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Activities of daily living in myotonic dystrophy type 1

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Objectives: The objective of this cross-sectional, observational study was to investigate performance of activities of daily living in patients with myotonic dystrophy type 1 (DM1).

Materials and Methods: Adults with genetically confirmed DM1 were recruited from Newcastle University (Newcastle upon Tyne, UK) and University College London Hospitals NHS Foundation Trust (London, UK). Data on activities of daily living were recorded through the DM1-Activ^{C} (scale scores range between 0 and 100, where a higher/lower score indicates a higher/lower ability).

Results: Our sample comprised 192 patients with DM1 (mean age: 46 years; 51% female). Patients reported most difficulties with running, carrying and putting down heavy objects, and standing on one leg, and least difficulties with eating soup, washing upper body, and taking a shower. Irrespective of the disease duration (mean: 20 years), most patients were able to perform basic and instrumental activities of daily living (eg personal hygiene and grooming, showering, eating, cleaning and shopping), with the exception of functional mobility/transfer tasks (eg walking uphill and running). The mean DM1-Activ^{C} total score was estimated at 71 (95% CI: 68-74). Estimated progenitor cytosine-thymine-guanine repeat length and age explained 27% of the variance in DM1-Activ^{C} total scores ($P < .001$).

Conclusions: We show that DM1 impairs performance of activities of daily living, in particular those requiring a high degree of muscle strength, stability and coordination.

Erik Landfeldt and Nikoletta Nikolenko contributed equally to this work.

Yet, across the evolution of the disease, the majority of patients will still be able to independently perform most basic and instrumental activities of daily living.

KEYWORDS
activities of daily living, quality of life, social participation

1 | INTRODUCTION

Myotonic dystrophy type 1 (DM1) is a rare, disabling neuromuscular disorder of varying severity caused by the expansion of the cytosine-thymine-guanine (CTG) triplet repeat in the *DMPK* gene.[1] Longer CTG triplets expansion has been shown to be related to greater disease severity and earlier age at onset.[2,3] DM1 is the most common muscular dystrophy with an estimated prevalence of 8 per 100 000.[4] Typical manifestations of DM1 include muscle weakness, myotonia and fatigue, but symptoms are heterogeneous and may also involve other organs and systems, such as the heart and eyes, and the endocrine, gastrointestinal and central nervous system.

In recent decades, the increased understanding of the underlying molecular pathology of DM1 has enabled the design of new targeted treatments, including antisense oligonucleotides, GSK3β inhibitors, and other pharmacological and genetic treatments.[5] This acceleration in therapy development has resulted in a pressing need to map out the natural history of the disease to inform the design of clinical trial programs, including the selection of appropriate clinical endpoints and tools that are fit for purpose to measure drug benefits.[6,7]

The DM1 activity and participation scale for clinical use (DM1-Activ^{C}) is a rating scale designed to measure self-reported performance of activities of daily living (eg brushing teeth, preparing meals and walking up a flight of stairs) in patients with DM1. The tool was initially developed in 2010,[8] but re-constructed in 2015,[9] and the current version encompasses a total of 25 items, each described in three levels. The DM1-Activ^{C} has been tested using modern psychometric analysis (ie Rasch analysis[10]) and has been shown to adhere to the epistemological requirements for stable measures.

Since its development, the DM1-Activ^{C} has been employed as part of a few studies,[11,12] and the instrument was also included in a recently completed multi-national trial in DM1 (ie the OPTIMISTIC trial).[13] However, to date, no study has reported results from the DM1-Activ^{C} beyond summary point estimates of mean instrument scores. Accordingly, the objective of this study was to investigate the impact of DM1 on activities of daily living as recorded using the DM1-Activ^{C} in patients with DM1 from the UK. A specific aim was to examine if the disease burden varies by sex, disease duration, and several clinical measures and biomarkers of the disease, including estimated progenitor CTG repeat length.

