HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2020 October 05.

Published in final edited form as:

Am J Med Genet A. 2018 November ; 176(11): 2350–2358. doi:10.1002/ajmg.a.40517.

The effect of steroid treatment on weight in nonambulatory males with Duchenne muscular dystrophy

Molly M. Lamb[1], **Bo Cai**[2], **Julie Royer**[3], **Shree Pandya**[4], **Aida Soim**[5], **Rodolfo Valdez**[6], **Carolyn DiGuiseppi**[1], **Katherine James**[1], **Nedra Whitehead**[7], **Holly Peay**[7], **Swamy Y. Venkatesh**[8], **Dennis Matthews**[9], **The Muscular Dystrophy Surveillance, Research, and Tracking Network (MD STAR*net*)**

[1]Department of Epidemiology, Colorado School of Public Health, Aurora, Colorado

[2]Department of Epidemiology and Biostatistics, Arnold School of Public Health, Columbia, South Carolina

[3]South Carolina Revenue and Fiscal Affairs Office, Columbia, South Carolina

[4]Department of Neurology, University of Rochester, Rochester, New York

[5]New York State Department of Health, Empire State Plaza, Albany, New York

[6]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

[7]Department of Social, Statistical, and Environmental Sciences, RTI International, Raleigh-Durham, Durham, North Carolina

[8]Department of Neurology, University of South Carolina School of Medicine, Columbia, South Carolina

[9]Department of Pediatric Rehabilitation Medicine, Children's Hospital Colorado, Aurora, Colorado

Abstract

To describe the long-term effect of steroid treatment on weight in nonambulatory males with Duchenne Muscular Dystrophy (DMD), we identified 392 males age 7–29 years with 4,512 weights collected after ambulation loss (176 steroid-naïve and 216 treated with steroids ≥6 months) from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*). Comparisons were made between the weight growth curves for steroid-naïve males with DMD, steroid-treated males with DMD, and the US pediatric male population. Using linear mixed-effects models adjusted for race/ethnicity and birth year, we evaluated the association between weight-for-age and steroid treatment characteristics (age at initiation, dosing interval, cumulative duration, cumulative dose, type). The weight growth curves for steroid-naïve and steroid-treated nonambulatory males with DMD were wider than the US pediatric male growth

Correspondence: Molly M. Lamb, Colorado School of Public Health, University of Colorado Denver, Building 500,13001 East 17th Place, Mail Stop C245 Aurora, CO 80045. molly.lamb@ucdenver.edu.

Disclosures: The authors have no conflicts of interest.

SUPPORTING INFORMATION

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

curves. Mean weight-for-age *z* scores were lower in both steroid-naïve (mean = −1.3) and steroid-treated (mean = −0.02) nonambulatory males with DMD, compared to the US pediatric male population. Longer treatment duration and greater cumulative dose were significantly associated with lower mean weight-for-age *z* scores. Providers should consider the effect of steroid treatment on weight when making postambulation treatment decisions for males with DMD.

Keywords

corticosteroids; muscular dystrophy; nonambulatory; weight

1 | INTRODUCTION

As the result of improvements in treatment and management, the life expectancy of males with DMD has increased greatly over the past few decades. Males with DMD are now living into their third decade (Calvert, McKeever, Kinnear, & Britton, 2006; Rail & Grimm, 2012). Thus, males with DMD now have a much longer postambulation period, in which treatment decisions may need to be reevaluated as the risk/benefit balance of treatment shifts over time.

For decades, glucocorticoid ("steroid") treatment has been recommended for ambulatory males with DMD to preserve (Balaban, Matthews, Clayton, & Carry, 2005; Beenakker et al., 2005; Biggar, Harris, Eliasoph, & Alman, 2006; Henricson et al., 2013) or improve (Angelini etal., 1994; Fenichel etal., 1991; Mendell etal., 1989; Rahman, Hannan, Mondol, Bhoumick, & Haque, 2001) muscle strength and motor function (Gloss, Moxley 3rd, Ashwal, & Oskoui, 2016), and to prolong independent ambulation by 1–3 years (DeSilva, Drachman, Mellits, & Kuncl, 1987; Houde et al., 2008; King et al., 2007; Koeks et al., 2017; McDonald et al., 2017; Pradhan et al., 2006; Yilmaz, Karaduman, & Topaloglu, 2004). More recently, prolonged steroid treatment in males with DMD has been associated with preserved upper limb function (McDonald et al., 2017; Pane et al., 2015), reduced or delayed scoliosis onset (Alman, Raza, & Biggar, 2004; Balaban et al., 2005; Houde et al., 2008; King et al., 2007; Koeks et al., 2017; Lebel, Corston, McAdam, Biggar, & Alman, 2013; Yilmaz et al., 2004), preserved respiratory function (Balaban et al., 2005; Biggar et al., 2006; Henricson et al., 2013; Koeks et al., 2017; Machado et al., 2012; Silversides, Webb, Harris, & Biggar, 2003), delayed cardiomyopathy onset (Barber et al., 2013; Houde et al., 2008; Koeks et al., 2017; Markham, Kinnett, Wong, Woodrow Benson, & Cripe, 2008; Schram et al., 2013; Silversides et al., 2003), and prolonged survival (McDonald et al., 2017), albeit inconsistently. The most recent Care Considerations recommend continued steroid treatment in the nonambulatory stage of DMD due to the beneficial effects of steroid treatment on a variety of late-stage comorbidities (Birnkrant et al., 2018), and anecdotal evidence from clinicians suggests that prolonged steroid treatment in postambulatory males with DMD is becoming increasingly common.

While the evidence suggests that steroid treatment may benefit males with DMD across their lifespan, it may also cause a number of undesirable side effects (Matthews, Brassington, Kuntzer, Jichi, & Manzur, 2016), including weight gain (Lamb et al., 2016). This side effect

may exacerbate the complex natural history of weight gain and weight maintenance in males with DMD, in which excess weight gain and obesity in adolescence (Balaban et al., 2005; Griggs et al., 1993; Houde et al., 2008; Mendell et al., 1989; Moxley et al., Moxley 3rd et al., 2005) may be followed by underweight as they age and the disease progresses in both steroid-naïve (Davidson et al., 2014; Martigne et al., 2011) and steroid-treated males (Davidson et al., 2014) with DMD. Information on the postambulatory weight growth experience is sparse, both in steroid-naïve and steroid-treated males with DMD. Using the large, longitudinal Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*) surveillance cohort, we created and compared weight growth curves in nonambulatory males with DMD, for steroid-naïve males and males treated with steroids ≥6 months cumulatively in their lifetime leading up to each weight measurement. In addition, to better describe the side effects of steroid treatment in nonambulatory males with DMD, we examined associations between weight growth and steroid treatment characteristics among nonambulatory steroid-treated males with DMD.

