

Association of Muscle Strength and Walking Performance in Adult Patients With Pompe Disease

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Background. The loss of the ability to walk is among the most prominent signs of Pompe disease. The associations with muscle strength have not been described.

Objective. The objective of this study was to estimate the associations of walking performance with muscle strength in 4 specific lower extremity muscle groups along with other factors in adult patients with Pompe disease.

Design. This was a single-center, cross-sectional study.

Methods. Muscle strength (hand-held dynamometry of hip flexion and abduction and knee extension and flexion) and walking performance (unable to walk, able with aids, walking without aids but with a waddling gait, or walking without aids and with a normal gait) were assessed in 107 patients at their first visit. Relationships between walking performance and muscle strength were studied through multivariate analyses and regression modeling. Age, sex, body mass index (BMI), disease duration, and use of ventilator support were taken into account as potential confounders. The results were transformed into a nomogram to allow the probability of a patient having a certain level of walking performance to be calculated based on the values of the independent variables.

Results. Walking performance declined significantly with decreasing muscle strength of hip flexion and abduction and knee extension and flexion. The final selected model, including strength of the hip abductor and knee extensor, BMI, age, sex, and use of ventilation, predicted 66% of the cases accurately.

Limitations. These results are based on cross-sectional data and do not predict future changes.

Conclusions. In adult people with Pompe disease, walking performance can be explained by muscle strength, BMI, age, sex, and ventilation use. The proposed model gives insight into how an individual is expected to walk based on his or her risk factors and serves as a starting point to unraveling factors associated with walking performance and ultimately to developing a prognostic model.

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Pompe disease is a rare inheritable metabolic myopathy. It is caused by deficiency of the lysosomal enzyme acid α -glucosidase, which is needed to break down glycogen in the lysosomes. As a result, glycogen accumulates in several tissues, especially muscle cells. The disease presents as a broad clinical spectrum, with variable organ involvement, age of onset, and severity. The most severe form, seen in infants, results in death within the first year of life, while the disease progresses more slowly in children and adults.¹

In adults, Pompe disease is characterized by limb-girdle weakness and weakness of respiratory muscles (including the diaphragm). Patients develop Duchenne or Trendelenburg signs or a swayback posture. Eventually, patients lose the ability to walk and become wheelchair and/or respirator dependent.

The loss of the ability to walk is one of the most prominent signs and debilitating effects of Pompe disease and has been shown to be an important factor in determining patients' quality of life.² In general, retaining the ability to walk is important to maintain independence from caregivers.^{3,4}

Reduced walking performance has been shown to be related to decreased skeletal muscle strength in several populations, including patients with related neuromuscular diseases and the elderly.⁵⁻⁹ However, the associations between walking performance and muscle strength have not been described for patients with Pompe disease. Results from studies in other neuromuscular diseases cannot automatically be generalized to these patients, as the distribution of muscle weakness, and thus its effects on walking performance, differs.⁹ In addition, other risk factors, such as age, BMI, and respiratory status that might contribute to a reduced walking performance, are not well understood in patients with Pompe disease.

By modeling the relationship between walking performance on the one hand, and muscle strength and associated risk factors on the other, it will be possible to determine a patient's expected

position in the spectrum of walking performance. This can give the clinician a better feel for where the patient is in the disease process. Importantly, the model can serve as a starting point to further our understanding of the factors that determine walking performance in Pompe disease, and ultimately to develop a prognostic model for larger patient care planning efforts among the integrated rehabilitation team.

The aim of our study was to estimate the associations of walking performance with muscle strength of specific lower extremity muscle groups and with other factors in adult patients with Pompe disease.

Methods Participants

Adult patients with a confirmed diagnosis of Pompe disease were included in this study. All patients were first seen between December 2003 and August 2012 at the Center for Lysosomal and Metabolic Diseases of the Erasmus MC University Medical Center, Rotterdam, the national referral center for patients with Pompe disease in the Netherlands. Patients were excluded if they had co-morbidities that affected their walking performance.

On visiting the center, patients were subjected to a standardized set of outcome tests, including assessment of muscle strength and motor function tests encompassing the ability to walk. Data from the patients' first visit to the center was analyzed retrospectively. We also recorded age, sex, height, weight, and disease duration (time since diagnosis) for each patient. All patients signed informed consent.

