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ORIGINAL ARTICLE

Functional abilities, respiratory and cardiac function in a large cohort of adults with Duchenne muscular dystrophy treated with glucocorticoids

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Abstract

Background and purpose: The transition to adult services, and subsequent glucocorticoid management, is critical in adults with Duchenne muscular dystrophy. This study aims (1) to describe treatment, functional abilities, respiratory and cardiac status during transition to adulthood and adult stages; and (2) to explore the association between glucocorticoid treatment after loss of ambulation (LOA) and late-stage clinical outcomes.

Methods: This was a retrospective single-centre study on individuals with Duchenne muscular dystrophy (≥16 years old) between 1986 and 2022. Logistic regression, Cox proportional hazards models and survival analyses were conducted utilizing data from clinical records.

Results: In all, 112 individuals were included. Mean age was 23.4 ± 5.2 years and mean follow-up was 18.5 ± 5.5 years. At last assessment, 47.2% were on glucocorticoids; the mean dose of prednisone was 0.38 ± 0.13 mg/kg/day and of deflazacort 0.43 ± 0.16 mg/kg/day. At age 16 years, motor function limitations included using a manual wheelchair (89.7%), standing (87.9%), transferring from a wheelchair (86.2%) and turning in bed (53.4%); 77.5% had a peak cough flow <270 L/min, 53.3% a forced vital capacity percentage of predicted <50% and 40.3% a left ventricular ejection fraction <50%. Glucocorticoids after LOA reduced the risk and delayed the time to difficulties balancing in the wheelchair, loss of hand to mouth function, forced vital capacity percentage of predicted <30% and forced vital capacity <1 L and were associated with lower frequency of left ventricular ejection fraction <50%, without differences between prednisone and deflazacort. Glucocorticoid dose did not differ by functional, respiratory or cardiac status.

Conclusion: Glucocorticoids after LOA preserve late-stage functional abilities, respiratory and cardiac function. It is suggested using functional abilities, respiratory and cardiac status at transition stages for adult services planning.

KEYWORDS
cardiac function in adults with DMD, EK scale in adults with DMD, glucocorticoid dose in adults with DMD, respiratory function in adults with DMD, transition to adulthood in DMD

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an inherited X-linked recessive neuromuscular disorder due to variants in the *DMD* gene [1] leading to absence of the structural protein dystrophin [2], progressive limb girdle muscle weakness, loss of ambulation (LOA) by age 10–14 years [3], dilated cardiomyopathy and respiratory insufficiency [2].

The natural history of individuals with DMD has changed over the past 30 years due to the implementation of standards of care (SoC) [4] in terms of ventilatory support, glucocorticoid treatment, proactive cardiac intervention and multidisciplinary care. At the John Walton Muscular Dystrophy Research Centre (JWMDRC) glucocorticoids were introduced as part of the treatment of individuals with DMD in the 1990s [5]. Glucocorticoids have increased life expectancy from a mean age of 19 years in the 1960s [6] to a current mean age of 24.0–28.1 years [7–9]. Novel therapeutic approaches are under investigation in DMD and their long-term effect on motor function and life expectancy remains to be explored [10, 11].

Glucocorticoids [12] delay the age of LOA by 2–3 years [3, 13], preserve upper limb, cardiac and respiratory function and reduce orthopaedic complications [14–17]. The 2018 SoC for DMD recommends continuing glucocorticoids during non-ambulatory stages and states that older glucocorticoid-naïve individuals might benefit from glucocorticoid initiation [4]. However, glucocorticoid usage decreases after LOA, with only 15% and 4.4% of individuals in their 20s and 30s, respectively, being on glucocorticoids [16]. The optimal regimen, type and dose in adults with DMD remains elusive [18].

Individuals with DMD typically transition to adult neurology or neuromuscular services at ages 14–18 [19, 20]. This process is expected to be a continuum of a multidisciplinary and supporting programme initiated at the time of diagnosis and extends to the transition period to adult services until the last stages of the condition [19]. Recently, SoC for adults with DMD in the UK have been published [21]. Informing adult services about specific clinical features of this group is essential for planning and delivery of appropriate care, impacting quality of life and survival. In our neuromuscular centre, transition is within the same team; however, there are dedicated transition clinics for some specialties, such as respiratory clinics.

This study aims (1) to describe treatment, functional abilities, respiratory and cardiac status of individuals with DMD during the transition to adult services and in adult stages; and (2) to explore the association between glucocorticoid treatment after LOA and late-stage clinical outcomes.

MATERIALS AND METHODS

This is a retrospective study of adults with DMD followed up at a highly specialized service in neuromuscular diseases, the JWMDRC, UK. Individuals were assessed every 6–12 months by clinicians and physiotherapists specialized in neuromuscular diseases. Clinical notes were reviewed to collect demographic, genetic, treatment [4, 5, 22–24], functional abilities (Egen Klassifikation [EK] scale version 2) [25–27], respiratory and cardiac data [28].

The inclusion criteria were (i) males genetically diagnosed with DMD ≥16 years old at last assessment (LA) and (ii) ambulant or non-ambulant at LA. LOA was defined as the age at which the individual was reported as a fulltime wheelchair user with no subsequent ambulation [29].

The glucocorticoid status after LOA, hereinafter glucocorticoid status, was classified as prednisone/prednisolone (PDN), deflazacort (DFZ) or glucocorticoid-naïve—this last category included individuals who discontinued glucocorticoids before or at LOA.

Study approval was obtained from the Newcastle upon Tyne Hospitals Register Audit, Newcastle Upon Tyne, UK (Caldicott approval number 8275), and the study conforms with World Medical Association Declaration of Helsinki.

Statistical analysis

Data were expressed as number and percentage for categorical variables and as mean ± SD and/or median and interquartile range for quantitative variables, as appropriate.

Logistic regression and Cox proportional hazards models explored the associations between glucocorticoid status and functional, respiratory and cardiac milestones. Time to late-stage milestones after LOA were explored by survival analysis. No multiple comparisons correction was performed.

Statistical analysis was performed using IBM SPSS statistics version 28. Adjusted survival analysis for late-stage disease milestones was conducted in R (R Core Team, 2023) and figures were produced using the package adjustedCurves version 0.10.1 [30]. A level of significance of $p < 0.05$ was used in all the analyses.

Extended materials and methods and statistical analysis are available in Appendix 1.

RESULTS

A total of 112 individuals with DMD were included. The mean age at LA was 23.4 ± 5.2 years and 86.6% (97/112) were ≥18 years old (Table 1). The cohort's dates of birth extended from June 1971 to December 2005, and the study period extended from July 1986 (date of the first genetic diagnosis) to July 2022 (date of last individual follow-up) (Table 1). Eighty-six individuals (77.0%) were born before the year 2000, the time when more consistent SoC, including routine glucocorticoid prescription, were implemented [31, 32] (Appendix S1).

The most frequent *DMD* variants were out of frame deletions (67.9%, 76/112). Amongst them, 76.3% (58/76) were amenable to exon skipping. Specifically, out of frame deletions amenable to skipping exon 51 were the most frequent (26.0%, 15/58) (Appendix S1).

TABLE 1 Demographics and disease milestones data

Total cohort[a]	***n***	**112**
Demographics, Mean SD (min-max) [y][b]		
Age at genetic diagnosis	108/112	5.4 ± 3.2 (0.0 - 19.0)
Age at last assessment	112/112	23.4 ± 5.2 (16.1 - 39.2)
Age of death	47/47	25.0 ± 5.1 (17.2 - 37.0)
Age of LOA	112/112	12.1 ± 3.1 (6.4 - 21.3)
Follow up time since genetic diagnosis	108/112	18.5 ± 5.5 (4.4 - 33.8)
Follow up time since LOA	110/112	11.4 ± 6.2 (0.5 - 29.2)
Glucocorticoid treatment related time/ages, Mean SD (min-max) [y]		
GC duration	84/84	10.7 ± 6.0 (0.5 - 19.5)
Time on GC after LOA, PDN group	26/28	7.0 ± 4.0 (7.3, 0.9 – 16.0)*,c
Time on GC after LOA, DFZ group	44/44	8.0 ± 4.4 (8.0, 0.3 – 16.1)*,c
Age of GC initiation	82/84	7.9 ± 3.9 (3.3 - 27.0)
Before LOA	73/75	7.00 ± 2.3 (3.3 - 16.5)
After LOA	9/9	16.1 ± 5.6 (10.2 - 27.0)
Age of stopping GC	31/31	12.7 ± 4.9 (6.9 - 35.0)
Before LOA	10/10	9.7 ± 2.3 (6.9 - 14.5)
After LOA	21/21	14.2 ± 5.5 (8.6 - 35.0)
Age of switching GC	13/13	13.2 ± 3.1 (8.5 - 17.3)
Time to stopping GC from LOA	21/21	3.4 ± 2.6 (0.3 - 10.1)
Time to stopping GC before LOA	10/10	2.4 ± 2.8 (0.8 - 8.1)
Respiratory function related time/ages, Mean SD (min-max) [y]		
Age of individuals with FVC ≤ 1 litre	66/67	17.2 ± 5.1 (6.8 - 28.2)
Individuals on GC after LOA	32/67	18.4 ± 6.0 (7.0 – 28.2)
Individuals not on GC after LOA	34/67	15.5 ± 4.4 (9.0 – 25.2)
Age of Nocturnal NIV	67/67	18.5 ± 3.8 (11.8 – 35.8)
Age of Daytime NIV	21/24	22.5 ± 4.8 (12.9 - 34.7)
Cardiac function related time/ages, Mean SD (min-max)		
Age of LEVF<50% or FS<25% [y]	60/60	18.1 ± 5.0 (10.2 - 38.0)
Age ACEI/ARAII initiated [y]	106/112	15.2 ± 4.0 (5.0 – 38.8)
Perindopril dose at last follow up[d] [mg/d]	71/71	6.7 ± 2.3 (1.2 – 12.0)

Abbreviations: ACE, Angiotensin-converting enzyme inhibitors; ARAII, Angiotensin II receptor antagonists; DFZ, deflazacort; FS, fractional shortening; GC, Glucocorticoid; LOA, loss of ambulation; LVEF, left ventricular ejection fraction; Max, maximum; Min, minimum; NIV, Non-invasive ventilation; PDN, prednisone/ prednisolone; SD, standard deviation.