2 | MATERIALS AND METHODS

2.1 | Study population and sample

The MD STAR*net* is a population-based surveillance system that aims to identify all individuals with childhood-onset DMD or Becker muscular dystrophy born between 1982 and 2011 and who have ever resided in an MD STAR*net* site. Details of the surveillance methodology and case classification have been published previously (Mathews et al., 2010; Miller et al., 2006). Briefly, cases were retrospectively identified in Arizona, Colorado, Iowa, and western New York starting in 2004, Georgia in 2005, and Hawaii in 2008. Annual medical record abstraction was completed through December 31, 2011 for those cases identified prior to September 2011, and through December 31, 2012 for those cases identified between September and December 2011. The case-finding methodology used by MD STAR*net* was based on active review of source records in neuromuscular clinics, hospital discharge databases, private physician practices, service sites for children with special health care needs, and birth defect surveillance programs (Miller et al., 2006). Each participating site obtained permission for case finding and medical record abstraction either through institutional review board approval or by state-mandated public health reporting.

Duchenne or Becker Muscular Dystrophy (DBMD) case definitions were assigned following independent neuromuscular specialist clinician review of critical diagnostic elements of each abstracted case record. Case definitions included “definite,” “probable,” “possible,” “asymptomatic,” or “affected female” (Mathews et al., 2010). We selected “probable” and “definite” DBMD cases for analysis. “Probable” DBMD cases (9% of analysis cohort) had recorded clinical symptoms related to a dystrophinopathy, an elevated creatine kinase, and an X-linked pedigree consistent with a dystrophinopathy. “Definite” DBMD cases (91% of analysis cohort) also had a confirmed dystrophin mutation, a muscle biopsy showing absent dystrophin, or an X-linked pedigree and an affected family member with a dystrophin mutation or diagnostic muscle biopsy. In our analysis cohort, the percentage of males that had a “probable” DMD diagnosis did not differ significantly between steroid-treated (6.7%) and steroid-naïve (12.2%) boys (chi-square $p = .06$). Affected males were categorized as

having a Duchenne phenotype if the following criteria were met: (1) ambulation ceased before 12 years of age or 16 years of age, when prior to cessation, any steroid use or continuous steroid use of at least 24 months was ascertainable, respectively; or (2) observation of an out-of-frame DMD mutation consistent with a Duchenne phenotype or a Western blot showing less than or equal to 5% dystrophin; or (3) onset of symptoms occurred before 5 years of age. Subjects not meeting this definition of Duchenne phenotype were excluded from analyses. Subjects from Hawaii were excluded due to very small sample size and incomplete follow-up. Cohort exclusions and selection of cases for the analyses were made according to the flowchart detailed in Figure 1. Of the 1,054 subjects in the MD STAR*net* surveillance dataset, 392 nonambulatory males with DMD with clinic visits that occurred between ages 7 and 29 years were selected for these analyses.

2.2 | Growth data

Weight data were obtained from annual medical record abstraction. The analysis cohort contained 1,832 weight records for 176 nonambulatory (defined as full-time wheelchair use or first report that ambulation had ceased) steroid-naïve males with DMD, and 2,596 weight records for 209 nonambulatory males with DMD who were treated with steroids for ≥6 months. We excluded growth measurements collected between 1 day and 6 months of cumulative steroid treatment (daily or intermittent regimens) from our analyses, because the effect of steroids on weight is gradual and may not be evident until at least 6 months of treatment. Records of males with DMD who had been treated with steroids for at least 6 months, then discontinued steroid treatment, were included in the “steroid-treated” group. There were seven males with DMD who had nonambulatory weight records collected both before and after steroid initiation. The 84 steroid-naïve records from these males were included in the steroid-naïve analysis, and the 92 records collected from these males after 6 months of steroid treatment were included in the steroid-treated analysis (Figure 1). When comparing the weight growth curves between steroid-treated and steroid-naïve nonambulatory males with DMD, we excluded the seven males that had both steroid-naïve and steroid-treated records, due to a potential change in the slope of their growth curve shortly after the initiation of steroid treatment.

2.3 | Steroid treatment

Steroid age at initiation, cumulative duration, cumulative dosage, and dosing interval were abstracted from medical records and calculated as follows. Cumulative duration of steroid treatment was calculated as a count of days during which the child was determined to have been treated with steroids, based on recorded steroid start and stop dates (if applicable), and was calculated for each clinic visit at which weight was collected, to determine the total length of exposure to steroid treatment for that weight measurement. The number of days was converted into number of years for analysis. Cumulative dose of steroids was calculated as the actual dosing interval (in days) multiplied by the dose of steroid multiplied by the duration of treatment, calculated for each reported steroid treatment regimen, and summed over each reported change in steroid dose (reported as mg/kg), and was determined for each clinic visit at which weight was collected. For prediction models, steroid dosing interval was dichotomized from recorded dosing intervals to “at least daily” or “less than daily,” and was determined for each clinic visit at which weight was collected. Each steroid treatment

variable was calculated for prednisone and deflazacort separately, to determine if these two steroids had differential effects on weight growth.

2.4 | Growth curve analysis

To create weight growth curves, we calculated weight-for-age in 6 month intervals from age 8.5 to 21.0 years in steroid-naïve males, and 8.5–22.5 years in steroid-treated males using the same methodology as the CDC growth charts (Kuczmarski et al., 2002). The small number of nonambulatory weight records collected before age 8.5 years (due to the fact that most boys with DMD were still ambulatory at these younger ages) made the growth curve calculation unstable and prone to excessive influence of a single outlier, so we began the growth curve calculations at age 8.5 years. To compare the weights of males with DMD to general US population males, we restricted our dataset to weights collected prior to age 20 years, because the CDC growth charts only specify weight percentiles up to 20 years of age due to flattening of the growth curves in adulthood. We then created growth curves (10th, 25th, 50th, 75th, and 90th percentiles) for steroid-naïve and steroid-treated nonambulatory males with DMD. If more than one growth measurement was available for an individual in a given 6 month interval, the measurements for that individual in that interval were averaged, and the average value was used in growth curve creation.