Outcome Measures

Walking performance was classified in 4 categories (unable to walk, walking with aids, walking without aids but with a waddling gait, or walking without aids and with a normal gait) according to the item "walking 10 meters" of the Quick Motor Function Test (QMFT).¹⁰ This item was assessed by asking patients to walk a 10-m course at their usual pace. Use of aids (canes or walkers) was allowed for this test, but

patients were challenged to achieve the maximum performance; ie, those who used a wheelchair but could still walk 10 meters were asked to do so. Patients were classified as unable to walk when they were fully dependent on a wheelchair (ie, they could not walk more than a few steps without a walking aid). Patients who used a wheelchair but were capable of walking 10 meters were scored as "able to walk with aids." Normal gait was considered as a gait pattern without a Trendelenburg or Duchenne sign or swayback.

Skeletal muscle strength exerted during maximal voluntary eccentric contractions was measured by hand-held dynamometry (HHD) (Cytec dynamometer; CIT Technics, Groningen, the Netherlands). The lower proximal muscle groups—hip flexors, hip abductors, knee flexors, and knee extensors—were tested using the break test technique. Specifics of the test positions, stabilization, and dynamometer placement have been described elsewhere.¹³ Muscles were tested separately for each leg, and values were averaged for the 2 legs. The absolute HHD values were used and expressed in Newtons (N). All measurements were carried out by 3 physicians specially trained to perform HHD and connected to our center.

Data Analysis

Median muscle strength values were plotted against the 4 levels of walking performance using box plots. Differences in muscle strength were assessed using the Kruskal-Wallis test. When this was significant, the Mann-Whitney test was used to identify which of the groups differed.

Ordered logistic regression was used to build a model describing the independent variable walking performance, based on the dependent variables: muscle strength of the 4 lower extremity muscle groups, age, sex, body mass index (BMI), disease duration, and use of ventilator support.^{3,14,15}

A step backward method was used, starting with a full model containing all possible independent variables. Variables that did not contribute to the

