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Selected clinical and demographic factors and all-cause mortality among individuals with Duchenne muscular dystrophy in the Muscular Dystrophy Surveillance, Tracking, and Research Network

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Abstract

Population-based estimates of survival among individuals with Duchenne muscular dystrophy (DMD) living in the United States are lacking. It is also unclear whether the association between glucocorticoid use and all-cause mortality persists in the context of other common treatments (cardiac medication, cough-assist, bilevel positive airway pressure, and scoliosis surgery) observed to delay mortality. Among 526 individuals identified by the Muscular Dystrophy Surveillance, Tracking, and Research Network, the estimated median survival time from birth was 23.7 years. Current glucocorticoid users had a lower hazard of mortality than non-users. Individuals who ever had scoliosis surgery had a lower hazard of mortality than individuals who did not have scoliosis surgery. Individuals who ever used cough assist had a lower hazard of mortality than individuals who never used cough assist. Non-Hispanic Black individuals had a higher hazard of mortality than non-Hispanic White individuals. No differences in hazards of mortality were observed between ever versus never use of cardiac medication and ever versus never use of bilevel positive airway pressure. The glucocorticoid observation is consistent with the 2018 Care Considerations statement that glucocorticoid use continues in the non-ambulatory phase. Our observations may inform the clinical care of individuals living with DMD.

Keywords

Duchenne Muscular Dystrophy; Mortality; Survival

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular disorder caused by mutations in the dystrophin gene. It is the most common childhood-onset muscular dystrophy (MD) and, has a prevalence of 1 in 10,000 males aged 5-24 years [1]. DMD has a median diagnosis age of five years in the United States [2]. DMD is characterized by progressive skeletal and cardiac muscle weakness with a mean age at loss of independent ambulation of 9.5 years [3] and mean age at cardiomyopathy onset of 14.3 years [4]. Although several European studies estimated the median age of death to be in the early 20’s, [5-7] a population-based estimate of survival among individuals with DMD in the United States is lacking.

Currently no cure for DMD exists, but treatments and interventions are available to slow progression and delay the development of comorbidities. Previous studies have reported lower mortality among glucocorticoid users as compared to non-users, suggesting a delay in mortality [8-11]. However, it is unclear what the association between glucocorticoids and mortality is in the context of other common treatments observed to delay mortality, including angiotensin-converting enzyme (ACE) inhibitors and beta blockers,[12, 13] scoliosis surgery,[14-16] cough assist machines[17, 18] and mechanical ventilation [7, 18-26]. A better understanding of survival estimates and how treatments and interventions influence these estimates could inform the care of individuals with DMD. The objective of this study was to use data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*), a population-based surveillance program for MD funded by the Centers for Disease Control and Prevention, to estimate survival and assess

the associations between all-cause mortality and race/ethnicity, glucocorticoids, cardiac medications, cough assist, scoliosis surgery, and bilevel positive airway pressure (BiPAP) among males with DMD.

2. Patients and Methods

The full methodology for MD STAR*net* has been described previously [27, 28]. MD STAR*net* started in 2002 with the purpose of determining the prevalence of childhood-onset dystrophinopathy and collecting information on clinical practices and health outcomes, including mortality. Beginning in 2004, MD STAR*net* retrospectively identified and longitudinally followed all individuals diagnosed with Duchenne or Becker muscular dystrophy (DBMD), born since January 1, 1982, diagnosed by age 21, and who resided in four United States sites: Arizona, Colorado, Iowa, and 12 counties in western New York State. Georgia was added to the surveillance program in 2006 and Hawaii in 2008.

Trained abstractors reviewed medical records from neuromuscular clinics, emergency departments, and hospitals, and abstracted data on demographics, signs, and symptoms of dystrophinopathy, clinical and diagnostic tests, health outcomes, and medical treatments. Information from vital records was also obtained. Annual medical record abstraction was conducted through December 2011. For individuals identified during September 2011 through December 2011, record abstraction was conducted through 2012 to ensure a minimum of one year follow-up.

During data collection, a committee of neuromuscular clinical experts reviewed abstracted diagnostic data to assign each individual a case status (definite, probable, possible, asymptomatic, affected female, or not DBMD) [27]. At the end of data collection, MD STAR*net* investigators created an algorithm that used diagnostic and clinical information to classify phenotype for each individual as DMD, Becker Muscular Dystrophy (BMD), affected-female, termination, or unable to determine [29]. Investigators also used mobility information (month and year of full-time wheelchair use) to define date at loss of ambulation.