2 | MATERIALS AND METHODS

2.1 | Study design and patient sample

This study was based on a sample of patients with genetically confirmed DM1 recruited from two sites in the UK (Newcastle University, Newcastle upon Tyne, and University College London Hospitals NHS Foundation Trust, London) as part of the Myotonic Dystrophy Type 1 Deep Phenotyping to Improve Delivery of Personalized Medicine and Assist in the Planning, Design and Recruitment of Clinical Trials (PhenoDM1) study (ClinicalTrials.gov identifier: NCT02831504). To be eligible to participate, all patients were required to meet the following inclusion criteria: (a) ≥18 years of age, (b) genetically confirmed diagnosis of DM1 and (c) ability to perform the 10 m walking test at selected pace without any assistance (walking devices allowed). All participants provided informed consent to participate in the study, and ethical approval was granted by the Newcastle and North Tyneside Ethics Committee (reference: NE/15/0178).

2.2 | Study procedures and outcome measures

Eligible patients were asked to complete the DM1-Activ^{C} as part of the study visits. We also recorded data from patients concerning their basic demographic and clinical characteristics as shown in Table 1. As an outcome measure of functional ability, the 6MWT was included for comparison. The test was performed in a 25-m long corridor in Newcastle and 20-m long corridor in London. Per currently agreed procedures,[6] patients received feedback every minute of the current test time (ie the time left of the total 6-minute test time).

2.3 | Genetic analysis

Recent studies[14] have shown that the length of the repeat expansion at birth as expressed by the progenitor allele is the most relevant predictor of disease onset and severity later in life, while disease progression is closely related to the rate of somatic expansion over time within different tissues (approximated as the difference between modal length at the time of DNA sampling and the progenitor allele, where the modal allele length is the most common repeat length in that tissue at time of sampling). For our analysis, we included both CTG repeat counts from blood DNA (ie the

TABLE 1 Demographic and clinical characteristics of the patient sample

Age, mean (SD) years	46 (13)
Sex, female	97 (51%)
Age at first symptoms, mean (SD) years*	26 (16)
Disease duration, mean (SD) years**	20 (12)
Type of DM1***	
Classical	135 (73%)
Congenital	9 (5%)
Late onset	40 (22%)
Part-time wheelchair dependency	25 (13%)
Six-minute walk test result, mean (SD) metres*	420 (152)
Muscular Impairment Rating Scale (MIRS) score	
I	21 (11%)
II	55 (29%)
III	41 (21%)
IV	57 (30%)
V	18 (9%)
Education, mean (SD) years completed****	15 (3)
Current occupation	
Employed	79 (41%)
Retired	26 (14%)
Long-term sick leave	45 (23%)
Unemployed/other	42 (22%)

Note: Data presented as n (%) if not specified otherwise. Total sample: n = 192, excluding missing values for n = 9 patients (*), n = 10 patients (**), n = 8 patients (***), and n = 5 patients (****). Myotonic dystrophy type 1 (DM1).

estimated progenitor and modal allele length) to allow comparison of data. CTG repeat length was estimated from blood DNA by the small-pool PCR assay as described by Gomes-Pereira et al[15] using the CTG repeat-flanking primers DM-C and DM-DR.[14,16] Replicate reactions were separated by gel electrophoresis, Southern blotted and hybridized using a ^{32}P-labelled 56 × CTG repeat probe. Bands were detected by autoradiography and sized by comparison against the DNA molecular weight marker, using CLIQS software (TotalLab UK Ltd.). The bottom edge of the expanded allele bands was used to determine the estimated progenitor allele length.[14] The densest part of the expanded allele bands was used to estimate the modal allele length at the time of DNA sampling (ie CTG modal alleles). The CTG repeat length analysis was only available for patients recruited via Newcastle University, Newcastle upon Tyne.