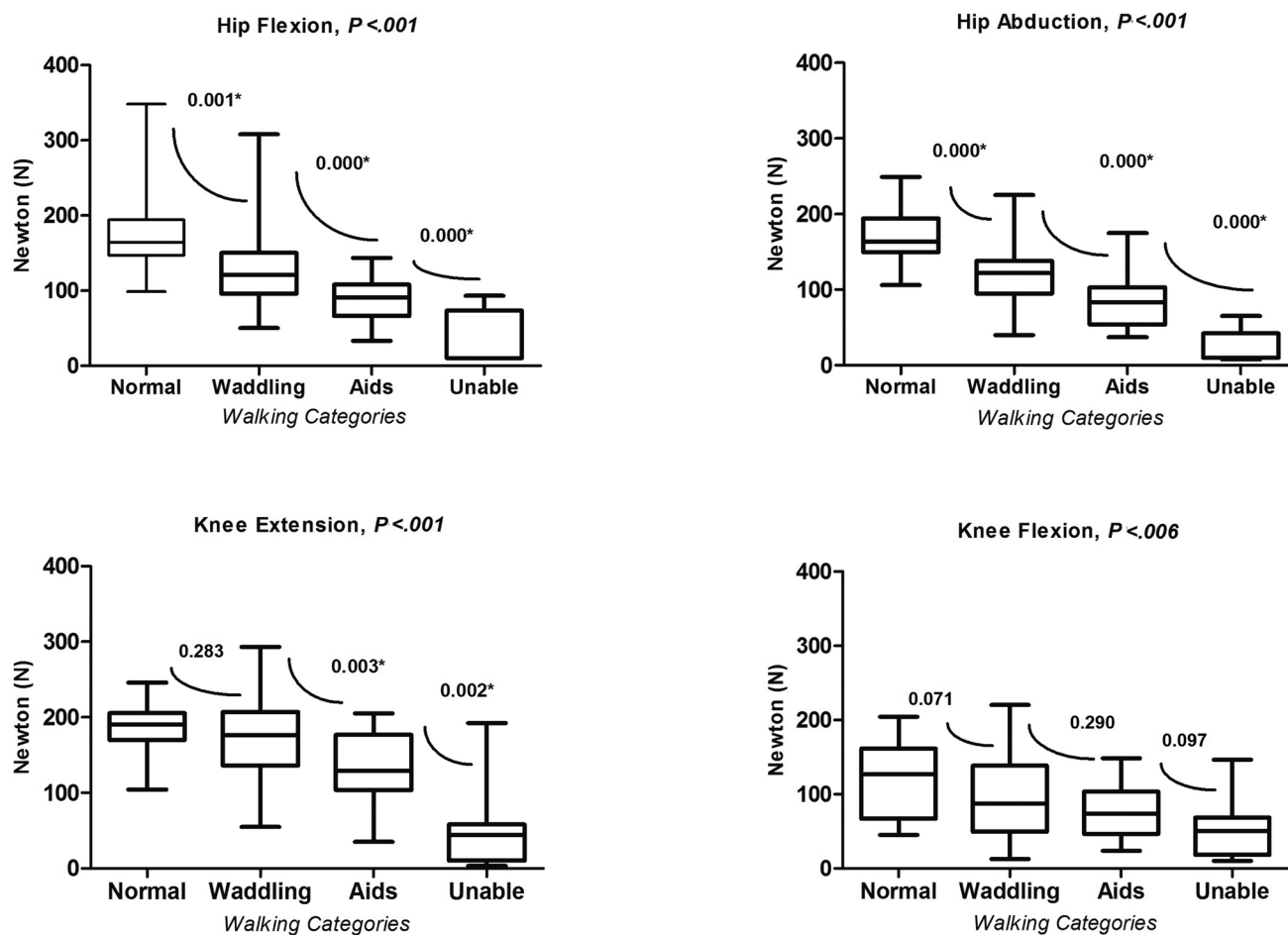


Figure 1.

Relationship between lower extremity muscle strength (expressed in Newtons [N]) and walking performance. Unable = fully dependent on a wheelchair; aids = walking with walking aids; waddling = walking without aids with waddling gait; normal = walking with normal gait pattern. The P value for differences between any of the groups (Kruskal-Wallis test) is shown at the top of each graph, whereas differences between adjacent groups (Mann-Whitney test) are indicated by the bridging lines (* = significant differences between adjacent groups).

model were excluded at a cut-off significance level of 0.20.

Internal validation of the (full and subsequent) models was assessed using the bootstrap technique with 1000 samples. As measures of predictive ability, we used the area under the receiver operating characteristic curve (AUC, discriminative ability), Nagelkerke R^2 (goodness of fit), the calibration slope, and the Brier score (predictive accuracy). The most parsimonious model that performed satisfactorily in the validation step was reported here.

Next, based on this model, a nomogram was constructed that allows the chance

of being in 1 of the 4 levels of walking performance to be calculated directly from given specific values of the independent variables.

Differences in patient characteristics and muscle strength were tested using SPSS for Windows (release 21.0; SPSS Inc, Chicago, Illinois, USA). All other statistical analyses were performed with *R: A Language and Environment for Statistical Computing*, version 3.2.2, using the rms package (rms: Regression Modeling Strategies, Frank E Harrell Jr, R package version 4.4-1, 2015). Visualization was performed using GraphPad Prism version 5 (GraphPad Software, La Jolla, California, USA) and the rms package.

Results

Participants

During the study period, 108 adult patients with Pompe disease were first seen at the national referral center and examined. One patient was excluded from the analyses because this patient had Pompe disease in combination with spina bifida, both interfering with muscle strength.

Table 1 presents the characteristics of the 107 included patients at their first visit to the center. Patients had a median age of 50 years (minimum = 25 y; maximum = 76 y) and had symptoms for a median of 15 years. Twenty-eight percent were ventilator dependent. In

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Table 1.
Characteristics of 107 Adult Patients With Pompe Disease

Patient Characteristics at First Visit to Referral Center	Study Population (N = 107)
Sex (male), no. (%)	55 (51.4%)
Age (y), median (minimum–maximum)	50 (25–76)
BMI (kg/m ²), median (minimum–maximum)	24.1 (15–48)
Disease duration (y), median (minimum–maximum)	15 (2–48)
Walking performance, no. (%)	
Unable to walk	12 (11.2%)
Walking aids	30 (28%)
Walking without aids with waddling gait	46 (43%)
Normal gait	19 (17.8%)
Respiratory support at first visit, no. (%)	
No ventilator use	77 (72%)
Ventilator dependent	30 (28%)

terms of walking performance, 11% were fully dependent on a wheelchair, 28% used walking aids, 43% walked with an abnormal gait without aids, and the remainder (18%) had a normal walking pattern. None had started treatment with enzyme replacement therapy (ERT) at the time of examination for this study.

