

**Running head: MS physiological and perceived fall risk**

**Title: The relationship between physiological and perceived fall risk in people with multiple sclerosis: Implications for assessment and management**

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**Authors:** Hilary Gunn PhD<sup>1\*</sup>, Michelle Cameron MD<sup>2</sup>, Phu Hoang PhD<sup>3,4</sup>, Stephen Lord PhD<sup>3</sup>, Steve Shaw PhD<sup>1</sup>, Jennifer Freeman PhD<sup>1</sup>

**Academic Institutions:**

1: School of Health Professions, Plymouth University, UK

2: Oregon Health & Science University and VA Portland Health Care Service, Portland, Oregon, USA

3: Neuroscience Research Australia, Sydney, Australia

4: Australian Catholic University, Sydney, Australia

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2 **Title: The relationship between physiological and perceived fall risk in people**  
3 **with multiple sclerosis: implications for assessment and management**

4

5 **Abstract**

6 **Objective**

7 This study evaluated the relationship between physiological and perceived fall risk in  
8 people with MS.

9 **Design**

10 Secondary analysis of data from prospective cohort studies undertaken in Australia,  
11 United Kingdom and the United States.

12 **Setting**

13 Community

14 **Participants**

15 416 ambulatory people with MS (age 51.5 ±12.0 years; 73% female; 62% relapsing-  
16 remitting MS; 13.7 ±9.9 years disease duration).

17 **Interventions**

18 Not applicable

19 **Outcome measures**

20 All participants completed measures of physiological (Physiological Profile  
21 Assessment (PPA)) and perceived (Falls Efficacy Scale-international (FESi)) fall risk  
22 and prospectively recorded falls for three months.

23 **Results**

24 155 (37%) of the participants were recurrent fallers (≥2 falls). Mean PPA and FESi  
25 scores were high (PPA 2.14±1.87, FESi 34.27±11.18). The PPA and the FESi  
26 independently predicted faller classification in logistic regression, which indicated

27 that the odds of being classified as a recurrent faller significantly increased with  
28 increasing scores (PPA Odds Ratio 1.30 (95%CI 1.17-1.46), FESi Odds Ratio 1.05  
29 (95% CI 1.03-1.07)).

30 Classification and regression tree analysis divided the sample into four groups based  
31 on cut-off values for the PPA: (1) low physiological/ low perceived risk (PPA <2.83,  
32 FESi <27.5), (2) low physiological/ high perceived risk (PPA <2.83, FESi >27.5), (3)  
33 high physiological/ low perceived risk (PPA >2.83, FESi <35.5), and (4) high  
34 physiological/ high perceived risk (PPA <2.83, FESi >35.5). Over 50% of participants  
35 had a disparity between perceived and physiological fall risk; most were in group 2. It  
36 is possible that physiological risk factors not detected by the PPA may also be  
37 influential.

### 38 **Conclusion**

39 This study highlights the importance of considering *both* physiological and perceived  
40 fall risk in MS, and that further research is needed to explore the complex inter-  
41 relationships of perceptual and physiological risk factors in this population. This  
42 study also supports the importance of developing behavioral and physical  
43 interventions which can be tailored to the individual's need.

44

### 45 **300 words**

46 **Keywords:** Multiple sclerosis; Accidental falls; Physiological balance; Rehabilitation;  
47 Cohort study

48

### 49 **Abbreviations:**

50 AUS: Australia; CART: Classification and Regression Tree; EDSS: Expanded  
51 Disability Status Scale; MS: Multiple sclerosis; PPA: Physiological Profile

52 Assessment; SWIMS: South-West Impact of MS study; UK: United Kingdom; US:

53 United States

54

55

## 56 **Introduction**

57

58 Multiple sclerosis (MS) affects approximately 2.3 million people worldwide<sup>1</sup>. People  
59 with MS consistently report impaired mobility is one of their most concerning  
60 problems<sup>2</sup>, impacting not only access to the community but also quality of life<sup>3</sup>.

61 Impaired balance and falls are common in people MS and contribute to mobility  
62 loss<sup>4,5</sup>. Given the significant economic, personal, and social costs associated with  
63 impaired mobility, balance and falls<sup>3</sup>, effective interventions are a high priority<sup>6</sup>.

64

65 Evidence from other populations suggests that individualised fall risk-factor  
66 identification is important for developing targeted interventions to optimise  
67 rehabilitation outcomes<sup>7</sup>. Identified risk factors for falls in people with MS include  
68 physiological attributes such as gait disturbance, spasticity, slow reaction time, and  
69 increased postural sway<sup>8,9</sup> as well as psychological factors such as fear of falling<sup>12</sup>  
70 and reduced falls self-efficacy<sup>13 12</sup>. The Physiological Profile Assessment (PPA), a  
71 standardised five-item test of sensorimotor and balance performance which includes  
72 measures of proprioception, reaction time, visual contrast sensitivity, muscle  
73 strength, and postural sway, can measure physiological contributors to fall risk<sup>13</sup>.

74 Although the PPA was originally developed to assess fall risk in older adults, it has  
75 been validated in people with MS, where scores show moderate correlation with fall  
76 risk<sup>8,9</sup>. MS specific, age adjusted reference values for the PPA composite scores  
77 have also been established<sup>14</sup>. The Falls Efficacy Scale-international (FESi)<sup>15</sup>, a 16  
78 item questionnaire, is recommended as a measure of perceived risk of falls. The  
79 FESi has established validity and reliability in people with MS<sup>16,17</sup> and FESi scores

80 are associated with prospectively recorded falls in this group (Odds Ratio (OR) 1.22,  
81 95% Confidence Interval (CI) 1.04-1.43)<sup>18</sup>.