2.4 | Statistical analysis

We calculated the distribution of replies across all items and levels within the DM1-Activ^{C} and the corresponding mean item scores, ranging from 0 ("Not possible to perform") to 2 ("Possible, without any difficulty"), as well as the mean transformed total instrument score (ranging between 0 and 100, where a higher/lower score indicates a higher/lower ability to perform activities of daily living). We related the total score to two previously derived[9] threshold values (amended for the transformed scale): ≤30 (indicating severe limitations in activities of daily living) and >70 (indicating relatively few limitations). We summarized the three most difficult activities (ie the items with the lowest mean scores), as well as the three easies activities (ie the items with the highest mean scores), in the pooled sample and by patient age (ie <30 years vs ≥30 years, as limitations in activities of daily living, as well as the DM1-Activ^{C} scoring algorithm, have been shown to be different for these strata[9]), respectively. We also calculated the proportion of patients able to perform (with or without help) included activities of daily living (ie "Possible, without any difficulty" or "Possible, but with some difficulty" vs "Not possible to perform"). We compared the proportion of patients able to perform (with or without help) included activities of daily living across four categories of disease duration (<10, 10-20, 20-30 and ≥30 years, measured from onset) using the chi-squared test, and compared DM1-Activ^{C} total scores by sex and type of DM1 defined based on age at onset of disease (congenital: ≤11 months; classical: 12 months–40 years; and late adult: >40 years, with a Muscular Impairment Rating Scale (MIRS) score <III, and <150 CTG repeats) using Welch's *t* test. We also estimated Pearson's correlation coefficients to investigate the crude relationship between DM1-Activ^{C} total scores and disease duration, CTG repeat length, MIRS score and 6MWT result, respectively, and also derived linear trends using the ordinary least squares method. Finally, to further explore the relationship between estimated progenitor CTG repeat

length and performance of activities of daily living, we fitted an ordinary least squares regression model to the study data, with the mean DM1-Activ^C total score as the dependent variable and estimated progenitor CTG repeat length and age, as well as an interaction variable between estimated progenitor CTG repeat length and age, as independent variables (with estimated progenitor CTG repeat length normalized by log transformation).[14] The significance level was set to 0.05, Bonferroni adjusted for multiple comparisons: 0.05/20 = 0.003. All analyses were conducted in Stata 14.

3 | RESULTS

A total of n = 192 adult patients with DM1 met the study inclusion criteria and completed the DM1-Activ^C in accordance with the instructions. Summary descriptive statistics of the sample are presented in Table 1. Mean estimated progenitor and modal allele length, available for n = 104 and n = 102 patients, respectively, were 245 CTG repeats (SD: 178, range: 54-916) and 479 CTG repeats (SD: 346, range: 57-1441).

The distribution of replies to the DM1-Activ^C is presented in Figure 1, sorted by mean item score (ranging between 0 and 2). Patients were able, although with some difficulty, to perform most activities of daily living captured by the scale. The three most difficult activities (ie the items with the lowest mean scores) were "Run" (mean item score: 1.0), "Carry and put down heavy object (10 kg)" (1.1) and "Stand on one leg" (1.2). The three easiest activities were "Eat soup" (1.9), followed by "Wash your upper body" (1.9) and "Take a shower" (1.8). In patients <30 years of age (n = 19), the three most difficult activities were "Carry and put down heavy object (10 kg)" (0.8), "Vacuum clean" (1.3) and "Stand up from squatting position" (1.3), and the three easiest "Eat soup" (1.9) and "Dress your lower body" (1.8), and "Take a shower" (1.8). Results for patients ≥30 years of age (n = 173) were identical to estimates for the total sample.

The mean DM1-Activ^C total score was estimated at 71 (SD: 21, range: 28-100, 95% CI: 68-74). Approximately 1% (2 of 192) scored ≤30 (indicating severe limitations in activities of daily living) and 47% (91 of 192) >70 (indicating relatively few limitations). There were no significant differences between women and men in estimated mean DM1-Activ^C total scores (70 vs 72, P = .530). The mean score was 72 (95% CI: 68-75) for patients with classical DM1, 51 (36-66) for congenital DM1, and 73 (67-80) for late onset DM1 (classical vs congenital: P = .015; classical vs late onset: P = .618; and congenital vs late onset: P = .010).

