HHS Public Access

Author manuscript

J Child Neurol. Author manuscript; available in PMC 2024 March 12.

Published in final edited form as:

J Child Neurol. 2021 October ; 36(12): 1095–1102. doi:10.1177/08830738211047019.

Health Profile of Preterm Males With Duchenne Muscular Dystrophy

Aida Soim, PhD, MD[1], **Bailey Wallace, MPH**[2,3], **Nedra Whitehead, PhD**[4], **Michael G. Smith, DrPH**[5], **Joshua R. Mann, MD, MPH**[6], **Shiny Thomas, MBBS, MPH**[1], **Emma Ciafaloni, MD**[7], **Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*)**

[1]New York State Department of Health, Albany, NY, USA

[2]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA

[3]Oak Ridge Institute for Science and Education, Atlanta, GA, USA

[4]RTI International, Atlanta, GA, USA

[5]East Tennessee State University College of Public Health, Johnson City, TN, USA

[6]John D. Bower School of Population Health and University of Mississippi School of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

[7]University of Rochester, Rochester, NY, USA

Abstract

In this retrospective cohort study, we characterize the health profile of preterm males with Duchenne muscular dystrophy. Major clinical milestones (ambulation cessation, assisted ventilation use, and onset of left ventricular dysfunction) and corticosteroids use in males with Duchenne muscular dystrophy identified through a population-based surveillance system were analyzed using Kaplan-Meier survival curves and Cox proportional hazards modeling. The adjusted risk of receiving any respiratory intervention among preterm males with Duchenne muscular dystrophy was 87% higher than among the corresponding full-term males with Duchenne muscular dystrophy. The adjusted risks for ambulation cessation and left ventricular dysfunction were modestly elevated among preterm compared to full-term males, but the 95%

Corresponding Author: Aida Soim, PhD, Center for Environmental Health, Bureau of Environmental and Occupational Epidemiology, Birth Defects Lifespan Studies Section, Empire State Plaza, Corning Tower, Room 1203, Albany, NY 12237, USA. aida.soim@health.ny.gov.

Author Contributions

AS conceptualized and designed the study, carried out all data analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

BW replicated all data analyses (as per Muscular Dystrophy Surveillance Tracking and Research Network policies) and assisted with study design.

NW, MGS, JRM, ST, and EC approved the study design and assisted with data analyses.

All authors reviewed and revised the manuscript and approved the final version as submitted and agree to be accountable for all aspects of the work.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Data collection was approved by the Institutional Review Board at the University of Arizona and the Hawaii Department of Health, and through public health authority in Colorado, Georgia, Iowa, and western New York State.

confidence intervals contained the null. No difference in the start of corticosteroid use between preterm and full-term Duchenne muscular dystrophy males was observed. Overall, the disease course seems to be similar between preterm and full-term males with Duchenne muscular dystrophy; however, pulmonary function seems to be affected earlier among preterm males with Duchenne muscular dystrophy.

Keywords

Duchenne muscular dystrophy; preterm; pediatric; children epidemiology

Introduction

Duchenne muscular dystrophy is an X-linked recessive disorder with a prevalence of 1 in 3600 to 6000 live male births.[1] Duchenne muscular dystrophy is the result of the disruption of dystrophin in the dystrophin-glycoprotein complex.[2] Males with Duchenne muscular dystrophy experience a progressive loss of muscle function resulting in a number of physical challenges, such as a decline in mobility with eventual need for a wheelchair by age 12 years, limitations in performing daily activities, and respiratory and/or cardiac complications.[3-5]

Preterm birth is defined as delivery before 37 completed weeks of gestation. In 2018, preterm birth affected about 1 in 10 infants born in the United States.[6] Babies born prematurely are vulnerable to a wide array of long-term conditions, such as neurodevelopmental disabilities, chronic diseases including chronic respiratory complications, cognitive impairment, visual and hearing impairments, behavioral and socioemotional problems, and poor health and growth.[7-10]

We hypothesized that because of the increased vulnerability to health problems, preterm males with Duchenne muscular dystrophy may reach impaired clinical milestones (loss of ambulation, use of assisted ventilation, and left ventricular dysfunction) at a younger age. In addition, in a previous study, we observed that a definitive Duchenne muscular dystrophy diagnosis was determined 8 months earlier among preterm than full-term males.[11] Earlier diagnosis may be beneficial by allowing earlier initiation of corticosteroid treatment, which has a significant beneficial effect on slowing disease progression. We hypothesized that preterm males with Duchenne muscular dystrophy may start corticosteroid treatment earlier than full-term males with Duchenne muscular dystrophy.[12] To test these hypotheses, our study compared males with Duchenne muscular dystrophy who were born prematurely to those born full-term on these clinical milestones as well as the timing of corticosteroid treatment.

Materials and Methods

Study Design

We conducted a retrospective cohort study to evaluate and compare 3 major clinical milestones of Duchenne muscular dystrophy—loss of ambulation, use of assisted ventilation, and left ventricular dysfunction—and the start of corticosteroid treatment

between males with Duchenne muscular dystrophy who were born preterm to those born full-term.

Study Population and Data Sources

The study sample consisted of preterm and full-term males with Duchenne muscular dystrophy identified through the Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet). The surveillance methodology of MD STARnet has previously been described.[13] Briefly, the MD STARnet is a population-based surveillance system consisting of individuals with childhood-onset (before age 21 years) Duchenne or Becker muscular dystrophy born between January 1, 1982, and December 31, 2011, who resided in surveillance regions in Arizona, Colorado, Iowa, Georgia, Hawaii, and a 12-county area in western New York State during any part of that time period.

Individuals with Duchenne or Becker muscular dystrophy were identified through multiple sources of data: neuromuscular clinics, hospitals and hospital discharge databases, private physicians, service sites for children with special care needs, and birth defects surveillance programs. Once identified, trained abstractors collected data from medical records on demographic characteristics (date and place of birth, race/ethnicity, gestational age at birth, vital status, and date of death), clinical data, family history of muscular dystrophy, and diagnostic tests such as creatine kinase, muscle biopsy, or genetic tests. Data managers linked eligible individuals to birth certificate records, and where available, birth certificate records were the preferred data source for demographic characteristics.