82

83 In some people, physiological and perceived fall risk differ. Delbaere et al.  
84 highlighted such disparities in a cohort of community dwelling older adults<sup>19</sup>. They  
85 proposed categorizing individuals into four distinct groups based on their  
86 physiological fall risk as measured by the PPA, and their perceived fall risk as  
87 measured by the FESi. This study also identified cut-off points in the two measures  
88 to identify the different groupings. These findings are relevant to practice, and may  
89 inform patient management. For example, providing challenging balance exercise to  
90 people with high perceived risk but relatively low physiological risk may heighten  
91 their feelings of concern, and potentially reduce engagement in the program. In  
92 contrast, approaches aimed at increasing self-efficacy and use of falls management  
93 strategies are unlikely to be effective in people who do not perceive themselves to be  
94 at high risk of falling.

95

96 Although there is increasing evidence identifying MS-specific risk factors for falling,  
97 little is currently known about the relationship between perceived and physiological  
98 fall risk. Our aim was to evaluate this relationship using a similar methodology to  
99 Delbaere et al.<sup>19</sup>. The specific objectives were to assess whether there are  
100 disparities between perceived and physiological fall risk in people with MS, and to  
101 explore potential contributory factors. The findings could be used to guide  
102 individualised assessment and development of tailored fall risk management  
103 strategies.

104

105 **Methods**

106

107 *Data Sources*

108 This analysis used data from prospective cohort studies of falls and fall risk in people  
109 with MS carried out in Australia (AUS)<sup>8</sup>, the United Kingdom (UK)<sup>9</sup> and the United  
110 States (US)<sup>20</sup>. All relevant local ethical permissions were obtained for all three  
111 studies (AUS: HC09253; UK: 10/H0203/66 and US: E7244W). All participants gave  
112 written informed consent.

113

114 *Participants*

115 Study participants were 416 people with MS (210 AUS, 148 UK and 58 US)  
116 diagnosed by standardized criteria<sup>21,22</sup> and aged 18 years and older. All MS  
117 subtypes were included. In the UK and the US samples, disease severity was  
118 measured using the Expanded Disability Status Scale (EDSS)<sup>23</sup>, assessed either  
119 face-to-face by a trained clinician or using the self-report EDSS by telephone  
120 interview<sup>24</sup>. In Australia, the Disease Steps Scale<sup>25</sup> was used during a face-to-face  
121 assessment and converted to EDSS by mobility criteria<sup>26</sup>.

122

123 Common exclusion criteria were inability to understand and sign an informed  
124 consent or being unable to follow test instructions. Additional local inclusion criteria  
125 were:

- 126
- 127 • Australia: ability to stand unsupported for 30 seconds and walk 10 metres with  
128 or without a mobility aid (i.e. Disease Steps 0-5).
  - UK: EDSS score between 3.5 and 6.5.

- 129       • US: EDSS score of 6.0 or less, upper age limit of 50, relapse free for 30 days  
130           prior to baseline examination.

131

### 132 *Recruitment*

133 The Australian sample was recruited in a single out-patient MS physiotherapy clinic  
134 in Sydney. The UK sample was recruited via invitation letters from their local  
135 neurologist and an advertisement in the newsletter of the South West Impact of MS  
136 (SWIMS) project<sup>27</sup> which is accessed by over 1500 people with MS living in the  
137 South West of England. The US sample was recruited from specialty MS center  
138 outpatient clinics at a Department of Veterans Affairs medical centre, a university  
139 medical centre in the Northwest of the United States and the surrounding  
140 community.

### 141 *Measures*

142 Demographic data including age, gender, years since MS diagnosis, MS subtype,  
143 use of walking aids, and retrospective fall history were collected at baseline using a  
144 structured questionnaire.

145

### 146 Physiological fall risk: Physiological Profile Assessment (PPA)

147 The PPA was developed as a low-tech, clinically feasible method to assess fall risk<sup>13</sup>  
148 in older adults and has been shown to predict falls in people with MS<sup>8,9</sup>. The five  
149 components of the PPA are: (1) proprioception, measured with a lower limb  
150 matching task; (2) quadriceps muscle strength, measured isometrically in the  
151 dominant leg while participants are seated; (3) simple reaction time, measured with a  
152 light as stimulus and a finger press response; (4) visual contrast sensitivity as  
153 measured by the Melbourne edge test; and (5) postural sway, measured with a sway



154 meter recording displacements of the body at the level of the pelvis while participants  
155 stand on a foam rubber mat with eyes open. The five PPA components are  
156 weighted to compute a composite PPA fall-risk score expressed in standard (z-  
157 score) units; with higher scores indicating worse performance.

158

159 Perceived fall risk: Falls Efficacy Scale–international (FESi)<sup>15</sup>

160 The FESi is a 16-item questionnaire that asks participants to indicate their level of  
161 concern about falling for a range of activities of daily living (such as cleaning the  
162 house or going out on a social event). Each activity is scored on a four-point scale (1  
163 = not at all concerned to 4 = very concerned).