We found disease duration to be significantly associated with the mean DM1-Activ^C total score (ρ = −0.29, P < .001). Specifically, the mean score in patients with a duration of <10 years was estimated at 79 (SD: 22, 95% CI: 71-86, n = 40), between 10 and 20 years at 75 (SD: 19, 95% CI: 70-80, n = 57), between 20 and 30 years at 67 (SD: 21, 95% CI: 60-73, n = 46) and ≥ 30 years at 62 (SD: 20, 95% CI: 56-69, n = 39). Figure 2 presents the proportion of patients able (with or without difficulties) to perform the activities of daily living exhibiting the largest change across categories of disease duration (ie <10 years vs ≥30 years). Results for additional tasks covered by the scale, exhibiting a mean change across categories of disease duration of <2.10 percentage units, are presented as supplemental material online.

Results from our correlation analysis showed that DM1-Activ^C total score was significantly associated with estimated progenitor CTG repeat length (ie the length of the repeat expansion at birth) (ρ = −0.36, P < .001), modal allele CTG repeat length (ie the length of the repeat expansion at DNA sampling) (ρ = −0.42, P < .001), MIRS score (ρ = −0.61, P < .001) and 6MWT result (ρ = 0.70, P < .001). Scatter plots for these variable-pairs, as well as crude linear trends, are presented in Figure 3. Outcomes from our regression analysis also showed that the estimated progenitor CTG repeat length and age were able to explain 27% of the variance in DM1-Activ^C total scores (R^2 = .27, P < .001). In total, five patients had CTG repeat interruptions, and their mean DM1-Activ^C total score was 62 (SD: 15, range 48-84, 95% CI: 43-81).

4 | DISCUSSION

Our results show that most men and women with DM1 experience some limitations in performance of many common household and leisure tasks (Figure 1), but also reveal that only a few activities were impaired in a progressive pattern from onset. In particular, irrespective of the duration of the disease, the vast majority of patients in our sample were still able to perform *basic* activities of daily living (eg personal hygiene and grooming, showering, and eating), with the exception of functional mobility/transfers (eg walking uphill and running). Additionally, most patients (>80% per task) were able to perform *instrumental* activities of daily living (eg cleaning and shopping), as well as visiting family or friends. In general, across the evolution of the disease, the activities affected the most were those with major demands of muscle strength, stability and coordination, for example standing on one leg, carrying and putting down heavy objects, and running. Yet, even after 30 years of onset of symptoms, almost half of our cohort were still able, although with some problems, to perform the most difficult tasks studied.

We found the order of examined items in terms of difficulty to be broadly comparable to the ranking from the previous Rasch analysis of the DM1-Activ^C.[9] However, when comparing our results with the Rasch study, it is important to keep in mind that we only considered patients that were able to walk a minimum of 10 m without the assistance of somebody else and who had the capacity to understand the study information and consent to participating in the study, which means that the most functionally and cognitively impaired patients were not included. Future research should aim to also include patients with lower levels of ability, as well as explore changes over time to further broaden the understanding of the impact of DM1 across the evolution of the disease.

The CTG repeat length in the PhenoDM1 patient cohort was found to correlate with DM1-Activ^C total score, MIRS and the 6MWT. Yet, all three measures varied markedly between individuals in the cohort. The estimated inherited, or progenitor, allele length