*Mean SD (median, min max) [y]

[a]Frequency of individuals by birth decade (year): 1971 – 1979, $n=2$; 1980 -1989, $n=21$; 1990 – 1999, $n=63$; 2000 – 2005, $n=26$.

[b]Demographics and disease milestones data for individuals born before and after the year 2000 available on Appendix S1.

[c]Mean time on GC after LOA between individuals on PDN and DFZ, Independent sample T test, $p=0.6$

[d]One hundred and six individuals were receiving ACEI/ARAII at last assessment, of whom 75 were on Perindopril. Therefore, the mean dose of Perindopril at last assessment is reported.

Glucocorticoid treatment

Glucocorticoid prescription, regimen and type

Twenty-eight individuals (25.0%, 28/112) were glucocorticoid-naïve (Figure 1a). Glucocorticoids were initiated in childhood for 67.0% (75/112) of the individuals, with daily PDN being the most frequent regimen/type (50.0%, 56/112). The mean age of glucocorticoid initiation was 7.0 ± 2.3 years (median 6.7 years) (Table 1).

In the assessment prior to LOA, 58.0% (65/112) of the individuals were on glucocorticoids, with daily PDN constituting 30.4% (34/112) (Figure 1a). Ten individuals discontinued glucocorticoids before LOA, at a mean age of 10.0 ± 2.5 years (Figure 1b). Five of them were on daily PDN, three on daily DFZ and two on PDN 10 days on/10 days off. None of these re-initiated glucocorticoids after LOA.

Nine individuals initiated glucocorticoids after LOA, at a mean age of 16.1 ± 5.6 years. In three of them, glucocorticoids were prescribed as part of a pilot study of glucocorticoids in non-ambulant individuals with DMD [33]. In total, 66.1% (74/112) of the individuals were taking glucocorticoids after LOA. Daily DFZ was the most frequent glucocorticoid regimen/type, constituting 39.3% (44/112) of the individuals (Figure 1a). At LA, 47.2% (53/112) remained on glucocorticoids, as 21 out of the 74 individuals had discontinued glucocorticoids (Figure 1a).

Glucocorticoid management after LOA

After LOA, the most frequent glucocorticoid adjustments were a reduction in the dose (22.3% [25/112]) and maintenance of the dose (21.4% [24/112]) of the same glucocorticoid regimen and type. These adjustments represented 38.5% (25/65) and 37.0% (24/65) respectively of the individuals on glucocorticoids at the assessment prior to LOA. Twelve individuals switched glucocorticoid type after LOA, all from PDN to DFZ, 21 discontinued glucocorticoid after LOA (Figure 1b).

Weight gain was the main reason for glucocorticoid dose and type adjustments and discontinuation (49.1%, 29/59, Appendix S3). Additionally, behavioural side effects were the main cause of discontinuing glucocorticoids before or at LOA (4/10 individuals).

At glucocorticoid initiation, 48.0% (36/75) of the individuals were on the recommended glucocorticoid dose (0.75 mg/kg/day for PDN and 0.9 mg/kg/day for DFZ). At the assessment prior to LOA, only 4.6% (3/65) of the individuals were on the glucocorticoid recommended dose. After LOA, the glucocorticoid dose was possibly or definitively associated with adrenal suppression in 97.3% (72/74). Glucocorticoid doses at various stages are shown in Table 2 and Appendix S2.

Glucocorticoid side effects

Overweight, osteoporosis and delayed puberty were the most frequent side effects, reported in 62.8% (54/84), 54.7% (47/84) and

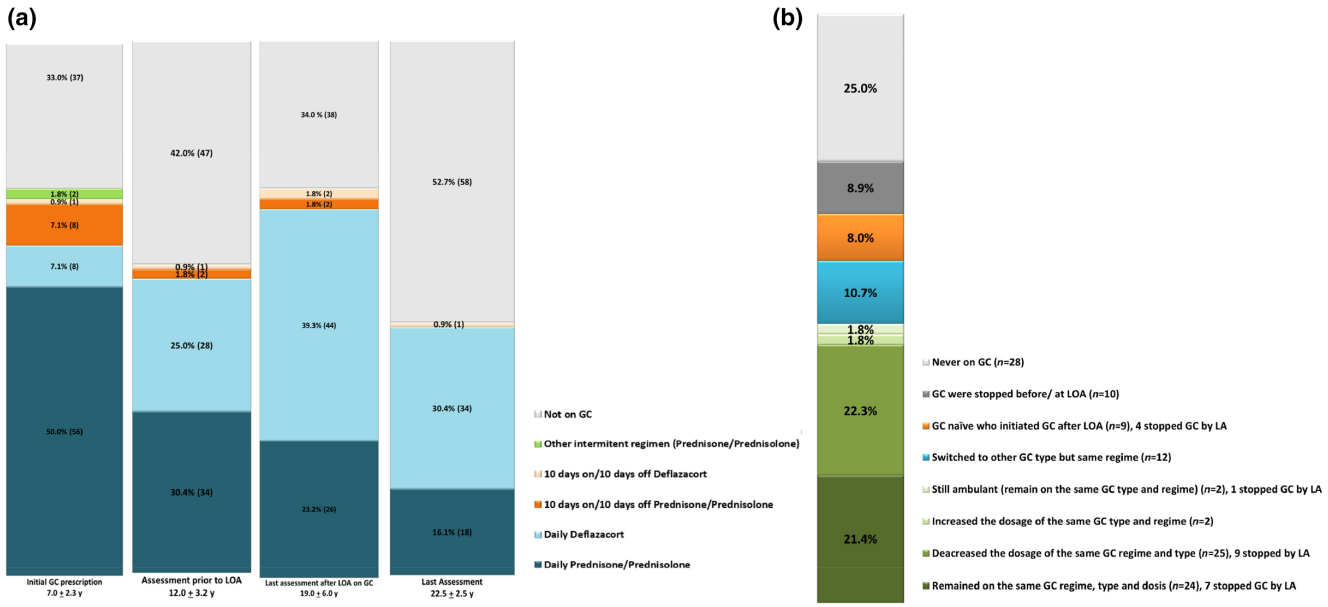


FIGURE 1 (a) Glucocorticoid type and regimen prescribed at four time points of follow-up: initial prescription, assessment prior to LOA, LA after LOA on GC and LA. (b) Variations in GC prescription after LOA. To label an increment or decrement on GC dose after LOA, an increment or reduction of ≥25% of the GC dose (mg/kg/day) was considered, as suggested by the 2018 Standards of Care in DMD [4]. Abbreviations: GC, glucocorticoid; LA, last assessment; LOA, loss of ambulation. Last assessment after LOA on GC signifies that the glucocorticoid status of all individuals was evaluated at the point when those who were on glucocorticoids (and subsequently stopped them at the last assessment) received this treatment for the last time.

TABLE 2 Glucocorticoid dosage.

Glucocorticoid type	Dose (mg/kg/day) Mean, SD (min–max), median	Percentage of recommended dose[a] Mean, SD (min–max), median	Total daily dose (mg/day) Mean, SD (min–max), median
Prednisone/prednisolone			
First prescription ($n=60/66$)[b]	0.70 ± 0.10 (0.25–0.81), 0.75	94.0 ± 13.5 (33.1–108.1), 100.0	17.1 ± 5.1 (10.0–45.0), 15.0
Assessment prior to LOA ($n=34/36$)[b]	0.52 ± 0.16 (0.15–1.05), 0.50	69.2 ± 21.0 (20.1–140.0), 67.0	22.3 ± 5.03 (12.5–32.4), 20.0
Last assessment after LOA on GC ($n=27/28$)[c]	0.38 ± 0.12 (0.14–0.58), 0.40	NA	19.0 ± 6.2 (7.0–30.0), 20.0
Last assessment ($n=18/18$)	0.38 ± 0.13 (0.14–0.58), 0.37	NA	18.3 ± 6.2 (6.6–30.0), 18.7
Deflazacort			
First prescription ($n=7/9$)[b]	0.87 ± 0.24 (0.46–1.07), 0.90	96.3 ± 26.5 (51.1–119.4), 100.0	26.8 ± 7.4 (18.0–35.0), 27.0
Assessment prior to LOA ($n=29/29$)[b]	0.61 ± 0.23 (0.31–1.28), 0.55	67.5 ± 26.0 (34.2–143.0), 61.2	28.1 ± 7.4 (12.0–46.0), 27.0
Last assessment after LOA on GC ($n=46/46$)[c]	0.42 ± 0.16 (0.05–0.75), 0.43	NA	25.0 ± 8.0 (3.00–40.00), 24.0
Last assessment ($n=35/35$)	0.43 ± 0.16 (0.05–0.75), 0.44	NA	21.0 ± 7.0 (2.5–33.3), 20.0

Note: Numbers in parenthesis represent the number of individuals in whom dose data were available over the total individuals by GC at each time point.
Abbreviations: GC, glucocorticoid; SoC, standards of care; LOA, loss of ambulation; NA, not applicable.

[a]The recommended doses are 0.75 mg/kg/day for prednisone/prednisolone and 0.9 mg/kg/day for deflazacort per 2018 SoC.

[b]The nine individuals who initiated GC after LOA were excluded from this analysis.

[c]Last assessment after LOA on GC: it signifies that the glucocorticoid status of all individuals was evaluated at the point when those who were on glucocorticoids (and subsequently stopped them at the last assessment) received this treatment for the last time.

54.7% (47/84) respectively amongst the 84 individuals exposed to any glucocorticoid regimen, type and dose during the study period (Appendix S4).

Functional abilities

Functional abilities

The mean age of LOA was 12.1 ± 3.1 years. At age 16 years, 84.8% (95/112) were non-ambulant, and this increased to 93.8% (105/112) at age 18 years. All ambulant individuals at the age of 16 and 18 years were on glucocorticoids. At LA, two individuals were still ambulant (both 17.0 years old and on glucocorticoids); 109 used a powered wheelchair and one was bedridden.

Egen Klassifikation scale data were available for 51.8% (58/112) of individuals by the age of 16 (mean age 16.0 ± 0.7 years), 59.8% (67/112) by the age of 18 (mean age 18.1 ± 0.9 years) and 86.6% (97/112) at LA (mean age 22.8 ± 5.5 years) (Figure 2 and Appendix S5).

