Longitudinal Relationships Between Moderate to Vigorous Physical Activity, Fatigue and Depression in Pediatric MS

Samantha Stephens, Shahriar Shams, Joshua Lee, Stephanie A. Grover, Giulia Longoni, Tara Berebaum,, Marcia Finlayson, Robert W. Motl, and E. Ann Yeh

Disclosures

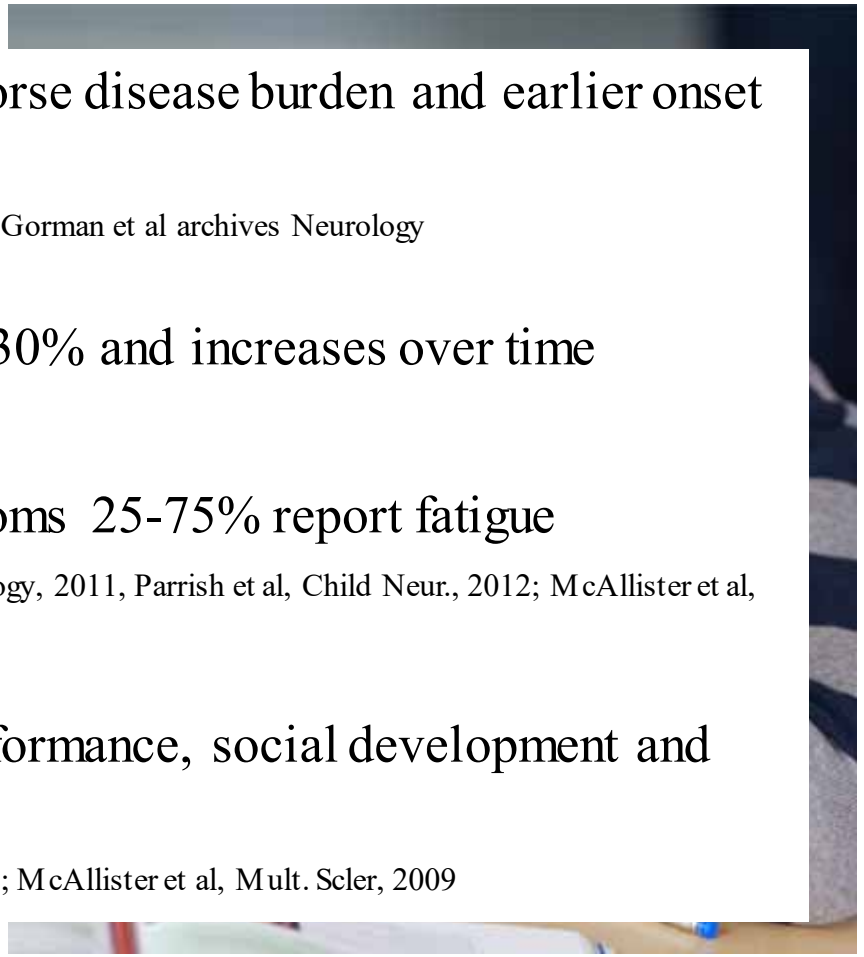
- S. Stephens no disclosures
- S.Shams no disclosures
- J. Lee no disclosures
- S.A. Grover no disclosures
- G. Longoni no disclosures
- M. Finlayson no disclosures
- R.W. Motl no disclosures
- EAY has received funds from NMSS, CIHI, CIHR, OIRM, MS Society of Canada, Mario Batali Foundation, SickKids Foundation, CBMH Innovation Fund, CMSC, Rare Diseases Foundation and Guthy Jackson Foundation. She serves as a relapse adjudicator for ACI. She has served on a scientific advisory panel for Juno Therapeutics and has received a speaker's honorarium from Novartis.

Learning Objective

- To gain an understanding of the relationship between physical activity participation and symptoms of depression and fatigue in children with demyelinating disorders over time.

