Supplementary Online Content

Joseph S, Wang C, Bushby K, et al; UK NorthStar Clinical Network. Fractures and linear growth in a nationwide cohort of boys with Duchenne muscular dystrophy with and without glucocorticoid treatment: results from the UK NorthStar database. *JAMA Neurol*. Published online March 11, 2019. doi:10.1001/jamaneurol.2019.0242

This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods

(a) NorthStar Database

At the inception of the database in 2006, only ambulant boys were included, but information of non-ambulant boys were captured since 2008. At the biannual clinical review, physicians and physiotherapists completed standardised proforma. Information on whether any new fracture had occurred since the previous visit, the presence of back pain and use of bisphosphonate were specifically recorded. Data entered into the database are entered by the clinician reviewing each subject and not be separate database officers.

The NorthStar network project and database were reviewed by the Sheffield Medical Research Ethics Committee in 2005 and 2006. The network and database, as clinical audit projects were approved by the Hammersmith and subsequently the Great Ormond Street Hospital Caldicott Guardians on behalf of the National Health Service.

No systematic information on subjects who declined consent to be part of the NorthStar database from all centres is kept. During the period of study of this present project, two out of 250 (0.8%) families in the two largest centres in the NorthStar network declined. Similarly, during the same period, only one out of the 91 (1.1%) families in Scotland declined.

(b) Subjects: Analysis of fracture, back pain height and body mass index according to age groups.

For the 832 subjects, study visits (not subjects) were categorized into the five age groups: Group A: < 5.0 years (n= 113), Group B: 5.0 to 7.9 years (n=384), Group C: 8.0 to 10.9 years (n=421), Group D: 11.0 to 13.9 years (n=299), and Group E: ≥ 14.0 years (n=160) [Figure1]. As it is possible for subjects to be in the different age groups depending on the duration of follow-up, the total number in groups A to E exceeds 832. Only information from the last visit in each age group for each subject with data on fracture, back pain, height and body mass index is used.

(c) Subjects: Glucocorticoid regimen

Of the 832 subjects, 564 (68%) had more than one assessment record and complete details on GC treatment, and were used to study fracture incidence [Figure1]. Subjects on intermittent therapy were on the ten days on, ten days off regimen. Those recorded as receiving "other" included unknown type or dose frequency were excluded (n=74). For analysis of fracture incidence and longitudinal growth, individuals were assigned to each GC regimen group if they stayed on the same GC regimen. If any changes in GC type or regimen occurred, they were assigned to the "mixed GC" group [Figure1].

Mean daily hydrocortisone equivalent dose for surface area over the observation period (in mg/m2/day) in daily deflazacort, daily prednisolone, intermittent deflazacort, intermittent prednisolone regimen were 46.5 mg/m2/day [12.8], 57.5 mg/m2/day [19.4], 20.6 mg/m2/day [5.4], and 30.6 mg/m2/day [10.7], respectively. Mean daily hydrocortisone equivalent dose for weight over the observation period (in mg/kg/day) in daily deflazacort, daily prednisolone, intermittent deflazacort, intermittent prednisolone regimen were 1.7 mg/kg/day [0.6], 2.4 mg/kg/day [0.5], 0.7 mg/kg/day [0.2], and 1.2 mg/kg/day [0.3], respectively. Mean cumulative hydrocortisone equivalent dose over the observation period (in mg/kg) in daily deflazacort, daily prednisolone, intermittent deflazacort, intermittent prednisolone regimen were 1367 mg/kg [1217], 2698 mg/kg [1819], 617 mg/kg [563], and 1014 mg/kg [805], respectively. Mean prescribed drug dose in daily deflazacort, daily prednisolone, intermittent deflazacort, intermittent prednisolone regimen over the observation period taking into account days of drug exposure were 0.6 mg/kg/day [0.2], 0.5 mg/kg/day [0.1], 0.3 mg/kg/day [0.1], and 0.3 mg/kg/day [0.1], respectively.