2.1 Public Health Authority and Institutional Review Board

In Colorado, Georgia, Iowa, and western New York state, public health authority permitted medical record abstraction for DBMD. Institutional review board approval was obtained for Arizona from the University of Arizona and for Hawaii from the Hawaii Department of Health, and when needed, other health care facilities where data collection occurred.

2.2 Outcomes

All-cause mortality was determined by using data from medical records, state death records, and the National Death Index. We focused on all-cause mortality because the majority of deaths in our study had muscular dystrophy or congenital myopathy listed as the underlying cause of death. For individuals without a record of death, the endpoint was their last clinic visit on or before December 31, 2011. We used birth as the start point for our time–to–event estimate of survival from birth. To examine the association between select demographic and clinical factors and death, we used two definitions of time to event that differed by start dates

and restricted the analysis to individuals who would be at risk for death. The first definition of time–to–event was from the date the individual turned age 10 years until their endpoint. In our analytical sample of individuals born from 1982–1999, no one died before age 10 years. This minimum age of death has been observed in another cohort [30]. The second definition of time–to–event was from the date of loss of ambulation until endpoint.

2.3 Exposures

Abstractors recorded full start and stop dates of glucocorticoid use and type (prednisone or deflazacort). For cardiac medication (ACE inhibitor or beta blocker), abstractors recorded the name of the medication and the year of use. Cardiac medication was only recorded for chronic use and not for an acute event like hospitalization. For cough assist machine and BiPAP, abstractors recorded month and year of use. Abstractors recorded the month and year during which scoliosis surgery was performed.

Race and ethnicity were collected and categorized for analysis as non-Hispanic White, non-Hispanic Black, Hispanic, and Other. Individuals who were Asian, Native Hawaiian, Pacific Islander, Native American, or Alaskan Native were included in the Other category because of small numbers. Individuals of multiple races or whose race and ethnicity were not documented were also included in the Other category. Information was also collected and categorized for analysis on surveillance area (Arizona, Colorado, Georgia, Iowa, and western New York), age at first signs and symptoms of dystrophinopathy in years (<1.5, 1.5– <3.0, 3.0– <5.0, and 5.0+), and birth year cohort (1982 –1984, 1985 –1989, 1990–1994, 1995–1999).

2.4 Analytical Sample

Inclusion and exclusion criteria for this study are displayed in Figure 1. There were 1054 individuals ascertained with dystrophinopathy by the MD STAR*net* surveillance system. We included only individuals with a case status categorized as definite or probable and classified as Duchenne phenotype. Because of incomplete case ascertainment, we excluded individuals from Hawaii. We excluded individuals born between 2000 –2011 because they were not old enough to have adequate time at risk. We also exclude the one individual whose death was noted in the medical record without a death date. For the analytic sample for survival from birth and the subsequent subsamples, we included individuals who were born during 1982-1999. For the analytical subsample with time since age 10 years, we also excluded those who were lost to follow-up before age 10 years. For the analytical subsample with time since loss of ambulation, we excluded individuals who were still ambulating, individuals whose age at loss of ambulation was missing, and individuals who were lost to follow-up before loss of ambulation. The two analytical subsamples were not mutually exclusive. Most of the individuals (404 of 407) who were in the analytical subsample for time since loss of ambulation models were also in the time since age 10 years analytic subsample (n=504).

2.5 Statistical Analysis

The Kaplan-Meier method was used to estimate survival probabilities and draw survival curves. Descriptive statistics were used to summarize mortality in each of the two analytical subsamples.

