THE NATURAL HISTORY OF BECKER MUSCULAR DYSTROPHY (BMD) – A LIVING SYSTEMATIC LITERATURE REVIEW

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BACKGROUND

- Becker muscular dystrophy (BMD) is caused primarily by in-frame mutations in the *DMD* gene; phenotype varies from asymptomatic to severe.[1-3]
- Progressive manifestations may include muscle weakness, loss of ambulation, cardiomyopathy, scoliosis, and respiratory insufficiency; cognitive disability may also be present yet nonprogressive. [1-3]

OBJECTIVE

- This study aimed to characterize the frequency and age at occurrence of key clinical milestones associated with BMD.

METHODS

Data collection

- A 'living' (periodically updated) systematic review initially conducted in 2019 was refreshed in 2022 using MEDLINE and EMBASE to identify articles describing the natural history of BMD.
- Articles published in patients with BMD, in English, from the year 2000 onwards were included.

Analysis & synthesis of data

Proportion of patients experiencing events

- The proportion of patients experiencing each milestone was reported by 'life-stage' age groups of 0-17, 18-40, and 41+ years using individual patient data (IPD) from those representative of the general BMD population (e.g., a study where subjects were enrolled consecutively from a neuromuscular clinic with no inclusion/exclusion criteria other than a a valid diagnosis of BMD).
  - For these analyses, data were extracted from tables/statements like "The patient was ambulating independently at age 22".
- Patients were reported by proportion per cognitive function level.

Mean age at event

- Mean age at clinical event was calculated using IPD and grouped data from patients experiencing the event.
- Data were extracted from populations both representative, and not, of the general BMD population (e.g., a "representative" study of consecutively-enrolled BMD patients vs. "non-representative" where inclusion of subjects with BMD was further restricted by criteria such as a certain genotype or decreased cardiac function).
  - For these analyses, data were extracted from information such as "The patient lost ambulation at age 15", or "The mean (SD) age at loss of ambulation for the group of 10 patients who lost ambulation was 30.2 (9.3) years".
- Results were visually compared to similar data for the allelic, more severe Duchenne muscular dystrophy (DMD).[4-9]

RESULTS

Systematic literature review

- From 4,948 abstracts screened, 175 publications were included.
- The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement guidelines were followed (**Figure 1**).[10]

Study and patient characteristics

- Half of the included studies were cross-sectional design; geographic regions of study primarily comprised Europe, Asia, and North America.
- Patients ranged in age from <1 to 88 years.
- Six percent of all included had corticosteroid use reported at baseline; however, use was poorly reported overall (76% of studies not reporting; **Table 1**).

Analysis & synthesis of data

Proportion experiencing events

- The proportion of patients with BMD experiencing events by 'life-stage' age groups (from IPD; **Figure 2**) varied by outcome.
  - The most frequently observed manifestations by age 41 years and older (used as a proxy for overall cumulative risk) were muscle weakness (84.6%) and cardiomyopathy (71.4%).
  - Approximately half of all patients aged 41+ experienced respiratory insufficiency or scoliosis.
  - The least observed outcome by age 41+ was loss of ambulation, with 36.1% of 36 patients losing ambulation.
- Amongst 32 patients with BMD, 53.1% had normal cognitive function (n=17), 34.4% had reduced cognitive function (n=11), and 12.5% had cognitive disability (n=4).

Mean age at event

- Amongst those who experienced the event, mean (SD) age at event was estimated as follows:
  - **Symptom onset - 12.5 (10.3) years (n=971)**
  - Decreased cardiac function – 19.4 (5.8) years (n=81)
  - **Muscle weakness - 20.2 (11.5) years (n=161)**
  - **Scoliosis - 24.9 (3.1) years (n=3)**
  - Decreased ambulatory function – 26.6 (15.5) years (n=134)
  - Respiratory insufficiency - 29.5 (9.4) years (n=192)
  - **Cardiomyopathy - 32.2 (13.5) years (n=188)**
  - **Loss of ambulation - 33.5 (13.3) years (n=262)**
  - **Ventilation (invasive or non-invasive) - 35.2 (12.0) years (n=21)**
  - **Death - 56.1 (20.6) years (n=11)**
- The above results in **bold** (primary events) are visually compared to published DMD values (**Figure 3**); transitional, early-stage outcomes (not bold) are not visualized due to lack of comparison values available.