To produce percentile curves that could be directly compared, linear smoothing procedures modeled after the smoothing procedures used by the 2,000 CDC Growth Charts for the United States were applied in two stages to the irregular plots of the empirical percentile values (Kuczmarski et al., 2002). Graphical examinations were made to compare differences in weight-for-age growth curves among nonambulatory steroid-naïve males with DMD, nonambulatory steroid-treated males with DMD and general population US pediatric males. We also compared the mean weight-for-age z scores for nonambulatory steroid-naïve males with DMD, nonambulatory steroid-treated males with DMD, and general US pediatric population males (Kuczmarski et al., 2002) using Student's t tests.

Frequently, height was not directly measured in nonambulatory males with DMD due to muscle contractures; approximately two-thirds of the clinic records included in our analysis data set were missing height information. Therefore, due to likely bias in the existing height data, we only conducted an exploratory analysis comparing US pediatric male height-for-age z scores and BMI-for-age z scores with mean height-for-age and BMI-for-age z scores for steroid-naïve and steroid-treated nonambulatory males with DMD for whom height data were available. Due to lack of data, we did not construct height and BMI growth curves for this nonambulatory analysis cohort.

2.5 | Demographic comparisons and linear mixed-effects analysis

Demographic variables in steroid-treated and steroid-naïve nonambulatory males with DMD were compared using Student's t test for continuous variables and chi-square for categorical variables. Using a linear mixed-effects model to account for intrasubject correlation of repeated measures with an unstructured covariance matrix of weight in children as they age, we described associations between weight-for-age z scores and steroid treatment characteristics (age at initiation, dosing interval, cumulative duration, cumulative dose,

steroid type) in the nonambulatory males with DMD that were treated with steroids for ≥6 months. Stratified linear mixed-effects models were conducted for each steroid treatment characteristic. All models were adjusted for birth year and race/ethnicity to control for their confounding effects. SAS statistical package 9.4 (Cary, NC) was used for all analyses.

3 | RESULTS

Of the 392 nonambulatory males with DMD in our analysis cohort, 176 were steroid-naïve and 216 had been treated with steroids for ≥6 months. Demographic details of the analysis population can be found in Table 1. Weight and steroid treatment information were collected from multiple clinic records across the child's nonambulatory childhood and early adulthood; the mean age of clinic record was 15.2 years, with weight data for steroid-naïve males with DMD being collected at a slightly younger average age than steroid-treated males with DMD (15.1 years vs. 15.3 years, $p = .045$). Steroid treatment patterns varied widely in our analysis cohort. Subjects started and stopped steroid treatment up to 3 times throughout the observation period. While very few ($n = 7$) males with DMD in our analysis cohort initiated steroid treatment after ambulation loss, 39% of steroid-treated males with DMD in our analysis cohort discontinued steroid treatment around the time of ambulation loss. Non-Hispanic white males with DMD were more likely to be treated with steroids than Hispanic or non-Hispanic Black males with DMD ($p < .0001$). Mean cumulative length of steroid treatment was 5.6 years, and the difference between deflazacort treatment length (6.5 years) and prednisone treatment length (5.2 years) was not statistically significant ($p = .13$). Length of steroid treatment ranged from 0.58 to 17.4 years for deflazacort, and 0.50–17.1 years for prednisone.

Among both steroid-treated and steroid-naïve nonambulatory males with DMD, the ranges of their growth curves were wider than the growth curve of their peers from the US pediatric male population: weight-for-age range for US pediatric males at 20 years of age: 10th percentile = 59 kg, 90th percentile = 89 kg; weight-for-age range for nonambulatory steroid-naïve males with DMD at 20 years of age: 10th percentile = 29 kg, 90th percentile = 92 kg; weight-forage range for nonambulatory steroid-treated males with DMD at 20 years of age: 10th percentile = 39 kg, 90th percentile = 103 kg (Figure 2, Supporting Information Figure S1). Steroid-naïve nonambulatory males with DMD had significantly lower mean weight-for-age z scores compared with both steroid-treated nonambulatory males with DMD (−1.3 vs. −0.02, $p < .0001$) and the US pediatric male population (−1.3 vs. 0, $p < .0001$). The mean weight-for-age z score in steroid-treated nonambulatory males with DMD was only slightly lower than the US pediatric male population (−0.02 vs. 0, $p = .60$). At younger ages, the mean weight-for-age z scores in both steroid-naïve and steroid-treated nonambulatory males with DMD were greater than the US pediatric male population. However, as the nonambulatory males with DMD got older, their weight-for-age fell off compared with the US pediatric male population, likely because of progressive muscle wasting and replacement with fibrotic tissue. Means and selected growth curve percentiles of weight by age in steroid-naïve and steroid-treated nonambulatory males with DMD can be found in Supporting Information Tables S1 and S2.

The exploratory analysis showed mean height-for-age *z* scores for nonambulatory steroid-naïve males with DMD and nonambulatory steroid-treated males with DMD were below US pediatric male averages (−0.80 in steroid-naïive males with DMD, −0.84 in steroid-treated males with DMD). In the steroid-naïve males with DMD, mean BMI-for-age *z* scores were also low (−1.15) compared to US pediatric males, while in steroid-treated nonambulatory males with DMD, mean BMI-for-age *z* scores were higher compared to US pediatric males (0.16).

In nonambulatory males with DMD who were treated with steroids for ≥6 months, longer duration of treatment and greater cumulative dose were significantly associated with lower weight-for-age *z* scores. Age at steroid initiation was not significantly associated with weight-for-age *z* score. Dosing frequency was not associated with weight-for-age *z* score in males treated with deflazacort; however, in males treated with prednisone, at least daily dosing interval was associated with greater weight-for-age *z* score. There was no difference in weight-for-age *z* score between prednisone-treated males and deflazacort-treated males (Table 2).

4 | DISCUSSION

We describe, for the first time, the weight growth of postambulatory steroid-naïve and steroid-treated males with DMD. A comparison of the steroid-naïve to the steroid-treated weight growth curves shows that steroid treatment is associated with increased weight in the postambulatory stages of DMD. This increased weight often resulted in overweight in the nonambulatory adolescent males. Other studies have also noted a tendency toward obesity in both steroid-treated and steroid naïve adolescents with DMD (Balaban et al., 2005; Griggs et al., 1993; Houde et al., 2008; Mendell et al., 1989; Moxley 3rd et al., 2005). This increase in body mass likely differs in composition between steroid-treated and steroid naïve males with DMD. A longitudinal study of boys with DMD age 5–15 years showed that steroid treatment increased lean tissue mass, while steroid-naïve boys with DMD experienced a significant increase in body fat mass (Vuillerot et al., 2014).