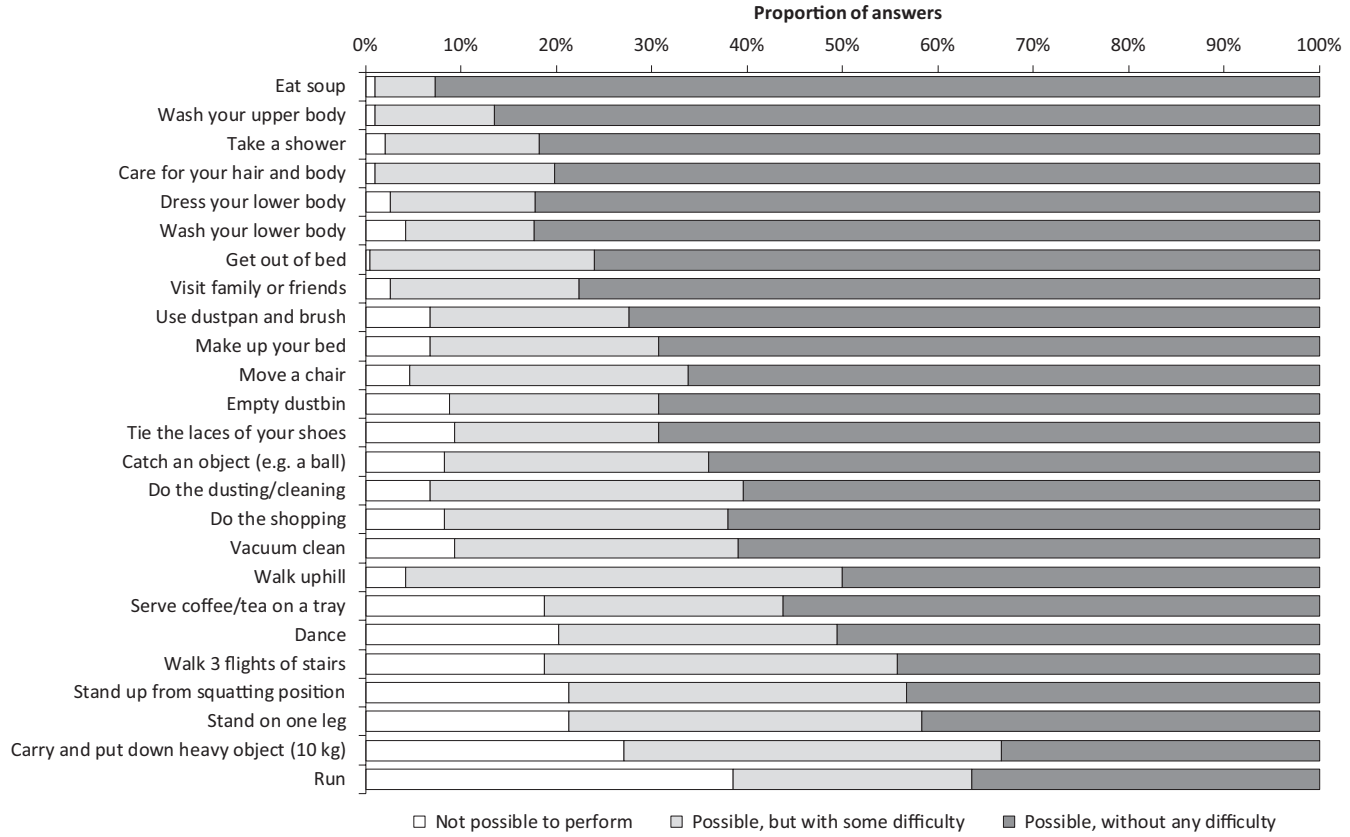

FIGURE 1 Distribution of replies to the DM1-Activ^C items. Note: The figure presents the distribution of replies to the DM1-Activ^C items, each described in three levels ("Not possible to perform, "Possible, but with some difficulty" and "Possible, without any difficulty")

was previously shown to be the single largest factor accounting for variation in age at disease onset, with a further contribution from somatic instability.[14] Although some of the variability in age at onset remains unexplained, this suggests that repeat length is the most important determinant of the underlying biology of the disease.

Five patients in the PhenoDM1 cohort were found to have AciI-sensitive variant repeat interruptions. These have previously been shown to result in reduced somatic instability and delayed disease onset.[17,18] Further, in several different phenotypic measures, individuals with variant repeats scored better.[17,18] This does not appear to be the case in the current study for the DM1-Activ^C total score, which did not differ significantly between individuals with and without variant repeats. However, the number of identified individuals bearing variant repeats in the cohort is relatively small. In any future natural history studies or clinical trials, it will be very important to identify any individuals with variant repeat interruptions, as they can profoundly alter symptoms and, potentially, response to therapies.