164

165 Falls

166 Falls were assessed retrospectively and prospectively. For retrospective assessment  
167 participants were asked if they had fallen in the previous three months (yes or no).  
168 For prospective assessment, participants recorded falls in the subsequent three  
169 months using a daily diary<sup>28</sup>. Participants received falls diary sheets, written  
170 instructions and reply-paid return envelopes; in AUS and USA these were returned  
171 monthly, the UK diaries were returned every two weeks. A reminder telephone call or  
172 email was sent to participants whose diary returns fell behind schedule<sup>28</sup>. In AUS, a  
173 fall was defined as “unintentionally coming to the ground or other lower level and  
174 other than as a consequence of sustaining a violent blow, loss of consciousness, or  
175 sudden onset of paralysis as in stroke or epileptic seizure”<sup>29</sup>. In the UK and US, a fall  
176 was defined as “a slip or trip in which participants came to rest on the ground or floor  
177 or lower level”<sup>15</sup>. In line with recommendations, recurrent fallers were defined as

178 those who fell twice or more in the three month retrospective and prospective  
179 periods<sup>30</sup>.

180

### 181 *Data analysis*

182 All statistical analyses were performed using SPSS V23 (IBM, Chicago, USA). Data  
183 were summarized using frequencies and percentages, mean and standard deviation  
184 or median and interquartile range (IQR) as appropriate. Given the low numbers of  
185 missing data, missing values were imputed using the overall mean from the rest of  
186 the sample<sup>31</sup>.

187

188 Baseline differences between the three geographical samples were assessed by  
189 either univariate analyses of variance (ANOVA) or by  $\chi^2$  tests. Subsequently, logistic  
190 regression was used to calculate univariate and bivariate odds ratios for the  
191 associations between physiological fall risk (PPA) and perceived fall risk (FESi) with  
192 fall classification.

193

194 A classification and regression tree (CART) analysis was undertaken to develop a  
195 framework to classify participants into groups based on their physiological and  
196 perceived fall risk. CART analysis aims to develop subsets of a data set, which are  
197 as homogenous as possible with respect to the target variable, through repeated  
198 analyses based on predictor variables<sup>32</sup>. Confirmation of the CART model was  
199 performed using cross-validation methods<sup>33</sup>. Subsequently, the associations  
200 between the CART groupings were explored. For categorical variables, the  
201 groupings were analysed using Fishers exact test. For continuous variables, the

202 differences between the CART groups were compared using ANOVA, with between  
203 group comparisons analysed using a Bonferroni corrected  $p$  value.

204

## 205 **Results**

206

207 A total of 416 participants were included in the analyses. Of these, 10 (<3%) had  
208 missing FESi data. Participants had a mean age of 52 years (range 21-84 years),  
209 305 (73%) were female, and 257 (62%) were classified as having relapsing-remitting  
210 MS (table 1). Approximately one third (155 participants, 37.3%) reported  $\geq 2$  falls in  
211 the three-month follow-up periods. There were significant differences between the  
212 cohorts for all characteristics except gender.

213

214 *Insert table 1 about here*

215

### 216 *Association between PPA/FESi and prospective falls*

217 Univariate logistic regression confirmed higher PPA and FESi scores increased the  
218 odds of being classified as a recurrent faller (PPA OR 1.30 (95%CI 1.17-1.46, FESi  
219 OR 1.05 (95% CI 1.03-1.07). Bivariate regression analysis demonstrated that both  
220 the PPA and FESi scores were independent predictors of recurrent falls, with PPA  
221 making the greater contribution to the model (standardised B, table 2). An overall  
222 indication of goodness of fit of the model was obtained through the use of the  
223 Hosmer and Lemeshow statistic. The non-significant result of  $\chi^2$  10.87, df 8  $p=0.21$   
224 indicates there is no evidence of lack of fit based on this statistic.

225

226 *Insert table 2 about here*

227

## 228 *Classification and regression tree analysis*

229 The CART analysis divided the sample into four groups (figure 1).

- 230 • Group 1: low physiological risk/low perceived risk;
- 231 • Group 2: low physiological risk/high perceived risk;
- 232 • Group 3: high physiological risk/low perceived risk;
- 233 • Group 4: high physiological risk/high perceived risk

234 The model and cross-validation samples performed similarly, with an overall model  
235 error rate of 0.31 (Standard error (SE) 0.02), compared with the cross-validation  
236 error rate of 0.35 (SE 0.02). The PPA cut-off point for splitting the group into low and  
237 high physiological risk was 2.83. This cut-off point classified most participants (69%  
238 (n=288)) as having 'low' physiological fall risk. The cut-off point to distinguish low  
239 and high levels of perceived fall risk using the FESi differed according to  
240 physiological risk; for those with a low physiological risk the FESi cut-off point was  
241 27.5, whilst for those with a high physiological risk the cut-off point was 35.5.

242 The two largest groups comprised participants with a high perceived fall risk (Groups  
243 2 and 4). In Group 4 (high physiological risk/ high perceived risk), 55 (64%)  
244 prospectively reported two or more falls, suggesting that these individuals were  
245 insightful about their level of risk. In contrast, in Group 2 (low physiological risk/ high  
246 perceived risk), 106 (63%) prospectively reported fewer than 2 falls. As with Group 4,  
247 most of the participants in Group 1 (low physiological/ low perceived risk) appeared  
248 to have an accurate perception of their fall risk, as 84% (n=100) had fewer than 2  
249 falls in the recording period. The smallest group were those classified as having high  
250 physiological risk, but low levels of perceived fall risk (Group 3, n=42). Of these, 18  
251 (43%) were classified as recurrent fallers.

252

253 *Insert Figure 1 about here*

254

255

256 *Associations between CART groupings and participant characteristics (table 3)*

257 Participants in Group 1 (low physiological risk/ low perceived risk) were, on average,

258 younger (mean age 47.2 (SD 12.6)) and less disabled (group median EDSS 2.5, IQR

259 2.0-3.5) than in the other groups. In contrast, Group 2 participants (low physiological

260 risk/ high perceived risk) were more likely to report having fallen in the previous year

261 than those in Group 1 (113 (67%) fallers in Group 2 compared with 56 (47% in

262 Group 1), and had similar rates of walking aid use to Groups 3 and 4 (those

263 classified at high physiological risk of falling). Groups 3 and 4 were similar to each

264 other except that Group 4 participants were more likely to report using a walking aid.