The growth curves of both steroid-naïve and steroid-treated males with DMD appeared to flatten out at a younger age than the growth curve of the US pediatric male population, perhaps due to the advancing muscle wasting that occurs as the disease progresses. Steroid treatment appeared to protect against underweight in the older males with DMD. The tendency toward underweight in the older steroid-naïve males with DMD that can be seen in the growth curves we created was also described in other studies (Davidson et al., 2014; Martigne et al., 2011), as it was the attenuating effect of steroid treatment on underweight in older males with DMD (Davidson et al., 2014).

It is worth noting that the weight-for-age *z* scores may not be a good proxy for obesity in this patient population. The height growth of ambulatory steroid-treated males with DMD is stunted (Lamb et al., 2016), due to both the DMD disease process and steroid treatment. Therefore, the weight in nonambulatory males with DMD in our analysis may still be higher than expected for their height, and could reach the obesity range despite their overall smaller size. We did not perform a formal analysis of height-for-age and BMI-for-age using the MD

STAR*net* cohort, due to a large amount of missing data and the strong possibility of selection bias–height could have been collected only for the children with fewer or less severe contractures. However, in an exploratory analysis of the available data from the MD STAR*net* cohort, the height-for-age *z* scores for nonambulatory steroid-naïve males with DMD were below US pediatric male averages. In the steroid-naïve males with DMD, BMI-for-age *z* scores were also low, while in steroid-treated nonambulatory males with DMD, BMI-for-age *z* scores were higher, but still not high enough to be of clinical concern, as defined by CDC growth charts.

As a male with DMD becomes increasingly disabled due to disease progression, excess weight gain may be a concern for its potential negative effects on health as well as the logistics of caregiving. Research thus far, however, suggests that the endocrine and physical effects of higher BMI do not appear to exacerbate or speed the development of DMD comorbidities, and may actually be protective (Canapari et al., 2015; Davidson et al., 2014; Janssen, Hendriks, Geurts, & de Groot, 2016; McKane et al., 2017). Nevertheless, excess weight does complicate the full assistance with daily care and transfers that these boys and men eventually require. Males with DMD and their families should be aware of the practical implications of the possible effects on weight, as well as the potential health benefits, when considering postambulatory steroid treatment.

Black and Hispanic nonambulatory males with DMD were significantly less likely to have had ≥6 months of steroid treatment compared to non-Hispanic white males with DMD. This treatment disparity has been observed previously in MD STAR*net* (Fox et al., 2015). The difference in steroid treatment by race/ethnicity may stem from lower treatment initiation rates (Fox et al., 2015), which could, in turn, be due to lower acceptance of the recommended treatment by families, lower rate of steroid treatment offered to minority populations, or lack of culturally sensitive presentation of treatment options. While MD STAR*net* does not have the appropriate data with which to test these hypotheses, other DMD cohorts could explore the presence of, and reasons for, this treatment disparity.

Our analysis of the association between steroid treatment characteristics and weight growth revealed an inverse association between steroid dose and weight, and between steroid treatment duration and weight. These findings are at odds with our previous findings in ambulatory males with DMD (Lamb et al., 2016). However, these findings are compatible if there is an acceleration of muscle wasting in the later stages of the disease process. Loss of muscle mass would reduce a subject's weight, and the weight-gaining effects of steroid treatment may eventually not be enough to offset the weight loss due to muscle wasting. Alternatively, these results could be the result of a selfselection effect. Weight gain is a major side effect of steroid treatment, and many subjects find this side effect so undesirable that they discontinue treatment. Thus, if only those males with DMD who did not gain much weight continued steroid treatment, while those who gained weight in excess were more likely to discontinue steroid treatment, then that may explain our observed inverse association between steroid dose and weight.

We did not find an association between dose frequency (at least daily vs. < daily) and weight in nonambulatory males with DMD who were treated with deflazacort; however, greater

dose frequency was associated with weight in those treated with prednisone, suggesting that dose frequency does not consistently modify this side effect of steroid treatment. Our findings are similar to those of other studies. A UK study found that a daily dose of prednisolone increased the prevalence of obesity among males with DMD (Ricotti et al., 2013), and a study performed by the Cooperative International Neuromuscular Research Group found increased BMIs in those treated with prednisone daily compared with those treated on weekends only, but their findings did not reach statistical significance (Escolar et al., 2011). Researchers and clinicians are not in agreement on the optimal steroid dosing regimen for DMD (Griggs et al., 2013). The FORDMD trial is currently testing different steroids and steroid dosing regimens to find the most effective treatment with the least side effects (Guglieri et al., 2017).

Strengths of this study include the classification of DMD using a standard protocol by a review committee consisting of neuromuscular specialist clinicians. These data are derived from a population-based cohort and are thus likely to be an accurate representation of males with DMD in the surveillance areas, which are scattered across the United States. Also, the MD STAR*net* surveillance methodology collects data longitudinally, which permits evaluation of growth throughout childhood and into adulthood. Adjustment for birth year enabled us to reduce cohort effects due to clinical practice shifts in prescribing steroids to males with DMD over the past few decades, and to potential acceleration in US children's growth (Ogden, Carroll, & Flegal, 2008).

A limitation of this study is the use of anthropometric measurements extracted retrospectively from medical records. The weights were likely collected with the patient in the wheelchair. It is standard clinical procedure to subtract the weight of the wheelchair. However, we cannot confirm that the chairs were weighed separately each time and if the weight of the wheelchair was subtracted appropriately from each of our nonambulatory weight measurements. We also relied on medical records for steroid treatment details, which may have been incomplete and may have resulted in misclassification of steroid treatment. We note that the clinic records in which steroid start and stop dates were recorded may not be complete, and may not reflect the true steroid exposure of the child due to incomplete reporting of steroid treatment compliance by the family. Thus, cumulative steroid duration and dose may be over or underestimated for each child. We note that neither the subjects nor the persons measuring knew that the anthropometric data being collected or steroid dosing information being recorded would be used to explore the association between weight and steroid treatment; thus the misclassification is likely to be nondifferential, and would bias our results toward the null hypothesis (no association). MD STAR*net* could not extract body fat measurements from clinic records; these measures are not routinely collected in males with DMD. This deficiency, combined with the large amount of missing height data, prevented us from more accurately describing the obesity status and fat mass of the subjects in our analysis. The loss to follow-up rate (defined as no clinic visit at which weight was measured within the last 3 years of data collection or 3 years prior to death, whichever occurred first) in males that died during the follow-up period was 23.71%, and the loss to follow-up rate in males that did not die during the follow up period was 14.58%. Thus, it is possible that the males with DMD nearing the end of their life may be underrepresented in these analyses. Finally, the finding of a lower rate of steroid treatment in non-white

nonambulatory males with DMD limits the generalizability of our findings, as does the fact that the analysis cohort was drawn from surveillance sites, and not the entire United States.

