Progression of disease burden among boys with Duchenne muscular dystrophy (DMD) according to ambulatory status and age at loss of ambulation (LoA)

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Background & Objective:

- **Duchenne muscular dystrophy (DMD)** is an X-linked disease affecting the dystrophin protein found in muscles.[1]
  - Individuals with DMD often begin to show **symptoms of muscle weakness** and **delays in or inability to achieve physical developmental milestones** as young children.[1]
- DMD progression is marked by **progressive loss of lower and upper extremity strength and function**, **pulmonary** and **cardiac disease**, eventually requiring ventilation and feeding tubes, and then death in young adulthood.[1] Treatment with glucocorticoids has been associated with delayed ambulation loss and reduced risk of death.[2]
- While progression of DMD through clinical milestones is well documented, **few studies explore how loss of ambulation (LoA) is associated with other outcomes in DMD**. This is particularly important as, for example, progression of disease-related milestones has been shown to differ with age at LoA (AaLoA).[2]
- Moreover, existing studies tend to be short-term and focused on clinical endpoints; **broader examinations of patient burden of disease are lacking.**

Objective:

This study aimed to characterize disease progression in boys with DMD according to ambulatory status and AaLoA.

Methods:

Data source & study population

- CINRG-DNHS (**C**ooperative **I**nternational **N**euromuscular **R**esearch **G**roup - **D**uchenne **N**atural **H**istory **S**tudy, NCT00468832) was a prospective, longitudinal study in which patients with DMD were followed up between 2006 and 2016.
  - In total, 440 patients with DMD received standard of care (corticosteroid or palliative therapies) across 20 centers in nine countries.[2,3]
- In the present observational study, all patients with LoA data were identified from the CINRG DNHS and included for analysis**.**
  - **LoA** was defined by self/parent-reported full-time wheelchair use.
- Included individuals were divided into **three AaLoA groups**:
  - <10 years
  - 10-13 years
  - >13 years
- Patients who were missing AaLoA data, but who remained ambulant throughout the study and were at least 13 years old at their last visit, were also included, as AaLoA >13 years could be inferred.

Data analysis

- Disease burden was measured with the **Major Adverse Dystrophinopathy Events (MADE)** score:
  - This score was developed by clinical experts to capture disease burden across body systems and severities, and comprises **cardiac, myopathy, nutrition status, and respiratory domains**.[4]
  - Scores were calculated for each visit by summing across scoring items (missing items contributed 0 points), with **higher scores indicating higher disease burden** (max: 92 points).
  - A "non-myopathy MADE score" was also calculated using only the pulmonary, cardiac, and nutrition domains to build composite outcomes that reflect the variables deemed most important by clinical experts (max: 75 points).
- Least-squares (LS) mean change (and 95% confidence interval [CI]) in MADE scores per 1-year age increase were calculated for overall MADE and non-myopathy MADE scores.
  - These were calculated for the overall study population and by AaLoA category, for the time periods during which patients were non-ambulatory and ambulatory.
- **MADE change per 1-year age increase** was estimated using unadjusted and adjusted linear mixed models (LMM).

Methods continued:

Unadjusted LMM:

- Fitted to optimize restricted maximum likelihood, and included parameters for:
  - Age at visit (continuous)
  - Patient-level AaLoA (<10 years, 10-13 years, or >13 years)
  - Ambulation status at visit (ambulatory vs. non-ambulatory)
  - Interactions for age/AaLoA, age/ambulation status, and ambulation status/AaLoA.
- Random intercepts and slopes (relative to age) were used to account for patient-level effects across repeated visits.

Adjusted LMM:

- Specified the same way as the unadjusted model, but also included fixed effects for:
  - Patient age at diagnosis (tertiles)
  - Cumulative glucocorticosteroid use at the time of the visit (never to <1 month, 1 month to <1 year, ≥1 year).

Results:

Participant characteristics

- Among 290 included patients (2,599 visits), mean (SD) age at enrollment was 13.1 (5.6) years (**Table 1**).
  - AaLoA <10 years: n=73
  - AaLoA 10-13 years: n=126
  - AaLoA >13 years: n=91
- Patients were primarily enrolled from the **United States (US, 42.1%**) and **non-US Americas** (**27.2%**).
- At enrollment, 51.0% of patients were non-ambulatory; non-ambulatory patients at baseline comprised 69.9% of those with AaLoA <10 years, 59.5% of those with AaLoA 10-13 years, and 24.2% of those with AaLoA >13 years.
- Across all AaLoA categories, mean (SD) overall MADE score at enrollment was 12.8 (11.0)
  - Mean (SD) non-myopathy MADE score was 7.6 (7.9) (**Table 1**).