For individuals identified before September 2011, follow-up abstraction was conducted annually until December 2011, or time of death, or until the person moved outside of the MD STAR*net* site catchment areas. To ensure at least 1 year of follow-up, individuals identified between September 2011 and December 2011 were followed through December 2012. Data collection was approved through the public health authorities in Colorado, Georgia, Iowa, and western New York State and by the Institutional Review Board at the University of Arizona and the Hawaii State Department of Health.

Neuromuscular physicians reviewed clinical data to classify cases as definite, probable, possible, or asymptomatic. For the purpose of this study, we included only males with a definite or probable classification of Duchenne muscular dystrophy.[14] The definite case classification was assigned if there were documented clinical symptoms referable to a childhood-onset dystrophinopathy and direct support of the diagnosis by at least 1 of the following: (1) a positive genetic test for dystrophin mutation; (2) a muscle biopsy demonstrating abnormal dystrophin; or (3) an elevated creatine kinase and an affected maternal male relative with a positive muscle biopsy or a dystrophin mutation. The probable case classification was assigned using the following criteria: documented clinical symptoms referable to a dystrophinopathy, elevated creatine kinase, and a family history of X-linked dystrophinopathy but no confirmatory genetic testing. We used age at loss of mobility, molecular testing results, and age at symptom onset to classify individuals as having Duchenne muscular dystrophy as described by Andrews et al.[15]

Figure 1 shows the exclusion criteria for our study cohort. We excluded residents of Hawaii because of incomplete case ascertainment and follow-up, asymptomatic individuals or those with a possible case classification, individuals with severe comorbid conditions that could potentially influence the decline in ability to ambulate (eg, cerebral palsy, spina bifida, microcephaly, encephalopathy), siblings of first-born males with Duchenne muscular dystrophy to maintain independence between observations, males with Becker muscular dystrophy, individuals with missing data on gestational age, and individuals not born in MD STAR*net* site catchment areas or with inconsistent data on ambulation due to incomplete follow-up data. The analytic sample comprised 399 males with Duchenne muscular dystrophy, of which 43 were preterm and 356 were full-term. Among the preterm group, 8 (18.6%) were very preterm (28-31 weeks of gestation) and 35 (81.4%) were moderately preterm (32-36 weeks of gestation).

Variables

Using gestational age at birth as recorded in the birth certificate or medical record, we created a preterm variable (yes [gestational age at birth <37 weeks] / no [gestational age at birth ≥37 weeks]). We analyzed the following clinical events as they were documented in the medical record: age at loss of ambulation, age at first pulmonary intervention (noninvasive ventilation, use of mechanical insufflation-exsufflation devices, tracheostomy, or any intervention), age at onset of left ventricular dysfunction (defined as an ejection fraction below 55% or, if missing, shortening fraction below 28%), and age at first corticosteroid use. We defined corticosteroid use (yes/no) as use for 1 or more days regardless of the type of corticosteroid. We used date of birth and dates at first documentation of each clinical event to estimate time to the event. To calculate time to first documented use of corticosteroid, we used the date of definitive diagnosis and the date of the first documented use of corticosteroid. We determined the age at diagnosis to be the minimum value of the age at first abnormal creatine kinase, age at muscle biopsy, or age at positive DNA test.

Censoring and Loss to Follow-up

An individual was considered lost to follow-up if his last clinic visit was more than 3 years prior to the end of the surveillance period and he was alive at the end of the study. For deceased individuals, if their last clinic visit was more than 3 years before their date of death, they were considered lost to follow-up. Males who did not have the specific clinical event being analyzed and who were not lost to follow-up were right-censored using age at the end of the surveillance period. Observations for males who were lost to follow-up and alive at the end of the study were censored at the date of the last clinic visit, whereas observations for males who were deceased were censored at date of death.

Statistical Analysis

We used Fisher exact test to compare the distribution of categorical variables. Because the age of preterm males with Duchenne muscular dystrophy at various milestones was not normally distributed, we used median, interquartile range, and minimum and maximum values to describe continuous outcomes, and the Wilcoxon rank-sum test to compare median values. We used the log-rank test from Kaplan-Meier curve estimation to assess time-to-event differences for each clinical milestone and corticosteroid use. We used Cox

proportional hazard models to estimate crude and adjusted hazards ratios with full-term males as the referent group. Based on the findings in the bivariable analysis, we adjusted for surveillance site (Arizona, Colorado, Georgia, Iowa, western New York State). To check for violations of the proportional hazard assumption, we assessed the influence of time by including the product of surveillance site and time in the model. The product term was not statistically significant in any of the Cox proportional hazard models. To evaluate whether very preterm males with Duchenne muscular dystrophy are at a higher risk for any pulmonary intervention, we conducted subanalyses among a subset that included only very preterm males and with full-term males as the referent group. We set the significance level for all statistical tests to $\alpha = 0.05$. Analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC).

Results

Table 1 shows the distribution of race/ethnicity, MD STAR*net* site, and use of corticosteroid treatment for preterm and full-term males. The distributions were similar for race/ethnicity and corticosteroid use. Higher percentages of preterm pregnancies were identified in Arizona and Georgia; the lowest percentage was from Iowa.

Median ages at loss of ambulation, any pulmonary intervention, left ventricular dysfunction, and corticosteroid use were not significantly different for preterm and full-term males (Table 2). For specific types of pulmonary interventions, only the median age at which the use of mechanical insufflation-exsufflation devices was initiated differed significantly for preterm and full-term males. Because of small counts among preterm males for individual pulmonary interventions, we only included any pulmonary intervention in our time-to-event analyses. Median age at the last clinical visit was 2 years earlier for preterm males compared to full-term, whereas median age at diagnosis was 10 months earlier for preterm males compared to full-term; the differences were not statistically significant.

Figures 2 through 5 show the Kaplan-Meier curves that compare the risk of a clinical event between preterm and full-term males for (1) loss of ambulation; (2) pulmonary intervention; (3) left ventricular dysfunction; and (4) start of corticosteroid use. Although none of the log-rank tests were statistically significant, the median time to loss of ambulation for full-term males was 8 months longer than preterm males. Conversely, median times to pulmonary intervention and left ventricular dysfunction were 13 and 7 months earlier, respectively, among preterm compared with full-term males. Compared with preterm males, full-term males received corticosteroid treatment on average 18 months earlier. Figure 6 shows the Kaplan-Meier curves that compare time from birth to diagnosis for preterm and full-term males with Duchenne muscular dystrophy. The median time to diagnosis was 9 months earlier among preterm compared to full-term males; however, the log-rank test was not statistically significant.