265 The distribution of participants amongst the CART groupings varied with recruiting

266 site, with proportionally more participants from the USA in Group 1, and a greater

267 proportion of UK participants in Groups 2 and 4.

268

269 *Insert table 3 about here*

270

## 271 **Discussion**

272

273 To our knowledge this paper presents the first analysis of the relationship between

274 physiological and perceived fall risk and prospectively reported falls in people with

275 MS. The cohort included ambulatory people with a range of disability levels and all

276 MS subtypes.

277

278 Our cohort's mean PPA score was 2.14 (SD 1.87), mean FESi score was 34.27  
279 (SD 11.18) and 37.3% of the group fell at least twice in 3 months. These values are  
280 all high compared to similar aged healthy individuals<sup>14</sup>, and other groups at  
281 increased risk of falling (including people following a stroke<sup>34</sup> and older adults<sup>35</sup>). The  
282 mean PPA and FESi values in this cohort were also higher than those reported in  
283 other MS cohorts (e.g. Sosnoff et al<sup>36</sup> and Carling et al<sup>37</sup>). These differences most  
284 likely relate to differences in sample characteristics. Our study had a higher  
285 proportion of people with SPMS than Sosnoff et al's cohort<sup>36</sup> (proportion of people  
286 with SPMS 24% vs. 15%) and a lower average EDSS than Carling et al's cohort<sup>37</sup>  
287 (Median EDSS 4.0, IQR 2.5 vs. 6.0, IQR 3.5).

288

289 The CART analysis categorized the cohort into four groups based on physiological  
290 and perceived fall risk scores and identified cut-off values for high and low risk.  
291 These cut-off values are higher than those obtained in Delbaere's analysis in older  
292 adults<sup>19</sup>. It is possible that this is because our MS cohort were able to develop  
293 strategies to manage their physical impairments more effectively to avoid falls than  
294 older people. However, the high overall values of perceived fall risk highlight that  
295 falls are an 'ever present reality' for most people with MS<sup>38,p151</sup>, thus the cut-off to  
296 differentiate those with a 'high' or 'low' perceived fall risk is made against a  
297 background of high concern across the cohort. As cut-off values to distinguish fallers  
298 and non-fallers in the PPA or FESi have not previously been reported in MS, further  
299 research to explore the validity of our results, particularly of the proposed cut-offs, is  
300 recommended.

301

302 In our analysis, over half of the participants had disparities between physiological  
303 and perceived risk (i.e. those in Groups 2 and 3). This is in contrast to Delbaere's  
304 study, where over two thirds had concurrent physiological and perceived fall risk<sup>19</sup>.  
305 Various factors could underlie the greater disparity in our cohort. Importantly,  
306 cognitive impairment, which is common in people with MS<sup>39</sup>, may have contributed to  
307 the disparity between physiological and perceived risk factors. Whilst all three  
308 samples collected cognitive data, variations in the measures used meant we were  
309 unable to include this factor in our study. Exploration of this in future studies is  
310 important as it is likely that this could influence management.

311

312 In our analysis, 63 (37%) of the participants in Group 2 (low physiological/ high  
313 perceived risk) were classified as recurrent fallers, which represents 41% of  
314 recurrent fallers across the whole cohort. Although these individuals were classified  
315 by the PPA as having 'low' physiological risk, the cut-off point (2.83) was relatively  
316 high and it is likely that for at least some of them, physiological factors in addition to  
317 those assessed by the PPA contributed to fall risk. For example, impaired gait,  
318 spasticity and dual task interference have all been identified as fall risk factors in  
319 prospective MS cohort studies but are not captured by the PPA<sup>8,9,12</sup>. It is essential  
320 that the complexity of factors contributing to risk of falls is recognised during the  
321 assessment process and when developing falls management interventions.

322

323 Conversely, over 60% (n=106) of Group 2 (low physiological/ high perceived risk) did  
324 not report recurrent falls. Despite the moderate level of disability within this group  
325 (median EDSS 4.0 (IQR 2.5-5.5)), 107 people (63%) reported using walking aids,  
326 which was a similar proportion to those doing so who were classified at high

327 physiological risk of falls. Whilst the three-month reporting period may have been  
328 too short to capture recurrent falls in some individuals, it could be that the high level  
329 of perceived risk made people take less risk. This emphasises the importance of  
330 evaluating individual's perceptions, alongside early education about fall prevention,  
331 with a key aim of maintaining physical activity levels and avoiding activity  
332 curtailment<sup>40,41</sup>. Accurate long-term monitoring, and interventions focused on  
333 increasing confidence and knowledge about effective risk management could be  
334 particularly appropriate for these individuals.

335

336 While perceived risk was greater than physiological risk for most participants with a  
337 disparity, 42 (10%) individuals were classified as having a high physiological risk but  
338 low perceived fall risk (Group 3). Within this group, over half reported no falls,  
339 suggesting their lower levels of concern were probably justified, for example they  
340 may have adopted effective fall prevention strategies. However, given the high mean  
341 PPA in this group, it is likely that encouraging the non-recurrent fallers to address  
342 modifiable risk factors would still be warranted to prevent future falls. In contrast, 18  
343 individuals in Group 3 reported recurrent falls. Identifying people who see  
344 themselves as being at unduly low risk is important, since it is known that the  
345 perceived relevance of a programme influences engagement<sup>42-44</sup>. For these  
346 individuals, it may be that management could initially focus on identifying problems  
347 with balance and stability before then supporting the participant to undertake  
348 appropriate risk management decisions based on an accurate assessment of their  
349 physical ability.