At age 16 years, common motor function impairments included 87.9% (51/58) needing support to stand or were unable to do so (EK scale scores 1, 2 and 3), 86.2% (50/58) needing assistance transferring from a wheelchair (EK scale scores 2 and 3), 89.7% (46/58) taking more than 10 min to move using a manual wheelchair or needing a powered one (EK scale scores 1, 2 and 3) and 53.4% (31/58) who could not turn in bed by themselves (EK scale scores 2 and 3) (Figure 2).

Preserved abilities at LA included: balancing in the wheelchair (42.3%, 41/97, EK scale scores 0 and 1), hand-tomouth function (39.2%, 38/97, EK scale score 0 and 1), joystick control (62.8%, 54/86, EK scale score 0), hand use (87.8%, 79/90, EK scale score 0, 1 and 2), speaking (60.4%, 58/96, EK scale score 0) and swallowing (59.6%, 58/97, EK scale score 0) (Figure 2).

Functional abilities and glucocorticoid treatment after LOA

Individuals on either PDN or DFZ at LA had lower odds ratio (OR) of scoring worse on various EK scale domains compared to glucocorticoid-naïve individuals: transferring from a wheelchair, balancing in a wheelchair, head control, moving arms against gravity, using hands and arms for eating, using a joystick, using hands, coughing, time to eat a meal, adapting food texture and swallowing. Detailed statistical results for each model are available in Appendix S6. No differences were found between PDN and DFZ except for transferring from a wheelchair, balancing in a wheelchair and moving the arms against gravity favouring DFZ (Appendix S6).

At LOA, one individual had wheelchair balancing limitations and two had lost hand-tomouth function, excluding them from survival analysis. Of the remaining individuals, those on either PDN or DFZ had a lower risk and delayed time to balance in a wheelchair with limitations (EK scale scores 2 or 3) (Cox proportional model, hazard ratio [HR] PDN 0.29, 95% confidence interval [CI] 0.09–0.92; HR DFZ 0.17, 95% CI 0.06–0.45; both $p<0.05$; adjusted survival curves

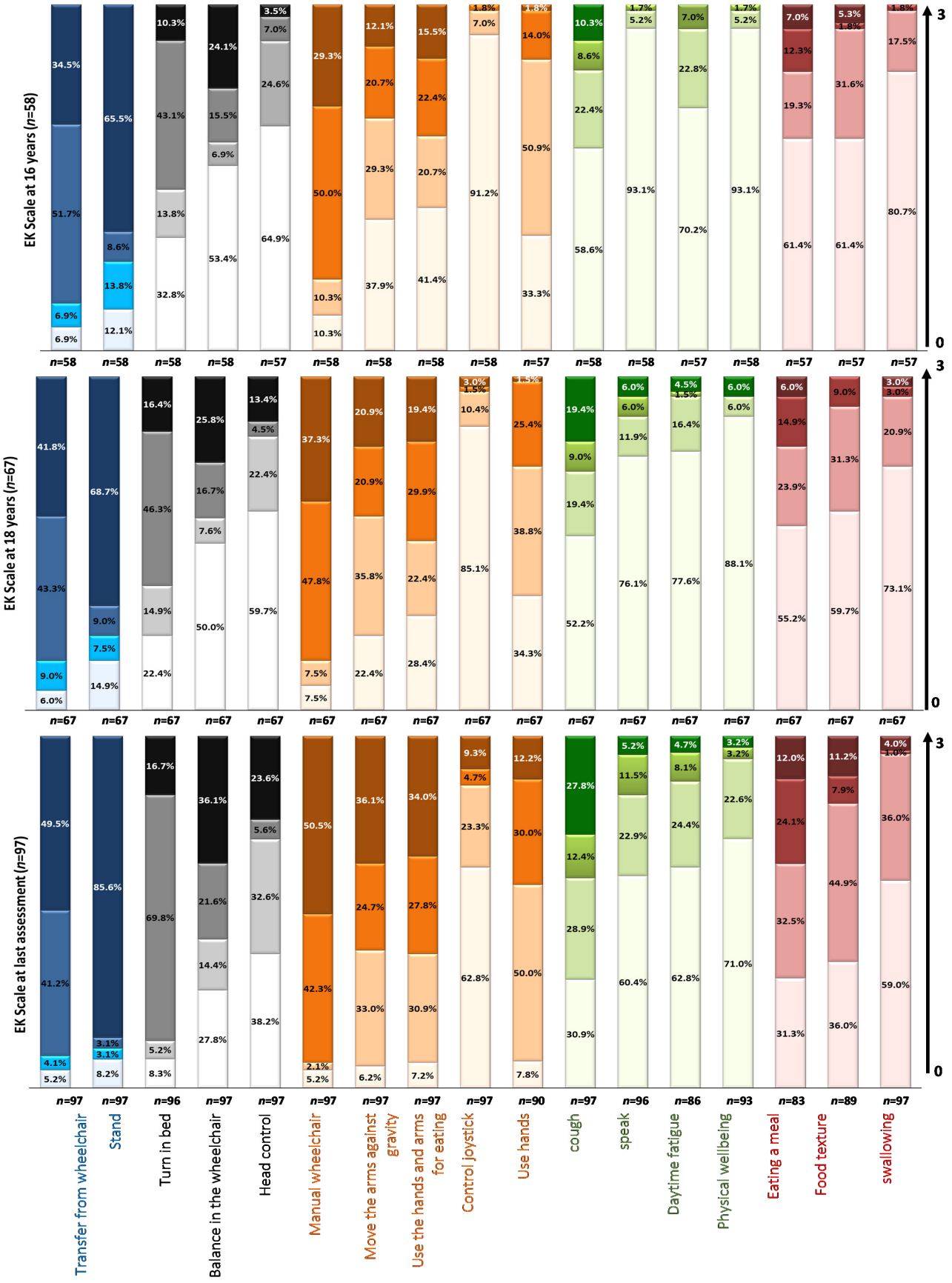


FIGURE 2 The bar graphs depict scores on the 17 domains of the Egen Klassifikation scale version 2 at the age of 16 years, 18 years and at last assessment. All individuals were non-ambulant. Darker colours indicate higher scores on the EK scale domains, signifying poorer performance. Domains in blue represent motor function abilities associated predominantly with lower limb strength; in grey motor function abilities associated predominantly with axial strength; in orange motor function abilities associated predominantly with upper limb strength; in green abilities associated predominantly with respiratory muscle strength; and in red abilities associated predominantly with oropharyngeal muscle strength. Within each colour group, domains are arranged in order of impairment. The first EK scale publication was in 2001 [25], so EK scale data at age 16 years old were available for individuals born since 1985.

difference, glucocorticoid-naïve vs. PDN −3.90 years, glucocorticoid-naïve vs. DFZ −5.02 years, both $p < 0.01$) and loss of hand to mouth function (EK scale scores 2 or 3) (Cox proportional model, HR PDN 0.37, 95% CI 0.12–0.76; HR DFZ 0.17, 95% CI 0.05–0.51; both $p < 0.05$; adjusted survival curves difference, glucocorticoid-naïve vs. PDN −3.20 years, $p < 0.04$; glucocorticoid-naïve vs. DFZ −5.04 years, $p < 0.01$) compared to glucocorticoid-naïve individuals, without differences between DFZ and PDN (Figure 3).

No significant differences were identified on the mean glucocorticoid dose at LA between individuals who scored 0 (complete preservation of functional ability) versus individuals who scored 1, 2 and 3 on each domain of the EK scale (ANCOVA $p > 0.05$, data not shown).

Respiratory function

Respiratory function

At age 16 years, 53.3% (57/107) had a forced vital capacity percentage of predicted (FVCpp) <50% rising to 84.7% (94/111) at LA. Sixteen individuals on glucocorticoids had an FVCpp >50% at LA and three of them had an FVCpp >80% (Figure 4). The peak cough flow (PCF) was the most commonly impaired respiratory parameter, dropping below 270 L/min in 77.5% (79/102).

At the age of 16 years, 20.5% (23/112) of the individuals were on ventilatory support rising to 59.8% (67/112) at LA. Of these, 41 required night-time non-invasive ventilation (NIV), 18 intermittent night-time/daytime NIV, one individual used NIV exclusively in daytime, three used NIV 24 h and four were tracheostomized. Of the 67 individuals on ventilatory support at LA, four had an FVCpp >50% but NIV was prescribed due to nocturnal hypoventilation symptoms (Figure 4 and Appendix S7).

Respiratory function and glucocorticoid treatment after LOA

Individuals on either PDN or DFZ at LA had lower odds of having low FVCpp (ordinal logistic regression, OR PDN 0.17, OR DFZ 0.15, both $p < 0.05$), forced vital capacity (FVC) ≤1 L (binary logistic regression, OR PDN 0.14, OR DFZ 0.15, both $p < 0.001$) and requiring ventilatory support at LA (binary logistic regression, OR PDN 0.18, OR DFZ 0.17, both $p < 0.05$) compared to glucocorticoid-naïve individuals, without differences between PDN and DFZ (Appendix S6).

At LOA, eight individuals had an FVCpp between 50% and 30% and 10 an FVCpp <30% excluding them from survival analysis. Individuals on PDN had a lower risk of an FVCpp <50% compared to glucocorticoid-naïve individuals (Cox proportional model, HR PDN 0.55, 95% CI 0.31–0.98, $p < 0.04$). No differences were identified between individuals on DFZ and glucocorticoid-naïve individuals nor between PDN versus DFZ (Appendix S8). However, individuals on either PDN or DFZ had a lower risk and delayed time to an FVCpp <30% compared to glucocorticoid-naïve individuals (Cox proportional model, HR PDN 0.41, 95% CI 0.20–0.83; HR DFZ 0.52, 95% CI 0.30–0.91; both $p < 0.05$; adjusted survival curves difference, glucocorticoid-naïve vs. PDN −3.30 years, glucocorticoid-naïve vs. DFZ −2.40 years, both $p < 0.01$), without differences between PDN versus DFZ (Figure 5).

Six individuals with an FVC ≤1 L at LOA were excluded from the survival analysis. Amongst the remaining 106 individuals, those on either PDN or DFZ had a lower risk and delayed time to a FVC <1 L (Cox proportional model, HR PDN 0.37, 95% CI 0.18–0.75; HR DFZ 0.37, 95% CI 0.21–0.67; both $p < 0.01$; adjusted survival curves difference, glucocorticoid-naïve vs. PDN −4.23 years, glucocorticoid-naïve vs. DFZ −4.13 years, both $p < 0.01$), without differences between PDN versus DFZ (Appendix S8).