Adjusting for surveillance site, Cox proportional modeling showed preterm males were 1.87 times as likely as full-term males to have a pulmonary intervention. The Cox proportional hazard model estimate of the analysis conducted on the subset including only the very preterm males was as follows: adjusted hazard ratio = 2.85, 95% confidence interval:

0.61, 1.42. In addition, adjusted hazard ratios for ambulation cessation and left ventricular dysfunction were modestly elevated among preterm compared to full-term males; however, the confidence intervals contained the null. No time difference in the start of corticosteroid use was observed between preterm and full-term males with Duchenne muscular dystrophy (Table 3).

Discussion

We conducted a retrospective cohort study to characterize the health profile of preterm males with Duchenne muscular dystrophy and to investigate whether major clinical milestones (loss of ambulation, use of assisted ventilation, and left ventricular dysfunction) or corticosteroid use differed between preterm and full-term males.

Age at Loss of Ambulation

The absence of or a defect in dystrophin in males with Duchenne muscular dystrophy results in muscle degeneration and loss of ambulation. About 63% of full-term and 65% of preterm males with Duchenne muscular dystrophy in our sample had lost ambulation, and the median age at loss of ambulation was about 10 years for individuals in both groups. The loss of ambulation at age 10 years among full-term males in our study is consistent with the age of loss at ambulation among males with Duchenne muscular dystrophy in most other studies,[16-19] but lower than the median age at loss of ambulation of 13 years observed among individuals in the UK NorthStar Network and data base.[20] The difference could be due to differences in demographic characteristics between the 2 study samples (data not shown in the study by Ricotti et al). Our study showed a modest but not significantly higher risk of losing ambulation within the study period among preterm compared to full-term males with Duchenne muscular dystrophy.

Age at Intervention for Pulmonary Function

Decline in respiratory function in males with Duchenne muscular dystrophy is a major cause of morbidity and mortality resulting from progressive respiratory muscle failure, decreased lung volume and chest wall compliance, atelectasis and fibrosis, and airway obstruction.[21,22] In time, individuals with Duchenne muscular dystrophy are unable to inhale and exhale fully or to cough effectively.[23] As vital capacity decreases, mechanical insufflation-exsufflation devices are considered standard of care.[21]

In our cohort, the first use of noninvasive ventilation was reported at about 16 years of age in both preterm and full-term males with Duchenne muscular dystrophy, which corresponds to the early nonambulatory stage. In the late nonambulatory stage, coughing in individuals with Duchenne muscular dystrophy becomes weak and requires manual and mechanical assistance.[21] Though we observed the use of mechanical insufflation-exsufflation devices at a median age of 18 years among full-term males with Duchenne muscular dystrophy, corresponding to the late nonambulatory stage, the median age for mechanical insufflation-exsufflation device use among preterm individuals with Duchenne muscular dystrophy was 14 years. Cox proportional hazards modeling showed an 87% increase in the risk of any respiratory intervention within the study period among preterm males compared to full-term

individuals with Duchenne muscular dystrophy. In addition, the risk was even higher among early preterm males (adjusted hazard ratio = 2.85); however, the estimate was imprecise because of the small number of early preterm males with Duchenne muscular dystrophy in our analytic sample.

One explanation of our findings could be that, in general, preterm individuals are at a higher risk of developing chronic respiratory complications than their full-term counterparts. Although mostly the early preterm infants are at an increased risk of developing bronchopulmonary dysplasia, moderate preterm infants are also at increased risk of adverse health effects across the life span.[8] Even late preterm infants have increased respiratory complications and lung function impairment that persist in childhood and into early adulthood.[24] Lung immaturity and diminished oxygen exchange capacity resulting from preterm birth may worsen the impact of Duchenne muscular dystrophy on pulmonary function; however, further investigation into the existence and biological mechanism of an additive effect of Duchenne muscular dystrophy and prematurity on pulmonary functioning is warranted. Alternatively, males who were born preterm could have had more interactions with the health care system and/or a higher level of attention on the part of clinicians who may worry that being preterm will hasten Duchenne muscular dystrophy–related decline and therefore be more proactive in providing pulmonary function support.

Age at Onset of Left Ventricular Dysfunction

Along with respiratory issues, cardiovascular complications contribute to both morbidity and mortality among males with Duchenne muscular dystrophy.[25] Most individuals with Duchenne muscular dystrophy develop left ventricular dysfunction between 10 and 15 years of age.[26] In our study, 32% of full-term and 26% of preterm males with Duchenne muscular dystrophy developed left ventricular dysfunction. The median age at first documentation of left ventricular dysfunction was about 15 years for both full-term and preterm males with Duchenne muscular dystrophy. Similar findings were observed by Connuck et al (mean age 14.4 years) and van den Bergen et al (mean age 15 years).[19,27]

Preterm birth is associated with an increased risk of cardiovascular comorbidities, including changes in cardiovascular structure and function.[28,29] Preterm birth may have a direct effect on myocardial tissue characterized by reduction in myocardial functional reserve, mainly among babies born before 31 weeks of gestation.[28] However, our Cox proportional hazard models showed no higher risk of left ventricular dysfunction in the study period among those with preterm birth compared to full-term birth. One explanation of the null hazard ratio could be the lack of statistical power because of the small number (n = 8) of very preterm males with Duchenne muscular dystrophy in our data set.

Age at Start of Corticosteroid Use

Corticosteroids are used in individuals with Duchenne muscular dystrophy to improve muscle strength, motor function, and pulmonary function, as well as to delay left ventricular dysfunction.[30] In our analytic sample, 62% of full-term and a slightly lower percent (58%) of preterm males with Duchenne muscular dystrophy reported corticosteroid use, and the median age at the start of corticosteroid treatment was about the same for both groups (6.5

years). The results are consistent with other studies that have reported the average age of corticosteroid initiation as 6.5 years[19] and 5.9 years.[31] For our analytic sample, the hazard for corticosteroid use was similar between preterm and full-term males with Duchenne muscular dystrophy (hazard ratio = 0.93, 95% confidence interval: 0.61, 1.42).