Impact of Multiple Sclerosis

- Children with MS experience worse disease burden and earlier onset of disability than adults.
  - Renoux et al, NEJM.2007; Yeh et al, Brain, 2009; Gorman et al archives Neurology
- Cognitive impairment occurs in 30% and increases over time
  - Amato et. al, 2008 Neurology
- 30-50% report depressive symptoms 25-75% report fatigue
  - Amato et al, Neurology, 2008;Amato et al, Neurology, 2011, Parrish et al, Child Neur., 2012; McAllister et al, Mult. Scler, 2009
- Negatively affects academic performance, social development and life
  - Amato et al, 2008; Parrish et al, Child Neur., 2012; McAllister et al, Mult. Scler, 2009



What factors may effect depression and fatigue over time?

- Vigorous physical activity associated with lower disease burden
  -Grover et al, Neurology 2015
- Moderate to vigorous intensity physical activity is inversely related with fatigue and depression
  - Grover et al, J Peds 2016
- Knowledge related to longitudinal impact of moderate to vigorous physical activity is needed to plan non pharmacological therapeutic interventions

Research Question

Is moderate to vigorous physical activity participation in children with multiple sclerosis (MS) predictive of symptoms of depression and fatigue over time?

Does the relationship differ between youth with MS and monophasic demyelination (mono-ADS)?

Research Design

Study Design

- Prospective longitudinal study

- Consecutive enrollment of patients attending tertiary pediatric MS center 09/2013-03/2017

Inclusion/ Exclusion criteria

Inclusion Criteria

- Diagnosis of MS (McDonald Criteria) or mono-ADS
- < 18 years of age at first visit

Exclusion Criteria

- Diagnosis other than MS or mono-ADS
- > 18 years of age at first visit
- Unable to read or understand English at a level allowing for accurate completion of questionnaires

Methods

- **Clinical Covariates**
  - Disability (Expanded Disability Status Scale)
  - Number of demyelinating events
  - Disease duration
- **Depressive symptoms**
  - Center for Epidemiologic Studies Depression Scale for Children (CES-DC)
- **Fatigue**
  - Pediatric Quality of Life Multidimensional Fatigue Module (PedQL-MFS)
- **Physical Activity**
  - Godin Leisure Time Exercise Questionnaire

Analysis

- Joint modeling approach for multivariate longitudinal data
- Where: $Y1_{\text{depression}}ij = \mu1(tij) + a1i + \varepsilon1ij$