One individual on nocturnal NIV at LOA was excluded from the survival analysis. Individuals on PDN after LOA had a lower risk and later time of requiring ventilatory support compared to glucocorticoid-naïve individuals (Cox proportional model, HR PDN 0.49, 95% CI 0.26–0.97, $p = 0.03$; adjusted survival curves difference, glucocorticoid-naïve vs. PDN −3.81 years, $p < 0.01$), without differences between DFZ and glucocorticoid-naïve individuals nor between PDN versus DFZ (Appendix S8).

At LOA, the mean PCF was 206.4 ± 67.3 L/min (minimum 94.0 L/min, maximum 429.0 L/min) and 41% (46/112) had a PCF below 270 L/min. Only nine individuals had a PCF above 270 L/min at LA preventing formal statistical analysis. Eight of those individuals were on glucocorticoids and one discontinued glucocorticoids at the time of LOA (Figure 4).

No significant differences were identified on the mean glucocorticoid dose at LA by FVCpp, FVC ≤1 L or NIV status at LA (ANCOVA $p > 0.05$, data not shown).

Cardiac function

Cardiac function

By the age of 16 years, 40.3% (23/57) of the individuals had a left ventricular ejection fraction (LVEF) <50%, increasing to 61.2% (60/98) at LA (Figure 6).

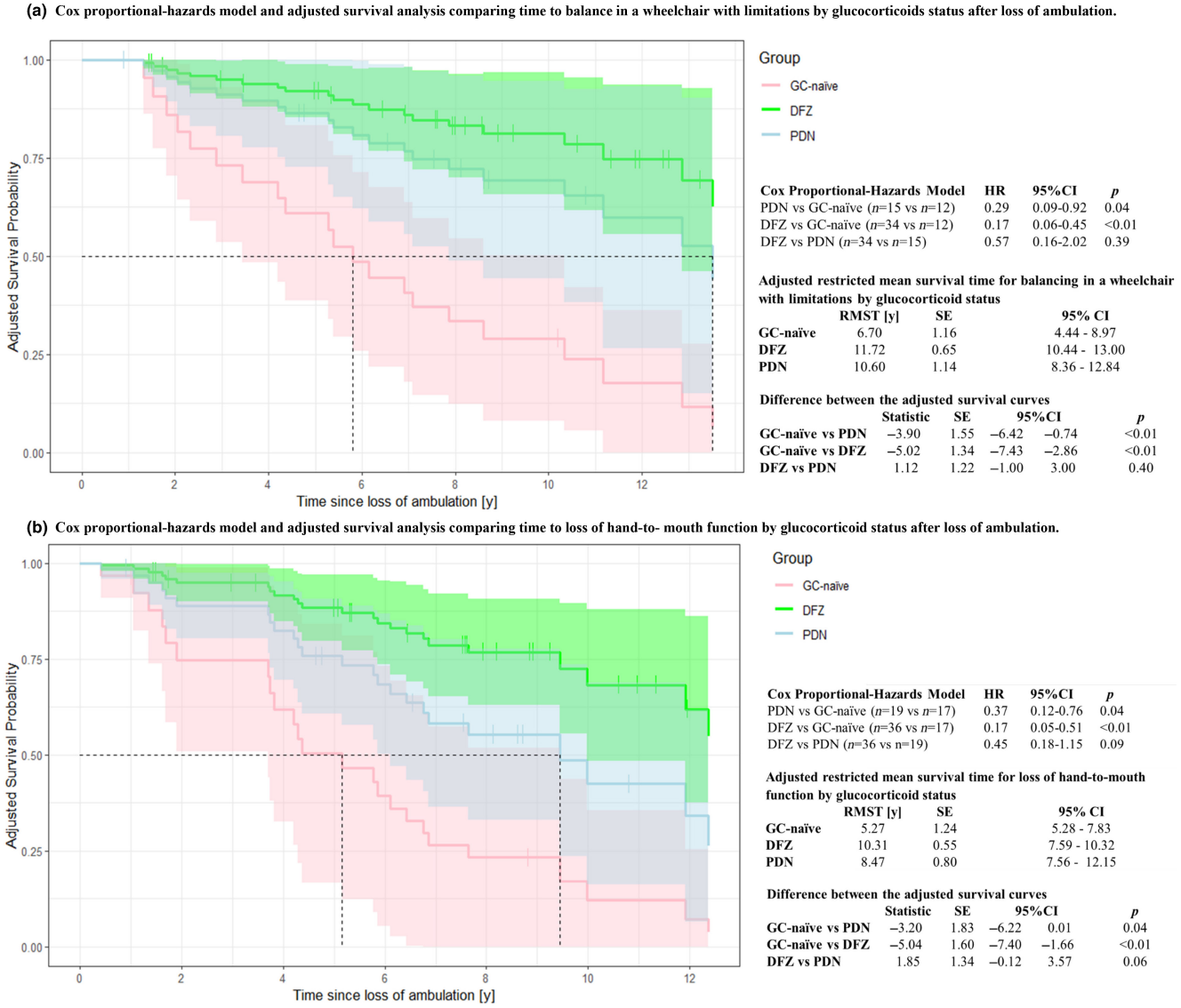
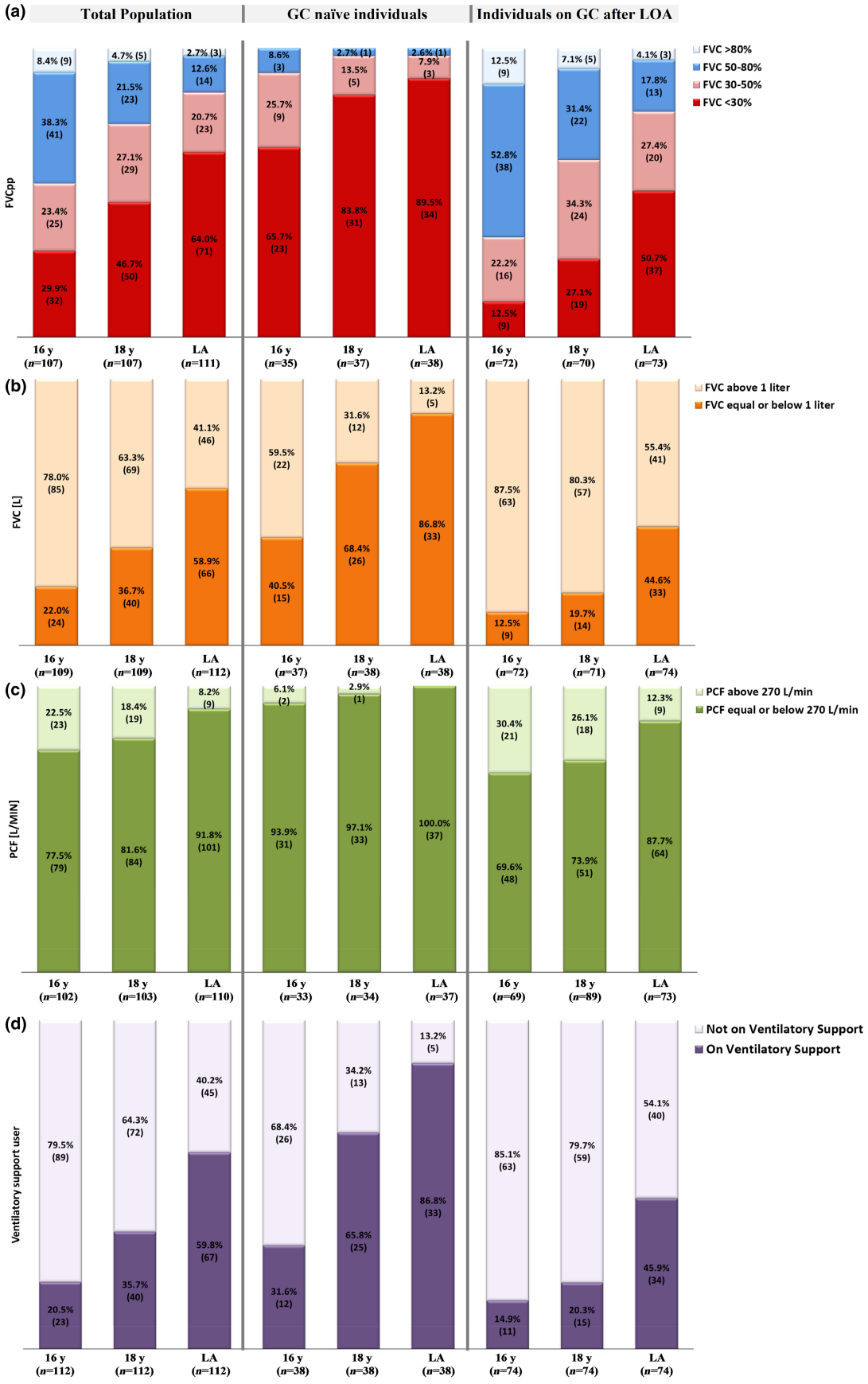


FIGURE 3 Cox proportional hazards model and adjusted survival analysis comparing time to late-stage functional ability milestones by glucocorticoid status after loss of ambulation. (a) Cox proportional hazards model and adjusted survival analysis to time to balance in a wheelchair with limitations by glucocorticoid status after loss of ambulation. Balance in a wheelchair with limitations was defined as scoring 2 or 3 on the 'Ability to balance in the wheelchair' domain of the Egen Klassifikation version 2 at last assessment. Restricted mean survival time was defined as the area under the curve of the survival function up to a time (time period after LOA 0–13.51 years). (b) Cox proportional hazards model and adjusted survival analysis to time to loss of hand to mouth function by glucocorticoid status after loss of ambulation. Loss of hand to mouth function was defined as scoring 2 or 3 on the 'Ability to move the arms' domain of the Egen Klassifikation version 2 at last assessment. Restricted mean survival time was defined as the area under the curve of the survival function up to a time (time period after LOA 0–12.35 years). Note: Dotted lines indicate the median survival time by glucocorticoid status after LOA, except for DFZ as its probability was never 50% or less. The Cox proportional hazards model had two model specifications, which differ only by the baseline glucocorticoid reference group (naïve or prednisone). 95% CI, 95% confidence interval lower bound–upper bound. Abbreviations: DFZ, deflazacort; GC, glucocorticoid; HR, hazard ratio; LOA, loss of ambulation; PDN, prednisone/prednisolone; RMST, restricted mean survival time; SE, standard error.