No previous studies have compared time to the major clinical milestones between preterm and full-term males with Duchenne muscular dystrophy, and thus, our findings cannot be directly compared with findings from other studies.

Strengths

To our knowledge, this is the first study that investigates whether a history of preterm birth is associated with reaching the major clinical milestones of Duchenne muscular dystrophy (loss of ambulation, use of assisted ventilation, and left ventricular dysfunction) at a younger age. We used a comprehensive population-based surveillance system to ascertain cases of males with Duchenne muscular dystrophy. Clinical data were reviewed by experienced neuromuscular physicians who assigned case definition consistently across all participant sites. In addition, diagnosis was confirmed by laboratory data and/or family pedigree. We obtained clinical data through abstraction of medical records, and thus, minimized recall bias.

Limitations

Our findings are not representative of the entire Duchenne muscular dystrophy population in the United States, as the participant sites in the MD STAR*net* cohort are from selected areas of the country. Because of the small number of preterm males with Duchenne muscular dystrophy in our study, we likely did not have the statistical power to detect differences with respect to the clinical milestones between the preterm and full-term males with Duchenne muscular dystrophy.

Conclusion

Owing to the decline in muscle function, males with Duchenne muscular dystrophy face numerous health challenges. Although these challenges may be amplified by prematurity, it appears that among males with Duchenne muscular dystrophy, preterm individuals cease ambulation, develop left ventricular dysfunction, and start using corticosteroids at about the same age as full-term individuals. However, the median age of cough machine use was 4 years younger among preterm males than full-term males; in addition, the risk of intervention for respiratory function among preterm is 87% higher than the hazard of intervention among full-term individuals with Duchenne muscular dystrophy. Clinicians may need to have heightened awareness of the potential need for respiratory support in males born preterm.

Acknowledgments

We thank study coordinators and data managers for assistance with data collection and management.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by Cooperative Agreement numbers DD000187, DD000189, DD000190, DD000191, 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.

References

1. 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. [PubMed: 19945913]
2. Koenig M, Hoffman EP, Bertelson CJ, Monaco AP, Feener C, Kunkel LM. Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. Cell. 1987;50(3):509–517. [PubMed: 3607877]
3. Cyrulnik SE, Fee RJ, De Vivo DC, Goldstein E, Hinton VJ. Delayed developmental language milestones in children with Duchenne's muscular dystrophy. J Pediatr. 2007;150(5):474–478. [PubMed: 17452219]
4. Yiu EM, Kornberg AJ. Duchenne muscular dystrophy. Neurol India. 2008;56(3):236–247. [PubMed: 18974549]
5. Zebracki K, Drotar D. Pain and activity limitations in children with Duchenne or Becker muscular dystrophy. Dev Med Child Neurol. 2008;50(7):546–552. [PubMed: 18611207]
6. Centers for Disease Control and Prevention. Preterm births. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm. (Accessed on April 21, 2020)
7. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75–84. [PubMed: 18177778]
8. Islam JY, Keller RL, Aschner JL, Hartert TV, Moore PE. Understanding the short- and long-term respiratory outcomes of prematurity and bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2015;192(2):134–156. [PubMed: 26038806]
9. Kerkhof GF, Willemsen RH, Leunissen RW, Breukhoven PE, Hokken-Koelega AC. Health profile of young adults born preterm: negative effects of rapid weight gain in early life. J Clin Endocrinol Metab. 2012;97(12):4498–4506. [PubMed: 22993033]
10. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet. 2003;361(9363):1089–1097. [PubMed: 12672313]
11. Soim A, Smith MG, Kwon JM, Mann JR, Thomas S, Ciafaloni E. Is there a delay in diagnosis of Duchenne muscular dystrophy among preterm-born males? J Child Neurol. 2018;33 (8):537–545. [PubMed: 29759004]
12. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gas-trointestinal and nutritional management. Lancet Neurol. 2018;17 (3):251–267. [PubMed: 29395989]
13. Miller LA, Romitti PA, Cunniff C, et al. The muscular dystrophy surveillance tracking and research network (MD STARnet): surveillance methodology. Birth Defects Res A Clin Mol Teratol. 2006;76(11):793–797. [PubMed: 17036307]
14. Mathews KD, Cunniff C, Kantamneni JR, et al. Muscular dystrophy surveillance tracking and research network (MD STARnet): case definition in surveillance for childhood-onset Duchenne/Becker muscular dystrophy. J Child Neurol. 2010;25(9):1098–1102. [PubMed: 20817884]
15. Andrews JG, Lamb MM, Conway K, et al. Diagnostic accuracy of phenotype classification in Duchenne and Becker muscular dystrophy using medical record Data1. J Neuromuscul Dis. 2018;5-(4) :481–495. [PubMed: 30320597]
16. Magri F, Del Bo R, D'Angelo MG, et al. Clinical and molecular characterization of a cohort of patients with novel nucleotide alterations of the dystrophin gene detected by direct sequencing. BMC Med Genet. 2011;12:37. [PubMed: 21396098]
17. Martigne L, Salleron J, Mayer M, et al. Natural evolution of weight status in Duchenne muscular dystrophy: a retrospective audit. Br J Nutr. 2011;105(10):1486–1491. [PubMed: 21272404]