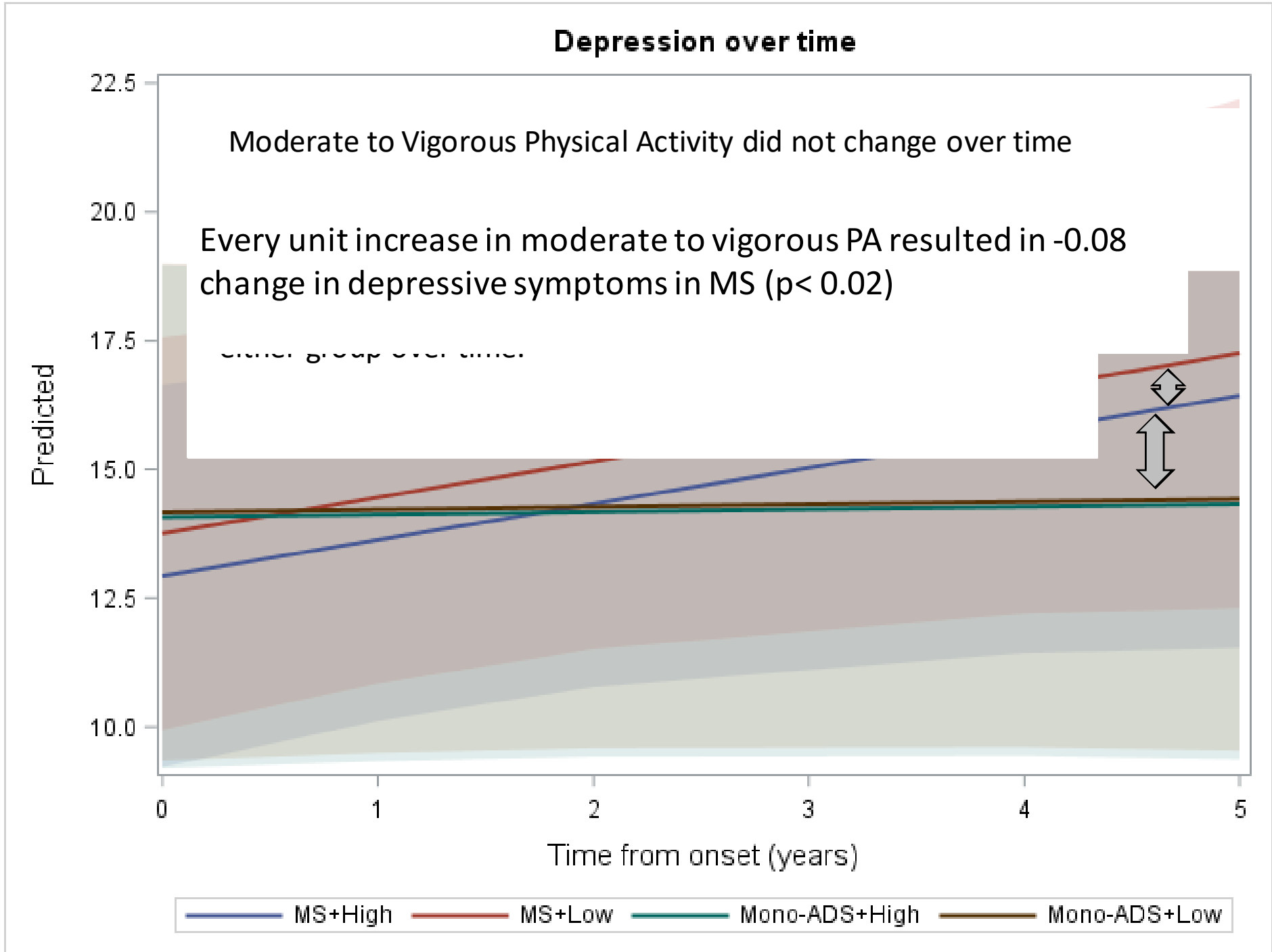
  $Y2_{\text{fatigue}}ij = \mu2(tij) + a2i + \varepsilon2ij$
- **Fixed Effect Terms:** $\mu k(tij) = \beta k0 + \beta k1 * \#events * d\_group + \beta k2 * age\ at\ onset + \beta k3 * time\ from\ onset + \beta k4 * gender + \beta k5 * mvpa * d\_group$
- **Random Effect Term:** $a1i$ and $a2i$ = subject level intercept terms for response $Y1$ and $Y2$.