Cox proportional hazard models with time-varying covariates were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). We treated our samples as fixed cohorts with right censoring because our exposures of interest were either static (demographics) or information that would be routinely collected by a clinic in a new patient's history. The counting process method [31, 32] was applied to code the time-varying treatment variables, which could change yearly. Current glucocorticoid use was defined as any day of use in a given year. Cardiac medication use, cough assist machine use, and BiPAP use were defined as ever used, and scoliosis surgery was defined as ever occurred. Years prior to the start of cardiac medications, cough assist machine use, BiPAP use, and scoliosis surgery were entered as never use to avoid immortal time bias [33]. If cardiac medications, cough assist machine use, BiPAP use, or first scoliosis surgery occurred before the start of follow-up time (age 10 or loss of ambulation), they were coded as ever used for each year of follow-up. We decided to include all treatment variables, race/ethnicity, surveillance site, and age at first signs and symptoms into each multivariate model *a priori.*

For all individuals who died, treatment information from the date of the last clinic visit until date of death was unknown. We assumed that use of glucocorticoids, cardiac medication, cough assist machine, BiPAP, and scoliosis surgery did not start during this time period. For individuals who were using glucocorticoids at the time of their last clinic visit (n=12), the duration of glucocorticoid usage from last clinic visit until death was unknown. To account for this missing period of glucocorticoid usage, a multiple imputation technique was used in our study [34]. We assumed that the missing period of glucocorticoid usage was missing at random and generated 500 imputed data sets utilizing multiple imputation by chained equations through the MICE package [35] in R software (R Foundation for Statistical Computing, version 3.5.0). The missing period of glucocorticoid use was imputed by predictive mean matching based on the covariates: race/ethnicity, birth year cohort, age at first signs and symptoms of DMD, and surveillance area. After imputation, we applied a Cox proportional hazards model for each dataset and then we performed multiple imputation inference for all the data sets through the function MIcombine in the Mitools package [36] in R software. MIcombine function in the Mitools package computed Rubin's degrees-of-freedom estimate and rate of missing information.

To assess the association between glucocorticoid use prior to start of risk and all-cause mortality, a Cox proportional hazard model examined cumulative duration of glucocorticoid use by age 10 years (no glucocorticoid use or less than 6 months of use, 6 months – 24 months, and greater than 24 months) and the hazard of death. In an exploratory analysis, a Cox-proportional hazard model was used to compare the hazard of death since age 10 years between individuals who only used prednisone to individuals who only used deflazacort, and to individuals who used both prednisone and deflazacort.

Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC) and R software (R Foundation for Statistical Computing, version 3.5.0).

3. Results

3.1 Survival from Birth

The estimated median survival from birth for the 526 individuals born from 1982-1999 was 23.7 years (95% CI=22.3, 24.2) (Figure 2).

3.2 Frequencies and distribution of demographic and clinical variables

Frequencies of demographic and clinical variables for the 504 individuals included in the time since age 10 years analytic subsample and the 407 individuals included in the time since loss of ambulation analytic subsample are displayed in Table 1a. Most individuals in each subsample were born during 1990–1999 and were non-Hispanic White. A slightly higher percentage of individuals in the time since loss of ambulation subsample ever used cardiac medications, ever used a cough assist machine, ever had scoliosis surgery, and ever used a BiPAP machine than the individuals in the time since age 10 years subsample. However, a lower percentage of individuals in the time since loss of ambulation subsample used glucocorticoids than individuals in the time since age 10 years subsample. The subsamples had similar percentages of individuals who died, 27% (n=136) in the time since age 10 years subsample and 27.8% (n=113) in the time since loss of ambulation subsample. The distribution of age of death and length of follow-up time among those who were censored were also similar between the two subsamples (Table 1b).

3.3. Analytical Sample Time Since Age 10 years

Since no one died before age 10, the survival curve from time since age 10 years was similar to the survival curve from birth. The estimated median survival time since age 10 years was 13.7 years (95% CI=12.3–14.2), (Supplementary Figure A.1). The unadjusted and adjusted HRs and corresponding 95% CIs for the associations between clinical and demographic factors and all-cause mortality in the time since age 10 years models are displayed in Table 2. After adjustment, non-Hispanic Black individuals had more than twice the hazard of death than non-Hispanic White individuals [aHR= 2.09, (95% CI=1.11– 3.92)]. In any given year, individuals who ever used a cough assist machine had a 45% lower hazard of death than individuals who never used a cough assist machine [aHR=0.55, (95% CI=0.32–0.93)], and individuals who ever had scoliosis surgery had a 42% lower hazard of death than individuals who never had scoliosis surgery [aHR=0.58, (95% CI=0.39–0.86)]. In any given year, individuals who were currently using glucocorticoids had an 83% lower hazard of death than individuals who were not currently using glucocorticoids [aHR=0.17, (95% CI=0.08–0.38)]. No difference in hazard of death was seen among individuals who ever used cardiac medications as compared to individuals who did not use cardiac medications and among individuals who ever used a BiPAP machine as compared to individuals who did not use a BiPAP machine.

