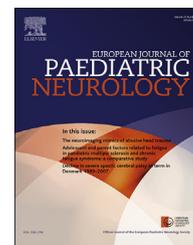




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Official Journal of the European Paediatric Neurology Society



## Original article

# Two-minute versus 6-minute walk distances during 6-minute walk test in neuromuscular disease: Is the 2-minute walk test an effective alternative to a 6-minute walk test?



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## ARTICLE INFO

## Article history:

Received 5 April 2018

Received in revised form

1 October 2018

Accepted 2 October 2018

## Keywords:

2-min walk test

6-min walk test

Neuromuscular disorders

Pediatrics

## ABSTRACT

Functional tests such as Motor Function Measure-32 (MFM-32), supine to stand, ascend/descend stairs permit the assessment of task-specific motor function in neuromuscular disease (NMD). The 6-min walk test (6MWT), though functional, is primarily used to assess endurance and disease progression in children with neuromuscular disorders. Barriers to 6MWT administration, in this population, can include reduced attention span due to age and inability to tolerate test length due to weakness. We propose task-specific functional deficits are related to endurance. Additionally, the 2-min walk test (2MWT) could effectively replace the 6MWT in this population. Seventy-seven participants, ages 5–18, with a variety of neuromuscular disorders performed the 6MWT, timed functional tests (TFT), and the MFM-32. Correlation and paired t-test analyses were used to compare the distance walked in the first 2 min (2MWD) to the distance walked in the entire 6 min (6MWD) and to the functional outcome measures above. The 2MWD strongly correlated with 6MWD and the other outcome measures. Paired t-test analysis also showed that the 2MWD did not differ from the distance walked in the last 2 min of the 6MWT. Although equivalence testing could not reject the claim that this difference exceeded the upper practical limit of 9.5 m, it only showed a modest overestimation of the 4-6MWD compared with the 2MWD. Together, our results support the ability of the 2MWD to predict the 6MWD, specifically in the pediatric neuromuscular disease population.

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<https://doi.org/10.1016/j.ejpn.2018.10.001>

1090-3798/Published by Elsevier Ltd on behalf of European Paediatric Neurology Society.

## 1. Introduction

The 6-min walk test (6MWT) was originally developed to assess walking capability, disease progression, and treatment efficacy<sup>1</sup> in adults with cardiopulmonary conditions.<sup>2</sup> It is now also used in individuals with neuromuscular disorders including Duchenne muscular dystrophy (DMD), Kennedy's disease, inclusion body myositis, and spinal muscular atrophy and in other neurological disorders such as multiple sclerosis.<sup>3–7</sup> Although previous work supports the validity and reliability of the 6MWT in the neuromuscular disease population, the length of this test limits the ability of participants to complete the assessment. Thirty percent of adolescents with neuromuscular disease (NMD) were shown to have behavioral challenges about three times greater than children without NMD.<sup>8</sup> Therefore, behavioral concerns (i.e., personality disorders, social problems, attention deficits, anxiety, and/or depression),<sup>8</sup> reduced ambulatory ability, and cognitive impairment, especially when fatigued, are of particular concern in the pediatric population. Thus, the 6MWT may not serve as an effective measure for monitoring disease progression and functional ability in the pediatric population.<sup>9,10</sup> However, the 2MWT is of shorter duration, objective, easily administered, and provides a standardized evaluation of functional capacity in populations with reduced ambulatory capability, including adults with neuromuscular disease.<sup>11–16</sup>

The 2-min walk test (2MWT, independent of 6MWT) has been used as an endurance measure in the aged population and in individuals with lower extremity amputations, cystic fibrosis, traumatic brain injury, and neurological disorders.<sup>11–18</sup> In support, a strong correlation between the distance walked in the 2MWT and 6MWT was observed in participants with sporadic inclusion body myositis<sup>11</sup> and a range of neuromuscular diseases.<sup>1</sup> Studies also showed strong predictability of 6MWT performance based on 2MWT results and vice versa.<sup>1,11</sup> Kosak and Smith<sup>19</sup> compared the validity of the 2, 6, and 12-min walk tests in adults recovering from a stroke and showed the distance walked in 2 min is highly correlated ( $r = 1.00$ ) with distance walked in 6 ( $r = 1.00$ ) and 12 min ( $r = 1.00$ ). We propose the results of this study will support the 2MWT as an effective alternative to the 6MWT in pediatric populations affected by neuromuscular disease, without compromising reliability. To date, the 2MWT has been shown to be reliable in pediatric patients with DMD compared to the 6MWT.<sup>10</sup> Similar results have been reported in pediatric patients with congenital myotonic dystrophy using the first 2-min distance of the 6MWT.<sup>20</sup>