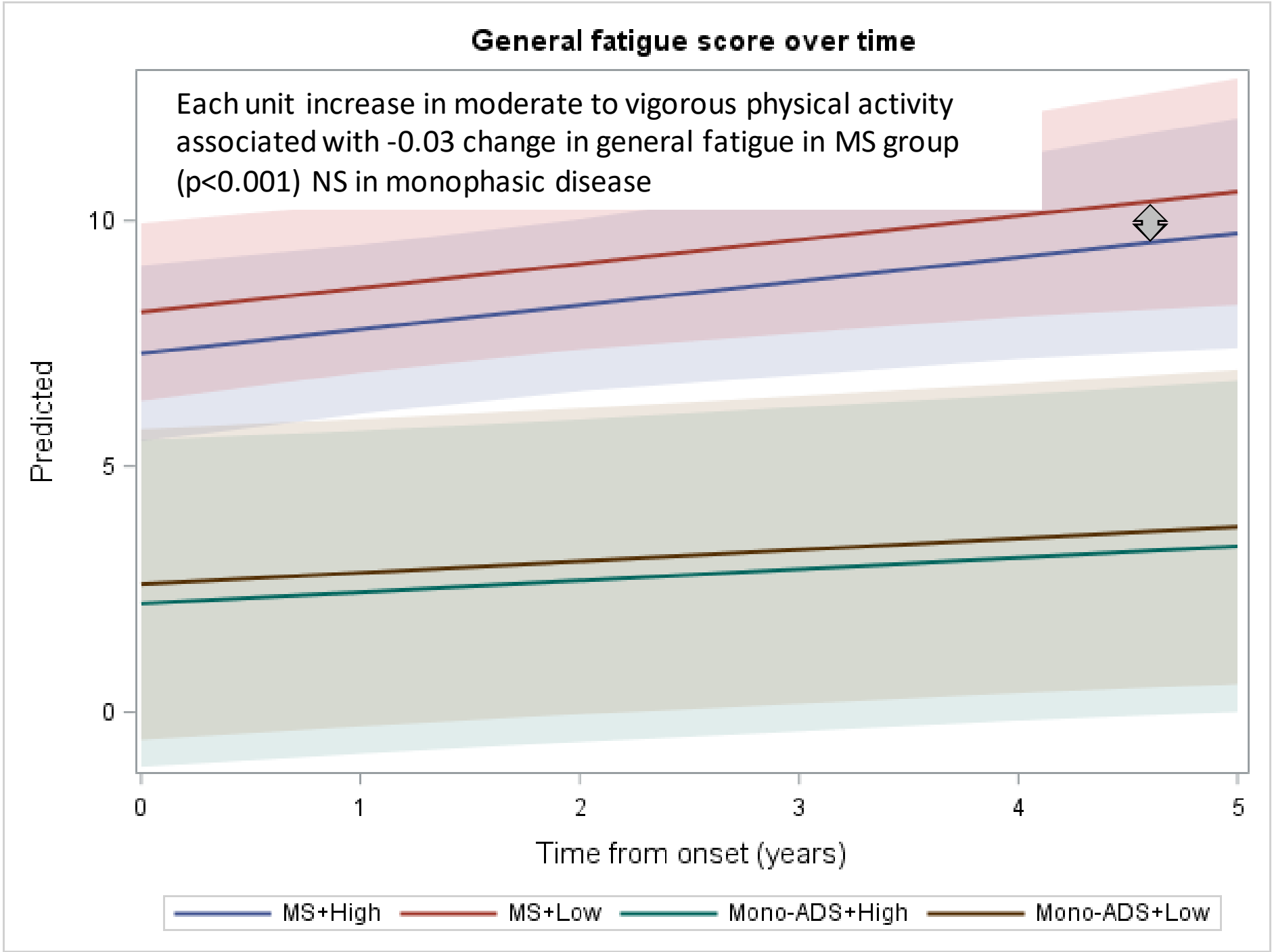
Visit 1 Demographic & Clinical Characteristics

Characteristic	Group		
	MS (N=49)	mono-ADS(N=134)	P-Value
Gender (N, % female)	35 (71%)	67 (50%)	< 0.01
Age at onset	13.6 (3.0)	9.0 (4.0)	<0.0001
Age (Mean, SD)	15.5 (1.7)	12.0 (3.6)	<0.0001
EDSS	1.5 (1.0)	1.3 (1.6)	NS
Number of Demyelinating Events	2.3 (2.5)	1.0 (0.0)	<0.0001
Total Fatigue	22 (12)	16 (12)	0.007
Depressive Symptoms	15 (10)	10 (7.0)	0.02

Physical Activity Level at Visit 1

Physical Activity	Group		
	MS (N=49)	**Mono-Ads (N=134)**	P-Value
Light Activity (unit/week)	9 (8)	13 (9)	0.23
Moderate Activity (unit/week)	16 (12)	18 (11)	0.28
Vigorous Activity (unit/Week)	20 (21)	31 (22)	0.004
MVPA (unit/week)	36 (30)	49 (29)	0.02