Cumulative duration of glucocorticoid use by age 10 years was not associated with hazard of death during follow-up. The crude HR comparing individuals who used glucocorticoids

between 6 months and 24 months (n=80) to individuals who never use glucocorticoids or used them less than six months (n=283) was 0.91 (95% CI=0.54–1.53). The crude HR comparing individuals who used glucocorticoids for more than 24 months (n=141) to individuals who never used glucocorticoids or used them less than six months was 0.88 (95% CI=0.58–1.32).

In an exploratory analysis, we examined glucocorticoid type and the hazard of death in the time since age 10 years subsample and did not observe a statistical association. The crude HR of comparing individuals who only used deflazacort (n=35) to individuals who only used prednisone (n=135) was 0.97 (95%=0.29–3.26). The crude HR comparing individuals who used both deflazacort and prednisone (n=50) to individuals who only used prednisone was also not statistically different [HR=0.67, (95%CI=0.25–1.78)]

3.4 Analytic Sample Time Since Loss of Ambulation

The estimated median survival time since loss of ambulation was 12.5 years (95% CI=11.8–13.5 years) (Figure 3). The associations between clinical and demographic factors and all-cause mortality were similar to those observed in the time since age 10 years subsample (Table 3). Cumulative duration of glucocorticoid use by loss of ambulation was not associated with hazard of death during follow-up. The crude HR comparing individuals who used glucocorticoids between 6 months and 24 months (n=54) to individuals who never use glucocorticoids or used them less than six months (n=216) was 0.81 (95% CI=0.42–1.57). The crude HR comparing individuals who used glucocorticoids for more than 24 months (n=137) to individuals who never used glucocorticoids or used them less than six months was 0.94 (95% CI=0.61–1.44).

4. Discussion

In our population-based study of 526 individuals born during 1982–1999 and diagnosed with DMD, the estimated median age at death was 23.7 years. A similar median age of death of 24 years was observed among a cohort of individuals born between 1970 and 1980 in Germany [7] and almost half of individuals in an Italian cohort born between 1981 and 1990 survived until age 25 years [6]. A recent Chilean study observed over half of individuals survived to 20 years [30]. Among individuals who died from DMD in England and Wales between 1993 and 1999, the median age of death was 18 years [5]. A Mexican study of individuals with medical records available in 2011, found the mean age of death to be 19 years among those who died [37]. A recent meta-analysis of life expectancy at birth, also estimated the median age at death as 23.7 from samples that contained both individuals who did use mechanical ventilation along with individuals who did not [26].

We observed that in any given year starting at age 10 years, controlling for other factors, individuals who were currently using glucocorticoids were 83% less likely to die than individuals who were not currently using glucocorticoids. Similarly, in any given year after loss of ambulation, individuals who were currently using glucocorticoids were 77% less likely to die. These observations are consistent with 2018 DMD Care Considerations that individuals may benefit from continued glucocorticoid use in the non-ambulatory stage or initiating glucocorticoid use in the non-ambulatory stage [38]. Prior studies have

observed lower mortality among individuals with DMD using glucocorticoids as compared to non-users. However, these studies did not examine the association in the context of other therapies or interventions used. A 2013 Montreal study of 86 individuals, born between 1972-2006 and who were on cardiac medications, reported individuals using glucocorticoids had a lower hazard of death than individuals not using glucocorticoids [HR=0.24, [95%CI=0.07–0.91)] [10]. This association was adjusted for left ventricular ejection fraction. A 2006 Canadian study of individuals 10-18 years of age observed that 12 of 34 (35%) individuals not treated with deflazacort died whereas only 2 of the 40 individuals (5%) treated with deflazacort died [8]. In 2018, the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study reported that individuals treated with glucocorticoids (n=369) for at least 1 year had a lower odds of death than individuals with no history of glucocorticoid use [odds ratio (OR)=0.47, (95% CI=0.22–1.00)] [9]. This association was not adjusted for any other demographic or treatment factors. A recent North American multi-center retrospective study among 408 individuals reported lower odds of death, adjusted for age, among individuals using glucocorticoids as compared to non-users [OR=0.36, (95% CI=0.15 ▫ 0.82)] [11].