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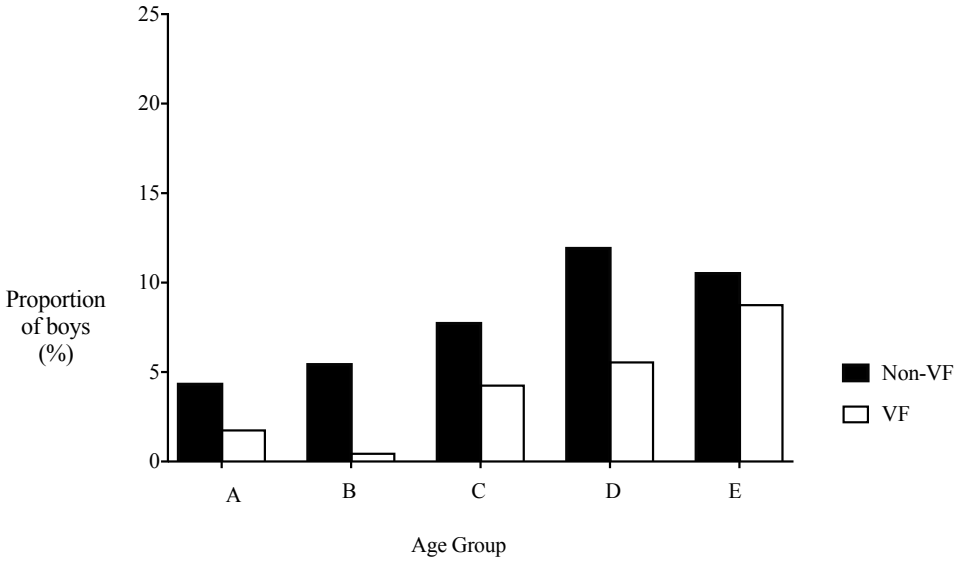
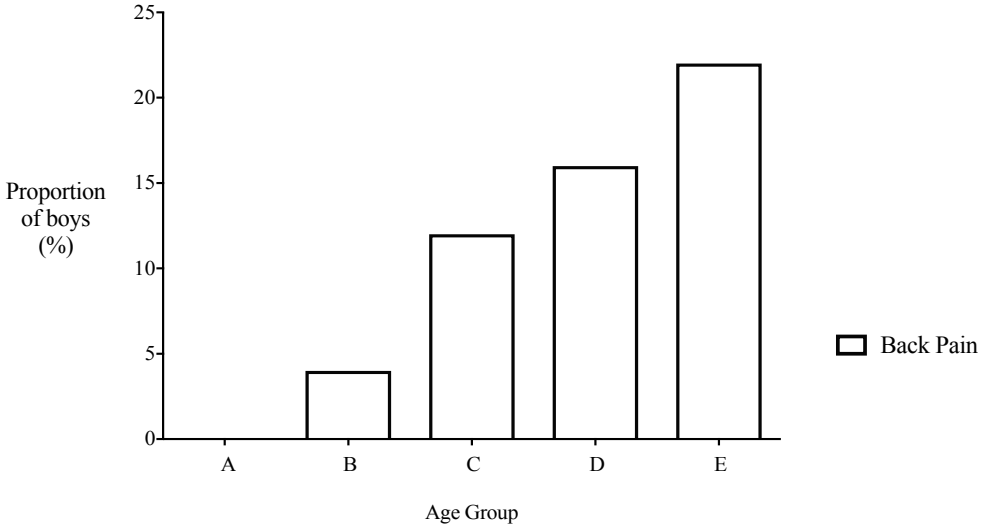
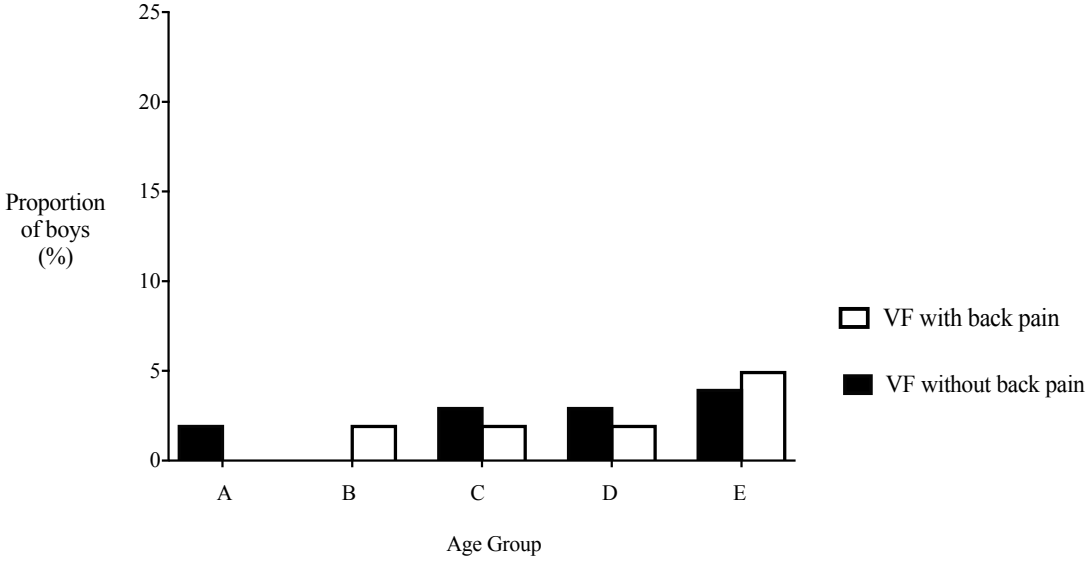


eFigure 1a



eFigure 1b



eFigure 1c

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eFigure 1 **New fracture occurrence according to age groups**