350



351 Individuals in Groups 1 and 4 were classified as having concurrent physiological and  
352 perceived fall risk. Within Group 1, some participants reported falling despite being  
353 classified as having both low physiological and low perceived risk of falling. These  
354 participants, on average, were relatively young with a low disease severity. It is  
355 postulated that an early intervention approach, which emphasizes health promotion  
356 alongside preventative strategies, would be beneficial for this group to minimise the  
357 long-term negative impact that falls may have on participation levels and quality of  
358 life. Group 4 participants had the highest level of disability, greatest proportion of  
359 individuals with progressive MS and the highest proportion of people reporting  
360 having fallen in the past year. It is likely that falls management interventions for these  
361 individuals would need to address multiple risk factors, carefully balancing benefit  
362 and burden.

363

### 364 **Study Limitations**

365 This study has several limitations. Firstly, our cohort comprised participants who  
366 were recruited to separate studies in three countries. It is likely that the variations in  
367 recruitment criteria and baseline characteristics between the groups contributes to  
368 the different proportions of participants from each country seen in the CART  
369 analyses, however, other social or geographical factors cannot be discounted.

370 In addition, our sample did not include any individuals with an EDSS >6.5. It is likely  
371 that the factors contributing to falls in non-ambulatory individuals are different from  
372 those in ambulatory individuals<sup>45</sup>. The findings may therefore not generalize to  
373 people whose mobility is severely affected. In addition, while our analysis was able  
374 to explore the relationship between physiological and perceived fall risk as indicated  
375 by the PPA and the FESi, both of these measures do not capture all of the complex

376 factors contributing to fall risk in MS. Given the high rate of comorbidities<sup>46</sup>, and the  
377 prevalence of issues such as cognitive dysfunction and depression<sup>39</sup>, further  
378 exploration is warranted. In addition, limitations in the PPA and the FESi could result  
379 in inaccurate classification for some individuals. For example, the PPA may not  
380 detect subtle balance deficits that can be captured by instrumented tests<sup>47</sup> and, may  
381 not capture MS-specific physiological risk factors (e.g. spasticity, internuclear  
382 ophthalmoplegia), that may be significant. Finally, it is important to emphasize that,  
383 while this analysis presents cut-off points which classify individuals into groups  
384 based on physiological and perceived fall risk, the results represent an *estimate* of  
385 values which could differentiate those at lower and higher risk. Our intention was to  
386 provide an initial exploration of the relationship between physiological and perceived  
387 fall risk in MS, and to suggest ways that assessment findings could be used to inform  
388 therapists' management plans. It is likely that other factors, not included within our  
389 analyses, such as cognition, disability level and physical environment, may also  
390 influence falls. Additional work to evaluate the relationship between the multiple  
391 factors that are likely to influence risk of falling and engagement with fall prevention  
392 activities is essential.

393

## 394 **Conclusion**

395

396 These findings highlight the importance of considering both physiological and  
397 perceived fall risk when evaluating people with MS. Whilst both the PPA and the  
398 FESi independently predicted falls in this cohort, the subsequent classification and  
399 regression tree analysis highlighted an interrelationship between the two factors  
400 which could have important implications for management. These findings are

401 consistent with the geriatrics literature and its growing focus on targeted,  
402 individualized fall prevention, addressing both factors<sup>48</sup>. These findings also  
403 underline the complexity of falls in MS and the importance of detailed description,  
404 evaluation and targeting of fall prevention interventions to optimize their  
405 effectiveness.

406

407 3695 words

408 **Conflict of interests**

409 Stephen Lord declares the Physiological Profile Assessment (NeuRA FallScreen) is  
410 commercially available through Neuroscience Research Australia.

411

412

## References

1. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor B V, et al. 2014. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology*. 83(11):1022–4.
2. Jones CA, Pohar SL, Warren S, Turpin KVL, Warren KG. 2008. The burden of multiple sclerosis: a community health survey. *Health Qual Life Outcomes*. 6(1):1.
3. Sutliff MH. 2010. Contribution of impaired mobility to patient burden in multiple sclerosis. *Curr Med Res Opin*. 26(1):109–19.
4. Soyuer F, Mirza M, Erkorkmaz U. 2006. Balance performance in three forms of multiple sclerosis. *Neurol Res*. 28(5):555–62.
5. Gunn H, Creanor S, Haas B, Marsden J, Freeman J. 2014. Frequency, characteristics and consequences of falls in multiple sclerosis: findings from a cohort study. *Arch Phys Med Rehabil*. 95(2):538–45.
6. Royal College of Physicians. 2011. The national audit of services for people with multiple sclerosis 2011. 2011.
7. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. 2012. Interventions for preventing falls in older people living in the community.
8. Hoang PD, Cameron MH, Gandevia SC, Lord SR. 2013. Neuropsychological, balance and mobility risk factors for falls in people with multiple sclerosis: a prospective cohort study. *Arch Phys Med Rehabil*. 95(3):480–6.
9. Gunn H, Creanor S, Haas B, Marsden JF, Freeman J. 2013. Risk factors for falls in Multiple Sclerosis: an Observational Study. *Mult Scler*. 19(14):1913–22.

