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Research Article

Physical activity and functional limitations in pediatric multiple sclerosis: Are fatigue and depression confounding variables?

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Abstract.
PURPOSE: Pediatric-onset multiple sclerosis (MS) is associated with risk for functional limitations defined as the perceived reduction in capacity for undertaking activities of daily living. Moderate-to-vigorous physical activity (MVPA) has been associated with less frequent and less impactful functional limitations, but the symptoms of fatigue and depression have not been considered as potential confounding variables. This study examined whether fatigue and depression confound the association between MVPA and functional limitations among youth with pediatric MS.
METHODS: Participant data were accumulated from three ongoing observational studies. The combined sample included 65 cases of pediatric-onset MS (24 male/41 female, 16 ± 1.7 years of age). Data on self-report MVPA, functional limitations, depression, and fatigue were analyzed.
RESULTS: MVPA was significantly associated with functional limitations ($r = 0.45$), fatigue ($r = –0.28$), and depression ($r = –0.32$). Functional limitations were associated with fatigue ($r = –0.45$) and depressive symptoms ($r = –0.53$). MVPA was significantly correlated with functional limitations ($\beta = 0.27$, $p = 0.04$) even after accounting for general fatigue ($\beta = 0.08$, $p = 0.64$) and depressive symptoms ($\beta = –0.40$, $p = 0.03$) among those with pediatric MS.
CONCLUSION: Self-reported MVPA was associated with perceived functional limitations among youth with pediatric MS independent of perceived fatigue and depressive symptoms.

Keywords: Pediatric multiple sclerosis, physical activity, functional limitations, fatigue, depression.

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1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system most commonly diagnosed in adulthood, but 5% of cases in the United States have an onset before the age of 18 years [1]. Pediatric MS is characterized by higher annualized relapse rates, higher lesion volume, and earlier onset of irreversible disability when compared with adult-onset MS [2–4]. Symptomatic manifestations of pediatric MS include fatigue, depression, and cognitive impairment [5]. These symptoms may result in functional limitations (e.g., perceived reduction in capacity for performing desired daily activities) among those with MS [6, 7]. Indeed, adolescents with pediatric MS have reported both physical (e.g., fatigue, pain, falls) and mental (e.g., fear, anxiety) difficulties that impact participation in desired activities of daily living (i.e., functional limitations; [8]).

There is burgeoning interest in physical activity as a strategy for managing the manifestations of pediatric MS [9]. For example, prior research indicated that physical activity participation, particularly levels of moderate-to-vigorous physical activity (MVPA), was associated with relapse rate and brain MRI lesion volume among youth with MS [10]. Physical activity was further associated with functional limitations among youth with MS [11].

Higher physical activity has been associated with lower fatigue and depression among those with pediatric MS [12), and those symptoms are associated with functional limitations among adults with MS [13, 14]. Accordingly, the symptoms of fatigue and depression may confound the relationship between physical activity and functional limitations among those with pediatric MS. If this is the case, then the symptoms of fatigue and depression, rather than physical activity, would become a central target of interventions for managing functional limitations in pediatric MS.

The present study examined the association between physical activity and functional limitations at a single point in time, as measured using a self-report inventory of disability and function, among youth with pediatric MS. It further examined symptoms of fatigue and depression as confounding variables (i.e., variables associated with both physical activity and functional limitations, thereby resulting in a spurious association between the two variables). Of note, this study focused on physical activity as confounding variables. However, there are multiple interpretations of third variables (e.g., mediators or moderators) that are impossible to tease apart in a cross-sectional exploration.

Researchers anticipated that levels of MVPA would be significantly associated with functional limitations, and that both variables would be associated with symptoms of fatigue and depression. Further, it was expected that the association between MVPA and functional limitations would be independent of fatigue and depression, and thereby highlight an independent association between MVPA and functional limitations in pediatric-onset MS.

2. Methods

2.1. Ethical considerations

The present study was approved by the Institutional Review Board as a secondary data analysis prior to data retrieval.

2.2. Participants and procedures

Participant data were accumulated from three ongoing observational studies. Participants were recruited through clinics in Canada and the United States. They were eligible for inclusion if they were between 12 and 19 years of age at time of data collection, were <18 years of age at time of symptom onset, received treatment within six months of their initial symptom onset, had a confirmed diagnosis of pediatric MS according to international diagnostic criteria [15], had a score of <4.0 on the Expanded Disability Status Scale (EDSS), and were fluent in English. Youth with MS were excluded if they were unable to communicate in English, had experienced a relapse within the previous 30 days of enrollment, or had severe respiratory problems or known cyanotic congenital heart disease.