Association Between Walking Performance and Lower Proximal Muscle Strength

Figure 1 shows the differences between each of the consecutive walking categories in strength of the hip flexors, hip abductors, knee extensors, and knee flexors. Walking performance declined with decreasing muscle strength. This was most obvious for the hip flexors and hip abductors, where muscle strength differed significantly between each consecutive level of walking performance ($P < .01$). For knee extension, no significant difference in strength of the knee extensors was found between patients with a waddling gait and those walking normally. For strength of knee flexors, there were no differences between any of the consecutive walking categories.

Table 2 displays the patients' muscle strength values and other risk factors across the 4 walking categories. Besides reduced muscle strength, patients with more impaired walking performance were older, had been symptomatic for

longer, and were more often ventilated compared to those with normal/less impaired walking performance. Also, higher BMI and male sex seemed to be more frequent in the more impaired patients.

Stepwise backward elimination of the variables in Table 2 ($P < .20$) resulted in an ordered logistic regression model containing the variables strength of the hip abductors and knee extensors, sex, age, ventilation use, and BMI. This was the most parsimonious model and also performed well on internal validation (AUC, discriminative ability = 0.76; Nagelkerke R^2 for goodness of fit = 0.66; calibration slope = 0.86; Brier score for predictive accuracy [lower is better] = 0.14). Higher strength of the hip abductors (odds ratio [OR] = 1.042; 95% CI = 1.026–1.057) and knee extensors (OR = 1.011; 95% CI = 1.001–1.022), lower age (OR = 0.968; 95% CI = 0.931–1.005), lower BMI (OR = 0.837; 95% CI = 0.753–0.930), female sex (OR = 0.365; 95% CI = 0.137–0.972), and not using ventilator assistance (OR = 4.540; 95% CI = 1.379–14.950) are associated with the probability of being in a better walking category. The eAppendix (available at <https://academic.oup.com/ptj>) provides the regression and validation results for the different models that were generated, as well as further information on the interpretation of the validation coefficients.

Figure 2 (top) shows the results of this model transformed into a nomogram. This visualization of the model allows the probability of being in 1 of the 4 categories of walking performance to be calculated directly based on given values of the independent variables. The range of each independent variable is related to a corresponding number of points on a linear scale. The sum of the corresponding points for each variable (total points) corresponds with the probability for being in each of the 4 walking categories. Two example calculations, based on 2 of our patients, both with an observed waddling gait, are shown in Figure 2 (bottom).

Discussion

In adult patients with Pompe disease, walking performance declines with decreasing strength of the lower extremities. This study shows that a patient's probability to have a certain level of walking performance can be calculated based on muscle strength and a number of other risk factors. The model we describe here enables clinicians to compare a patient's actual walking performance to that expected based on his or her risk factors, and thereby to counsel patients on their current disease status and possible supportive measures. It should be further expanded to encompass other factors and ultimately develop a prognostic model.

Walking performance declined most obviously with decreasing strength of the hip flexion and abduction. The strength of knee extension varied significantly between 3 of the 4 walking categories only, while knee flexion did not distinguish between any of the 4 consecutive categories. This is consistent with findings based on muscle-driven simulation that showed that gait was most affected by weakness of hip abductors and hip flexors, as well as plantar flexors, which are not usually affected in adult patients with Pompe disease.¹⁶ Observed muscle strength values overlapped considerably between the consecutive walking categories, indicating that other patient characteristics, such as sex and BMI, may affect walking performance also.^{14,15,17} Concerted contraction of