Although we observed an association between all-cause mortality and current glucocorticoid use during follow-up, we did not observe an association with cumulative glucocorticoid use prior to the start of risk at age 10 or at loss of ambulation. This suggests that to prolong survival, glucocorticoid use needs to occur during the time at risk for mortality. We also did not observe a difference in hazard of death between prednisone and deflazacort. However, our exploratory analysis did not adjust for any other demographic and clinical factors. Given that deflazacort was only recently approved to treat DMD in the United States, collecting recent data would be needed to fully compare these two glucocorticoids.

We did not observe an association between ever use of cardiac medications (ACE inhibitor or beta blocker) and all-cause mortality. However, we did not examine when cardiac medications were started. Timing of when ACE inhibitors are started may be an important predictor of survival. A Japanese retrospective study of 52 individuals with heart failure, observed that individuals who started on an ACE inhibitor and beta blocker prior to symptoms of heart failure had a higher survival rate at 5, 7, and 10 years of follow-up than those who started on an ACE inhibitor and beta blocker after symptoms of heart failure (P<.001) [13]. A recent analysis of data from the French DMD Heart Registry observed a lower hazard of death among individuals using prophylactic ACE inhibitors as compared to individuals not using prophylactic ACE inhibitors [39]. The analysis utilized a propensity-based approach to balance baseline confounders including glucocorticoid use, scoliosis surgery, and non-invasive intervention, although the number of individuals using these adjusted-for treatments was small. A 2007 double-blind French trial of 57 individuals with normal left ventricle ejection fraction were randomly assigned to receive perindopril or a placebo for 3 years. Subsequently, everyone received perindopril and was then followed for up to 10 years. Of the individuals who received perindopril early, 93% were alive as compared to 66% of the individuals who initially received the placebo (P=.02) [12]. Based on the results of the French trial, the 2018 Care Considerations recommended starting individuals on ACE inhibitors or angiotensin receptor blockers by age 10 years [40].

Progressive skeletal muscle weakness typically leads to scoliosis in individuals with DMD. Progression of scoliosis can compromise cardiac and respiratory function and is often treated by surgery [41]. We observed that in any given year after age 10 years, individuals who ever had scoliosis surgery were 42% less likely to die as compared to individuals who never had scoliosis surgery. Prior studies regarding scoliosis surgery have shown mixed results. A 2015 Cochrane review of scoliosis surgery in individuals with DMD determined that most studies did not observe that scoliosis surgery prolonged survival [41]. However, a few studies have observed that scoliosis surgery prolonged survival [14-16].

As DMD progresses, individuals develop a weakened cough which places them at risk of respiratory tract infections and pneumonia [42]. When forced vital capacity is <50%, peak cough flow is <270 L/min, or maximum expiratory pressure is less than 60 cm H_20, it is recommended that manual or mechanical cough assist begins [42]. Two studies have observed that non-invasive intermittent positive-pressure ventilation (NIPPV) along with mechanical cough assist prolonged survival [17, 18]. We observed that at any given year after loss of ambulation, those who ever used a cough assist machine were 54% less likely to die than individuals who never used a cough assist machine.

Previous observational studies have shown that mechanical ventilation prolongs survival in individuals with DMD [7, 18-25]. The field has credited mechanical ventilation with increasing median survival ages among individuals with DMD [6, 21, 26]. However, the one randomized control trial of NIPPV in individuals with DMD was discontinued because of increased mortality in the NIPPV group as compared to the control group [43]. Our study did not observe an association between ever use of BiPAP and all-cause mortality. Our measure of first BiPAP use may have not been a sensitive enough measure of NIPPV; we did not account for use during a 24-hour period. Our cohort may have been too young to see an association between mechanical ventilation and survival. Among individuals who did not die, the median age at last clinic visit was 17 years. Most individuals with DMD will start assisted ventilation by age 18–21 years [42].