Depression over time
Moderate to Vigorous Physical Activity did not change over time
Every unit increase in moderate to vigorous PA resulted in -0.08 change in depressive symptoms in MS (p< 0.02)
Predicted
22.5
20.0
17.5
15.0
12.5
10.0
0
1
2
3
4
5
Time from onset (years)
MS+High
MS+Low
Mono-ADS+High
Mono-ADS+Low


General fatigue score over time
Each unit increase in moderate to vigorous physical activity associated with -0.03 change in general fatigue in MS group (p<0.001) NS in monophasic disease
Predicted
10
5
0
0
1
2
3
4
5
Time from onset (years)
MS+High
MS+Low
Mono-ADS+High
Mono-ADS+Low

Symptom Reduction	Amount of MVPA	Examples
1 point reduction in depressive symptoms	2 x 15 minute sessions of moderate activity	
	1 x 15 minute session of vigorous activity	
1 point reduction in general fatigue	6 x 15 minute sessions of moderate activity	
	3 x 15 minute sessions of vigorous activity	

Conclusions

- Moderate to vigorous physical activity is associated with lower depressive symptoms and fatigue across time in children with MS
- Small changes in moderate to vigorous physical activity may result in symptom reductions
- Inform future intervention

Acknowledgements

SickKids | Centre for Brain & Mental Health


Shahriar Shams


Joshua Lee


Stephanie Grover


Giulia Longoni


Tara Berebaum


Marcia Finlayson

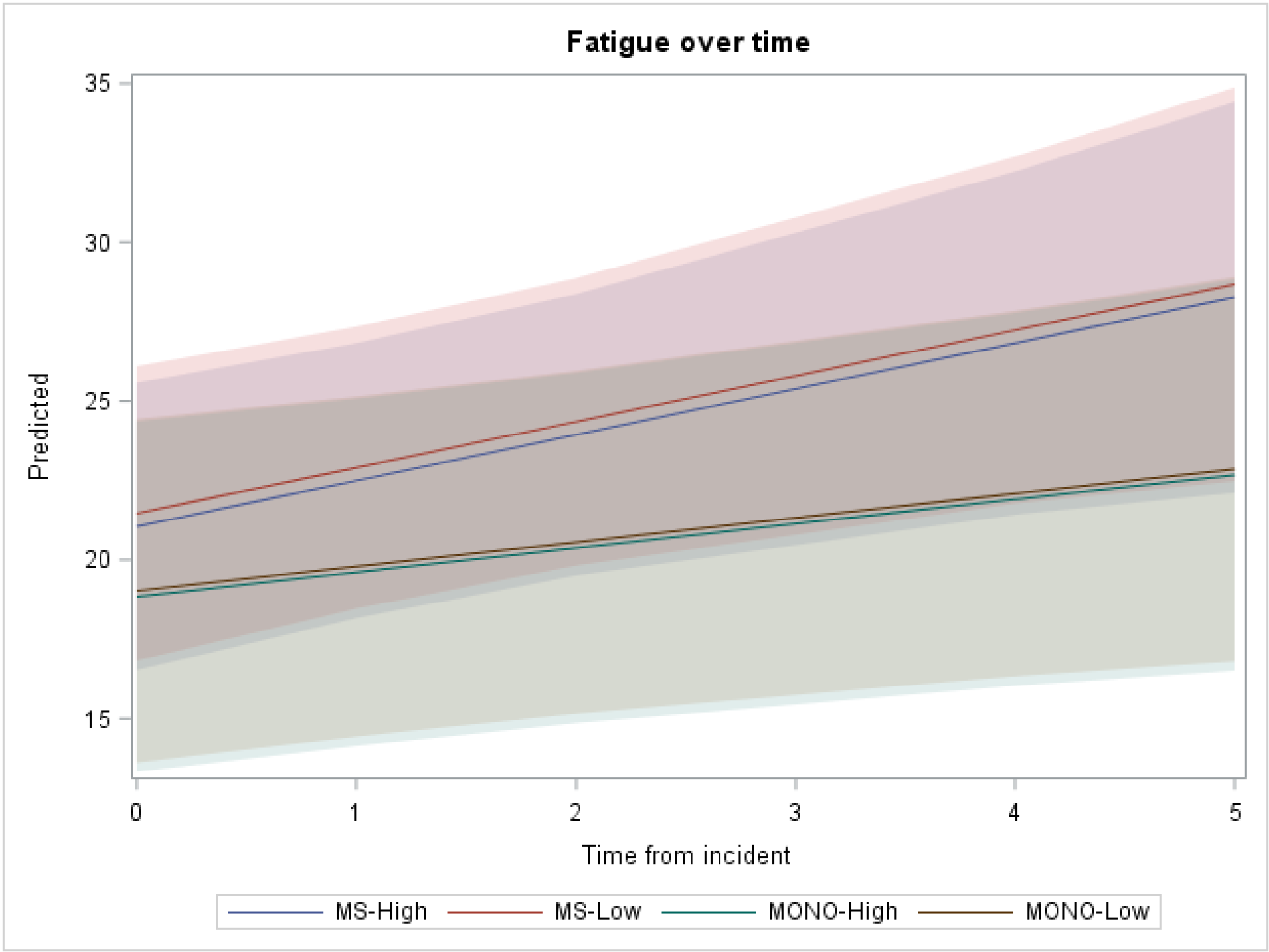

Robert Motl


Dr. Ann Yeh

CMSC
THE CONSORTIUM OF MULTIPLE SCLEROSIS CENTERS

MS Multiple Sclerosis Society of Canada

MS National Multiple Sclerosis Society


Fatigue over time
35
30
25
20
15
Predicted
0
1
2
3
4
5
Time from incident
MS-High
MS-Low
MONO-High
MONO-Low

Results: Depression and MVPA

- Depressive symptoms increased over time in children with MS (0.70 points/year, $p < 0.14$) but not in mono-ADS (0.05 points/year, $p < 0.25$)
- MVPA was stable through time