Table 2.Characteristics and Muscle Strength Across the 4 Walking Categories^a

	Normal (Walking Without Aids and With a Normal Gait) (n = 19)	Walking Without Aids With a Waddling Gait (n = 46)	Able With Aids (n = 30)	Unable to Walk (n = 12)	P
Muscle strength (N)					
Hip flexion	164.5 (99–348)	121.1 (50–308)	91.0 (33–144)	10 (10–93)	<.001 ^b
Hip abduction	163.5 (106–249)	121.8 (40–225)	83.5 (37–175)	10 (7–65)	<.001 ^b
Knee extension	190.5 (105–246)	176.5 (55–293)	129.1 (35–205)	49.0 (3–193)	<.001 ^b
Knee flexion	126.8 (45–204)	87.3 (13–220)	73.4 (24–149)	52.2 (10–147)	.006 ^b
Characteristics					
Age (y)	45.0 (25–72)	46.5 (25–68)	54.0 (26–71)	59.0 (33–76)	<.001 ^b
Body mass index	23.1 (19–29)	24.2 (17–48)	25.2 (20–38)	23.2 (15–28)	.074
Disease duration (y)	1.0 (0–27)	1.5 (0–19)	13.0 (0–30)	22.0 (0–32)	<.001 ^b
Ventilation (% yes)	5.3	15.2	60.0	83.3	<.001 ^b
Sex (% male)	36.8	54.3	43.3	83.3	.059

^aContinuous variables are shown as median and ranges (minimum to maximum) and compared with the Kruskal-Wallis test. Categorical values are expressed as percentages, and *P* values are calculated using chi-square analysis. N = Newtons.

^bSignificant differences between 1 or more of the walking categories.

muscle groups as a compensation for weakness may play a role as well.¹⁶ To compensate for weak quadriceps muscles, a hip extensor might be included for knee extensor strategy, ie, using the 2 joint characteristics of the hamstring muscle to move the knee toward extension.¹⁸ Therefore, we developed a multivariate regression model to describe walking performance.

The probability of being in 1 of the walking categories can be calculated best based on strength of the hip abduction and knee extension, age, sex, BMI, and respiratory support. From the 4 lower extremity muscle strength groups, only hip abduction and knee extension contributed to the final model because of the interdependence between the 4 groups. Despite disease duration being associated with disease severity,¹⁹ this variable did not contribute to the model after correcting for age. In our model, women had a higher chance of being in a better walking category. These sex differences were also found by De Vries et al.²⁰

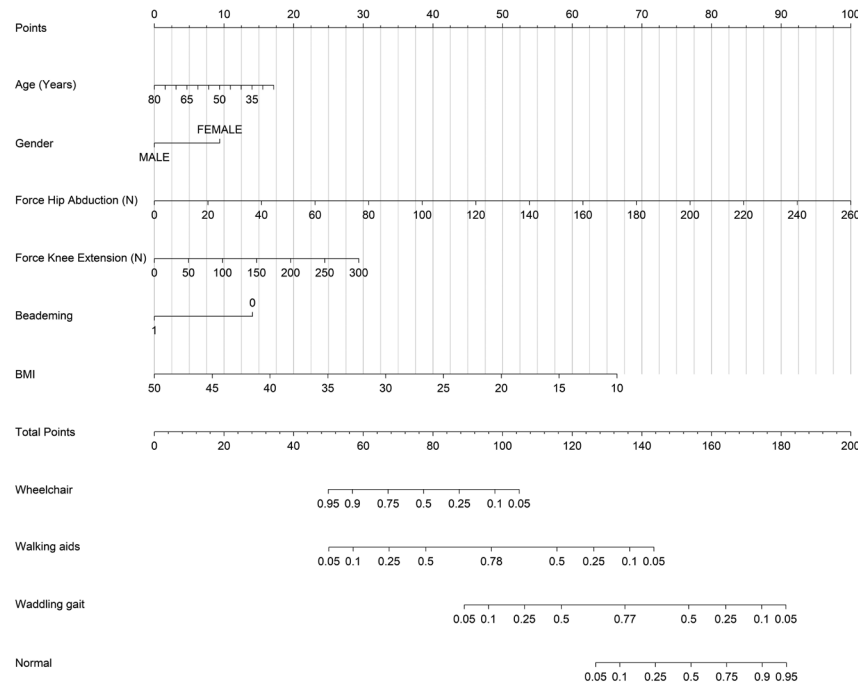
One of the perspectives of creating a multivariate model is the application in clinical practice, and therefore, the model was transformed into a

nomogram. By doing this, a patient's chance to have a certain level of walking performance can be calculated based on his or her risk factors. While a patient's actual walking performance can be observed, the nomogram allows a clinician to compare this to the probability of being in the 4 walking performance categories based on the patient's muscle strength and risk factors. This comparison has several potential clinical benefits. For example, in case the expected (ie, the walking category with the highest probability) and observed walking performance are the same, there are 2 options: (1) the probability of the expected walking category might be the clearly highest; or (2) the probability of the expected walking category is quite close to the probability of an adjacent walking category. In the first condition, a patient can be reassured. In the second condition, a patient can be advised to do strength training and/or lose weight in order to prolong this particular ambulant status. In case of a discrepancy between observed and expected walking performance, this might draw attention to the issues of overload (when the observed walking category is "higher" than the expected one) or underload (in case of a "lower" walking category than calculated).