All participants provided written informed consent and/or assent. Participants completed questionnaires measuring physical activity, functional limitations, fatigue, and depression at baseline sessions of three ongoing studies using computerized data management software (REDCap). Disease specific information including disease duration and disability level was extracted from medical records and entered onto a standardized case report form.

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2.3. Measures

2.3.1. Physical activity

Physical activity was measured with the Godin Leisure Time Exercise Questionnaire (GLTEQ) as scores for this have been validated for use among youth with pediatric MS [16]. The GLTEQ includes three items wherein participants report the number of bouts of light, moderate, and strenuous physical activity of 15+ minutes during a typical week. The GLTEQ is often scored by multiplying the number of light, moderate, and strenuous bouts by 3, 5, and 9 metabolic equivalents of task respectively and summing them into an overall physical activity score. The GLTEQ was scored as MVPA by summing only the moderate and strenuous scores into a health contribution score (HCS) [17].

2.3.2. Functional limitations

The concept of perceived functional limitations was measured using the Late Life Functional Disability Inventory (LLFDI) [18]. The LLFDI has been validated for use in adults with MS [19] and has been used in pediatric MS research [11]. The LFFDI has 15 items assessing three primary areas of function (i.e., basic lower extremity function, advanced lower extremity function, and upper extremity function). The overall LLFDI score is included in this analysis as a global marker of perceived function and includes all three subscales. The overall score is interpreted such that higher scores reflect fewer functional limitations (i.e., better perceived function), and thus a positive association with physical activity and negative associations with fatigue and depression were expected. The Cronbach's alpha coefficient for this sample was 0.95.

2.3.3. Fatigue

Fatigue was measured with the PedsQL Multidimensional Fatigue Scale. The PedsQL is frequently used in pediatric MS studies and has been validated for use in healthy pediatric populations [20]. The PedsQL includes 18 questions and is scored across three fatigue dimensions: general fatigue, sleep/rest fatigue, and cognitive fatigue. Items are scored on a 5-point Likert scale of 0 ('never') through 4 ('almost always'). They were linearly transformed from zero to 100 with higher scores representing more problems with fatigue. The general fatigue subscale was included as a global marker of fatigue for youth with pediatric MS. Negative associations with physical activity and function, and positive association with depression, were expected. The Cronbach's alpha coefficient for this sample was 0.90.

2.3.4. Depression

The Center for Epidemiological Studies Depression Scale for Children (CES-DC) was used to measure depressive symptoms [21]. The CES-DC includes 20 items rated on a scale of 1 ('rarely or none of the time') to 4 ('most or all of the time') with higher scores indicating more depressive symptoms. Negative associations were expected between CES-DC and with physical activity and function, and a positive association with fatigue. The Cronbach's alpha coefficient for this sample was 0.86.

2.4. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics, version 24. Descriptive statistics were reported as mean $\pm$ standard deviation for all normally distributed data, and median interquartile range for non-normal distributions. Normality was assessed visually using histograms. Bivariate correlations (Pearson's r) estimated the magnitude and direction of associations among MVPA (GLTEQ-HCS), functional limitations (LLFDI), fatigue (PedsQL), depression (CES-DC), and among clinical disease variables (i.e., disability and disease duration). Correlations were interpreted such that 0.1, 0.3, and 0.5 were considered weak, moderate, and strong, respectively. Hierarchical linear regression analysis was then performed wherein functional limitations (LLFDI) was regressed first on MVPA (GLTEQ-HCS), and then on MVPA with fatigue (PedsQL) and depression (CES-DC). EDSS was not controlled for in the statistical analyses based on overlapping conceptual content with LLFDI (e.g., both measures assess aspects of function and disability). Significant values were set *a priori* as $p < 0.05$ without corrections for multiple comparisons.