- For every unit increase in MVPA there was a decrease in depressive symptoms of - 0.08 ($p<0.02$) in children with MS

Interventional Implications

Based on our prediction model:

- A 10 unit increase in MVPA would result in ~ 1 point reduction in depressive symptoms

- This is equivalent to: 2 * 15 minute sessions of moderate activity, or 1 *15 minute session of vigorous activity per week.

Conclusions

- Fatigue increased twice as much in MS than Mono-Ads over time.
- MVPA decreased total fatigue in MS (N.S)
- Cognitive, Sleep/ Rest was lower in MS with higher MVPA
- General fatigue was lower in those with MS and Mono-Ads with higher MVPA over time
- Moderate increases in MVPA may be required to reduce cognitive, sleep or general fatigue in MS.

Conclusions

- Each 1 MET increase in MVPA results in a decrease in depressive symptoms and fatigue (NS) in MS patients over time.

- This effect was larger in MS patients and NS in Mono-ADS.

Research Objectives

2. Are symptoms of depression and fatigue predictive of physical activity level in pediatric MS and Mono-ADS?

Previous fatigue and MVPA

Solutions for Fixed Effects						
Effect	**d_group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		72.6139	10.4821	121	6.93	<.0001
fatigue*d_group	MS	-0.4160	0.2669	169	-1.56	0.1210
fatigue*d_group	Mono-ADS	0	.	.	.	.

Every 1 point increase in total fatigue recorded at previous visit resulted in decreased MVPA at next visit by ~0.4 MET.

Conclusions Objective 2

- Fatigue level at a previous visit was predictive of less MVPA at the next visit. (NS)

- Depressive symptoms were not predictive of MVPA at the next visit.

Future Research Implications

- Does an increase in 20 minutes per day of MVPA result in reduced Depressive symptoms in children with MS?

- Does reducing depression symptoms result in a decrease in fatigue (intervention)?

- Identification of other lifestyle factors for reducing fatigue (e.g. sleep).