18. Nakamura H, Kimura E, Mori-Yoshimura M, et al. Characteristics of Japanese Duchenne and Becker muscular dystrophy patients in a novel Japanese national registry of muscular dystrophy (Remudy). Orphanet J Rare Dis. 2013;8:60. [PubMed: 23601510]
19. van den Bergen JC, Ginjaar HB, van Essen AJ, et al. Forty-Five years of Duchenne muscular dystrophy in the Netherlands. J Neuromuscul Dis. 2014;1(1):99–109. [PubMed: 27858664]
20. Ricotti V, Ridout DA, Pane M, et al. The NorthStar ambulatory assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials. J Neurol Neurosurg Psychiatry. 2016;87(2):149–155. [PubMed: 25733532]
21. 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. [PubMed: 29395990]
22. Lo Mauro A, Aliverti A. Physiology of respiratory disturbances in muscular dystrophies. Breathe (Sheff). 2016;12(4):318–327. [PubMed: 28210319]
23. Mayer OH, Finkel RS, Rummey C, et al. Characterization of pulmonary function in Duchenne muscular dystrophy. Pediatr Pulmonol. 2015;50(5):487–494. [PubMed: 25755201]
24. Bolton CE, Bush A, Hurst JR, Kotecha S, McGarvey L. Lung consequences in adults born prematurely. Thorax. 2015;70 (6):574–580. [PubMed: 25825005]
25. McNally EM. New approaches in the therapy of cardiomyopathy in muscular dystrophy. Annu Rev Med. 2007;58(1):75–88. [PubMed: 17217326]
26. McNally EM. Cardiomyopathy in muscular dystrophy: when to treat? JAMA Cardiol. 2017;2(2):199. [PubMed: 27926775]
27. Connuck DM, Sleeper LA, Colan SD, et al. Characteristics and outcomes of cardiomyopathy in children with Duchenne or Becker muscular dystrophy: a comparative study from the Pediatric Cardiomyopathy Registry. Am Heart J. 2008;155 (6):998–1005. [PubMed: 18513510]
28. Burchert H, Lewandowski AJ. Preterm birth is a novel, independent risk factor for altered cardiac remodeling and early heart failure: is it time for a new cardiomyopathy? Curr Treat Options Cardiovasc Med. 2019;21(2):8. [PubMed: 30762137]
29. Luu TM, Katz SL, Leeson P, Thebaud B, Nuyt AM. Preterm birth: risk factor for early-onset chronic diseases. CMAJ. 2016;188 (10):736–746. [PubMed: 26644500]
30. Gloss D, Moxley RT 3rd, Ashwal S, Oskoui M. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86 (5):465–472. [PubMed: 26833937]
31. Cowen L, Mancini M, Martin A, Lucas A, Donovan JM. Variability and trends in corticosteroid use by male United States participants with Duchenne muscular dystrophy in the Duchenne Registry. BMC Neurol. 2019;19(1):84. [PubMed: 31046703]

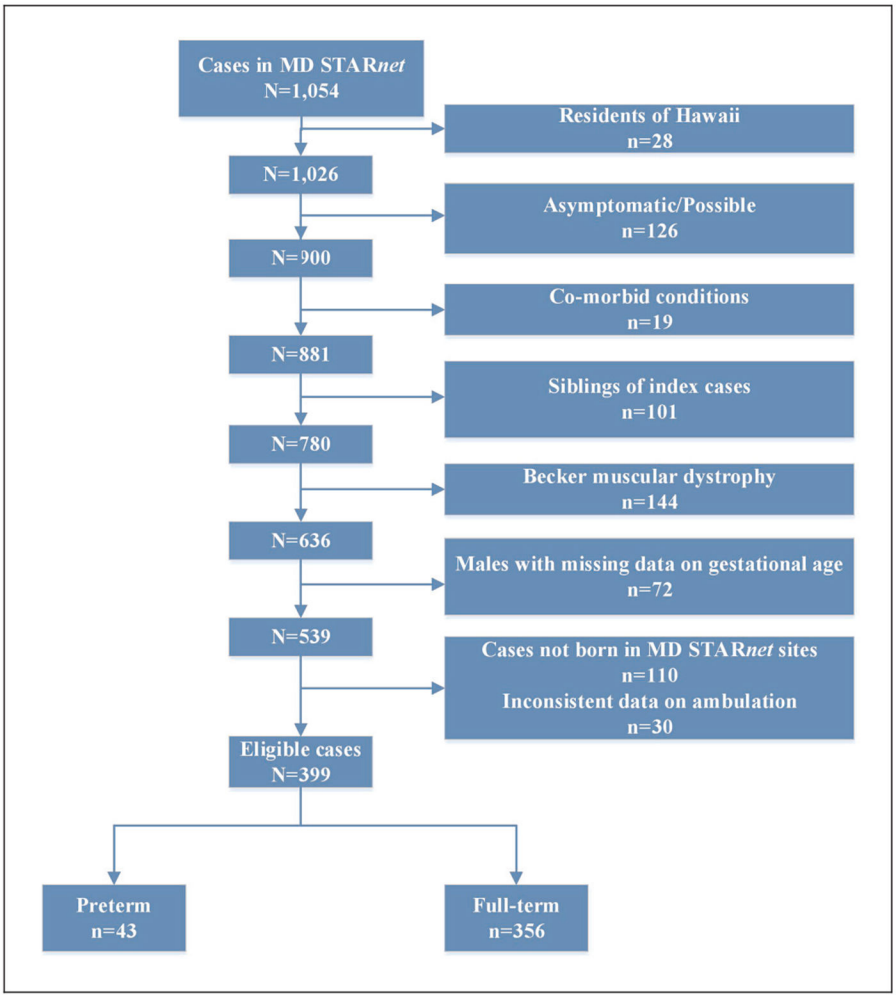

Figure 1.

Sample exclusion criteria for males from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*) cohort.