FIGURE 4 The bar graphs describe the respiratory profile and use of ventilatory support at three time points of follow-up. Numbers in parentheses represent the number of individuals in each group. (a) Distribution of individuals by FVCpp. Individuals with an FVCpp <50% are coloured in red. Individuals with an FVCpp ≥50% are coloured in blue. (b) Distribution of individuals by FVC <1 L (dark colour) or ≥1 L (light colour). (c) Distribution of individuals by PCF ≤270 L/min (dark colour) or >270 L/min (light colour). (d) Distribution of individuals by NIV user (dark colour) or non-user (light colour). Note: The GC-naïve group includes the 10 individuals who discontinued glucocorticoids before or at loss of ambulation. The three individuals on NIV 24 h and the four individuals on tracheostomy were labelled PCF ≤270 L/min and FVC ≤1 L at LA. Distribution of FVCpp at LA by GC type at LA: prednisone <30%, 13; 30%–50%, 10; 50%–80%, four; >80%, no individuals; deflazacort <30%, 24; 30%–50%, 10; 50%–80%, nine; >80%, three individuals. Abbreviations: FVC, forced vital capacity; FVCpp, forced vital capacity percentage of predicted; LA, last assessment; NIV, non-invasive ventilation; PCF, peak cough flow.

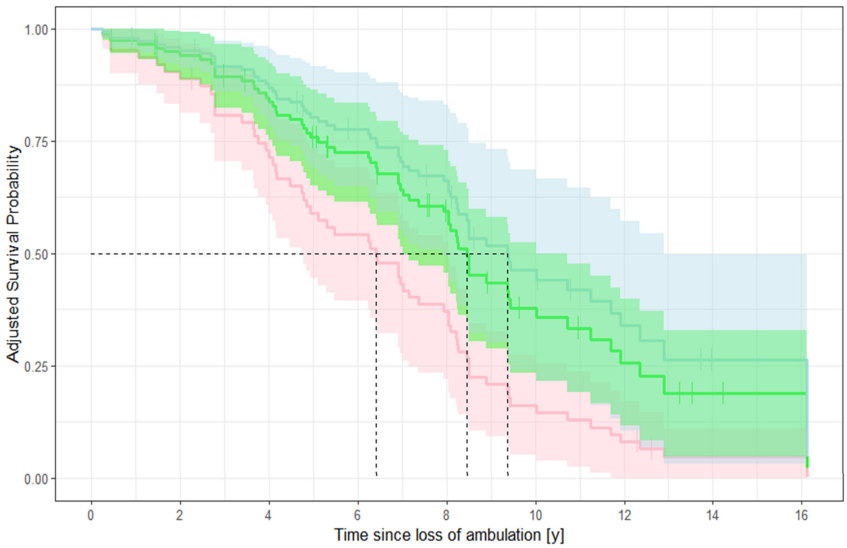


All except six individuals received angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARAII) during the study period. There were no significant differences in the mean age of ACEI/ARAII initiation or ACEI dose at LA by glucocorticoid status (Table 1). Amongst the individuals not on ACEI/ARAII, five had an LVEF ≥50% at LA and cardiac data were not available for one individual.

Cardiac function and glucocorticoid treatment after LOA

Individuals on either PDN or DFZ had lower odds of a LVEF <50% at LA compared to glucocorticoid-naïve individuals (binary logistic regression, OR PDN 0.27, OR DFZ 0.22, both $p < 0.05$), without differences between them (Appendix S6).

(a) **Cox proportional-hazards model and adjusted survival analysis comparing time to a forced vital capacity below 30% of predicted by glucocorticoids status after loss of ambulation.**



Cox Proportional-Hazards Model	HR	95%CI	p
PDN vs GC-naïve (*n*=25 vs *n*=31)	0.41	0.20-0.83	0.01
DFZ vs GC-naïve (*n*=43 vs *n*=31)	0.52	0.30-0.91	0.02
DFZ vs PDN (*n*=43 vs *n*=25)	1.23	0.61-2.61	0.52

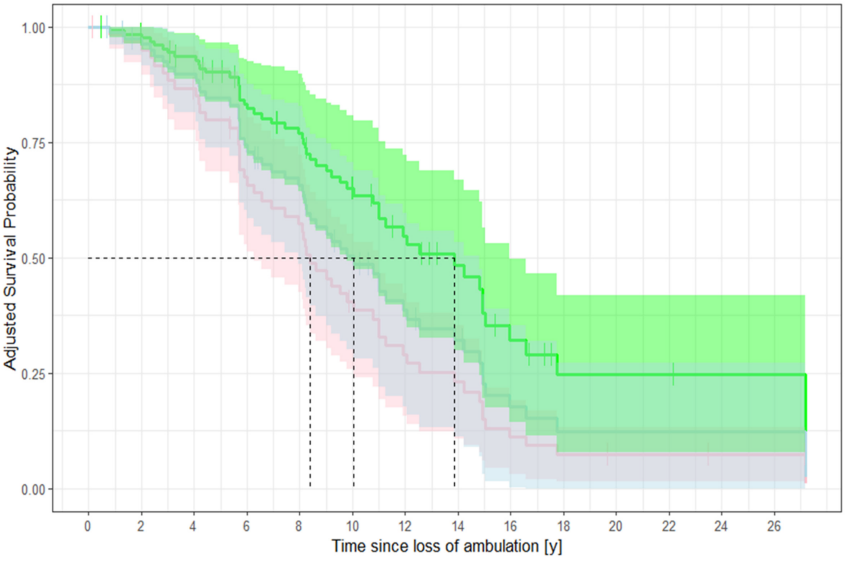
Adjusted restricted mean survival time for FVC<30% by glucocorticoid status

	RMST [y]	SE	95% CI
GC-naïve	6.55	0.65	5.28 - 7.83
DFZ	8.95	0.70	7.59 - 10.32
PDN	9.86	1.17	7.56 - 12.15

Difference between the adjusted survival curves

	Statistic	SE	95%CI		p
GC-naïve vs PDN	−3.30	1.37	−5.97	−0.58	<0.01
GC-naïve vs DFZ	−2.40	0.91	−3.64	−0.73	<0.01
DFZ vs PDN	−0.91	1.27	−3.16	1.76	0.48

(b) **Cox proportional-hazards model and adjusted survival analysis comparing time to time a left ventricular ejection fraction below 40% glucocorticoid status after loss of ambulation.**



Cox Proportional-Hazards Model	HR	95%CI	p
PDN vs GC-naïve (*n*=21 vs *n*=34)	0.74	0.35-1.57	0.44
DFZ vs GC-naïve (*n*=39 vs *n*=34)	0.46	0.24-0.88	0.02
DFZ vs PDN (*n*=39 vs *n*=21)	0.61	0.27-1.37	0.23

Adjusted restricted mean survival time for a LVEF<40% by glucocorticoid status

	RMST [y]	SE	95% CI
GC-naïve	9.91	0.78	8.38 - 11.44
DFZ	14.54	1.68	11.25 - 17.84
PDN	11.54	1.82	7.97 - 15.10

Difference between the adjusted survival curves

	Statistic	SE	95%CI		p
GC-naïve vs PDN	−1.62	1.93	−4.64	1.73	0.38
GC-naïve vs DFZ	−4.63	1.90	−7.58	−1.32	0.03
DFZ vs PDN	3.01	2.39	−1.06	7.37	0.21

FIGURE 5 Cox proportional hazards model and adjusted survival analysis comparing time to late-stage respiratory and cardiac milestones by glucocorticoid status after loss of ambulation. (a) Cox proportional hazards model and adjusted survival analysis comparing time to a FVCpp below 30% by glucocorticoid status after loss of ambulation. Restricted mean survival time was defined as the area under the curve of the survival function up to a time (time period after LOA 0–16.10 years). (b) Cox proportional hazards model and adjusted survival analysis comparing time to a LVEF below 40% by glucocorticoid status after loss of ambulation. Restricted mean survival time was defined as the area under the curve of the survival function up to a time (time period after LOA 0–27.10 years). Note: Dotted lines indicate the median survival time by glucocorticoid status after LOA. The Cox proportional hazards model had two model specifications, which differ only by the baseline glucocorticoid reference group (naïve or prednisone). 95% CI, 95% confidence interval lower bound–upper bound. Abbreviations: DFZ, deflazacort; FVCpp, forced vital capacity percentage of predicted; GC, glucocorticoid; HR, hazard ratio; LOA, loss of ambulation; LVEF, left ventricular ejection fraction; PDN, prednisone/prednisolone; RMST, restricted mean survival time; SE, standard error.