Other clinical endpoints often used in NMD to assess motor function and functional ability include Motor Function Measure-32 (MFM-32) and Timed Functional Tests (TFTs).<sup>21</sup> The MFM-32 is a valid and reliable assessment of motor function and disease progression. It contains three motor function domains including supine-to-stand (domain 1, D1), axial and proximal (domain 2, D2), and distal (domain 3, D3).<sup>22</sup> This assessment is complemented by TFTs.<sup>22</sup> TFTs such as 10 m walk/run, supine-to-stand, and stair ascent/descent are task-specific tests that have been shown to correlate with 6MWD in DMD.<sup>23</sup> Previous work, in Inclusion Body Myositis (IBM), has shown the 2MWT is highly correlated with the

6MWT and other functional tests including stair ascent/descent thus making the 2MWT a potential alternative to the 6MWT. Similar to other NMDs, some of the patients with IBM were unable to finish the 6MWT due to fatigue. As such, the authors propose the 2MWT as a better alternative given it is “less fatiguing and better tolerated.”<sup>11</sup>

The primary objective of this study is to establish the utility of the 2MWT based on the correlation between 2-min walk distance (2MWD, the first 2 min of the longer 6-min walk) and the 6-min walk distance (6MWD) in children with various neuromuscular disorders, who performed the 6MWT. We use the term “distance” in both cases (2MWD, 6MWD) to highlight the difference between our study testing and previous reports, in which the 2MWT and the 6MWT were administered separately. The secondary objective is to compare the 2MWD and 6MWD to motor performance tests including the timed floor-to-stand test, timed ascent and descent of stairs, and the MFM-32.

## 2. Materials and methods

### 2.1. Participants

A total of 77 participants ages 5 to 18 enrolled in two natural history protocols at the National Institutes of Health between 2010 and 2015 after obtaining informed consent and/or assent previously approved by the Institutional Review Board. A variety of neuromuscular disorders were represented in this sample, including collagen VI-related dystrophy (COL6-RD), laminin alpha 2-related dystrophy (LAMA2-RD), limb-girdle muscular dystrophy (LGMD), and RYR1-related myopathies (RYR1-RM), among other neuromuscular diagnoses (Table 1). All enrolled ambulatory participants were able to walk 10 m (m) without the use of assistive devices and/or ankle-foot orthoses. Participants were evaluated using a battery of functional tests, including the 6MWT, timed functional tests, and the MFM-32.

### 2.2. 6MWT

The 6MWT was administered as per the American Thoracic Society (ATS) guidelines,<sup>24</sup> with the exception of pulse oximetry and use of a 30 m corridor. The modified ATS guidelines

**Table 1 – Demographic data. Study participants are grouped by diagnosis. Gender breakdown, age range, and mean age are presented. Several additional diagnoses are represented in the “other” category, including giant axonal neuropathy, LMNA-related myopathy, ACTA1 myopathy, and SEPN1 congenital muscular dystrophy.**

	Gender		Total	Mean Age (years) ± SD
	Male	Female		
RYR1-RM	10	9	19	9.7 ± 2.59
COL6-RD	9	8	17	10.7 ± 3.48
LAMA2-RD	0	3	3	8.1 ± 4.77
LGMD	5	2	7	8.1 ± 2.65
Other	20	11	31	10.5 ± 2.64
<b>Total</b>	<b>44</b>	<b>33</b>	<b>77</b>	<b>10.1 ± 2.93</b>

for rest were also not used. Upon arrival to the testing site, participants rested for 5 min. Blood pressure and heart rate were measured pre-exercise, immediately post-exercise, and after a 5-min recovery. Participants were instructed to walk “as quickly and safely as possible” in a 50 m corridor for 6 min. Participants did not receive external motivation but were informed of the remaining time during the test. The use of orthotics and assistive devices was not permitted. Participants were also given small objects to drop at the end of each minute as a marker of distance walked in that minute. If participants required rest during the course of the test, they were permitted to do so without sitting or leaning against objects. A clinician trailed slightly behind the participants to ensure safety and avoid a pacing bias. If the protocol required participants to return for subsequent visits, only the first administration of the test was used for analysis.