3. Results

3.1. Demographics

Table 1 includes demographic information for the sample. The overall sample of youth with MS included 65 participants (24 males, 41 females) with a mean age of 16.2 ± 1.7 years, a median disability (EDSS) score of 1.5 [1], and a mean disease duration of 1.5 ± 1.7 years. The mean GLTEQ-HCS (i.e.,

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Table 1
Clinical characteristics of the sample

	Pediatric MS ($n = 65$)
Age (yrs)	16.2 ± 1.7
Sex (M/F)	24 / 41
Disease Duration (yrs)	1.5 ± 1.7
EDSS (median [IQR])	
Range of possible scores: 0–10 Interpretation: Higher EDSS is equivalent to higher degree of disability	1.5 [1]
Functional limitations	
Range of possible scores: 0–100 Interpretation: Higher scores indicate better perceived function	69.0 ± 9.4
MVPA	
Range of possible scores: 0–98 Interpretation: Higher scores indicate higher rates of MVPA	36.6 ± 25.8 METs
Fatigue	
Range of possible scores: 0–100 Interpretation: Higher scores indicate higher fatigue	74.6 ± 20.7
Depression	
Range of possible scores: 0–100 Interpretation: Higher scores indicate greater depression	13.7 ± 10.7

*EDSS: Expanded Disability Status Scale; F: female; IQR: interquartile range; M: male; MET: metabolic equivalent of task; MS: multiple sclerosis; yrs: years.

MVPA) was 36.5 ± 25.8. The mean functional limitations (LLFDI) score was 69.0 ± 9.4. The mean general fatigue (PedsQL) score was 74.6 ± 20.7 and mean depression (CES-DC) score was 13.7 ± 10.7.

3.2. Correlations

MVPA (GLTEQ-HCS) was significantly associated with functional limitations (LLFDI) ($r = 0.37$, $p < 0.001$), lower general fatigue ($r = –0.29$, $p = 0.02$), and fewer depressive symptoms ($r = –0.30$, $p = 0.02$) when controlling for age and sex. Function limitations (LLFDI) was moderately associated with general fatigue ($r = –0.32$, $p < 0.01$) and depressive symptoms ($r = –0.43$, $p < 0.001$) when controlling for age and sex.

Disability (EDSS) was associated with MVPA (GLTEQ-HCS; $r = –0.41$, $p = 0.001$) and functional limitations (LLFDI; $r = 0.37$, $p = 0.006$). Age was not associated with MVPA (GLTEQ-HCS; $r = –0.08$, $p = 0.53$), depressive symptoms ($r = 0.11$, $p = 0.34$), fatigue ($r = 0.13$, $p = 0.3$), or functional limitations (LLFDI; $r = 0.009$, $p = 0.95$). Participant sex was not associated with MVPA (GLTEQ-HCS; $r = –0.15$, $p = 0.24$) or functional limitations (LLFDI; $r = –0.09$, $p = –0.51$). In line with the lack of significant associations with age/sex, these variables were not included in the regression model.

Table 2
Regression – variables predicting functional limitations

	B	*SE B*	β	*p*-value	R^2	ΔR^2
Block 1				**0.004**	**0.14**	
HCS	0.13	0.04	0.37	0.004		
Block 2				**0.001**	**0.25**	**0.11**
HCS	0.09	0.05	0.27	**0.04**		
Fatigue	0.01	0.02	0.09	0.64		
Depression	–0.35	0.16	–0.40	**0.03**		

HCS: health contribution score.

3.3. Regressions

Step 1 of the hierarchical linear regression regressed functional limitations (LLFDI) on MVPA (GLTEQ-HCS; Table 2). This model explained 14% of variance in functional limitations among youth with pediatric MS ($R^2 = 0.14$), and GLTEQ-HCS was a statistically significant correlate of functional limitations in the regression equation ($\beta = 0.37$, $p = 0.004$).

Step 2 of the hierarchical linear regression regressed LLFDI on MVPA (GLTEQ-HCS), fatigue (PedsQL), and depression (CES-DC). The variables in Step 2 of the regression equation explained an additional 11% of variance in functional limitations over just MVPA in Step 1. The model including MVPA, fatigue, and depression tested in Step 2 explained 25% of variance in functional limitations for youth with pediatric MS ($R^2 = 0.25$, $\Delta R^2 = 0.11$). MVPA (GLTEQ-HCS) was still a significant correlate of functional limitations ($\beta = 0.27$, $p = 0.04$) when including fatigue ($\beta = 0.08$, $p = 0.64$) and depression ($\beta = –0.40$, $p = 0.03$). Of note, collinearity of fatigue (tolerance: 0.38, variance inflation factor: 2.6) and depression (tolerance: 0.39, VIF: 2.5) was not of significant concern in Step 2 of the regression.