(a) New fracture occurrence according to age group

Fractures are classified in VF or non-VF. New fracture occurrences are shown as percentage of boys with fracture in the five different age groups.

New fracture of all types occurred in 7/113 (6.0%) of group A (< 5 years), in 23/384 (6.0%) of group B (5.0 to 7.9 years), in 51/421 (12.0%) of group C (8.0 to 10.9 years), in 52/299 (17.0%) of group D (11 to 13.9 years) and in 31/160 (19.0%) of those in group E (≥ 14 years).

New non-VF occurred in 5/113 (4.0%) of group A (< 5 years), in 21/384 (6.0%) of group B (5.0 to 7.9 years), in 33/421 (8.0%) of group C (8.0 to 10.9 years), in 36/299 (12.0%) of group D (11 to 13.9 years) and in 17/160 (2.0%) of those in group E (≥ 14 years).

New VFs were present in 2/113 (2.0%) of group A (< 5 years), in 2/384 (0.5%) of group B (5.0 to 7.9 years), in 18/421 (4.0%) of group C (8.0 to 10.9 years), in 16/299 (5.0%) of group D (11.0 to 13.9 years) and in 14/169 (9.0%) of group E (≥ 14 years).

[VF: vertebral fracture]

(b) Reported back pain according to age group

Reported back pain is shown as percentage in the five different age groups.

Back pain was reported in 0/113 (0.0%) of group A (< 5 years), in 16/384 (4.0%) of group B: (5.0 to 7.9 years), in 51/421 (12.0%) of group C (8.0 to 10.9 years), in 48/299 (16.0%) of group D (11.0 to 13.9 years) and in 35/160 (22.0%) of group E (≥ 14 years)

(c) New VF with and without reported back pain according to age group

VF with and without reported back pain during clinic visits are shown as percentage in the five different age groups.

VFs without back pain were present in 2/113 (2.0%) of group A (< 5 years), in 0/384 (0.0%) of group B (5.0 to 7.9 years), in 11/421 (2.6%) of group C (8.0 to 10·9 years), in 10/299 (3·3%) of group D (11 to 13·9 years) and in 6/160 (4.0%) of group E (≥ 14 years).

VFs with back pain were present in 0/113 (0.0%) of group A (< 5 years), in 2/384 (0·5%) of group B (5·0 to 7·9 years), in 7/421 (2.0%) of group C (8·0 to 10·9 years), in 6/299 (2·0%) of group D (11 to 13·9 years) and in 8/160 (5·0%) of group E (≥ 14 years).

[VF: vertebral fracture]