- Other Slides

Total depression = total fatigue

Solutions for Fixed Effects

Effect	d_group	gender	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			5.9334	2.4001	155	2.47	0.0145
total_fatigue			0.4988	0.03115	246	16.01	<.0001
number_of_re*d_group	MS		0.6292	0.3072	246	2.05	0.0416
number_of_re*d_group	Mono-ADS		-2.3552	1.0955	246	-2.15	0.0325
age_at_onset			-0.1475	0.1512	246	-0.98	0.3303
time_4m_onset			-0.2614	0.1876	246	-1.39	0.1648
hcs*d_group	MS		-0.05447	0.01916	246	-2.84	0.0048
hcs*d_group	Mono-ADS		-0.00238	0.01560	246	-0.15	0.8790
gender		1	-0.1580	0.9784	246	-0.16	0.8719
gender		2	0	.	.	.	.
edss*d_group	MS		0.4764	0.5464	246	0.87	0.3841
edss*d_group	Mono-ADS		0.9068	0.4959	246	1.83	0.0687

Total Fatigue = Total Depression

Solutions for Fixed Effects

Effect	d_group	gender	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			2.6548	2.9690	155	0.89	0.3726
total_depression			0.7310	0.04851	248	15.07	<.0001
age_at_onset			0.6354	0.1989	248	3.19	0.0016
time_4m_onset			0.6591	0.2384	248	2.76	0.0061
hcs*d_group	MS		-0.00085	0.02334	248	-0.04	0.9710
hcs*d_group	Mono-ADS		-0.00621	0.01901	248	-0.33	0.7443
edss*d_group	MS		0.1700	0.6451	248	0.26	0.7924
edss*d_group	Mono-ADS		-0.5134	0.6312	248	-0.81	0.4168
gender		1	-1.5405	1.3619	248	-1.13	0.2591
gender		2	0	.	.	.	.

Physical Activity, MS Symptoms and Disease Activity: Cross-Sectional Results

- ↓ Physical Strenuous Activity
- ↑ Fatigue
- ↑ Depressive Symptoms
- ↑ Fatigue ↑ Depressive Symptoms
- ↑ Strenuous PA ↓ Disease Activity

Physical Activity as a Therapeutic Approach

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

Stephanie A. Grover, MSc
Berengere Aubert-Broche, PhD
Dumitru Fetco, MD
D. Louis Collins, PhD
Douglas L. Arnold, MD
Marcia Finlayson, PhD
Brenda L. Banwell, MD
Robert W. Motl, PhD
E. Ann Yeh, MD

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;

Effect	Outcome	Group	Estimate	SE	T-	p-
Time4monset*d_group*ot	Depression	MS	0.71	0.47	1.50	0.135
Time4monset*d_group*ot	Fatigue	MS	1.43	0.57	2.48	0.014
Time4monset*d_group*ot	Depression	Mono-ADS	0.042	0.25	0.16	0.870
Time4monset*d_group*ot	Fatigue	Mono-ADS	0.75	0.36	2.06	0.040
hcs*d_group*ot	Depression	MS	-0.083	0.026	-3.15	0.002
hcs*d_group*ot	Fatigue	MS	-0.040	0.031	-1.28	0.202
hcs*d_group*ot	Depression	Mono-ADS	-0.01	0.02	-0.49	0.623
hcs*d_group*ot	Fatigue	Mono-ADS	-0.019	0.026	-0.73	0.469

Characteristic	Group		
	MS (N=49)	Mono-Ads (N=134)	P-Value
General Fatigue	7.1 (4.4)	4.6 (4.2)	0.001
Cognitive Fatigue	6.7 (5)	5.3 (5.1)	0.10
Sleep/rest Fatigue	8.4 (4.7)	6.4 (4.3)	0.84

Methods

Relationship between Fatigue and Depression

- Fatigue and depression highly related
- Every 1 point increase in fatigue results in a 0.5 point increase in depressive symptoms
- Every 1 point increase in depressive symptoms results in a 0.7 point increase in fatigue.