### 2.3. Motor Function Measure-32

The MFM-32 is a 32-item test that quantifies functional capabilities in individuals with neuromuscular disorders.<sup>25</sup> This motor assessment has been validated in the congenital muscular dystrophy, congenital myopathy, and limb girdle muscular dystrophy populations.<sup>22</sup> The 32 items are scored on a 4-point Likert scale and are further divided into sub-categories including: D1 (13 items) standing and transfers, D2 (12 items) axial and proximal motor function, and D3 (7 items) distal motor function. Standing and transferring function was further analyzed in relation to the 6MWT. This subcategory includes hopping on one foot, running 10 m, walking on heels, etc.

### 2.4. Timed functional tests

Timed and graded functional tests were performed, including the floor-to-stand test, ascending 4 steps, and descending 4 steps. The TFT have been used as outcome measures in several neuromuscular disease clinical trials.<sup>26–28</sup> Taken together, these assessments capture functional ability as does the 6MWT.<sup>23</sup>

#### 2.4.1. Floor to stand

Participants were positioned in supine on a floor mat. They were instructed to stand up as quickly as possible without using external support. If external support was needed, a sturdy table or chair was used. The timer was started as soon as the test administrator said, “go” and stopped once the participant was in a standing position.

#### 2.4.2. Ascend & descend 4 steps

The ascend/descend step test was administered on a 4-step staircase with handrails. Participants were instructed to climb the steps as safely and quickly as they could once the test administrator said, “go.” Once the participants reached the top, they were asked to stop, at which point the timer was also stopped. Participants were then asked to descend the steps as safely and quickly as they could. The timer for the second part of the test began when the test administrator said, “go” and stopped once the participant reached the bottom.

### 2.5. Statistical analysis

Descriptive statistics are given in the form of mean ( $\pm$ SD) or N (%). Regression of 6MWD on 2MWD was used to define the predicted 6MWD, with R-squared measured to determine goodness of fit. Paired t-tests were used to compare 2MWD to predicted normative values. The Shapiro-Wilk test of Normality was used to assess 2MWD, 6MWD, and final 2 min’ distance (4–6 MWD) data for evidence of non-Normality. Pearson correlation was calculated for all pairs of timed distances and TFTs. Spearman correlation of timed distances and MFM-32 D1 and total score were also calculated. Equivalence testing with the two one-sided tests procedure (TOST) assessed comparability of 2MWD and 4–6MWD. The equivalence margin was set to 9.5 m, as this is one third of the minimal clinical important difference (MCID) established by McDonald et al. for the 6MWT.<sup>22</sup> While their study used a 30 m corridor and we used a 50 m corridor, it has been shown that 6-min walk distance is not affected by straight courses ranging between 15 m and 50 m.<sup>24</sup> Bland–Altman plots were also used to assess agreement between the 2MWD and 4–6MWD. Statistical significance was set as  $p < 0.05$ . All analyses were conducted in Stata 14.<sup>29</sup>

## 3. Results

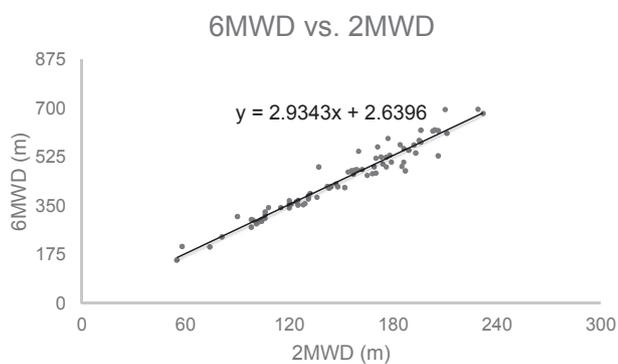
Seventy-seven participants completed the 6MWT. Of these, 73 participants had a measured 4–6MWD. Sixty-six participants completed the floor-to-stand test, 72 participants completed the timed ascent and descent of stairs, and 69 participants completed the MFM-32 (Table 2).