4. Discussion

This study examined associations between physical activity, functional limitations, and symptoms of fatigue and depression among youth with pediatric MS. MVPA and functional limitations were moderately and significantly correlated among youth with pediatric MS ($r = 0.45$, $p < 0.001$) such that higher MVPA was associated with better perceived function. MVPA was a significant correlate of functional limitations in the regression analysis and explained

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14% of the variance in this sample of youth with MS. These results confirm previous findings among adults with MS [22] and further align a smaller sample of those with pediatric MS included in the current study [11]. Indeed, physical activity is a significant predictor of functional limitations among adults with MS [13], yet directionality cannot be established in the current study based on the cross-sectional research design. Physical activity could be influencing functional limitations for those with pediatric MS, or vice versa. Such directionality could be teased out in future longitudinal research.

MVPA was a significant correlate of functional limitations in the second step of the regression that included symptoms of fatigue and depression. This result suggests that MVPA is an important correlate of functional limitations regardless of fatigue and depression for those with pediatric MS. This is especially useful information for clinicians developing and implementing interventions targeting functional limitations for this population. Such interventions might include MVPA for managing functional limitations in pediatric-onset MS.

Importantly, the symptoms of fatigue and depression along with MVPA accounted for 11% more variance in perceived functional limitations than MVPA alone, and depression had a statistically significant beta weight, whereas this was not the case for fatigue. This suggests that depression may be uniquely associated with functional limitations among those with pediatric MS. This is an important result as individuals with pediatric MS report higher rates of depressive symptoms than healthy peers and youth with similar demyelinating diseases (monophasic acquired demyelinating syndromes (mono-ADS; 10, 23). As such, symptoms of depression are important for clinicians and researchers to consider when assessing and addressing functional limitations among those with pediatric MS. The lack of significance of fatigue in the regression model suggests fatigue may not play a large role in perceptions of functional limitations for those with pediatric MS, but this finding warrants additional exploration.

4.1. Limitations

The authors acknowledge several important limitations of the present study. The cross-sectional design is a major limitation for conclusions regarding the temporal and causal nature of the association between MVPA and functional limitations. Indeed, MVPA could influence function, or function could influence MVPA, and these might be associated based on some third, unknown variable other than fatigue and depression. The small sample size in the present study limited the ability to thoroughly examine interactions between variables (i.e., depression and fatigue). Further, age was not associated with MVPA or functional limitations in the present study. This may be due to the low variance in age of included participants. Future studies will benefit from larger variance in age within samples to explore potential impacts of age.

The lack of a non-MS control group for establishing the specificity of generality of the association between MVPA and function is a potential limitation in the present study. An additional limitation is the use of a non-pediatric specific functional measure (LLFDI) although this measure has been used in pediatric MS research before [11] and validated for use in MS [20]. Future research would benefit from the use of a pediatric specific measure (e.g., the Functional Disability Inventory) to identify pediatric-specific aspects of function that may be impaired in pediatric MS. Use of device-measured physical activity in future studies will also be helpful in reducing the limitation of self-reported MVPA.

5. Conclusion

MVPA, as well as fatigue and depression, were associated with functional limitations among youth with pediatric MS, and MVPA continued to be a significant correlate of perceived functional limitations even after accounting for general fatigue and depressive symptoms. These results highlight a possible role of MVPA in managing functional limitations among those with pediatric MS regardless of rates of fatigue and depression. Future research should include experimental designs to test whether a change in MVPA results in a subsequent change in functional limitations for those with pediatric MS.

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Conflict of interest

The authors have no conflict of interest to report. Data collection for the present study was enabled by a pilot research grant from the National Multiple Sclerosis Society (NMSS).

References

[1] Waldman A, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M, Banwell B. Multiple sclerosis in children: An update on clinical diagnosis, therapeutic strategies, and research. Lancet Neurol. 2014;13(9):936-48. doi: 10.1016/s1474-4422(14)70093-6

[2] Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Arch Neurol. 2009;66(1):54-9. doi: 10.1001/archneurol.2008.505

[3] Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. N Engl J Med. 2007;356(25):2603-13. doi: 10.1056/NEJMoa067597

[4] Yeh EA, Weinstock-Guttman B, Ramanathan M, et al. Magnetic resonance imaging characteristics of children and adults with paediatric-onset multiple sclerosis. Brain. 2009;132(Pt 12):3392-400. doi: 10.1093/brain/awp278

[5] Waldman A, Ness J, Pohl D, et al. Pediatric multiple sclerosis: Clinical features and outcome. Neurology. 2016;87(9 Suppl 2):S74-81. doi: 10.1212/wnl.0000000000003028