Table 1. Baseline characteristics of boys and young men enrolled in the CINRG DNHS that had available AaLoA data (n=290 out of 440 participants)

Item	Overall (n=290)	Age at loss of ambulation		
		< 10 years (n=73)	10 - 13 years (n=126)	> 13 years (n=91)
Age in years, mean (SD)	13.1 (5.6)	12.6 (5.7)	13.6 (5.5)	12.8 (5.7)
Region, n (%)				
US	122 (42.1%)	43 (58.9%)	55 (43.7%)	24 (26.4%)
Americas (non-US)	79 (27.2%)	9 (12.3%)	32 (25.4%)	38 (41.8%)
Europe	36 (12.4%)	3 (4.1%)	15 (11.9%)	18 (19.8%)
Australia	21 (7.2%)	4 (5.5%)	8 (6.3%)	9 (9.9%)
India	32 (11.0%)	14 (19.2%)	16 (12.7%)	2 (2.2%)
Weight in kg, mean (SD)	43.3 (22.9)	45.0 (24.3)	44.9 (24.3)	39.7 (19.2)
Calculated height in cm, mean (SD)	143.9 (21.4)[a]	145.3 (22.1)[b]	146.6 (21.9)	139.1 (19.4)
Ambulatory status, n (%)				
Ambulatory	142 (49.0%)	22 (30.1%)	51 (40.5%)	69 (75.8%)
Non-ambulatory	148 (51.0%)	51 (69.9%)	75 (59.5%)	22 (24.2%)
Walker use, n (%)				
Occasionally	4 (1.4%)[c]	2 (2.9%)[d]	1 (0.8%)	1 (1.1%)
Previously but discontinued	38 (13.2%)[c]	11 (15.7%)[d]	20 (15.9%)	7 (7.7%)
Never use	245 (85.4%)[c]	57 (81.4%)[d]	105 (83.3%)	83 (91.2%)
Wheelchair use, n (%)				
Not used	104 (35.9%)	20 (27.4%)	37 (29.4%)	47 (51.6%)
Less than once per week	12 (4.1%)	0 (0.0%)	3 (2.4%)	9 (9.9%)
Once per week	4 (1.4%)	0 (0.0%)	2 (1.6%)	2 (2.2%)
3-5 times per week	4 (1.4%)	1 (1.4%)	1 (0.8%)	2 (2.2%)
Daily (part-time)	18 (6.2%)	1 (1.4%)	8 (6.3%)	9 (9.9%)
Daily (full-time)	148 (51.0%)	51 (69.9%)	75 (59.5%)	22 (24.2%)
Overall MADE score, max. 92 points				
Mean (SD)	12.8 (11.0)	17.0 (12.4)	13.5 (11.0)	8.5 (7.8)
Non-myopathy MADE score, max. 75 points				
Mean (SD)	7.6 (7.9)	9.4 (9.4)	8.0 (8.1)	5.6 (5.8)

Abbreviations: AaLoA=age at loss of ambulation; CINRG DNHS: Cooperative International Neuromuscular Research Group Duchenne Natural History Study; cm=centimeters; MADE=major adverse dystrophinopathy event; SD=standard deviation; US=United States.
Notes: [a]n=288; [b]n=71; [c]n=287; [d]n=70

Results continued:

Ambulatory period

- **While ambulatory**, **MADE score change** per 1-year age increase was **generally higher in the younger AaLoA groups,** indicating greater increases in burden.
  - Adjusted LS mean (95% CI) change per 1-year age increase:
    - For patients with AaLoA <10 years: **2.88 (2.40-3.35)**;
    - For 10-13 years: **2.38 (2.01-2.75)**; and
    - For >13 years: **1.86 (1.51-2.20) (Figure 1)**.
- Trends in disease burden with respect to AaLoA remained consistent for change in non-myopathy MADE score, with greater increases in non-myopathy burden among patients with younger AaLoA.
  - While ambulatory, adjusted LS mean (95% CI) change per 1-year age increase was:
    - AaLoA <10 years: **2.25 (1.81-2.69)**;
    - AaLoA 10-13 years: **1.77 (1.43-2.11)**; and
    - AaLoA >13 years: **1.39 (1.07-1.71) (Figure 1)**.