Comparing our results with previous research based on the DM1-Activ^C, selected outcomes of the scale have been described as part of three recently published studies. Similarly to our findings with respect to the 6MWT, DiPaolo et al[11] found the scale for the assessment and rating of ataxia (SARA) to be significantly associated with the DM1-Activ^C total score ($\rho = -0.75$, $P < .001$). Moreover, in a study investigating body composition in DM1, Sedehizadeh et al[12] estimated the mean DM1-Activ^C total score at 28 (using the first version of the scale[6]) in a sample of 38 patients with DM1 from the UK (mean age: 42 years; 47% female). However, due to differences in instrument versions, this point estimate is not easily comparable to our data. Finally, the DM1-Activ^C was the primary outcome measure in the OPTIMISTIC clinical trial,[13] but no scale data were published except for differences in total scores between examined interventions.

Our findings are broadly comparable to results from previous research of the impact on DM1 on activities of daily living quantified using measures other than the DM1-Activ^C. For example, Kierkegaard et al[19] found dependence in "personal activities" (eg feeding, bathing, dressing, toileting and transfer) and "instrumental activities" (eg shopping, cleaning, cooking and transportation) in 16% and 39% of patients, respectively, and participation restrictions in "social and lifestyle activities" (eg domestic chores, work/leisure and outdoor activities) in 52% of patients. Van Heugten et al[20] found most restrictions concerning sports/leisure activities and activities outside the home environment, but also housekeeping based on data recorded via the Utrecht Scale for Evaluation of Rehabilitation-Participation. Similar findings were described by Gagnon et al,[21] who found most impact in the "Recreation," "Mobility" and "Housing" domains (in addition to "Employment") based on the Assessment of Life Habits (LIFE-H) tool in a sample of Canadian adults with DM1.

In our sample, the crude mean DM1-Activ^C total score was similar for women and men with the disease. In contrast, previous