Mean distances walked were comparable for the initial 2 min at 149.8 m ( $\pm 40.3$ ) compared to the final 2 min 149.2 m ( $\pm 42.2$ ). The mean 6MWD was 442.1 m ( $\pm 121.6$ ). The scatterplot and regression line of 6MWD against 2MWD are given in Fig. 1. The 95% confidence interval for the slope of the regression was [2.77, 3.10]. The mean difference between the predicted 6MWD from the regression and that obtained by multiplying 2MWD by three (an assumption that speed was the same throughout the 6 min) was 7.2 m and was statistically significant ( $p < 0.0001$ ), but was smaller than the margin of equivalence of 9.5 m. Normative 2MWD values computed for each participant had mean 194.1 ( $\pm 14.3$ ) and were significantly larger than observed 2MWD ( $p < 0.001$ ).

Four participants were excluded from analyses comparing the 2MWD with the 4–6 MWD as intermediate distances were

**Table 2 – Mean values from outcome measures.**

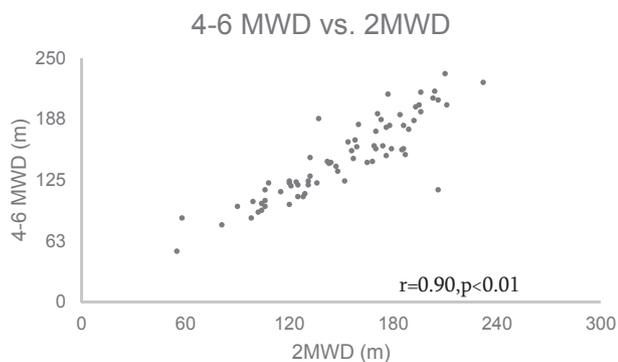
Activity (unit)	n	Mean $\pm$ SD
2MWD (m)	77	149.8 $\pm$ 40.3
6MWD (m)	77	442.1 $\pm$ 121.6
4–6MWD (m)	73	149 $\pm$ 4.93
Floor-to-Stand Time (s)	66	6.62 $\pm$ 4.54
Ascend 4 Steps Time (s)	72	4.35 $\pm$ 4.40
Descend 4 Steps Time (s)	72	3.05 $\pm$ 2.35
D1 MFM Standing & Transfers Score (%)	67	69.4 $\pm$ 22.7
MFM Total Score (%)	67	82.3 $\pm$ 14.2



**Fig. 1 – 6MWD vs. 2MWD with trend line.** This model displays each participant's 2MWD (x-axis) and 6MWD (y-axis). The regression equation estimates the relationship between the 2MWD and 6MWD. The regression equation has a slope of 2.93 and a y-intercept of 2.64.  $r = 0.90$ ,  $p < 0.01$ .

not recorded. With these four excluded, mean 2MWD was slightly higher at 152.4 m ( $\pm 39.3$ ). Among the 73 participants with both measurements, the 2MWD demonstrated a strong correlation with the 4–6 MWD ( $r = 0.90$ ,  $p < 0.0001$ ) (Fig. 2). The 2MWD and 4–6 MWD were not significantly different ( $p = 0.07$ ) with a mean difference of 5.07 m and 95% CI [-0.52, 10.65]. Equivalence testing rejected the lower margin of equivalence ( $p < 0.0001$ ) but failed to reject the claim that 2MWD was at least 9.5 m greater than 4–6 MWD ( $p = 0.0591$ ). The Bland–Altman plot for 2MWD and 4–6MWD showed strong agreement between both measurements, with 97% of the data falling within the limits of agreement (see Supplemental figure 1).

The distance walked in both 2 min and 6 min showed moderately strong inverse correlations with all four TFT tests ( $-0.7 < r < -0.6$ ). For each TFT test, both distances had comparable correlation coefficients and all correlations were significant at  $p < 0.0001$  (Table 3). Additionally, strong correlations existed between both the 2MWD and the 6MWD with the D1 category of the MFM-32 as well as MFM-32 total score (Table 3).