10. Tinetti ME, Richman D, Powell L. 1990. Falls Efficacy as a Measure of Fear of Falling. *J Gerontol.* 45(6):P239–43.
11. Batchelor F, Hill K, Mackintosh S, Said C. 2012. Falls efficacy and fear of falling in stroke: issues with measurement and interpretation. *Disabil Rehabil.* 34(8):704; author reply 705.
12. Nilsagard Y, Lundholm C, Denison E, Gunnarsson LG. 2009. Predicting accidental falls in people with multiple sclerosis- a longitudinal study. *Clin Rehabil.* 23(3):259–69.
13. Lord SR, Menz HB, Tiedemann A. 2003. A Physiological Profile Approach to Falls Risk Assessment and Prevention. *Phys Ther.* 83(3):237–52.
14. Hoang PD, Baysan M, Gunn H, Cameron M, Freeman J, Nitz J, et al. 2016. Fall risk in people with MS: A Physiological Profile Assessment study. *Mult Scler J - Exp Transl Clin.* 2(0):1898–912.
15. Lamb S, Jørstad-Stein E, Hauer K, Becker C. 2005. Development of a Common Outcome Data Set for Fall Injury Prevention Trials: The Prevention of Falls Network Europe Consensus. *J Am Geriatr Soc.* (9):1618–22.
16. Delbaere K, Close JCT, Mikolaizak AS, Sachdev PS, Brodaty H, Lord SR. 2010. The Falls Efficacy Scale International (FES-I). A comprehensive longitudinal validation study. *Age Ageing.* 39(2):210–6.
17. van Vliet R, Hoang P, Lord S, Gandevia S, Delbaere K. 2013. The Falls Efficacy Scale International: A Cross-Sectional Validation in People with Multiple Sclerosis. *Arch Phys Med Rehabil.* 94(5):883–9.
18. Mazumder R, Lambert WE, Nguyen T, Bourdette DN, Cameron MH. 2015. Fear of Falling is associated with Recurrent Falls in People with Multiple Sclerosis: A Longitudinal Cohort Study. *Int J MS Care.* (4):164–70.

19. Delbaere K, Close JCT, Brodaty H, Sachdev P, Lord SR. 2010. Determinants of disparities between perceived and physiological risk of falling among elderly people: cohort study. *BMJ*. 341:c4165.
20. Cameron MH, Thielman E, Mazumder R, Bourdette D. 2013. Predicting falls in people with multiple sclerosis: fall history is as accurate as more complex measures. *Mult Scler Int*. Sept 26(online article).
21. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. 1983. New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. *Ann Neurol*. 13(3):227–31.
22. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 69(2):292–302.
23. Kurtzke JF. 1983. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*. 33(11):1444-.
24. Lechner-Scott J, Kappos L, Hofman M, Polman CH, Ronner H, Montalban X, et al. 2003. Can the Expanded Disability Status Scale be assessed by telephone? *Mult Scler*. 9(2):154–9.
25. Hohol MJ, Orav EJ, Weiner HL. 1999. Disease steps in multiple sclerosis: a longitudinal study comparing Disease Steps and EDSS to evaluate disease progression. *Mult Scler J*. 5(5):349–54.
26. Learmonth Y, Motl R, Sandroff B, Pula J, Cadavid D. 2013. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMV Neurol*. :13:37.
27. Zajicek JP, Ingram WM, Vickery J, Creanor S, Wright DE, Hobart JC. 2010. Patient-orientated longitudinal study of multiple sclerosis in south west

- England (The South West Impact of Multiple Sclerosis Project, SWIMS) 1: protocol and baseline characteristics of cohort. *BMC Neurol.* 10(1):88.
28. Perry L, Kendrick D, Morris R, Dinan S, Masud T, Skelton D, et al. 2012. Completion and Return of Fall Diaries Varies With Participants' Level of Education, First Language, and Baseline Fall Risk. *Journals Gerontol Ser A Biol Sci Med Sci.* 67A(2):210–4.
  29. Gibson M, Isaacs B, Radebaugh T. 1987. The prevention of falls in later life. A report of the Kellogg International Work Group on the prevention of falls by the elderly. *Dan Med Bull.* 34:1–24.
  30. Coote S, Sosnoff JJ, Gunn H. 2014. Fall Incidence as the Primary Outcome in Multiple Sclerosis Falls-Prevention Trials. *Int J MS Care.* 16(4):178–84.
  31. van der Heijden GJMG, T. Donders AR, Stijnen T, Moons KGM. 2006. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: A clinical example. *J Clin Epidemiol.* 59(10):1102–9.
  32. Ture M, Kurt I, Turhan Kurum A, Ozdamar K. 2005. Comparing classification techniques for predicting essential hypertension. *Expert Syst Appl.* 29(3):583–8.
  33. Teng J-HH, Lin K-CC, Ho B-SS. 2007. Application of classification tree and logistic regression for the management and health intervention plans in a community-based study. *J Eval Clin Pract.* 13(5):741–8.
  34. Belgen B, Beninato M, Sullivan PE, Narielwalla K. 2006. The association of balance capacity and falls self-efficacy with history of falling in community-dwelling people with chronic stroke. *Arch Phys Med Rehabil.* 87(4):554–61.
  35. Siong K-H, Kwan MM-S, Lord SR, Lam AK-C, Tsang WW-N, Cheong AM-Y.