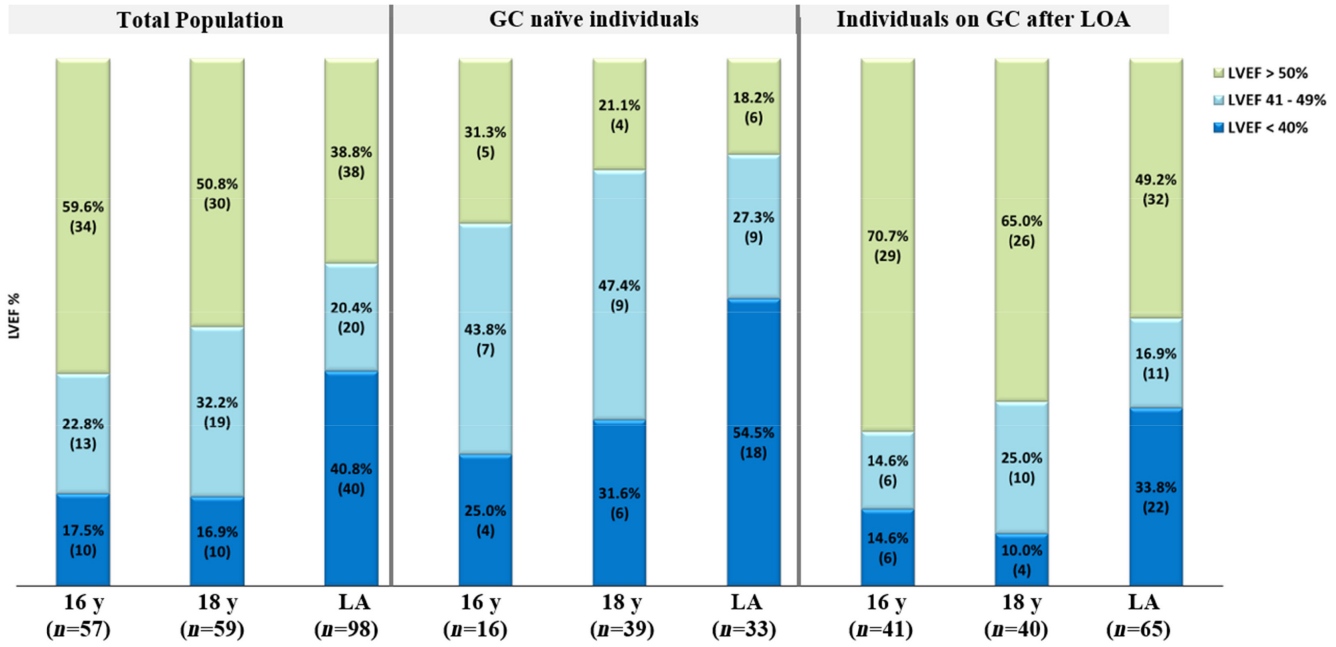


FIGURE 6 The bar graphs describe the cardiac function at three time points of follow-up. Numbers in parenthesis represent the number of individuals in each group. Heart failure (HF) was classified as per the European Society of Cardiology 2021: HF with reduced LVEF (LVEF <40%); HF with mildly reduced EF (LVEF 41%–49%) and HF with preserved EF (LVEF >50%). The GC-naïve group includes the 10 individuals who discontinued glucocorticoids before or at LOA. Abbreviations: GC, glucocorticoids; LOA, loss of ambulation; LVEF, left ventricular ejection fraction.

At LOA, 10 individuals had an LVEF <50% excluding them from survival analysis. Sixty-four individuals reached an LVEF <50% after LOA (glucocorticoid-naïve 16/28; PDN 20/46; DFZ 28/38). After adjusting by age at LA, the risk and time to a LVEF <50% since LOA did not differ between individuals on either PDN or DFZ and glucocorticoid-naïve individuals (Appendix S8). However, individuals on DFZ had a lower risk of a LVEF ≤40% versus glucocorticoid-naïve individuals (Cox proportional model, HR DFZ 0.46, 95% CI 0.24–0.88, $p=0.02$) (Figure 3). Despite individuals on glucocorticoids had a later mean time to a LVEF ≤40% after LOA compared to glucocorticoid-naïve individuals, this was only statistically significant for those on DFZ (adjusted survival curves difference, glucocorticoid-naïve vs. DFZ −4.63 years, $p=0.03$) (Figure 3).

No significant differences were identified on the mean glucocorticoid dose at LA for the LVEF ≤ vs. >50% and LVEF ≤ vs. >40% categories (ANCOVA $p>0.05$, data not shown).

Late stages

During the study period, 42.0% (47/112) of the individuals died (glucocorticoid-naïve 63.2% [24/38]; on PDN 25.0% [7/28]; on DFZ 34.8% [16/46]). The mean age of death was 25.0 ± 5.1 years (17.1–37.0). The cause of death was not reported in 53.1% (25/47) of the individuals (PDN 6/7, DFZ 8/16, glucocorticoid-naïve 11/24). All but four individuals developed cardiomyopathy before death, and all but 12 required ventilatory support (Appendix S9).

DISCUSSION

Effective planning and provision of resources required for clinical services for adult individuals with DMD and those in transition of care, in terms of multidisciplinary professionals, infrastructure, equipment and time allocation, is crucial for providing tailored and proactive care [8, 9, 34]. Functional abilities related to the lower limbs and axial muscles are compromised in individuals with DMD by the time of transition. More than 80% of our cohort required support or devices for transferring from a wheelchair and standing and 67.2% for turning in bed by the age of 16 years. Guidelines for adults with DMD recommend respiratory team referral if there are symptoms of nocturnal hypoventilation and/or an FVCpp <50% for NIV consideration [21]. Half of our individuals fulfil that criterion already by the age of 16 years. Cough augmentation devices are recommended for PCF <270 L/min, affecting over 70% of our cohort since age 16 [21]. Individuals with DMD should receive annual cardiac follow-up starting at age 10 [35]. Cardiomyopathy with reduced LVEF (<50%) was identified in 40.3% by the age of 16 years. These findings have important implications for the care and equipment planning of adult clinical services.

Our results provide evidence of the benefit of glucocorticoids in the late stages of DMD. Similar to the PRO-DMD-01 study [15], it was confirmed that individuals on either PDN or DFZ showed a lower risk and later time to a severe respiratory impairment (FVCpp <30% and FVC <1 L) and of losing hand-to-mouth function, even when exploring this in the period exclusively after LOA. In our study, glucocorticoids after LOA were associated with higher probabilities

of LVEF >50% at LA, although the risk and time to an LVEF <50% did not differ between glucocorticoid-treated and glucocorticoid-naïve individuals. The latter was a finding of the PRO-DMD-01 study. Differences in the criteria for time to event analysis between both studies might explain this discrepancy.

Differences between PDN and DFZ were not identified in terms of respiratory and cardiac function and slight differences were seen in specific functional abilities. Individuals on DFZ were associated with better performance in the EK scale domains assessing transfer, wheelchair balance and hand-to-mouth function, but without differences in the time to lose the last two late-stage milestones compared to individuals on PDN. Similar to us, the PRO-DMD-01 study did not report differences in the rate of decline or in the time to late stage respiratory, cardiac and hand-to-mouth function milestones between PDN and DFZ; however, individuals on DFZ showed a lesser decline in the performance of the upper limb scale [36]. Given that both studies are observational and non-randomized, it remains challenging to ascertain whether the positive impact of DFZ on the EK scale functional abilities and the performance of the upper limbs is influenced by the high prevalence of DFZ use amongst individuals or if it genuinely reflects a more favourable effect on late-stage motor functions.

Minimum and maximum effective glucocorticoid doses are based on paediatric populations [5, 37]. It is uncertain whether adult doses should be adjusted by weight or if they should receive fixed doses. In our study, most of the individuals were maintained on the same dose, or it was reduced after LOA. The glucocorticoid dose by functional abilities, respiratory or cardiac function at LA was not different. This might simply reflect the lack of guidance on dose adjustments in adulthood; therefore, individuals are maintained at similar doses. Although the glucocorticoid dose used in adults at LA were well below the recommended one at initiation of treatment, it was within a range associated with a possible or definite risk of adrenal axis suppression, emphasizing the relevance for a constant surveillance for this in the adult population.

One strength of the study is that, as a single-centre study, data collection was harmonized and consistent throughout the study period. However, the small sample size highlights the need for collaborative efforts to confirm these findings by gathering comprehensive, agreed outcomes in a larger number of adults with DMD to inform patient care and management.

Study limitations

The retrospective nature of the study results in missing and progressively available data reflecting adjustments in clinical practice and outcome measures over the years. Most of the individuals were on a daily glucocorticoid regimen, impeding investigations on the effect of different regimens in adulthood. The care recommendations regarding glucocorticoid prescription have changed over the long study period [4, 38–40] with older individuals not routinely treated with glucocorticoids or initiated at a later stage. The cumulative effect of glucocorticoid treatment was not investigated and might explain the lack of differences between glucocorticoid type after LOA. Finally, The low number of individuals who discontinued glucocorticoids before LOA ($n=10$) or initiated glucocorticoids after LOA ($n=9$) precluded their analysis as individual categories.

AUTHOR CONTRIBUTIONS

Marianela Schiava: Conceptualization; writing – original draft; writing – review and editing; formal analysis; visualization; investigation; validation. **Robert Muni Lofra:** Investigation; validation. **John P. Bourke:** Investigation; validation. **Jordi Díaz-Manera:** Investigation; validation. **Meredith K. James:** Investigation; validation. **Maha A. Elseed:** Investigation; validation. **Monika Malinova:** Investigation; validation. **Jassi Michel-Sodhi:** Investigation; validation. **Dionne Moat:** Investigation; validation. **Elisabetta Ghimenton:** Investigation; validation. **Michelle Mccallum:** Investigation. **Carla Florencia Bolaño Díaz:** Investigation; validation. **Anna Mayhew:** Investigation; validation. **Karen Wong:** Investigation; validation. **Mark Richardson:** Investigation; validation. **Giorgio Tasca:** Investigation; validation. **Gail Eglon:** Investigation; validation. **Michelle Eagle:** Investigation; validation. **Cathy Turner:** Validation. **Emma Heslop:** Validation. **Volker Straub:** Validation; investigation. **Chiara Marini Bettolo:** Investigation; validation. **Michela Guglieri:** Conceptualization; supervision; writing – review and editing; investigation; validation.

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FUNDING INFORMATION

No funding was received towards this work.

CONFLICT OF INTEREST STATEMENT

M. Guglieri has been participating in advisory boards for PTC Therapeutics, Capricor, Pfizer and NS Pharma. She had research collaborations with ReveraGen, PTC, Sarepta, Duchenne UK and MDUK through Newcastle University. She is or has been Principal Investigator for clinical trials with Roche, Italfarmaco, Santhera, ReveraGen, Summit, Pfizer, PTC Therapeutics. She received speaker honoraria from Italfarmaco, Roche, Novartis and Sarepta. M. Schiava has received a grant by UK Duchenne through Newcastle University. C. Marini Bettolo has received a grant by Duchenne UK through Newcastle University. R. Muni-Lofra has been participating in advisory boards for Biogen, Roche and Novartis and has delivered consultancy work for Pfizer, Italofarmaco, Sarepta, Summit and NS Pharma. AGM has served on medical/scientific advisory

boards for Regenxbio, Sarepta, Biogen and Roche; and has received fees for consulting and training services for Biogen, Roche, Novartis, Biohaven, PTC, Sarepta, Italfarmaco, Dyne, Pfizer, Summit, Catabasis, Santhera, Vision, Lysogene, Modis, Amicus, Analysis Group, MDUK and DUK. The rest of the authors report no competing interests.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