Our results suggest that prolonged steroid treatment is associated with increased weight gain/weight maintenance in nonambulatory males with DMD. The growth charts for nonambulatory males with DMD that we have provided herein should be useful to both clinicians and families as they monitor this major side effect of steroid treatment, and ponder initiation, continuation, or cessation of steroid treatment across the lifespan of a patient with DMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This publication was supported by the Cooperative Agreement numbers DD000187, DD000189, DD000190, DD000191, DD001116 and DD001117, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Diseases Control and Prevention or the Department of Health and Human Services.

Funding information:

Centers for Disease Control and Prevention, Grant/Award Numbers: DD000187, DD000189, DD000190, DD000191, DD001116 a, DD001117, DD001116, DD000191, DD000190, DD000189, DD000187

Abbreviations:

CDC	Centers for Disease Control and Prevention
DBMD	Duchenne or Becker Muscular Dystrophy
DMD	Duchenne Muscular Dystrophy
MD STAR*net*	Muscular Dystrophy Surveillance Tracking, and Research Network
Steroids	Glucocorticoids

REFERENCE

Alman BA, Raza SN, & Biggar WD (2004). Steroid treatment and the development of scoliosis in males with duchenne muscular dystrophy. The Journal of Bone and Joint Surgery. American Volume, 86-A(3), 519–524.

Angelini C, Pegoraro E, Turella E, Intino MT, Pini A, & Costa C (1994). Deflazacort in Duchenne dystrophy: Study of long-term effect. Muscle & Nerve, 17(4), 386–391. 10.1002/mus.880170405 [PubMed: 8170484]

Balaban B, Matthews DJ, Clayton GH, & Carry T (2005). Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: Long-term effect. American Journal of Physical Medicine & Rehabilitation, 84(11), 843–850. [PubMed: 16244521]

Barber BJ, Andrews JG, Lu Z, West NA, Meaney FJ, Price ET, … Cunniff C (2013). Oral corticosteroids and onset of cardiomyopathy in Duchenne muscular dystrophy. The Journal of Pediatrics, 163(4), 1080–1084e1081. 10.1016/j.jpeds.2013.05.060 [PubMed: 23866715]

Beenakker EA, Fock JM, Van Tol MJ, Maurits NM, Koopman HM, Brouwer OF, & Van der Hoeven JH (2005). Intermittent prednisone therapy in Duchenne muscular dystrophy: A randomized controlled trial. Archives of Neurology, 62(1), 128–132. 10.1001/archneur.62.1.128 [PubMed: 15642859]

Biggar WD, Harris VA, Eliasoph L, & Alman B (2006). Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. Neuromuscular Disorders, 16(4), 249–255. 10.1016/j.nmd.2006.01.010 [PubMed: 16545568]

Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, … Weber DR (2018). Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurology, 17(3), 251–267. 10.1016/s1474-4422(18)30024-3 [PubMed: 29395989]

Calvert LD, McKeever TM, Kinnear WJ, & Britton JR (2006). Trends in survival from muscular dystrophy in England and Wales and impact on respiratory services. Respiratory Medicine, 100(6), 1058–1063. 10.1016/j.rmed.2005.09.030 [PubMed: 16257521]

Canapari CA, Barrowman N, Hoey L, Walker SW, Townsend E, Tseng BS, & Katz SL (2015). Truncal fat distribution correlates with decreased vital capacity in Duchenne muscular dystrophy. Pediatric Pulmonology, 50(1), 63–70. 10.1002/ppul.23004 [PubMed: 24644236]

Davidson ZE, Ryan MM, Kornberg AJ, Sinclair K, Cairns A, Walker KZ, & Truby H (2014). Observations of body mass index in Duchenne muscular dystrophy: A longitudinal study. European Journal of Clinical Nutrition, 68(8), 892–897. 10.1038/ejcn.2014.93 [PubMed: 24824013]

DeSilva S, Drachman DB, Mellits D, & Kuncl RW (1987). Prednisone treatment in Duchenne muscular dystrophy. Long-term benefit. Archives of Neurology, 44(8), 818–822. [PubMed: 3632394]

Escolar DM, Hache LP, Clemens PR, Cnaan A, McDonald CM, Viswanathan V, … Connolly AM (2011). Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy. Neurology, 77(5), 444–452. 10.1212/WNL.0b013e318227b164 [PubMed: 21753160]

Fenichel GM, Florence JM, Pestronk A, Mendell JR, Moxley RT 3rd, Griggs RC, et al. (1991). Long-term benefit from prednisone therapy in Duchenne muscular dystrophy. Neurology, 41(12), 1874–1877. [PubMed: 1745340]

Fox DJ, Kumar A, West NA, DiRienzo AG, James KA, & Oleszek J (2015). Trends with corticosteroid use in males with Duchenne muscular dystrophy born 1982-2001. Journal of Child Neurology, 30(1), 21–26. 10.1177/0883073813517263 [PubMed: 24682290]

Gloss D, Moxley RT 3rd, Ashwal S, & Oskoui M (2016). Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the guideline development Subcommittee of the American Academy of neurology. Neurology, 86(5), 465–472. 10.1212/wnl.0000000000002337 [PubMed: 26833937]

Griggs RC, Herr BE, Reha A, Elfring G, Atkinson L, Cwik V, … Bushby K (2013). Corticosteroids in Duchenne muscular dystrophy: Major variations in practice. Muscle & Nerve, 48(1), 27–31. 10.1002/mus.23831 [PubMed: 23483575]

Griggs RC, Moxley RT 3rd, Mendell JR, Fenichel GM, Brooke MH, Pestronk A, et al. (1993). Duchenne dystrophy: Randomized, controlled trial of prednisone (18 months) and azathioprine (12 months). Neurology, 43(3 Pt 1), 520–527. [PubMed: 8450994]