**Fig. 2 – 4–6 MWD vs. 2MWD.** Correlation between distances walked in the first 2 min and last 2 min of the 6MWT.

**Table 3 – Correlation analysis of functional outcome measures.**

	n	Correlation Coefficient [95% CI]
2MWD & Supine to Stand Time	66	-0.62 [-0.75, -0.45]
6MWD & Supine to Stand Time	66	-0.62 [-0.75, -0.45]
2MWD & Ascend 4 Steps Time	72	-0.60 [-0.73, -0.43]
6MWD & Ascend 4 Steps Time	72	-0.61 [-0.74, -0.44]
2MWD & Descend 4 Steps Time	72	-0.60 [-0.73, -0.43]
6MWD & Descend 4 Steps time	72	-0.60 [-0.73, -0.43]
2MWD & D1 MFM	73	0.76 [0.64, 0.84]
Standing & Transfers Score		
6MWD & D1 MFM	73	0.75 [0.63, 0.84]
Standing & Transfers Score		
2MWD & MFM Total Score	69	0.71 [0.57, 0.81]
6MWD & MFM Total Score	69	0.72 [0.59, 0.82]

#### 4. Discussion

The 6MWT is used as a measure of endurance and function in pediatric populations with reduced ambulatory ability, resulting from neuromuscular diseases. The 2-min walk test (2MWT, independent of 6MWT) has been used in the aged population, individuals with lower extremity amputations, cystic fibrosis, traumatic brain injury, and neurological disorders as a measure of endurance.<sup>11–18</sup> It is also believed to serve as a potential alternative to the 6MWT in study populations that have issues with behavior, attention span, and/or the inability to tolerate test length due to weakness.<sup>8–10</sup> Two studies comparing 2MWT and 2MWD to 6MWT distances in DMD and congenital myotonic dystrophy populations, respectively, reported the 2MWT and 2MWD were reliable compared to 6MWT performance.<sup>10,20</sup> The findings of the current study support the potential of a 2MWT as an effective alternative to the 6MWT as a measure of function and performance in children with neuromuscular diseases. Our study demonstrated a strong correlation between the 2MWD and the 6MWD. This result was supported by equivalence testing confirming that 2MWD may modestly overestimate 4–6 min distance. Regression of 6MWD on 2MWD provided further support for approximating 6MWD with 2MWD multiplied by a factor of 3. The regression equation was  $6MWD = 2.93 * (2MWD) + 2.64$ , and the value 3 was within the 95% CI for the slope. These results consistently support the 2MWT as an alternative to the 6MWT for this population. A recent study established normative 2MWT distances in the pediatric population. As a result, separate prediction normative equations for boys and girls, incorporating age, height, and body mass, were established to account for the 40% variance in distance traveled during the 2MWT amongst children.<sup>30</sup> As expected, the children in this study ambulated significantly lower 2MWDs than the predicted normative values.

In addition to demonstrating the validity of the 2MWT as an endurance measure, we assessed the validity of the 2MWT as a functional measure. Both the 2MWD and the 6MWD were inversely correlated with the time taken to go from floor-to-stand, ascend 4 steps, and descend 4 steps. The correlation coefficients observed for both the 2 and 6-min walk distances were very similar, further confirming the validity of the 2MWT as a performance measure. The 2MWD and 6MWD also

showed a strong correlation with the D1 MFM-32 score. The D1 score was specifically assessed versus the other two domains of the MFM-32, because it measures standing and transfer capability in these individuals. These activities most closely resemble the type of function assessed in the 2MWT and 6MWT. This strong correlation provides further evidence for the use of the 2MWT as a functional measure.