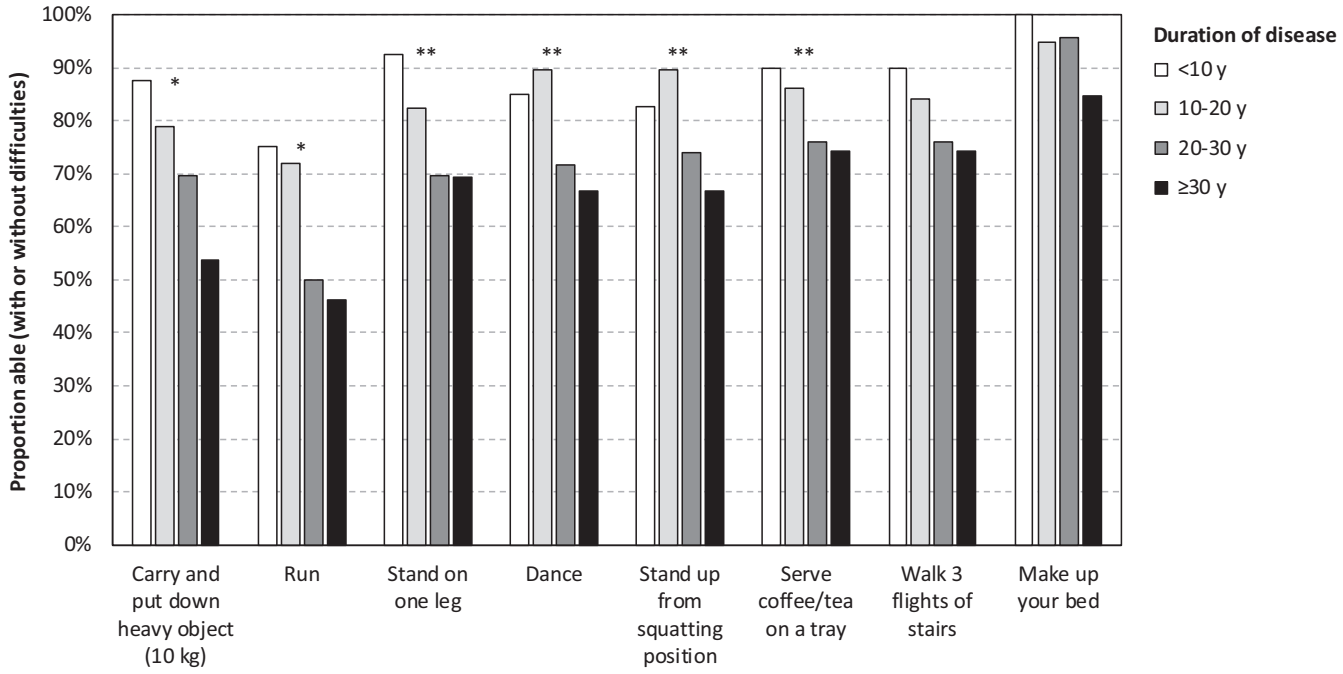

FIGURE 2 Proportion of patients able to perform selected activities of daily living, by disease duration. Note: The listed activities exhibited the largest change (in proportion of patients able with or without difficulties) across categories of disease duration (ie <10 y vs ≥30 y). Proportion able (with or without difficulties) refers to the second and third item-levels (vs the first level). *P-value <.010. **P-value <.050