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REFERENCES

1. Aartsma-Rus A, Hegde M, Ben-Omran T, et al. Evidence-based consensus and systematic review on reducing the time to diagnosis of Duchenne muscular dystrophy. *J Pediatr*. 2019;204:305-313.e14. doi:10.1016/j.jpeds.2018.10.043
2. Dongsheng D, Goemans N, Takeda S, Mercuri E, Aartsma-Rus A. Duchenne muscular dystrophy. *Nat Rev Dis Prim*. 2021;7(1):1-19. doi:10.1038/s41572-021-00248-3
3. Bello L, Morgenroth LP, Gordish-Dressman H, Hoffman EP, McDonald CM, Cirak S. DMD genotypes and loss of ambulation in the CINRG Duchenne natural history study. *Neurology*. 2016;87(4):401-409. doi:10.1212/WNL.0000000000002891
4. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. 2018;17(4):347-361. doi:10.1016/S1474-4422(18)30025-5
5. Griggs RC, Moxley RT, Mendell JR, et al. Prednisone in Duchenne dystrophy: a randomized, controlled trial defining the time course and dose response. *Arch Neurol*. 1991;48(4):383-388. doi:10.1001/archneur.1991.00530160047012
6. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscul Disord*. 2002;12(10):926-929. doi:10.1016/S0960-8966(02)00140-2
7. Ryder S, Leadley RM, Armstrong N, et al. The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. *Orphanet J Rare Dis*. 2017;12(79):1-21. doi:10.1186/s13023-017-0631-3
8. Broomfield J, Hill M, Guglieri M, Crowther M, Abrams K. Life expectancy in Duchenne muscular dystrophy: reproduced individual patient data meta-analysis. *Neurology*. 2021;97(23):e2. doi:10.1212/wnl.0000000000012910
9. Landfeldt E, Thompson R, Sejersen T, McMillan HJ, Kirschner J, Lochmüller H. Life expectancy at birth in Duchenne muscular dystrophy: a systematic review and meta-analysis. *Eur J Epidemiol*. 2020;35(7):643-653. doi:10.1007/s10654-020-00613-8
10. Yao S, Chen Z, Yu Y, et al. Current pharmacological strategies for Duchenne muscular dystrophy. *Front Cell Dev Biol*. 2021;9(August):1-22. doi:10.3389/fcell.2021.689533
11. Duan D, Systemic AAV. Micro-dystrophin gene therapy for Duchenne muscular dystrophy. *Mol Ther*. 2018;26(10):2337-2356. doi:10.1016/j.ymthe.2018.07.011
12. Guglieri M, Bushby K, Mcdermott MP, et al. Effect of different corticosteroid dosing regimens on clinical outcomes in boys with Duchenne muscular dystrophy: a randomized clinical trial. *JAMA*. 2022;327(15):1456-1468. doi:10.1001/jama.2022.4315
13. Henricson EK, Abresch RT, Cnaan A, et al. The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. *Muscle Nerve*. 2013;48(1):55-67. doi:10.1002/mus.23808
14. Ricotti V, Selby V, Ridout D, et al. Respiratory and upper limb function as outcome measures in ambulant and non-ambulant subjects with Duchenne muscular dystrophy: a prospective multicentre study. *Neuromuscul Disord*. 2019;29(4):261-268. doi:10.1016/j.nmd.2019.02.002
15. McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet*. 2018;391(10119):451-461. doi:10.1016/S0140-6736(17)32160-8
16. Koeks Z, Bladen CL, Salgado D, et al. Clinical outcomes in Duchenne muscular dystrophy: a study of 5345 patients from the TREAT-NMD DMD global database. *J Neuromuscul Dis*. 2017;4(4):293-306. doi:10.3233/JND-170280
17. McDonald CM, Gordish-Dressman H, Henricson EK, et al. Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: long-term natural history with and without glucocorticoids. *Neuromuscul Disord*. 2018;28(11):897-909. doi:10.1016/j.nmd.2018.07.004
18. Landfeldt E, Lindgren P, Bell CF, Schmitt C, Guglieri M, Europe PMC Funders Group. Compliance to care guidelines for Duchenne muscular dystrophy. *J Neuromuscul Dis*. 2016;2(1):63-72. doi:10.3233/JND-140053.Compliance
19. Wasilewska E, Małgorzewicz S, Sobierajska-Rek A, et al. Transition from childhood to adulthood in patients with Duchenne muscular dystrophy. *Fortschr Med*. 2020;56(9):1-13. doi:10.3390/medicina56090426
20. Abbott D, Carpenter J, Bushby K. Transition to adulthood for young men with Duchenne muscular dystrophy: research from the UK. *Neuromuscul Disord*. 2012;22(5):445-446. doi:10.1016/j.nmd.2012.02.004
21. Quinlivan R, Messer B, Murphy P, et al. Adult north star network (ANSN): consensus guideline for the standard of care of adults with Duchenne muscular dystrophy. *J Neuromuscul Dis*. 2021;8(6):899-926. doi:10.3233/JND-200609
22. Kinnett K, Noritz G. The PJ Nicholoff steroid protocol for Duchenne and Becker muscular dystrophy and adrenal suppression. *PLoS Curr*. 2017;9. doi:10.1371/currents.md.d18deef7dac96ed135e0dc8739917b6e
23. Parente L. Deflazacort: therapeutic index, relative potency and equivalent doses versus other corticosteroids. *BMC Pharmacol Toxicol*. 2017;18(1):1-8. doi:10.1186/s40360-016-0111-8
24. Biggar WD, Skalsky A, McDonald CM. Comparing deflazacort and prednisone in Duchenne muscular dystrophy. *J Neuromuscul Dis*. 2022;9(4):463-476. doi:10.3233/JND-210776
25. Steffensen B, Hyde S, Lyager S, Mattsson E. Validity of the EK scale: a functional assessment of non-ambulatory individuals with Duchenne muscular dystrophy or spinal muscular atrophy. *Physiother Res Int*. 2001;6(3):119-134. doi:10.1002/pri.221
26. Steffensen BF. Egen Klassifikation Scale II Manual. 2008 2:10–11. http://rcfm.dk/wp-content/uploads/2017/10/EK2_engelsk.pdf
27. Steffensen BF, Hyde SA, Attermann J, Mattsson E. Reliability of the EK scale, a functional test for non-ambulatory persons with Duchenne dystrophy. *Adv Physiother*. 2002;4(1):37-47. doi:10.1080/140381902317303195

28. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail*. 2021;23(3):352-380. doi:10.1002/ejhf.2115
29. Butterfield RJ, Kirkov S, Conway KM, et al. Evaluation of effects of continued corticosteroid treatment on cardiac and pulmonary function in non-ambulatory males with Duchenne muscular dystrophy from MD STARnet. *Muscle Nerve*. 2022;66(1):15-23. doi:10.1002/mus.27490
30. Denz R. Confounder-Adjusted Survival Curves and Cumulative Incidence Functions. 2023;April 20 (Version 0.10.1). doi:10.1002/sim.9681
31. Eagle M, Bourke J, Bullock R, et al. Managing Duchenne muscular dystrophy—the additive effect of spinal surgery and home nocturnal ventilation in improving survival. *Neuromuscul Disord*. 2007;17(6):470-475. doi:10.1016/j.nmd.2007.03.002
32. Ricotti V, Ridout DA, Scott E, et al. Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. *J Neurol Neurosurg Psychiatry*. 2013;84(6):698-705. doi:10.1136/jnnp-2012-303902
33. Eagle M, MCallum M, Guglieri M, Straub V, Bushby K. 10 years follow-up of early corticosteroid treatment of Duchenne muscular dystrophy—abstracts (G.P.1.02)/neuromuscular disorders 17 (2007). *Neuromuscul Disord*. 2007;17(9–10):772. doi:10.1016/j.nmd.2007.06.042
34. Lindsay S, McAdam L, Mahendiran T. Enablers and barriers of men with Duchenne muscular dystrophy transitioning from an adult clinic within a pediatric hospital. *Disabil Health J*. 2017;10(1):73-79. doi:10.1016/j.dhjo.2016.10.002
35. Bourke J, Turner C, Bradlow W, et al. Cardiac care of children with dystrophinopathy and females carrying DMD-gene variations. *Open Heart*. 2022;9(2):e001977. doi:10.1136/openhrt-2022-001977
36. McDonald CM, Mayer OH, Hor KN, et al. Functional and clinical outcomes associated with steroid treatment among non-ambulatory patients with Duchenne muscular dystrophy 1. *J Neuromuscul Dis*. 2023;10(1):67-79. doi:10.3233/JND-221575
37. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol*. 2010;9(1):77-93. doi:10.1016/S1474-4422(09)70271-6
38. Birnkrant DJ. The American College of Chest Physicians consensus statement on the respiratory and related management of patients with Duchenne muscular dystrophy undergoing anesthesia or sedation. *Pediatrics*. 2009;123(Suppl 4):242-244. doi:10.1542/peds.2008-2952J
39. Moxley RT, Ashwal S, Pandya S, et al. Practice parameter: corticosteroid treatment of Duchenne dystrophy—report of the quality standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Contin Lifelong Learn Neurol*. 2006;12(3):188-195.
40. Topaloglu H. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy: report of the guideline development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;87(2):238. doi:10.1212/01.wnl.0000489553.99227.18

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

MATERIALS AND METHODS AND STATISTICAL ANALYSIS, EXTENDED VERSION

MATERIALS AND METHODS

This is a retrospective study of adults with Duchenne muscular dystrophy (DMD) followed up at a highly specialized service in neuromuscular diseases, the John Walton Muscular Dystrophy Research Centre, Newcastle Upon Tyne, UK. Individuals were assessed every 6–12 months by clinicians and physiotherapists specialized in neuromuscular diseases. Individuals' clinical notes were reviewed to collect demographic, genetic, treatment [4, 5, 22–24], functional abilities, respiratory and cardiac data.

The inclusion criteria were (i) males genetically diagnosed with DMD ≥16 years old at last assessment (LA) and (ii) ambulant or non-ambulant at LA. Loss of ambulation (LOA) was defined as the age at which the individual was reported as a fulltime wheelchair user with no subsequent ambulation [29].

The glucocorticoid status after LOA, hereinafter glucocorticoid status, was classified as (a) individuals on prednisone/prednisolone (PDN), (b) individuals on deflazacort (DFZ), (c) glucocorticoid-naïve individuals (never received glucocorticoids) and (d) individuals who discontinued glucocorticoids before or at the time of LOA. As the focus was on the effect of glucocorticoids exclusively after LOA, individuals who discontinued glucocorticoids before or at LOA (10/112) were included in the glucocorticoid-naïve group.