Table 1. Baseline study and patient characteristics

Study characteristic	Number of studies	Percent (%)
Study design	**175**	**100%**
Cross-sectional	91	52%
Retrospective/prospective cohort*	10	6%
Clinical trial	14	8%
Case series	60	34%
Geographic region	**175**	**100%**
Europe	90	51%
Asia	36	21%
North America	24	14%
Middle East	8	5%
South America	10	6%
Global	5	3%
Africa	2	1%
Patient characteristic	**Number of patients**	**Percent (%)**
Corticosteroid use reported**	**4019**	**100%**
Yes	260	6%
No	697	17%
Mixed***	25	1%
Not stated	3037	76%
Age range	**0 to 88 years**	

*The period of follow up ranged from 3 weeks to 29 years
**Corticosteroid use reported for baseline where multiple timepoints reported
***Proportion treated not specified

Figure 1. PRISMA diagram

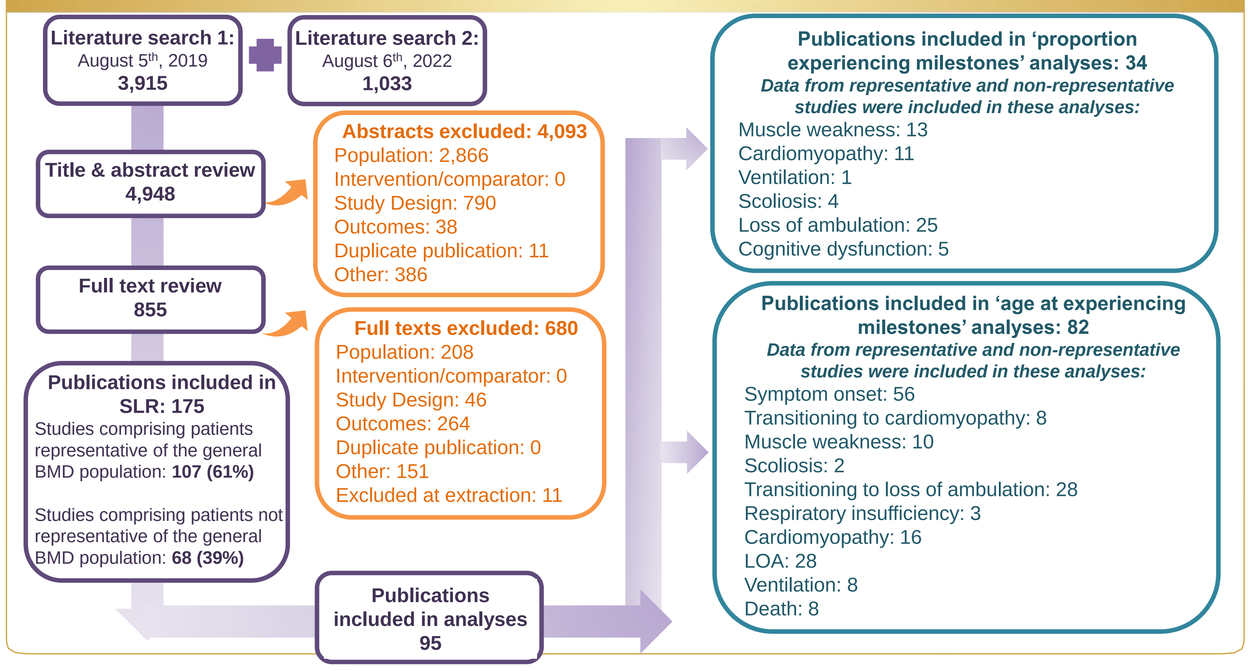
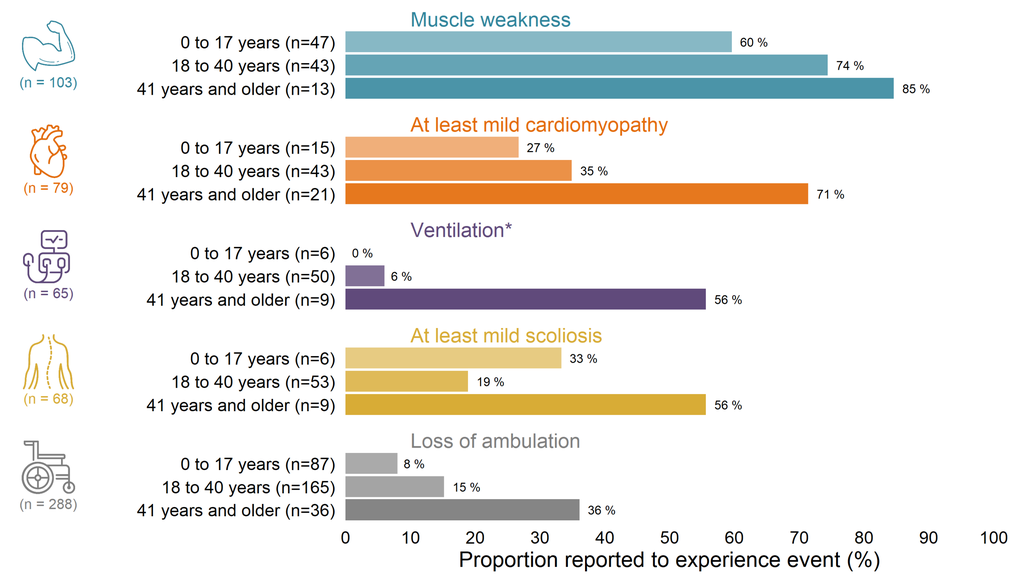
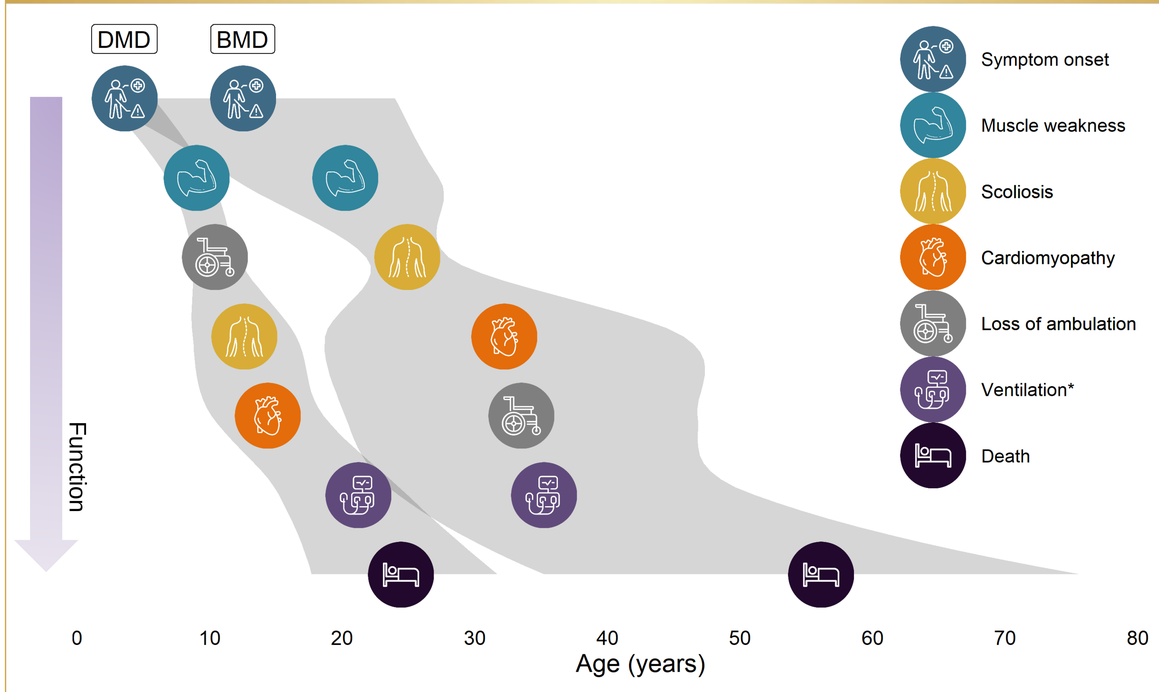