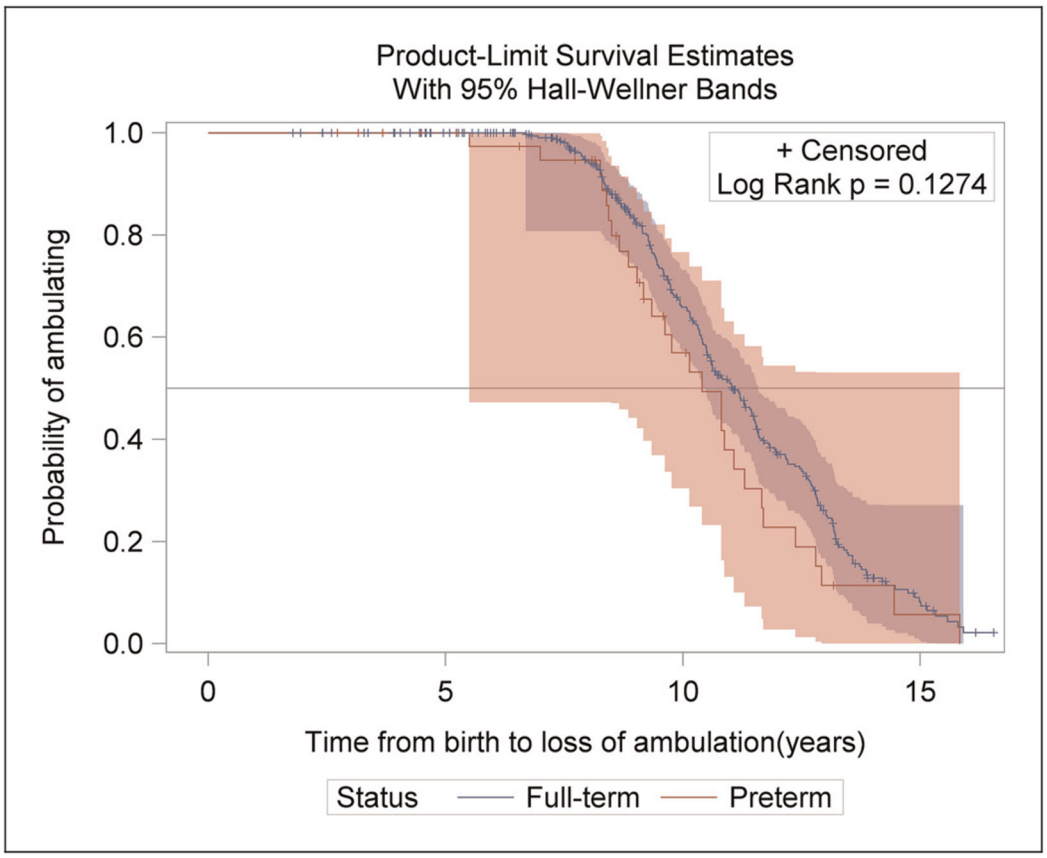

Figure 2.

Kaplan-Meier survival curves for the time to ambulation cessation among preterm and full-term born males with Duchenne muscular dystrophy, Muscular Dystrophy Surveillance, Tracking and Research Network.

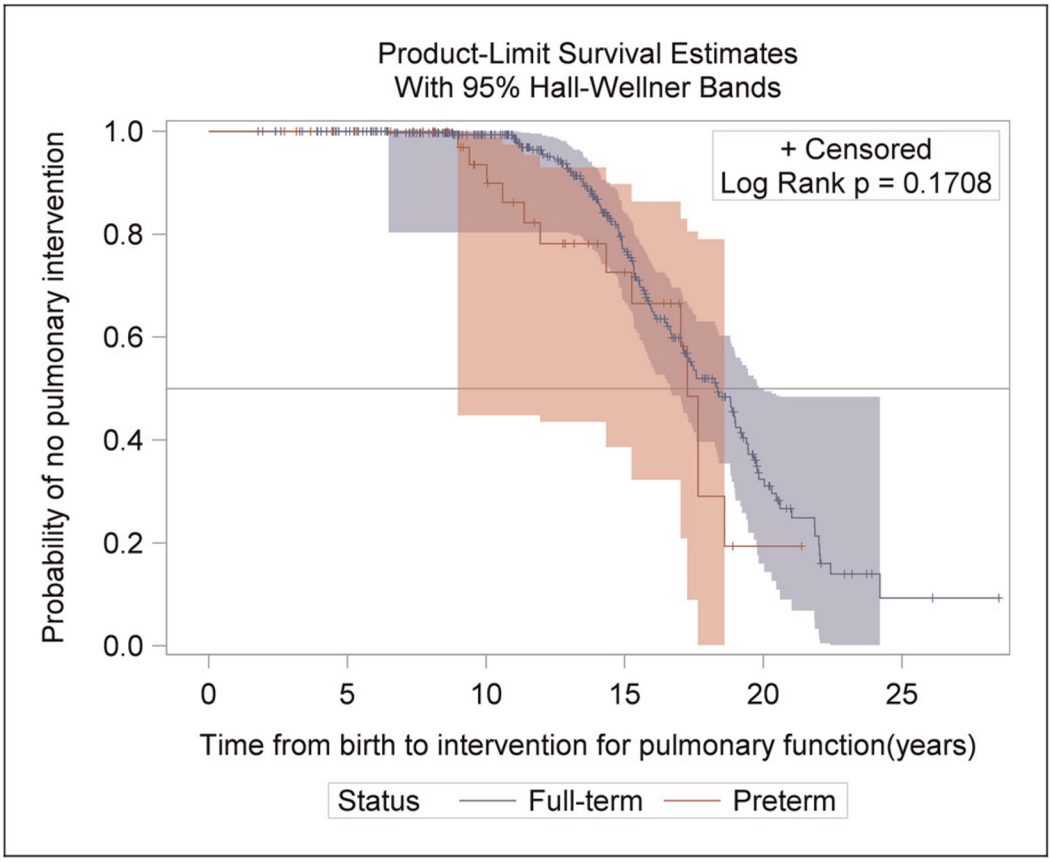

Figure 3.

Kaplan-Meier survival curves for the time to intervention for pulmonary function among preterm and full-term born males with Duchenne muscular dystrophy, Muscular Dystrophy Surveillance, Tracking and Research Network.