[6] Haley SM, Jette AM, Coster WJ, et al. Late Life Function and Disability Instrument: II. Development and evaluation of the function component. J Gerontol A Biol Sci Med Sci. 2002;57(4):M217-22. doi: 10.1093/gerona/57.4.m217

[7] Stuifbergen AK, Blozis SA, Harrison TC, Becker HA. Exercise, functional limitations, and quality of life: A longitudinal study of persons with multiple sclerosis. Arch Phys Med Rehabil. 2006;87(7):935-43. doi: 10.1016/j.apmr.2006.04.003

[8] Sikes EM, Richardson EV, Motl RW. A qualitative study of exercise and physical activity in adolescents with pediatric-onset multiple sclerosis. Int J MS Care. 2019;21(2):81-91. doi: 10.7224/1537-2073.2018-033

[9] Yeh EA, Kinnett-Hopkins D, Grover SA, Motl RW. Physical activity and pediatric multiple sclerosis: Developing a research agenda. Mult Scler. 2015;21(13):1618-25. doi: 10.1177/1352458515606526

[10] Grover SA, Aubert-Broche B, Fetco D, et al. Low levels of participation in vigorous physical activity in youth with ms and the association with fatigue and depression. Neurology. 2015;85(19):1663-9. doi: 10.1212/wnl.0000000000001939

[11] Grover SA, Sawicki CP, Kinnett-Hopkins D, et al. Physical activity and its correlates in youth with multiple sclerosis. J Pediatr. 2016;179:197-203. doi: 10.1016/j.jpeds.2016.08.104

[12] Stephens S, Shams S, Lee J, et al. Benefits of physical activity for depression and fatigue in multiple sclerosis: A longitudinal analysis. J Pediatr. 2019;209:226-232.e2. doi: 10.1016/j.jpeds.2019.01.040

[13] Motl RW, McAuley E. Symptom cluster as a predictor of physical activity in multiple sclerosis: Preliminary evidence. J Pain Symptom Manage. 2009;38(2):270-80. doi: 10.1016/j.jpainsymman.2008.08.004

[14] Beal CC, Stuifbergen AK, Brown A. Depression in multiple sclerosis: A longitudinal analysis. Arch Psychiatr Nurs. 2007;21(4):181-91. doi: 10.1016/j.apnu.2007.02.008

[15] Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: Revisions to the 2007 definitions. Mult Scler. 2013;19(10):1261-7. doi: 10.1177/1352458513484547

[16] Kinnett-Hopkins D, Grover SA, Yeh EA, Motl RW. Physical activity in pediatric onset multiple sclerosis: Validating a questionnaire for clinical practice and research. Mult Scler Relat Disord. 2016;10:26-9. doi: 10.1016/j.msard.2016.08.010

[17] Sikes EM, Richardson EV, Cederberg KJ, Sasaki JE, Sandroff BM, Motl RW. Use of the Godin leisure-time exercise questionnaire in multiple sclerosis research: A comprehensive narrative review. Disabil Rehabil. 2019;41(11):1243-67. doi: 10.1080/09638288.2018.1424956

[18] McAuley E, Konopack JF, Motl RW, Rosengren K, Morris KS. Measuring disability and function in older women: Psychometric properties of the late-life function and disability instrument. J Gerontol A Biol Sci Med Sci. 2005;60(7):901-9. doi: 10.1093/gerona/60.7.901

[19] Motl RW, McAuley E, Suh Y. Validity, invariance and responsiveness of a self-report measure of functional limitations and disability in multiple sclerosis. Disabil Rehabil. 2010;32(15):1260-71. doi: 10.3109/09638280903464463

[20] Varni JW, Seid M, Kurtin PS. PedsQL™ 4.0: Reliability and validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in healthy and patient populations. Med Care. 2001;39(8):800-12. doi: 10.1097/00005650-200108000-00006

[21] Weissman MM, Orvaschel H, Padian N. Children's symptom and social functioning self-report scales comparison of mothers' and children's reports. J Nerv Ment Dis. 1980;168(12):736-40. doi: 10.1097/00005053-198012000-00005

[22] Motl RW, McAuley E, Snook EM. Physical activity and quality of life in multiple sclerosis: Possible roles of social support, self-efficacy, and functional limitations. Rehabilitation Psychology. 2007;52(2):143-51. doi: 10.1037/0090-5550.52.2.143

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