2015. Fall risk in Chinese community-dwelling older adults: A physiological profile assessment study. *Geriatr Gerontol Int.* :259–65.
36. Sosnoff JJ, Finlayson M, McAuley E, Morrison S, Motl RW. 2014. Home-based exercise program and fall-risk reduction in older adults with multiple sclerosis: phase 1 randomized controlled trial. *Clin Rehabil.* 28(3):254–63.
37. Carling A, Forsberg A, Gunnarsson M, Nilsagard Y, Nilsagård Y. 2016. CoDuSe group exercise programme improves balance and reduces falls in people with multiple sclerosis: A multi-centre, randomized, controlled pilot study. *Mult Scler J.* 23(10):1–11.
38. Peterson EW, Kielhofner G, Tham K, von Koch L. 2010. Falls Self-Efficacy Among Adults With Multiple Sclerosis: A Phenomenological Study. Peterson EW, Kielhofner G, Tham K, von Koch L, editors. *OTJR Occup Particip Heal.* 30(4):148–58.
39. Marrie RA, Reingold S, Cohen J, Stuve O, Trojano M, Sorensen PS, et al. 2015. The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review. *Mult Scler.* 21(3):305–17.
40. Peterson EW, Cho CC, Finlayson ML. 2007. Fear of falling and associated activity curtailment among middle aged and older adults with multiple sclerosis. *Mult Scler.* 13(9):1168–75.
41. Matsuda PN, Shumway-Cook A, Ciol MA, Bombardier CH, Kartin DA. 2012. Understanding Falls in Multiple Sclerosis: Association of Mobility Status, Concerns About Falling, and Accumulated Impairments. *Phys Ther.* 92(3):407–15.
42. Peterson EW, Ben Ari E, Asano M, Finlayson ML. 2013. Fall Attributions among Middle Aged and Older Adults with Multiple Sclerosis. *Arch Phys Med*



- Rehabil. 94(5):890–5.
43. Bunn F, Dickinson A, Barnett-page E, Mcinnes E, Horton K. 2008. A systematic review of older people ' s perceptions of facilitators and barriers to participation in falls-prevention interventions A systematic review of older people's perceptions of facilitators and barriers to participation in falls-prevention inter. *Ageing Soc.* 28(4):449–72.
  44. Mihaljcic T, Haines TP, Ponsford JL, Stolwyk RJ. 2017. Investigating the relationship between reduced self-awareness of falls risk, rehabilitation engagement and falls in older adults. *Arch Gerontol Geriatr.* 69:38–44.
  45. Nelson AL, Groer S, Palacios P, Mitchell D, Sabharwal S, Kirby RL, et al. 2010. Wheelchair-Related Falls in Veterans With Spinal Cord Injury Residing in the Community: A Prospective Cohort Study. *Arch Phys Med Rehabil.* 91(8):1166–73.
  46. Marrie RA, Hanwell H. 2013. General health issues in multiple sclerosis: comorbidities, secondary conditions, and health behaviors. *Continuum (Minneap Minn).* 19(4 Multiple Sclerosis):1046–57.
  47. Martin CL, Phillips BA, Kilpatrick TJ, Butzkueven H, Tubridy N, McDonald E, et al. 2006. Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. *Mult Scler J.* 12(5):620–8.
  48. National Institute for Health and Clinical Excellence. 2013. Falls : assessment and prevention of falls in older people. NICE guideline 161. 2013.

1 **Figure Legends**

2

3 **Figure 1: Classification tree**

4 \*: "non-fallers" in this figure are those who reported ≤1 fall in the three-month reporting period

**Table 1: Sample Characteristics**

	Australia (n=210)	United Kingdom (n=148)	United States (n=58)	Total sample (n=416)
Age in years: Mean (range) <sup>*a</sup>	50.3 (21-73)	58 (33-84)	39.5 (22-50)	51.5 (21-84)
Gender F:M Ratio (%) <sup>ns; b</sup>	150:60 (71:29)	114:34 (77:23)	41:17 (71:29)	305:111 (73:27)
Years with MS: Mean (SD) <sup>*a</sup>	13.6 (8.9)	16.7 (10.9)	6.5 (5.8)	13.7 (9.9)
EDSS: Median (IQR) <sup>*a</sup>	3.5 (2.0-5.0)	5.5 (4.0-6.0)	3.0 (1.5-3.5)	4.0 (2.5-5.5)
Subtype: n (%) <sup>*b</sup>				
RRMS	160 (76.2)	42 (28.4)	55 (94.8)	257 (61.7)
SPMS	30 (14.3)	66 (44.6)	3 (5.2)	99 (23.8)
PPMS	19 (9.0)	37 (25)	0	56 (13.5)
Unknown	1 (0.5)	3 (2)	0	4 (0.9)
Mobility Aid Use: Y: N Ratio (%) <sup>*b</sup>	100:110 (48:52)	110:38 (74:26)	9:49 (16:84)	219:197 (53:47)
Retrospective falls history: Y:N (%) <sup>*b</sup>	152:58 (72:28)	85:63 (57:43)	30:28 (52:48)	267:149 (64:36)
Prospective falls history (3 months) n (%) <sup>*b</sup>				
0 falls	122 (58)	44 (30)	24 (41)	190 (46)
1 fall	31 (15)	26 (18)	14 (24)	71 (17)
2+ falls	57 (27)	78 (52)	20 (35)	155 (37)
PPA: Mean (SD) <sup>*a</sup>	2.32 (1.91)	2.45 (1.75)	0.74 (1.37)	2.14 (1.87)
FESi: Mean (SD) <sup>*a</sup>	34.93 (11.40)	37.06 (9.84)	25.59 (9.27)	34.37 (11.18)
F: Female; M: Male; n: Number; Y: Yes; N: No; SD: Standard Deviation; IQR: Inter-quartile range; EDSS: Expanded Disability Status Scale; RRMS: Relapsing-Remitting MS; SPMS: Secondary Progressive MS; PPMS: Primary Progressive MS; PPA: Physiological Profile Assessment; FESi: Falls Efficacy Scale (international);ns: no significant differences between the samples; *: significant differences between the samples; a: ANOVA; b: $\chi^2$				