In the current sample, our model predicted walking performance accurately in 66% of the cases. Hence, in around 34% of the cases the observed walking performance deviated from the model results. Other explanatory factors may play a role as well. For example, 1 of our patients had a high chance of walking with aids (70% chance), but was observed to walk with a waddling gait (ie, overloading). Further inspection showed us that this patient had a substantial scapula alata preventing the use of a walking stick. This comes at the price of a high fall risk, and alternative solutions to walking aids need to be searched for or a wheelchair recommended. This example illustrates that further factors may need to be incorporated to accurately predict walking performance in a prognostic model. In future research, it will be important to include instrumented gait analysis in order to identify compensatory movements for core and/or lower extremity muscle weakness.

Our analyses are based on a cohort of more than 100 adult patients with Pompe disease, which is very large given the rarity of the disease. However, to develop an accurate model, patient numbers are relatively small. Nevertheless, internal validation of the

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Case report patient I			Case report patient II		
Variables	Walking category	Chances	Variables	Walking category	Chances
42 yr female		25%	50 yr male		<5%
HA strength 128 N KE strength 147N No ventilation use		70%	HA strength 95N KE strength 175N No ventilation use		55%
BMI 22 kg/m ²		<5%	BMI 24 kg/m ²		40%
		<5%			<5%

Figure 2.

The probability of being in 1 of the 4 categories of walking performance can be calculated from the nomogram as follows. First, for each independent variable, the value is projected upward onto the "Points" scale to give the corresponding points. Next, these points are added and the total points are projected downward from the "Total points" scale to the scales giving the corresponding probabilities for being in 1 of the 4 walking categories. For example, case report I is a 42-year-old woman with a hip abduction (HA) strength of 128 Newtons (N) and knee extension (KE) of 147 N, who does not use a ventilator and has a body mass index (BMI) of 22 kg/m². In the first step, we project these values onto the top "Points" scale, counting 12 points for age, 9 for being female, 49 for HA strength, 14 for KE strength, 14 for being ventilator independent, and 45 for BMI. The total points value is 143. When drawing a vertical line downward, this gives a 70% chance of walking with a waddling gait, 25% chance of a normal gait, and <5% chance of other options.

model yielded a reasonable concordance between actual and estimated walking performance, and our model predicted walking performance accurately in 66% of the cases. A lack of external validation can be regarded as a limitation of our study. The model's validity in other cohorts of patients with Pompe disease remains to be studied. Furthermore, the nomogram was based on cross-sectional data rather than longitudinal data, and as a consequence, it does not provide information on a patient's prognosis or future walking performance. Another limitation is related to the measurement of muscle strength. HHD values were obtained using standard testing as described and widely used.¹³ Three testers (male and female) were involved in this study, where 1 performed the majority of the strength tests. The interrater reliability was not assessed, and whether this impacts the clinical utility of the nomogram remains to be determined. Finally, in Pompe disease, trunk muscles are frequently involved,¹⁵ which affects strength and performance of the lower extremities.²¹ Due to the lack of objective measurements of the core strength,²¹ this could not be included in our model. Although plantar flexors are known to be important for gait performance, we did not include these in our model. This was because they are known not to be severely affected in Pompe disease, which was supported by the data of our population, with all patients having values close to those seen in healthy people,¹³ which means that this would not add to the model.

This study shows that reduced walking performance in adult patients with Pompe disease is associated with reduced muscle strength of the lower extremities as well as with higher age, higher BMI, male sex, and ventilator use. We developed a model describing the chance to be in 1 of 4 walking categories. This model can support a clinician's subjective judgment on whether a patient—based on risk factors—is capable of more or less than what a patient shows in terms of walking performance. Moreover, it might serve as a first step toward developing a prognostic model.