Guglieri M, Bushby K, McDermott MP, Hart KA, Tawil R, Martens WB, … Griggs RC (2017). Developing standardized corticosteroid treatment for Duchenne muscular dystrophy. Contemporary Clinical Trials, 58, 34–39. 10.1016/j.cct.2017.04.008 [PubMed: 28450193]

Henricson EK, Abresch RT, Cnaan A, Hu F, Duong T, Arrieta A, … McDonald CM (2013). 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, 48(1), 55–67. 10.1002/mus.23808 [PubMed: 23649481]

Houde S, Filiatrault M, Fournier A, Dube J, D'Arcy S, Berube D, … Vanasse M (2008). Deflazacort use in Duchenne muscular dystrophy: An 8-year follow-up. Pediatric Neurology, 38(3), 200–206. 10.1016/j.pediatrneurol.2007.11.001 [PubMed: 18279756]

Janssen MM, Hendriks JC, Geurts AC, & de Groot IJ (2016). Variables associated with upper extremity function in patients with Duchenne muscular dystrophy. Journal of Neurology, 263(9), 1810–1818. 10.1007/s00415-016-8193-1 [PubMed: 27314968]

King WM, Ruttencutter R, Nagaraja HN, Matkovic V, Landoll J, Hoyle C, … Kissel JT (2007). Orthopedic outcomes of long-term daily corticosteroid treatment in Duchenne muscular dystrophy. Neurology, 68(19), 1607–1613. 10.1212/01.wnl.0000260974.41514.83 [PubMed: 17485648]

Koeks Z, Bladen CL, Salgado D, van Zwet E, Pogoryelova O, McMacken G, … Lochmuller H (2017). Clinical outcomes in Duchenne muscular dystrophy: A study of 5345 patients from the TREAT-NMD DMD global database. J Neuromuscul Dis, 4(4), 293–306. 10.3233/jnd-170280 [PubMed: 29125504]

Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, … Johnson CL (2002). 2000 CDC growth charts for the United States: Methods and development. Vital and Health Statistics, 11, 1–190.

Lamb MM, West NA, Ouyang L, Yang M, Weitzenkamp D, James K, … DiGuiseppi C (2016). Corticosteroid treatment and growth patterns in ambulatory males with Duchenne muscular dystrophy. The Journal of Pediatrics, 173, 207–213.e203. 10.1016/j.jpeds.2016.02.067 [PubMed: 27039228]

Lebel DE, Corston JA, McAdam LC, Biggar WD, & Alman BA (2013). Glucocorticoid treatment for the prevention of scoliosis in children with Duchenne muscular dystrophy: Long-term follow-up. The Journal of Bone and Joint Surgery. American Volume, 95(12), 1057–1061. 10.2106/jbjs.l.01577 [PubMed: 23783200]

Machado DL, Silva EC, Resende MB, Carvalho CR, Zanoteli E, & Reed UC (2012). Lung function monitoring in patients with duchenne muscular dystrophy on steroid therapy. BMC Research Notes, 5, 435 10.1186/1756-0500-5-435 [PubMed: 22889007]

Markham LW, Kinnett K, Wong BL, Woodrow Benson D, & Cripe LH (2008). Corticosteroid treatment retards development of ventricular dysfunction in Duchenne muscular dystrophy. Neuromuscular Disorders, 18(5), 365–370. 10.1016/j.nmd.2008.03.002 [PubMed: 18436445]

Martigne L, Salleron J, Mayer M, Cuisset JM, Carpentier A, Neve V, … Gottrand F (2011). Natural evolution of weight status in Duchenne muscular dystrophy: A retrospective audit. The British Journal of Nutrition, 105(10), 1486–1491. 10.1017/s0007114510005180 [PubMed: 21272404]

Mathews KD, Cunniff C, Kantamneni JR, Ciafaloni E, Miller T, Matthews D, … Romitti PA (2010). Muscular dystrophy surveillance tracking and research network (MD STARnet): Case definition in surveillance for childhood-onset Duchenne/Becker muscular dystrophy. Journal of Child Neurology, 25(9), 1098–1102. 10.1177/0883073810371001 [PubMed: 20817884]

Matthews E, Brassington R, Kuntzer T, Jichi F, & Manzur AY (2016). Corticosteroids for the treatment of Duchenne muscular dystrophy. Cochrane Database of Systematic Reviews, 5, CD003725 10.1002/14651858.CD003725.pub4

McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce NC, Hu F, … Gordish-Dressman H (2017). Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: A prospective cohort study. Lancet. 391(10119), 451–461. [PubMed: 29174484]

McKane M, Soslow JH, Xu M, Saville BR, Slaughter JC, Burnette WB, & Markham LW (2017). Does body mass index predict premature cardiomyopathy onset for Duchenne muscular dystrophy? Journal of Child Neurology, 32(5), 499–504. 10.1177/0883073816687422 [PubMed: 28084148]

Mendell JR, Moxley RT, Griggs RC, Brooke MH, Fenichel GM, Miller JP, et al. (1989). Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. New England Journal of Medicine, 320(24), 1592–1597. 10.1056/nejm198906153202405 [PubMed: 2657428]

Miller LA, Romitti PA, Cunniff C, Druschel C, Mathews KD, Meaney FJ, … Kenneson A (2006). The muscular dystrophy surveillance tracking and research network (MD STARnet): Surveillance methodology. Birth Defects Research. Part A, Clinical and Molecular Teratology, 76(11), 793–797. 10.1002/bdra.20279 [PubMed: 17036307]

Moxley RT 3rd, Ashwal S, Pandya S, Connolly A, Florence J, Mathews K, … Wade C (2005). 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. Neurology, 64(1), 13–20. 10.1212/01.wnl.0000148485.00049.b7 [PubMed: 15642897]

Ogden CL, Carroll MD, & Flegal KM (2008). High body mass index for age among US children and adolescents, 2003-2006. Journal of the American Medical Association, 299(20), 2401–2405. [PubMed: 18505949]

Pane M, Fanelli L, Mazzone ES, Olivieri G, D'Amico A, Messina S, … Mercuri E (2015). Benefits of glucocorticoids in non-ambulant boys/men with Duchenne muscular dystrophy: A multicentric longitudinal study using the performance of upper limb test. Neuromuscular Disorders, 25(10), 749–753. 10.1016/j.nmd.2015.07.009 [PubMed: 26248957]