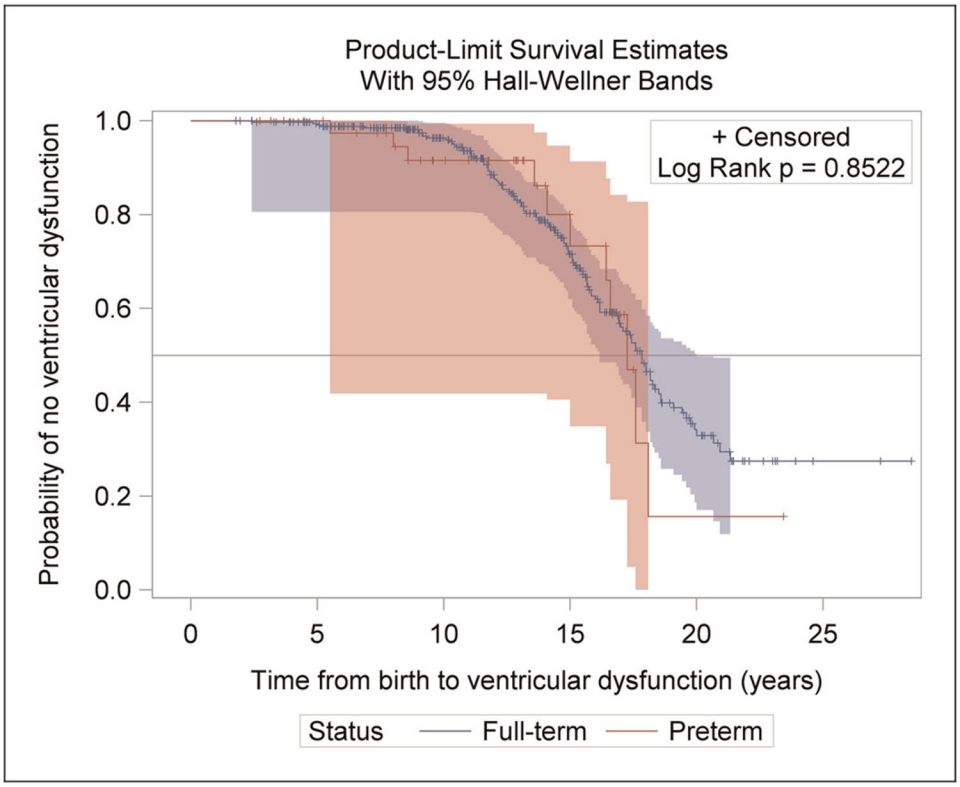

Figure 4.

KaplanMeier survival curves for the time to first documentation of left ventricular disfunction among preterm and full-term born males with Duchenne muscular dystrophy, Muscular Dystrophy Surveillance, Tracking and Research Network.

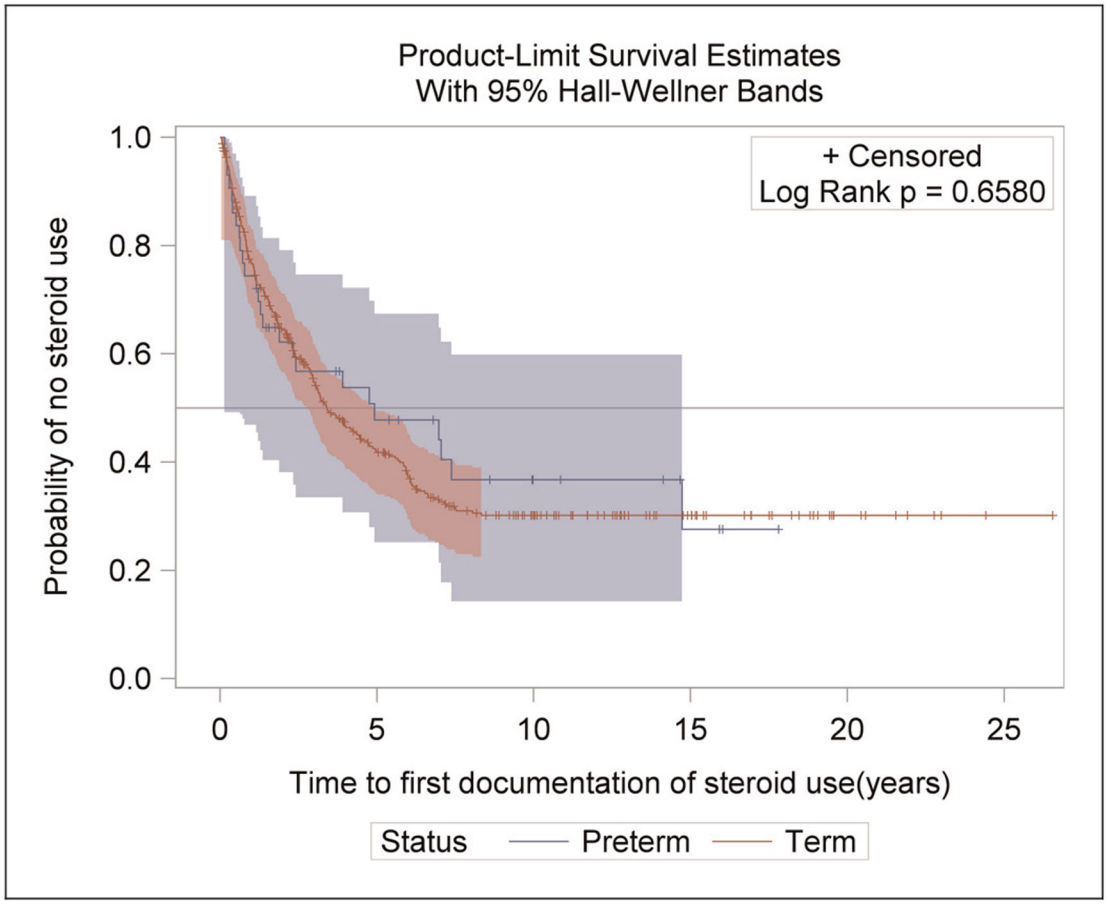

Figure 5.

Kaplan-Meier survival curves for the time from definitive diagnosis to first documentation of steroid use among preterm and full-term born males with Duchenne muscular dystrophy, Muscular Dystrophy Surveillance, Tracking and Research Network.

