclosures relevant to the manuscript. D. Collins has consulted for NeuroRX and is the cofounder of True Positive Medial Devices Inc. D. Arnold and M. Finlayson report no disclosures relevant to the manuscript. B. Banwell is an advisor to Biogen Idec, Novartis, Eli Lilly, and Sanofi-Aventis. She is also a chief editor for *Multiple Sclerosis and Related Disorders* and is on the editorial board for *Neurology*®. R. Motl receives funding from Biogen, Acorda, NMSS, and CMSS. He receives honoraria from EMD Serono. E. Yeh reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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