In our analytic sample, after adjusting for surveillance area and other clinical factors, non-Hispanic Black individuals had approximately twice the hazard of death as compared to non-Hispanic White individuals. The number of non-Hispanic Black individuals in this study was small and the majority came from one site. However, differences in mortality among Black individuals as compared to White individuals have been identified previously. An analysis of a national database of United States death certificates from 1983 to 1998 determined that the median age at MD-associated death for Black individuals was 23 years as compared to 27 years for White individuals [44]. A follow-up analysis that examined trends from 1986 through 2005 observed that White individuals had a larger improvement in age at MD-associated death over the time period than Black individuals [45]. The prior two analyses, along with a more recent analysis, observed the age-adjusted mortality rate for MD-associated deaths was lower in Black individuals than White individuals [44-46]. The lower age-adjusted mortality rate among Black individuals is most likely due to lower prevalence of DBMD [46]. Prior analyses of MD STAR*net* data observed that non-Hispanic Black individuals had a lower prevalence of DBMD than non-Hispanic White individuals [1, 47].

Our observed difference in mortality for non-Hispanic Black individuals as compared to non-Hispanic White individuals may be due to disparities in care. In a study of individuals with MD age 15-24, who were on Medicaid, living in South Carolina, and who accessed health care between 2000-2010, Black individuals had less overall health care utilization, less primary care utilization, and less outpatient services than White individuals [48]. Black individuals had higher emergency department usage and a higher incidence of hospitalizations than White individuals [48]. In the MD STAR*net* cohort, a combined group of non-Hispanic Black and Hispanic individuals were older at each step of the diagnostic process than non-Hispanic White individuals [49]. In the Duchenne Registry, non-Caucasian individuals were older at diagnosis than Caucasian individuals [50]. Differences in glucocorticoid usage have been observed in the MD STAR*net* cohort. Non-Hispanic Black individuals and Hispanic individuals were less likely to use glucocorticoids, were more likely to decline glucocorticoids after being offered, and were more likely to start glucocorticoids at later ages than non-Hispanic White individuals [51]. However, our association between all-cause mortality and race/ethnicity was adjusted for current glucocorticoid use. The difference in mortality that we observed among non-Hispanic Black individuals relative to non-Hispanic White individuals may be due to unmeasured clinical and social determinants of health.

Our study does have limitations. Although any day of glucocorticoid use was considered current use for that year, the median duration for glucocorticoid use since age 10 years was 3.3 years. Among individuals who did not die, the median age at last clinic visit was 16.9 years, which may have been too young to fully observe associations with some of the treatments. Only year of use was collected for non-glucocorticoid medications and therefore duration of cardiac medication use was unknown. Our study may be biased by uncontrolled confounding. We did not adjust for the reason or indication for treatment and our MD STAR*net* surveillance does not capture data on household income. For one group of models, we selected only individuals whose age at loss of ambulation was documented. This may have introduced selection bias. However, the results from this group of models were similar to the time since age 10 models. MD STARnet was not designed to be representative of the total United States population living with MD and our results may not be generalizable to populations outside the surveillance areas. Despite these limitations, our study has several strengths. This is one of the first population-based cohort studies to estimate DMD survival in select areas in the United States. Our large sample size and long-term follow-up allowed us to examine the association of a treatment while adjusting for other clinical and demographic factors.

5. Conclusion

Our population-based study estimated a median age of death of 23.7 years among individuals with DMD. We observed higher mortality among non-Hispanic Black individuals as compared to non-Hispanic White individuals. We did not observe associations between all-cause mortality and ever use of cardiac medications or ever use of BiPAP. Our study observed that glucocorticoids, cough assist, and scoliosis surgery prolonged survival. These associations occurred after loss of ambulation. The glucocorticoid observation is consistent with the 2018 Care Considerations statement that glucocorticoid use continues

in the non-ambulatory phase. Our observations may inform the clinical care of individuals living with DMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Interest:

Pangaja Paramsothy, Yinding Wang, Bo Cai, Kristin Conway, Shree Pandya, and Catharine Riley report none.

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Data Availability

Due to privacy concerns (detailed personal information was obtained from a small number of individuals living in a defined surveillance area), data from the MD STAR*net* are not

publicly available. Data used for this analysis are maintained at the Centers for Disease Control and Prevention.