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**Table 2: Logistic regression analysis examining association between physiological fall risk and perceived fall risk**

	B	S.E.	Wald	df	<i>p</i>	OR (95% CI)
PPA	0.196	0.061	10.51	1	0.001	1.217 (1.08-1.37)
FESi	0.034	0.010	10.64	1	0.001	1.035 (1.01-1.06)
Constant	-2.152	.367	34.47	1	<0.001	0.116

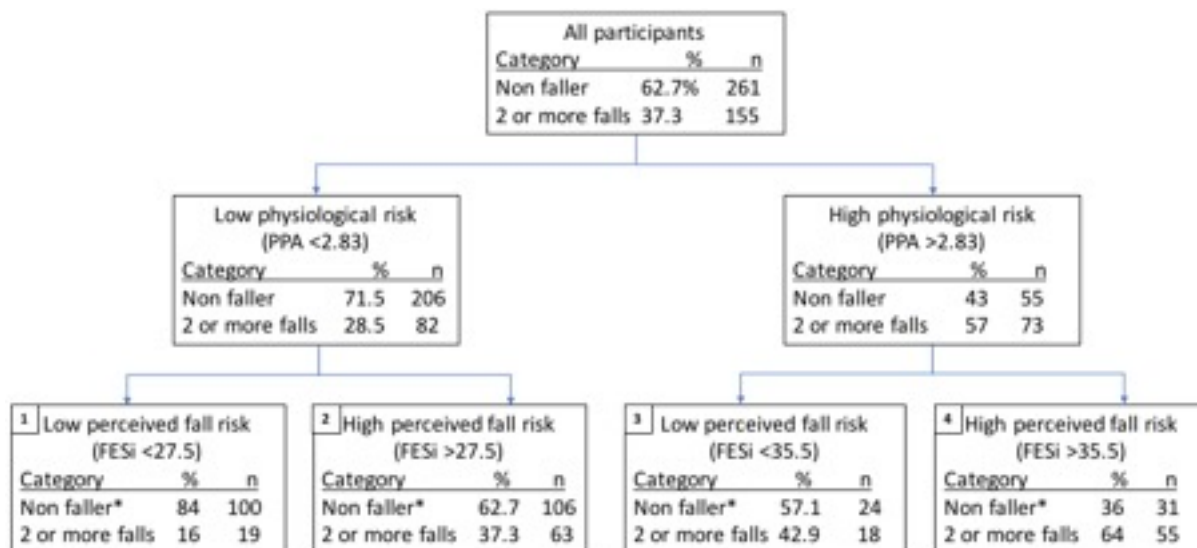
B: Standardised  $\beta$  coefficient; SE: Standard error; df: Degrees of freedom; OR: Odds ratio; CI: Confidence interval; PPA: Physiological Profile Assessment (physiological fall risk); FESi: Falls Efficacy Scale-international (perceived fall risk)

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**Table 3: Analysis of Classification and Regression Tree (CART) groupings**

	Low physiological fall risk			High physiological risk		
	Low perceived risk (n=119)	High perceived risk (n=169)	P value of difference	Low perceived risk (n= 42)	High perceived risk (n=86)	P value of difference
PPA (mean (SD))	0.77 (1.00)	1.38 (0.90)	<0.001 <sup>a</sup>	4.54 (1.41)	4.47 (1.27)	0.75 <sup>a</sup>
FESi (mean (SD))	22 (3.41)	38.7 (7.39)	<0.001 <sup>a</sup>	29 (4.71)	47 (6.99)	<0.001 <sup>a</sup>
EDSS (median (IQR))	2.5 (2.0-3.5)	4.0 (3.0-5.5)	<0.001 <sup>a</sup>	4.75 (3.5-6.0)	5.5 (4.0-6.0)	0.01 <sup>a</sup>
Age (mean (SD))	47 (12.6)	53 (11.2)	<0.001 <sup>a</sup>	54 (11.21)	55 (10.90)	0.57 <sup>a</sup>
Type of MS (n (%))						
	PP	6 (5)	<0.001 <sup>b</sup>	6 (14)	16 (19)	0.31 <sup>b</sup>
	RR	103 (87)		23 (55)	34 (40)	
	SP	9 (7)		13 (31)	35 (41)	
	Unknown	1 (1)		-	1 (1)	
Walking aid (n (%))						
	No aid	99 (83)	<0.001 <sup>b</sup>	17 (40)	19 (22)	0.07 <sup>b</sup>
	Any aid	20 (17)		25 (60)	67 (78)	
Self-report of any falls in the past year (n (%))						
	No falls	63 (53)	0.001 <sup>b</sup>	12 (29)	18 (21)	0.37 <sup>b</sup>
	≥1 fall	56 (47)		30 (71)	68 (79)	
Gender (n (%))						
	Male	37 (31)	0.35 <sup>b</sup>	8 (19)	23 (27)	0.38 <sup>b</sup>
	Female	82 (69)		34 (81)	63 (73)	
Site (n (%)) of cohort in each CART group						
	Australia	59 (28)	<0.001 <sup>b</sup>	25 (12)	44 (21)	0.32 <sup>b</sup>
	UK	21 (14)		16 (11)	39 (26)	
	USA	39 (67)		1 (2)	3 (5)	

<sup>a</sup>: analysis using ANOVA; <sup>b</sup>: analysis using Fisher's exact test;



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