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Disclosures

The authors completed the ICJME Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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References

- van der Ploeg AT, Reuser AJ. Pompe's disease. *Lancet*. 2008;372:1342–1353.
- Hagemans ML, Winkel LP, Van Doorn PA, et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. *Brain*. 2005;128:671–677.
- Shin H, Liu PY, Panton LB, Ilich JZ. Physical performance in relation to body composition and bone mineral density in healthy, overweight, and obese postmenopausal women. *J Geriatr Phys Ther*. 2014;37:7–16.
- Kuptniratsaikul V, Tosayanonda O, Nilganuwong S, Thamalikitkul V. The efficacy of a muscle exercise program to improve functional performance of the knee in patients with osteoarthritis. *J Med Assoc Thai*. 2002;85:33–40.
- Buchner DM, Larson EB, Wagner EH, Koepsell TD, de Lateur BJ. Evidence for a non-linear relationship between leg strength and gait speed. *Age Ageing*. 1996;25:386–391.
- Hasegawa R, Islam MM, Lee SC, Koizumi D, Rogers ME, Takeshima N. Threshold of lower body muscular strength necessary to perform ADL independently in community-dwelling older adults. *Clin Rehabil*. 2008;22:902–910.
- Jette DU, Slavin MD, Andres PL, Munsat TL. The relationship of lower-limb muscle force to walking ability in patients with amyotrophic lateral sclerosis. *Phys Ther*. 1999;79:672–681.
- Slavin MD, Jette DU, Andres PL, Munsat TL. Lower extremity muscle force measures and functional ambulation in patients with amyotrophic lateral sclerosis. *Arch Phys Med Rehabil*. 1998;79:950–954.
- Alfano LN, Lowes LP, Flanigan KM, Mendell JR. Correlation of knee strength to functional outcomes in Becker muscular dystrophy. *Muscle Nerve*. 2013;47:550–554.
- van Capelle CI, van der Beek NA, de Vries JM, et al. The quick motor function test: a new tool to rate clinical severity and motor function in Pompe patients. *J Inheret Metab Dis*. 2012;35:317–323.
- Bohannon RW. Make tests and break tests of elbow flexor muscle strength. *Phys Ther*. 1988;68:193–194.
- Lu YM, Lin JH, Hsiao SF, Liu MF, Chen SM, Lue YJ. The relative and absolute reliability of leg muscle strength testing by a handheld dynamometer. *J Strength Cond Res*. 2011;25:1065–1071.
- van der Ploeg RJ, Fidler V, Oosterhuis HJ. Hand-held myometry: reference values. *J Neurol Neurosurg Psychiatry*. 1991;54:244–247.
- Auyeung TW, Lee SW, Leung J, Kwok T, Woo J. Age-associated decline of muscle mass, grip strength and gait speed: a 4-year longitudinal study of 3018 community-dwelling older Chinese. *Geriatr Gerontol Int*. 2014;14(Suppl 1):76–84.
- van der Beek NA, de Vries JM, Hagemans ML, et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. *Orphanet J Rare Dis*. 2012;7:88.
- van der Krogt MM, Delp SL, Schwartz MH. How robust is human gait to muscle weakness? *Gait Posture*. 2012;36:113–119.
- Serra AJ, de Carvalho Pde T, Lanza F, et al. Correlation of six-minute walking performance with quality of life is domain- and gender-specific in healthy older adults. *PLoS One*. 2015;10:e0117359.
- Schmid S, Schweizer K, Romkes J, Lorenzetti S, Brunner R. Secondary gait deviations in patients with and without neurological involvement: a systematic review. *Gait Posture*. 2013;37:480–493.
- Hagemans ML, Winkel LP, Hop WC, Reuser AJ, Van Doorn PA, Van der Ploeg AT. Disease severity in children and adults with Pompe disease related to age and disease duration. *Neurology*. 2005;64:2139–2141.
- de Vries JM, van der Beek NA, Hop WC, et al. Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: an open-label single-center study. *Orphanet J Rare Dis*. 2012;7:73.
- Willson JD, Dougherty CP, Ireland ML, Davis IM. Core stability and its relationship to lower extremity function and injury. *J Am Acad Orthop Surg*. 2005;13:316–325.