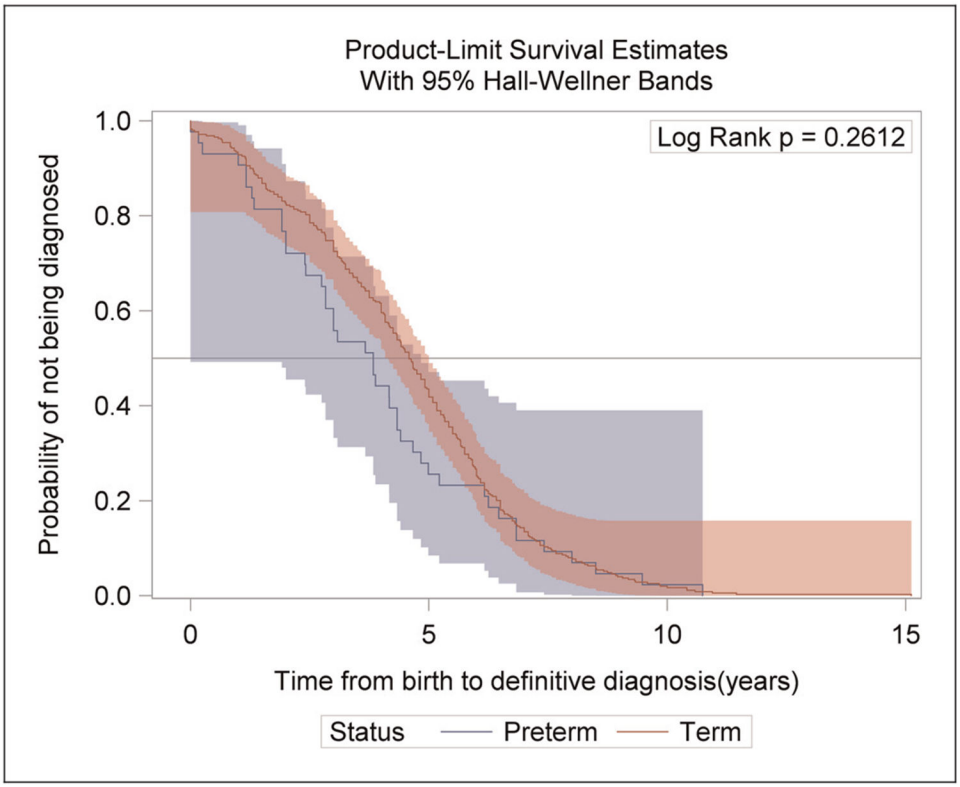

Figure 6.

Kaplan-Meier survival curves for the time from birth to definitive diagnosis for preterm and full-term born males with Duchenne muscular dystrophy, Muscular Dystrophy Surveillance, Tracking and Research Network.

Table 1.

Sociodemographic Characteristics by Preterm Birth Status for Males With Duchenne Muscular Dystrophy in the MD STAR*net* Cohort, 1982-2011.

	Full-term males (n = 356)		Preterm males (n = 43)		
Sociodemographic characteristics	**n**	**%**	**n**	**%**	***P* value[a]**
Race/ethnicity					.53
White non-Hispanic	231	64.9	28	65.1	
Black non-Hispanic	30	8.4	2	4.7	
Hispanic or Latino	67	18.8	7	16.3	
Other[b]	28	7.9	6	13.9	
MD STAR*net* site					.16
Arizona	70	19.7	14	32.5	
Colorado	71	19.9	7	16.3	
Georgia	102	28.7	13	30.2	
Iowa	55	15.5	2	4.7	
Western New York State	58	16.3	7	16.3	
Corticosteroid use					
Never	135	37.9	18	41.9	.62
Ever	221	62.1	25	58.1	

Abbreviation: MD STAR*net*, Muscular Dystrophy Surveillance Tracking and Research Network.

[a]Fisher exact test.

[b]Other includes Asian or Hawaiian or Pacific Islander, multiple, Native American or American Indian or Alaska Native, other, unknown.

Table 2.

Median Age (Years) and Interquartile Range at Various Diagnostic Steps for Males Born Full-Term and Preterm With Duchenne Muscular Dystrophy, MD STAR*net*, 1982-2011.

	Full-term males (n = 356)			Preterm males (n = 43)				
	n (%)	Median age, y (IQR)	Min, Max, y	n (%)	Median age, y (IQR)	Min, Max, y	*P* value[a]	*P* value[b]
Age at loss of ambulation	225 (63.2)	10.4 (3.1)	6.7, 15.9	28 (65.1)	9.9 (2.9)	5.5, 15.8	.87	.28
Age at assisted ventilation								
Noninvasive ventilation	94 (26.4)	15.7 (3.6)	6.5, 22.4	10 (23.3)	16.3 (6.3)	8.9, 18.6	.72	.73[c]
Cough machine	72 (20.2)	18.1 (4.8)	8.8, 25.5	8 (18.6)	13.9 (4.9)	10.0, 18.6	>.99	**.05** [c]
Tracheostomy	23 (6.5)	17.5 (3.4)	12.7, 25.9	3 (6.9)	19.5 (1.6)	18.9, 20.6	.75	0.42[c,d]
Any intervention	113(31.7)	15.5 (4.4)	6.5, 24.2	13 (30.2)	14.3 (6.7)	8.9, 18.6	>.99	.22[c]
Age at onset of LVD	114 (32.0)	14.5 (5.1)	2.4, 21.3	11 (25.6)	15.0 (8.7)	5.5, 18.1	.49	.98
Age at first corticosteroid use	221 (62.1)	6.6 (2.6)	2.7, 14.2	25 (58.1)	6.5 (3.0)	4.3, 14.7	.62	.67
Age at last clinical visit	356 (100)	13.9 (9.3)	1.9, 27.9	43 (100)	11.74 (8.2)	2.3, 22.9	–	.12
Age at diagnosis	356 (100)	4.6 (3.2)	0, 15.1	43 (100)	3.8 (3.2)	0, 10.7	–	.11

Abbreviations: IQR, interquartile range; LVD, left ventricular dysfunction; Max, maximum age; Min, minimum age; MD STARnet, Muscular Dystrophy Surveillance, Tracking, and Research Network.

[a] Fisher exact test of independence.

[b] Wilcoxon rank-sum test.

[c] Holm-Bonferroni correction.

[d] Wilcoxon rank-sum exact test.

Table 3.

Crude and Adjusted Hazard Ratios of the Association Between Preterm Birth Status and Time to major Clinical Milestones among Males With Duchenne Muscular Dystrophy, MD STAR*net*, 1982-2011.

Cox proportional hazard models[a]	**cHR (95% CI)**	**aHR (95%)**[b]
Time from birth to loss of ambulation	1.36 (0.92, 2.01)	1.28 (0.86, 1.91)
Time from birth to first respiratory intervention	1.50 (0.84, 2.67)	1.87 (1.02, 3.42)
Time from birth to onset of LVD	1.06 (0.60, 1.97)	1.13 (0.60, 2.13)
Time from diagnosis to first corticosteroid use	0.91 (0.60, 1.38)	0.97 (0.64, 1.48)

Abbreviations: aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; LVD, left ventricular dysfunction; MD STAR*net*, Muscular Dystrophy Surveillance, Tracking, and Research Network.

[a] Reference: full-term birth.

[b] Adjusted for: surveillance site (reference: Georgia).