Functional abilities were explored through the Egen Klassifikation (EK) scale version 2, a 17-domain scale validated in non-ambulant individuals with DMD [25–27]. Each domain is scored from 0 to 3, with higher scores representing lower function. The EK scale was assessed at each clinical appointment after LOA.

Lung function was classified based on the forced vital capacity percentage of predicted (FVCpp) as <30%, 30%–50%, 50%–80% and >80%.

Heart failure (HF) was classified according to the European Society of Cardiology 2021: HF with reduced left ventricular ejection fraction (LVEF ≤40%); HF with mildly reduced LVEF (41%–49%); and HF with preserved LVEF (≥50%) [28].

The glucocorticoid management, in terms of glucocorticoid regimen, type and dose, after LOA was explored. An increment or decrement in glucocorticoid dose after LOA was considered as a change ≥25% of the glucocorticoid dose (mg/kg/day) compared to the glucocorticoid dose at the LA prior to LOA, as suggested by the 2018

SoC [4]. As the minimal effective dose of glucocorticoids in adults with DMD has not been established, the glucocorticoid dose after LOA was reported in relation to its ability to suppress the hypothalamus–pituitary–adrenal axis (no suppression, possible suppression or definitive suppression), as suggested by the PJ Nicholoff steroid protocol for Duchenne and Becker muscular dystrophy and adrenal suppression [22] and due to the relevant clinical implication of adrenal suppression in individuals with DMD.

Study approval was obtained from the Newcastle upon Tyne Hospitals Register Audit, Newcastle Upon Tyne, UK (Caldicott approval number 8275), and the study conforms with World Medical Association Declaration of Helsinki.

STATISTICAL ANALYSIS

Data were expressed as number and percentage for categorical variables and as mean ± SD and/or median and interquartile range for quantitative variables.

The association between glucocorticoid status and functional abilities, respiratory and cardiac status at LA was explored. An ordinal logistic regression was conducted to investigate the association between glucocorticoid status and the EK scale score on each domain (0, 1, 2 or 3) at LA, adjusting by age at LA. Similarly, an ordinal logistic regression was conducted to investigate the association between glucocorticoid status and FVCpp at LA (FVCpp >80%, 80%–50%, 50%–30% and <30%), adjusting by age at LA. A binary logistic regression was conducted to investigate the association between glucocorticoid status and forced vital capacity (FVC) ≤1 L, use of ventilatory support and LVEF <50% at LA, adjusting by age at LA. No multiple comparisons correction was performed.

The time to late-stage disease milestones by glucocorticoid status was explored through a Cox proportional hazards ratio (HR point estimate with 95% confidence interval [CI]) and survival analyses. The late-stage disease milestones explored included: balancing on a wheelchair with limitations (balance on a wheelchair with limitations was defined as scoring 2 or 3 on the 'Ability to balance in the wheelchair' domain of the EK version 2 at LA), loss of hand-to-mouth function (loss of hand-to-mouth function was defined as scoring 2 or 3 on the 'Ability to move the arms' domain of the EK version 2 at LA), FVCpp <50%, FVCpp <30%, FVC <1 L, use of ventilatory assistance, LVEF <50% and LVEF <40%. Cox model covariates included age at LA and glucocorticoid status. Individuals who had reached a milestone prior to or at the time of LOA, or by the time of the first available assessment and who were still ambulant at LA, were excluded from the analysis. No multiple comparisons correction was performed.

An analysis of covariance, adjusted by the age at LA, with Bonferroni correction for multiple comparisons, was used to explore the mean differences in glucocorticoid dose (mg/kg/day) at LA between categories on each domain of the EK scale (3, 2 or 1 vs. 0), FVCpp categories (FVCpp >80%, 80%–50% or 50%–30% vs. <30%), FVC ≤ or >1 L, ventilatory support (user vs. not user), LVEF < or ≥50% and LVEF < or ≥40% at LA. To homogenize glucocorticoid dose comparisons amongst individuals, DFZ doses were converted to PDN and adjusted by weight following recommended equivalences (5 mg PDN is equal to 6 mg DFZ) and expressed in mg/kg/day [23, 24].

Statistical analysis was performed using IBM SPSS statistics version 28. Adjusted survival analysis for late-stage disease milestones were conducted in R (R Core Team, 2023) and figures were produced using the package adjustedCurves version 0.10.1 [30]. A level of significance of $p < 0.05$ was used in all the analyses.

Egen Klassifikation (EK) scale version 2

The EK scale is a validated scale in non-ambulant individuals with DMD and is conducted on each outpatient clinical appointment since LOA as a conversation in which the tested individual with DMD and/or a helper are interviewed by the evaluator about how the individual functions in the 17 domains. Each domain is scored from 0 to 3 and the EK scale total score ranges from 0 to 51 based on the individual's performance in the last 2 weeks from the appointment. Higherscores, both overall and for each individual item, indicate greater functional impairment.

Score	**Ability to use wheelchair. How do you get around indoors and outdoors?**
0	Able to use a manual wheelchair on flat ground, 10 m <1 min
1	Able to use a manual wheelchair on flat ground, 10 m >1 min
2	Unable to use manual wheelchair, requires power wheelchair
3	Uses power wheelchair, but occasionally has difficulty steering
	Unknown
	Ability to transfer from wheelchair. How do you transfer from your wheelchair to a bed?
0	Able to transfer from wheelchair without help
1	Able to transfer independently from wheelchair, with use of aid
2	Needs assistance to transfer with or without additional aids (hoist, easy glide)
3	Needs to be lifted with support of head when transferring from wheelchair
	Unknown
	Ability to stand. Do you sometimes stand? How do you do this?
0	Able to stand with knees supported, as when using braces
1	Able to stand with knees and hips supported, as when using standing aids
2	Able to stand with full body support
3	Unable to be stood
	Unknown
	Ability to balance in the wheelchair. Can you bend forwards and to the sides and return to the upright position?

0	Able to push himself upright from complete forward flexion by pushing up with hands
1	Able to move the upper part of the body ≥30° in all directions from the upright position, but cannot push himself upright as above
2	Able to move the upper part of the body <30° from one side to the other
3	Unable to change position of the upper part of the body, cannot sit without total support of the trunk and head
	Unknown
	Ability to move the arms. Can you move your fingers, hands and arms against gravity?
0	Able to raise the arms above the head with or without compensatory movements
1	Unable to lift the arms above the head, but able to raise the forearms against gravity, i.e., hand to mouth with/without elbow support
2	Unable to lift the forearms against gravity, but able to use the hands against gravity when the forearm is supported
3	Unable to move the hands against gravity but able to use the fingers
	Unknown
	Ability to use the hands and arms for eating. Can you describe how you eat?
0	Able to eat and drink without elbow support
1	Eats or drinks with support at elbow
2	Eats and drinks with elbow support; with reinforcement of the opposite hand + or − aids
3	Has to be fed
	Unknown
	Ability to turn in bed. How do you turn in bed during the night?
0	Able to turn himself in bed with bedclothes
1	Needs some help to turn in bed or can turn in some directions
2	Unable to turn himself in bed. Has to be turned 0–3 times during the night
3	Unable to turn himself in bed. Has to be turned ≥4 times during the night
	Unknown
	Ability to cough. How do you cough when you have to?
0	Able to cough effectively
1	Has difficulty to cough and sometimes needs manual reinforcement. Able to clear throat
2	Always needs help with coughing. Only possible to cough in certain positions and with manual reinforcement, air-stacking etc.
3	Unable to cough, needs suction and/or hyperventilation techniques or IPPB in order to keep airways clear
	Unknown
	Ability to speak. Can you speak so that what you say can be understood if you sit at the back of a large room?
0	Powerful speech. Able to sing and speak loudly
1	Speaks normally, but cannot raise his voice
2	Speaks with quiet voice and needs a breath after 3–5 words
3	Speech is difficult to understand except to close relatives
	Unknown
	Physical well-being. This relates to respiratory insufficiency only (see manual). Use the categories as questions
0	No complaints, feels good
1	Easily tires. Has difficulty resting in a chair or in bed
2	Has loss of weight, loss of appetite, scared of falling asleep at night, sleeps badly
3	Experience additional symptoms to score 2: change of mood, stomach ache, palpitations, perspiring
	Unknown
	Daytime fatigue. Do you have to organize your day or take a rest to avoid getting too tired?
0	Doesn't get tired during day
1	Need to limit activity to avoid getting too tired
2	Need to limit my activity and have a rest period to avoid getting too tired
3	Get tired during day even if I rest and limit activity
	Unknown
	Head control. How much head support do you need in your wheelchair?
0	Does not need head support
1	Needs head support when going up and down slope (15° standard ramp)
2	Needs head support when driving wheelchair
3	When sitting still in a wheelchair needs head support
	Unknown
	Ability to control joystick. What kind of joystick do you use to control your chair?
0	Uses a standard joystick without special adaptation
1	Uses an adapted joystick or has adjusted wheelchair in order to use joystick
2	Uses other techniques for steering than joystick such as blowing/sucking systems or scanned driving
3	Unable to operate wheelchair. Needs another person to operate it
	Unknown
	Food textures. Do you have to modify your food in any way in order to eat it?
0	Eats all textures of food

1	Eats cut up or small pieces of food or avoids hard/chewy foods
2	Eats minced/pureed food
3	Main intake consists of being tube fed
	Unknown
	Eating a meal (with or without assistance). How long does it take to complete a whole meal?
0	Able to consume a whole meal in the same time as others sharing the meal
1	Able to consume a whole meal in the same time as others only with encouragement or needs some additional time (approximately 10 min)
2	Able to consume a whole meal but requires substantially more time compared to others eating the same meal (15 min or more extra)
3	Unable to consume a whole meal even with additional time, assistance
	Unknown
	Swallowing. Do you ever have problems with swallowing?
0	Never has problems when swallowing and never chokes on food/drink
1	May experience occasional (less than once a month) problems swallowing certain types of food or occasionally chokes
2	Has regular trouble swallowing food/drink or chokes on food/drink (more than once a month)
3	Has trouble swallowing saliva or secretions
	Unknown
	Hand function. Which of these activities can you do?
0	Can unscrew the lid of a water or fizzy drink bottle and break the seal
1	Can write two lines or use computer keyboard
2	Can write signature or send text or use remote control
3	Cannot use hands
	Unknown

Note: References 25–27.

Abbreviation: IPPB, intermittent positive pressure breathing.