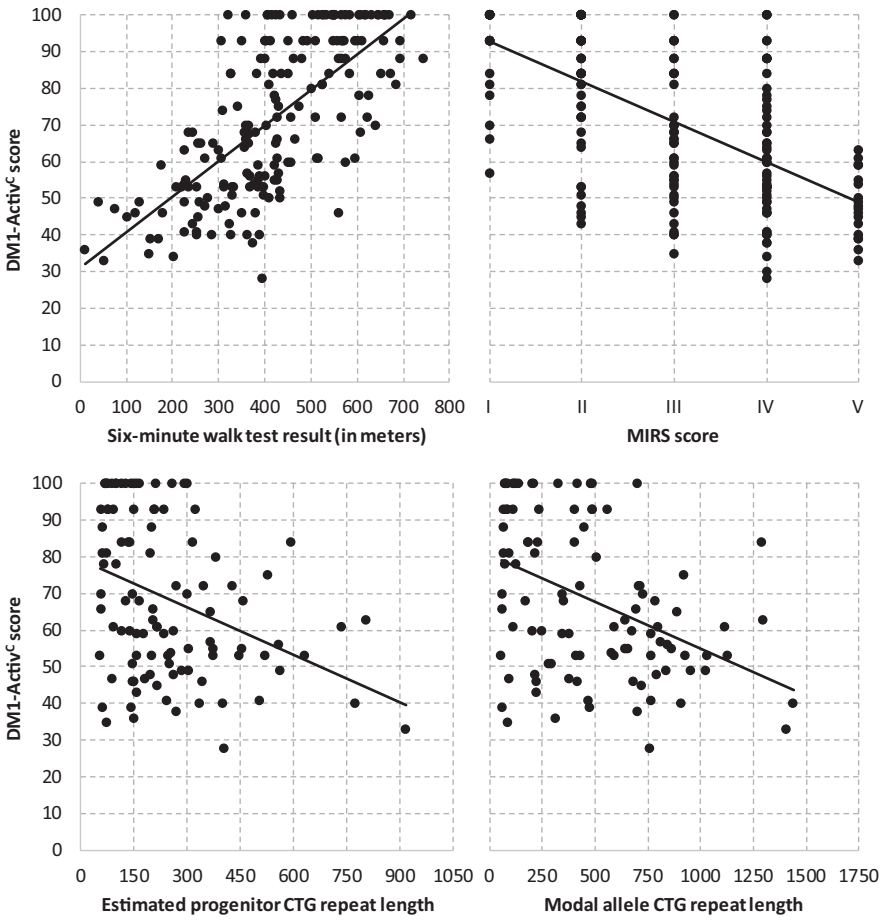

FIGURE 3 Association between 6MWT result, MIRS score, cytosine-thymine-guanine (CTG) repeat length and DM1-Activ^C total score. Note: Six-minute walk test (6MWT) result was available for n = 183 patients. Estimated progenitor and modal allele CTG repeat length were available for n = 104 and n = 102 patients, respectively. The Muscular Impairment Rating Scale (MIRS). DM1-Activ^C scores range from 0 to 100, where a higher/lower score represents a higher/lower ability to perform activities of daily living. Linear trend line for 6MWT: $y = 31.077 + 0.097x$ ($R^2 = .49$). Linear trend line for MIRS: $y = 103.769 - 10.996x$ ($R^2 = .33$). Linear trend line for estimated progenitor CTG repeat length: $y = 78.938 - 0.043x$ ($R^2 = .13$). Linear trend line for modal allele CTG repeat length: $y = 80.618 - 0.026x$ ($R^2 = .18$)

research[22] has indicated that men are subject to greater morbidity, including more severe muscular disability and cognitive impairment, and higher mortality. In our previous work,[23] we found that that a larger proportion of women with DM1 experienced considerable fatigue and depressive feelings; however, there was no difference between sexes with respect to the overall disease burden. Based on our data, it was not possible to further analyse potential sources for these inconsistent findings, but future studies of these topics are warranted.

A limitation of our study concerns the fact that we interpreted limitations in activities of daily living in relation to full ability, despite the fact that a non-trivial proportion of members of the general population also experience some impairment. Additionally, it is worth noting that the DM1-Activ^{C} data may be subject to bias due to, for example, incorrect reporting. However, per the study criteria, patients with significant cognitive impairment were not eligible to participate, which should help minimize errors associated with the data collection.

In conclusion, we show that DM1 impairs performance of activities of daily living, in particular those requiring a high degree of muscle strength, stability, and coordination. Yet, across the evolution of the disease, the majority of patients will still be able to perform most basic and instrumental activities of daily living.

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CONFLICT OF INTEREST

This study has been supported by the National Institute of Health Research (NIHR) under the RD-TRC programme and by the Wyck Foundation. Dr Landfeldt is an employee of ICON plc (Stockholm, Sweden), outside the submitted work. Dr Monckton reports having a research contract with Newcastle University during the conduct of the study; personal fees from AMO Pharma, Vertex, Charles River, BridgeBio, Small molecule RNA, and personal fees for scientific advisory board membership from Triplet Therapeutics and LoQus23, outside the submitted work. Dr Monckton is on the scientific advisory board of the Myotonic Dystrophy Foundation and is a scientific advisor to the Myotonic Dystrophy Support Group. Dr Faber reports research support from the European Union's Horizon 2020 research and innovation programme Marie Sklodowska-Curie grant for PAIN-Net, Molecule-to-man pain network (grant no. 721841), the European Union 7th Framework Programme (grant n°602273) for the PROPANE study, Prinses Beatrix Spierfonds, and Grifols and Lamepro for a trial on IVIg in small fibre neuropathy, outside the submitted work. Dr Faber has participated in steering committees for studies in small fibre neuropathy of Biogen/Convergence and Vertex outside the submitted work. Dr Merkies received funding for research from the Talecris Talents programme, the GSB CIDP Foundation International, Princes Beatrix foundation, and from the European Union 7th Framework Programme (grant n°602273) outside the submitted work. Furthermore, a research foundation at the University of Maastricht received honoraria on behalf of Dr Merkies for participation in steering committees of the Talecris ICE Study, LFB, CSL Behring, Novartis, Grifols, and Octapharma outside the submitted work. Dr Merkies serves on the editorial board of the Journal of Peripheral Nervous system, is a member of the Inflammatory Neuropathy Consortium (INC), and member of the Peripheral Nerve Society. Dr Turner reports financial support from the Biomedical Research Council and the National Brain Appeal. Dr Lochmüller is an investigator of the Medical Research Council UK Centre for Neuromuscular Diseases (reference G1002274, grant ID 98482). The other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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