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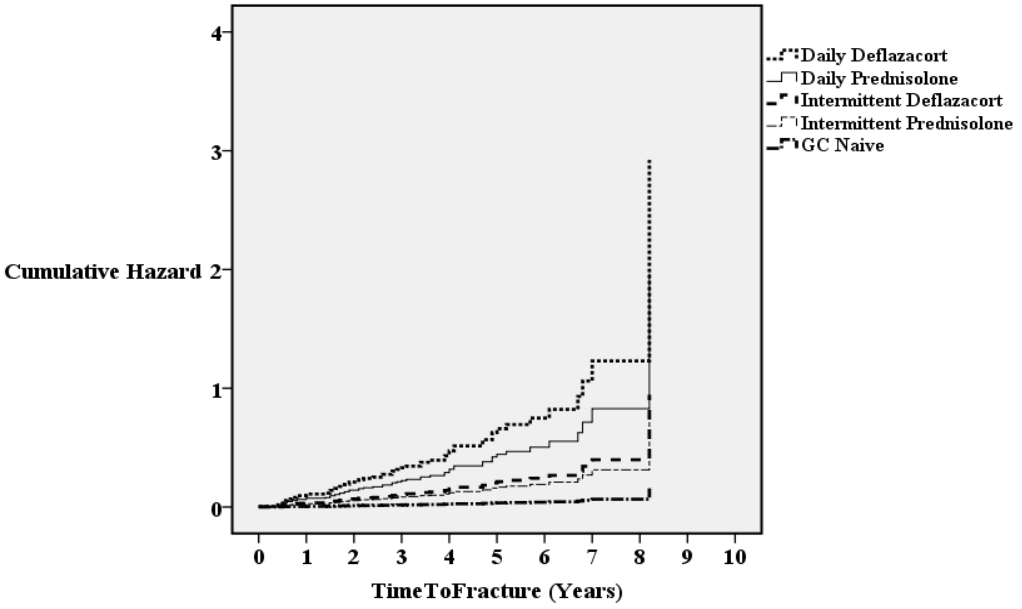
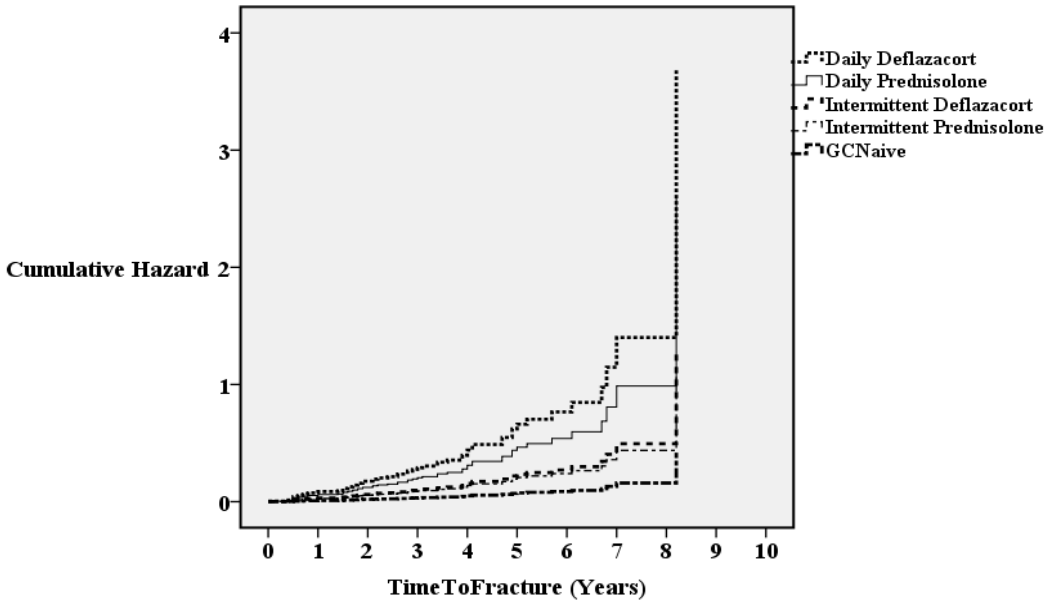


eFigure 2a



eFigure 2b

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eFigure 2: **Multivariate cox regression analysis of cumulative hazard according to GC regimen**

(a) Hazard ratio of sustaining the first fracture was analysed using multivariate cox regression adjusting for age at last assessment, average hydrocortisone equivalent (mg/kg/day), mobility status and bisphosphonate use prior to the first fracture.

(b) Hazard ratio of sustaining the first fracture was analysed using multivariate cox regression adjusting for age at last assessment, cumulative hydrocortisone equivalent (mg/kg), mobility status and bisphosphonate use prior to the first fracture.

[GC: glucocorticoid]

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	Change in Ht SDS			Change in BMI SDS		
	B	**95% CI**	**p-value**	**B**	**95% CI**	**p-value**
Daily deflazacort	-0.69	-1.20, -0.17	0.01*	0.04	-0.54, 0.63	0.88
Pulsed deflazacort	0.18	-1.06, 1.42	0.77	-0.00	-0.94, 0.94	0.99
Daily prednisolone	-0.39	-0.89, 0.05	0.12	0.65	0.14, 1.15	0.01*
Pulsed prednisolone	0.15	-0.24, 0.54	0.44	-0.01	-0.42, 0.41	0.99

eTable1: Multivariate analysis of the impact of glucocorticoid regimen on changes in growth parameters

The impact of different GC regimens on changes in Ht SDS and BMI SDS was evaluated using multivariate linear regression analysis adjusting for Ht/ BMI SDS at baseline, age at baseline and duration of follow-up. (GC naïve designated as reference category)

[Ht: height; BMI: body mass index; SDS: standard deviation score; B: beta; CI: confidence interval; GC: glucocorticoid]

* $p < 0.05$

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