Figure 2. Proportion of patients with BMD experiencing milestones by 'life stage' age groups from IPD



Abbreviations: BMD = Becker muscular dystrophy; IPD – individual patient data
*Ventilation included both invasive or non-invasive types

Figure 3. Mean (SD) age at experiencing milestones amongst patients with BMD who experienced the event from IPD and grouped data; DMD values for comparison[4-9]



Abbreviations: BMD = Becker muscular dystrophy; DMD = Duchenne muscular dystrophy; IPD = individual patient data; SD = standard deviation; *Ventilation included both invasive or non-invasive types

DISCUSSION

Conclusions

- In many of these patients, key BMD-related events such as requiring ventilatory support and loss of ambulation were not observed; cardiomyopathy and scoliosis were eventually observed in approximately half of patients.
- In patients for whom clinical events occurred, age at occurrence was variable.

Limitations

- As only patients with BMD who experienced the events (**Figure 3**) are included in the calculation of mean age at event occurrence, rather than all patients who did and did not experience the events (as would be included in a survival analysis), age at event will be biased toward a younger age than would be observed in a real-world cohort.
- Ability to classify patients by distinct milestones was limited by heterogeneity in reporting.

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POSTER & REFERENCE LIST FOR THE 95 STUDIES INCLUDED IN THE ANALYSES PRESENTED CAN BE FOUND:

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