Pradhan S, Ghosh D, Srivastava NK, Kumar A, Mittal B, Pandey CM, & Singh U (2006). Prednisolone in Duchenne muscular dystrophy with imminent loss of ambulation. Journal of Neurology, 253(10), 1309–1316. 10.1007/s00415-006-0212-1 [PubMed: 16786214]

Rahman MM, Hannan MA, Mondol BA, Bhoumick NB, & Haque A (2001). Prednisolone in Duchenne muscular dystrophy. Bangladesh Medical Research Council Bulletin, 27(1), 38–42. [PubMed: 11692899]

Rall S, & Grimm T (2012). Survival in Duchenne muscular dystrophy. Acta Myol, 31(2), 117–120. [PubMed: 23097602]

Ricotti V, Ridout DA, Scott E, Quinlivan R, Robb SA, Manzur AY, & Muntoni F (2013). Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. Journal of Neurology, Neurosurgery, and Psychiatry, 84(6), 698–705. 10.1136/jnnp-2012-303902

Schram G, Fournier A, Leduc H, Dahdah N, Therien J, Vanasse M, & Khairy P (2013). All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. Journal of the American College of Cardiology, 61(9), 948–954. 10.1016/j.jacc.2012.12.008 [PubMed: 23352781]

Silversides CK, Webb GD, Harris VA, & Biggar DW (2003). Effects of deflazacort on left ventricular function in patients with Duchenne muscular dystrophy. American Journal of Cardiology, 91(6), 769–772. [PubMed: 12633823]

Vuillerot C, Braillon P, Fontaine-Carbonnel S, Rippert P, Andre E, Iwaz J, … Berard C (2014). Influence of a two-year steroid treatment on body composition as measured by dual X-ray absorptiometry in boys with Duchenne muscular dystrophy. Neuromuscular Disorders, 24(6), 467–473. 10.1016/j.nmd.2014.03.002 [PubMed: 24780149]

Yilmaz O, Karaduman A, & Topaloglu H (2004). Prednisolone therapy in Duchenne muscular dystrophy prolongs ambulation and prevents scoliosis. European Journal of Neurology, 11(8), 541–544. 10.1111/j.1468-1331.2004.00866.x [PubMed: 15272899]

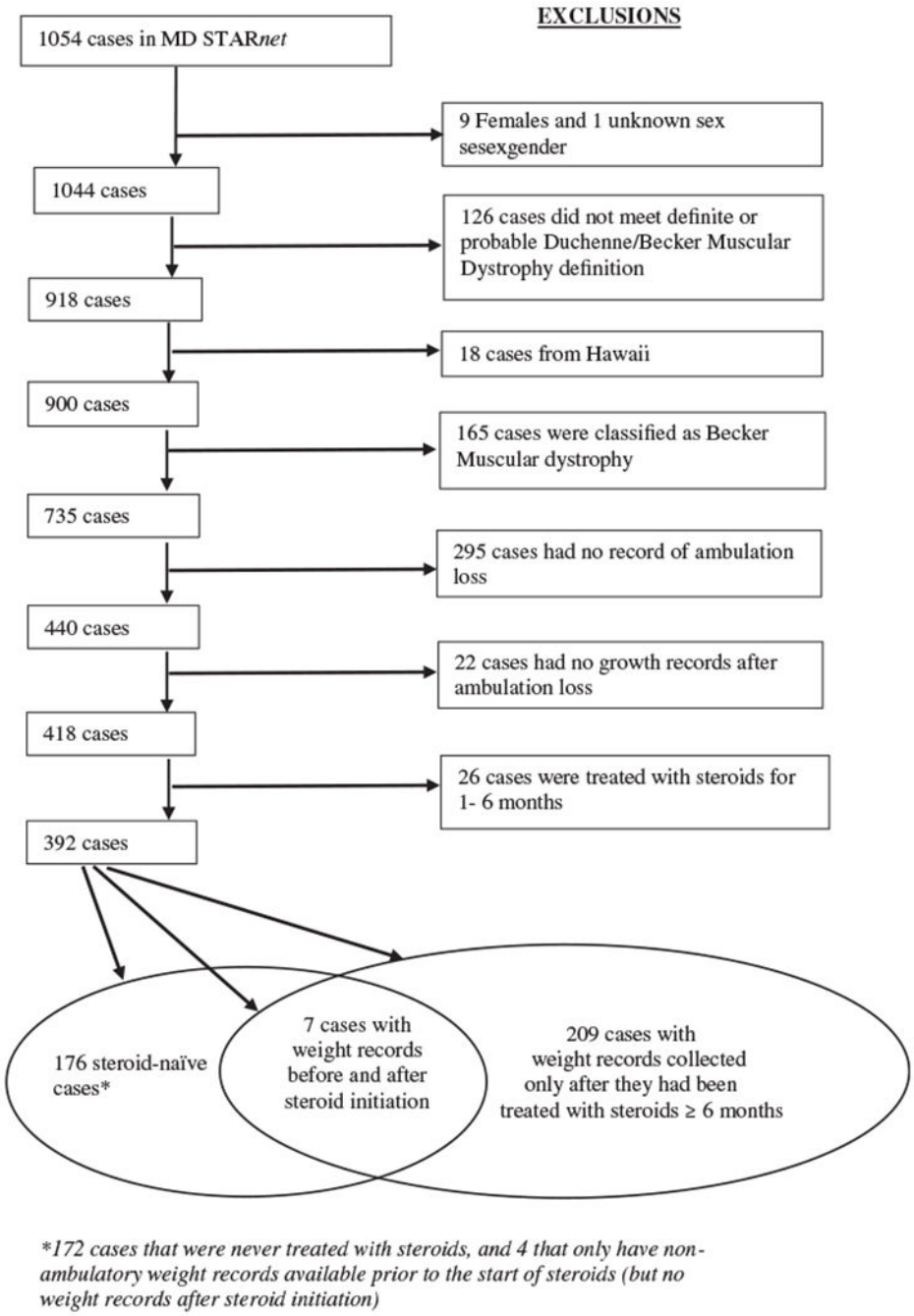

FIGURE 1.