One of the major concerns with the 2MWT is that children may walk at a faster pace given the shorter time frame. However, Alfano et al. showed 2MWT walking velocity was highly correlated with 6MWT velocity in IBM, yet the velocities were significantly different. Given the velocities were highly correlated, the authors were able to use linear regression to obtain an equation that allowed for the conversion of 2MWT performance to 6MWT.<sup>11</sup> Based on these results, a linear regression model can be used to resolve the concern of faster walking speeds in a 2MWT. Since we used the first 2 min of the 6MWT and did not conduct a separate 2MWT, we compared the distance traveled and walking speed at different time points to confirm that our participants maintained an even pace throughout the test. Table 4 shows walking velocities at each minute interval. Among participants with 2MWT and 4–6 MWT data, they ambulated a mean distance of 152 m in the first 2 min and 149 m in the last 2 min of the test, walking at an average velocity of 1.27 m/s and 1.24 m/s for the first two and last 2 min respectively. While the distance walked during these time frames correlated very strongly at 0.896, the velocity decreased by 2.3% in the last 2 min from the first 2 min (Table 4). Andersen et al.<sup>1</sup> reports a decrease in the walking speed from the first to the 6th minute by 1.4% in healthy adult controls. Equivalence testing between the first 2 min and last 2 min revealed that differences in these distances were not statistically significant and did not reach the equivalence margin. Since this equivalence margin was derived from a 6MWT MCID and not a 2MWT MCID, we wanted to further assess this relationship using a Bland–Altman plot. Bland Altman suggests two measures, 2-min and 6-min walking velocities, are considered in agreement if 95% of the data fall within  $\pm 2s$ , where  $s$  is the standard deviation.<sup>31</sup> In our plot, there were only 3 data points that fell outside the upper and lower limits.

#### 4.1. Limitations

While these results support the use of the 2MWT as a substitute for the 6MWT, there is concern that comparing the initial 2MWT to the total 6MWT could produce a pacing effect. Participants may have selected a faster walking speed had they been asked to walk for 2 min as opposed to 6 min.

**Table 4 – 6MWT velocities at each minute interval.**

Minute	Velocity (m/s)	Std. Dev.	p-value
1	1.32	0.36	–
2	1.23	0.34	0.0005
3	1.24	0.35	0.0013
4	1.24	0.34	0.0003
5	1.26	0.37	0.0408
6	1.24	0.35	0.0105

P-values are from pairwise comparisons of each minute interval to the first minute.

However, this concern has been addressed by use of a linear regression model given the high correlation between 2 and 6 min speeds.<sup>11</sup> Another option is a follow-up study that compares the 2MWT and 6MWT in NMD. The tests would be administered on different days to provide adequate recovery time to avoid the effects of fatigue.

Another limitation is the lack of MCID values for these specific populations. We used the only published pediatric neuromuscular MCID values available, from the DMD population which may not apply to all neuromuscular disorders of childhood. Furthermore, the MCID we used to compare the 2MWT and 4–6MWT was extrapolated from the 6MWT MCID. A follow-up study might explore the MCID specific to a 2MWT in our sample population. Additionally, a study of separate NMDs including at least 10 participants per NMD would enable subgroup analyses to determine whether the results from this study are consistent.

## 5. Conclusion

Our findings suggest that the 2MWT may replace the 6MWT as a measure of both endurance and functional ability in a pediatric population with neuromuscular disease given the high correlation between 2MWT and 6MWT. The shorter duration of the 2MWT is conducive to individuals with muscle weakness and fatigue. The 2MWT has similar utility to the 6MWT, serving as an optimal measure for tracking patients with progressive NMD over time; yet it requires less time thus less fatiguing to the patient. Additionally, both the 6MWT and the 2MWT, in our study, showed strong correlations with the functional measures, including MFM-32 and TFTs, valid measures shown to be demonstrative functional ability in NMD. Therefore, the aforementioned functional measures can be used to assess functional ability in NMD.

## Conflicts of interest

None declared.

## Funding

This work was supported by the NIH intramural research funds from the Clinical Center; the National Institute of Neurological Disorders and Stroke (NCT1568658); and the National Institute of Nursing Research (NCT02362425).

## Acknowledgements

We thank the patients for their commitment of time and effort in participating in this research. We are grateful to Carmel Nichols and Ching-Yi Shieh for their statistical analyses. We thank the Congenital Muscular Dystrophy Clinical Outcome Measures (CMD COM) Team: Leslie Nelson, Bonnie Hodsdon, Rebecca Parks, Roxanna Bendixen, Michelle McGuire, Tina Duong, Michelle Hsia, KC Keller, Donovan Lott, Irene C. Chrismer, Melody M. Linton, Jeff Elliott, Jahannaz Dastgir,

Linda Hynan, Elizabeth Hartnett, Gilberto M. Averion, James Collins, Eunice Kim, Angela Kokkinis, Veronica Hinton, Diana Bharucha, Carole Vuillerot, Anne Rutkowski. We also thank Joan Austin.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejpn.2018.10.001>.

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