Non-ambulatory period

- **While non-ambulatory**, **MADE score change** per 1-year age increase was also **higher among patients with younger AaLoA**.
  - Adjusted LS mean (95% CI) change per 1-year age increase:
    - AaLoA <10 years: **2.95 (2.56-3.35)**;
    - AaLoA 10-13 years: **2.45 (2.16-2.74)**; and
    - AaLoA >13 years: **1.93 (1.55-2.31) (Figure 2).**
- Similarly, non-myopathy MADE scores indicated higher increases in non-myopathy burden among patients with younger AaLoA.
  - Adjusted LS mean (95% CI) change per 1-year age increase:
    - AaLoA <10 years: **2.64 (2.27-3.01);**
    - AaLoA 10-13 years: **2.17 (1.90-2.44)**; and
    - AaLoA >13 years: **1.78 (1.43-2.14)** (**Figure 2**).
- Compared to the ambulatory period, slightly greater increases in burden were observed across AaLoA groups in the non-ambulatory period, especially in non-myopathy MADE scores, suggesting faster worsening of burden while non-ambulatory. However, statistical testing was not conducted.

Figure 1. Estimated yearly overall and non-myopathy MADE score change by AaLoA for CINRG DNHS patients during their ambulatory period

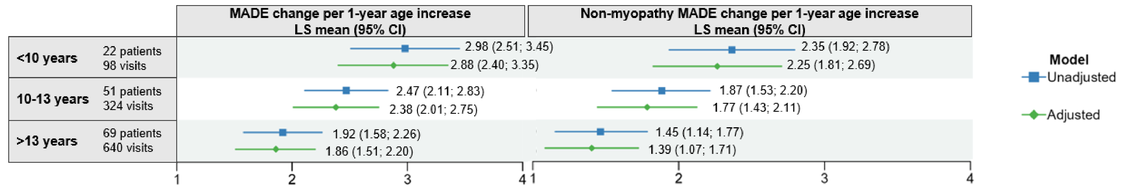
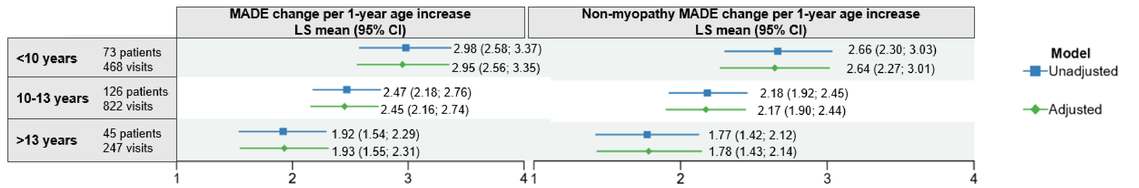


Figure 2. Estimated yearly overall and non-myopathy MADE score change by AaLoA for CINRG DNHS patients during their non-ambulatory period



Abbreviations: AaLoA=age at loss of ambulation; CI=confidence interval; CINRG DNHS=Cooperative International Neuromuscular Research Group Duchenne Natural History Study; LS=least squares; MADE=major adverse dystrophinopathy event; SD=standard deviation

Discussion:

- This analysis of data from a prospective, longitudinal study in DMD demonstrated that patients with later AaLoA had slower disease progression, as indicated by smaller increases in MADE & non-myopathy MADE scores.
- Disease progression also appeared slightly slower while patients were ambulatory compared to when they were non-ambulatory.
- Despite data limitations, results were derived from a substantial number of visits (>2,500 visits) over long-term follow-up.

Limitations:

- Standard care varied across sites, including use of steroids and cardiac testing. In particular, cardiac test results likely underestimate the prevalence of reduced cardiac function, which is a component of the MADE score. Missing data for MADE score components could possibly underestimate burden.
- As non-ambulatory status was defined as full-time wheelchair use, lack of access to wheelchairs may have influenced classification of non-ambulatory status, particularly in low income or developing settings.
- Given the inclusion only of patients with LoA data, sample sizes were small and resulting estimates may not generalize to other populations, or to the CINRG DNHS population as a whole.

Conclusion:

The study findings suggest that therapies that delay LoA may also delay progression of other DMD morbidities.

References:

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