Flowchart of exclusions to produce the analysis cohort for comparison of weight growth curves in nonambulatory males with Duchenne muscular dystrophy: The MD STAR*net*

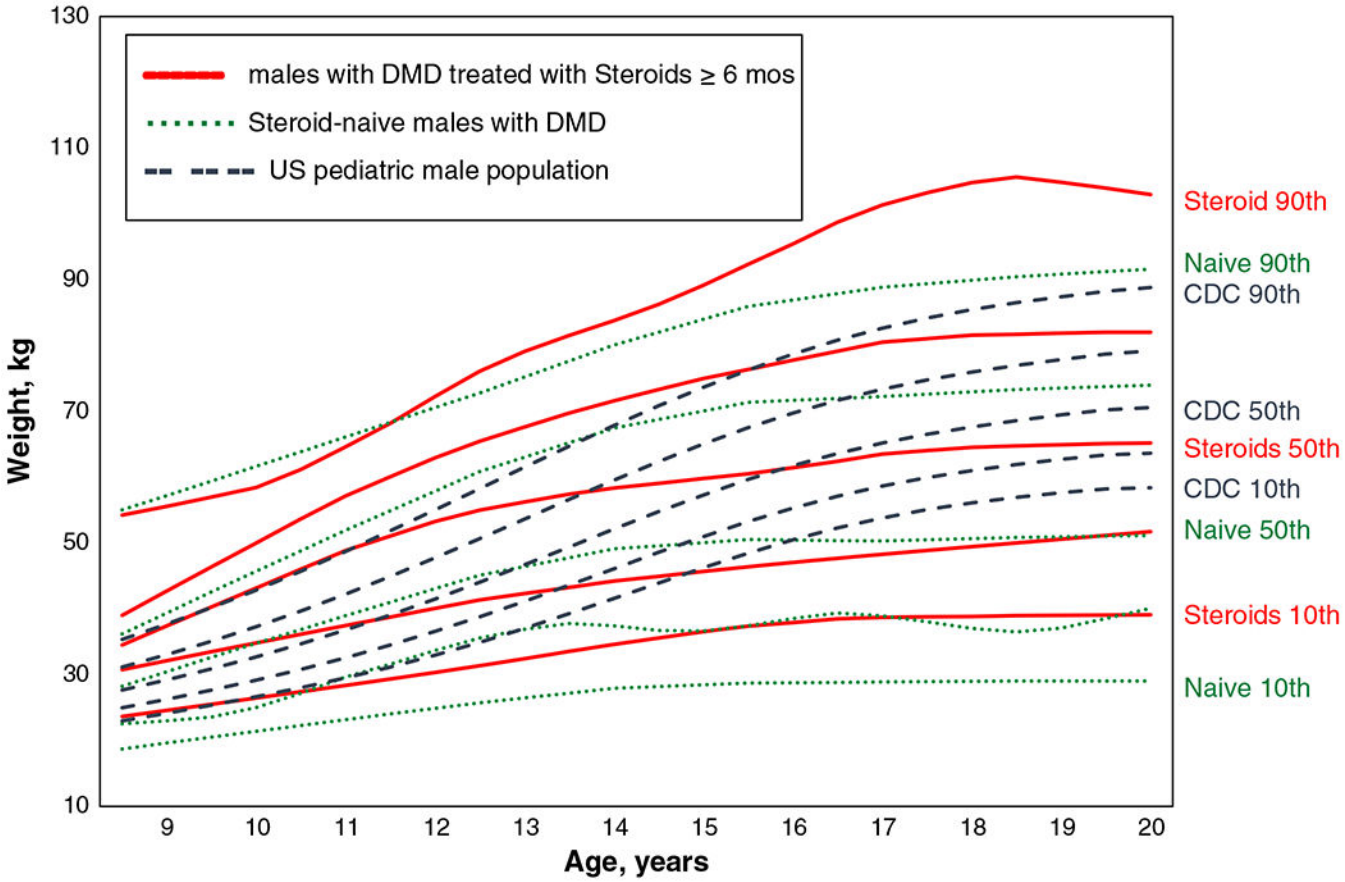

FIGURE 2.

Weight growth curves in nonambulatory males with Duchenne muscular dystrophy who were either steroid-naïve or were treated with corticosteroids for ≥6 months, compared with weight growth curves for the US pediatric male population: The MD STAR*net* [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1

Demographic and steroid treatment characteristics of nonambulatory steroid-naïve and steroid-treated males with Duchenne muscular dystrophy age 7–29 years (n = 392 subjects): The MD STAR*net*

	Steroid-Naïve *N* = 176	**Steroid-treated *N* = 216**	***p* value**[a]
	Mean (SD)	**Mean (SD)**	
Age	15.1 (3.7)	15.3 (3.7)	.59
Age at steroid initiation (years)		7.6 (2.4)	
Treated with prednisone only Treated with		7.6 (2.5)	
Deflazacort only		(1.8)	
Age at most recent visit (years)		(4.2)	
Treated with prednisone only Treated with		(3.8)	
Deflazacort only	16.9 (4.4)	17.1 (4.2)	.36
	***N* (%)**	***N* (%)**	
Race/ethnicity:	75 (42.6%)		< .0001
Non-Hispanic white		146 (67.6%)	
Hispanic	60 (34.1%)	34 (15.7%)	
Black	22 (12.5%)	9 (4.2%)	
	10 (5.7%)	5 (2.3%)	
Other unknown	9 (5.1%)	22 (10.2%)	
Steroid treatment at most recent observation		94 (43.5%)	
Type of steroid used: Prednisone		146 (67.5%)	
Deflazacort		31 (14.4%)	
Both (not concurrently)		33 (15.3%)	
Not specified		6 (2.8%)	

[a] *p* value obtained from Student's *t* test for continuous data, and chi-square test for categorical data.

TABLE 2

Linear mixed-effects analyses of steroid treatment and weight *z* scores calculated using the CDC growth charts among nonambulatory males with Duchenne muscular dystrophy: The MD STAR*net*

	Weight *z* score	
	Estimate (SE)[a]	***p* value**
Prednisone		
Age at initiation (years)	−0.09 (0.07)	.22
At least daily dosing (vs.< daily)	0.29 (0.05)	.047
Duration of use (years)	−0.10 (0.02)	<.0001
Cumulative dose (mg)	−0.00002 (2.8 E - 6)	<.0001
Deflazacort		
Age at initiation (years)	0.03 (0.13)	.84
At least daily dosing (vs.< daily)	−0.64 (0.42)	.12
Duration of use (years)	−0.15 (0.03)	<.0001
Cumulative dose (mg)	−0.00001 (2.5E-6)	<.0001
Drug comparison		
Deflazacort vs. prednisone (ref)	0.17 (0.39)	.66

[a]Adjusted for year of birth and race/ethnicity.