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Highlights:

- Estimated 50% survival until age 23.7 years and 12.5 years after loss of ambulation
- After loss of ambulation, glucocorticoid users had lower risk of death than non-users
- Lower risk of death observed among ever-users of cough assist and scoliosis surgery
- Non-Hispanic Black males had higher risk of death than Non-Hispanic White males
- Cardiac medication and bilevel positive airway pressure were not associated with death

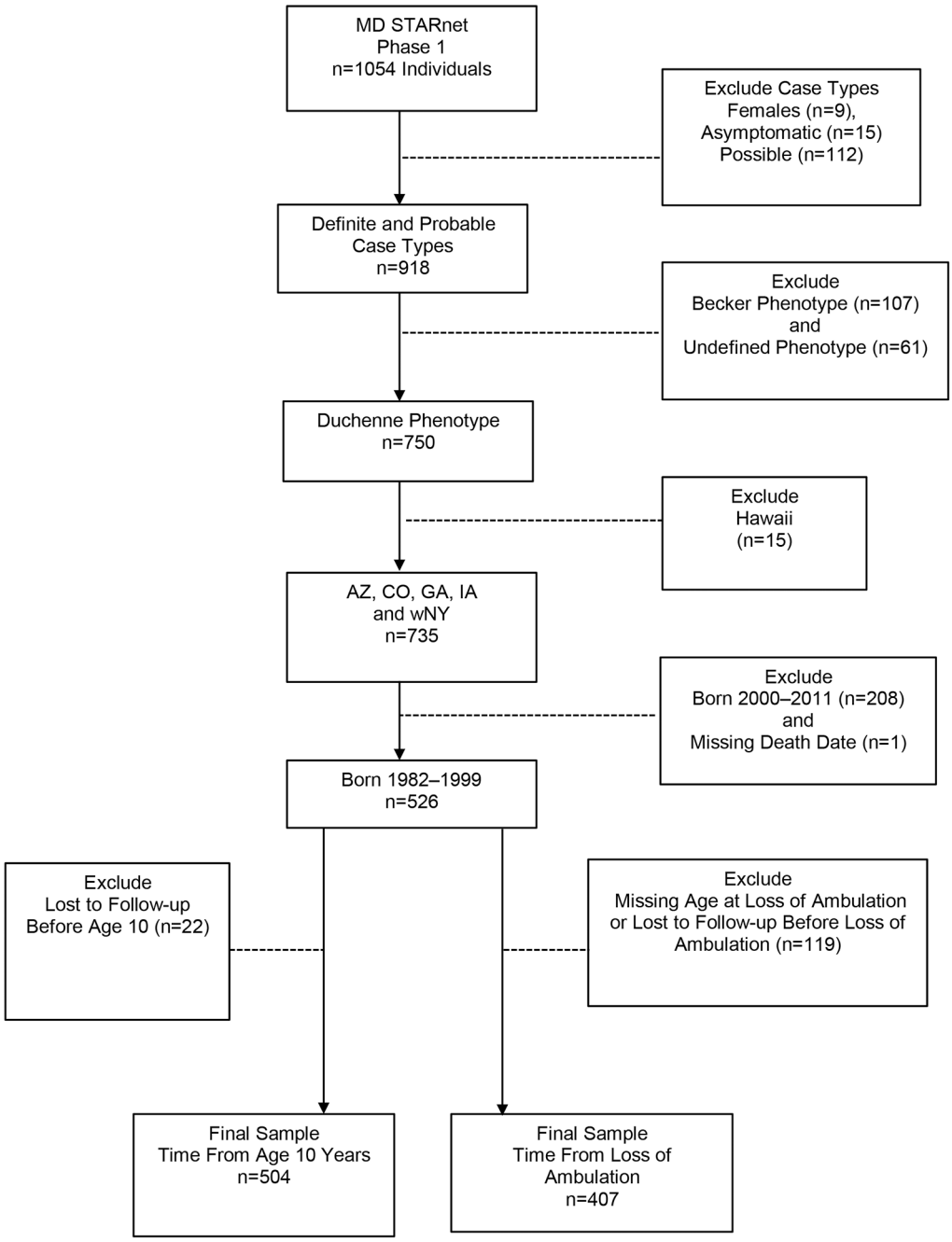

Figure 1.

Inclusion and Exclusion Criteria, Muscular Dystrophy Surveillance, Tracking, and Research Network,1982-2011

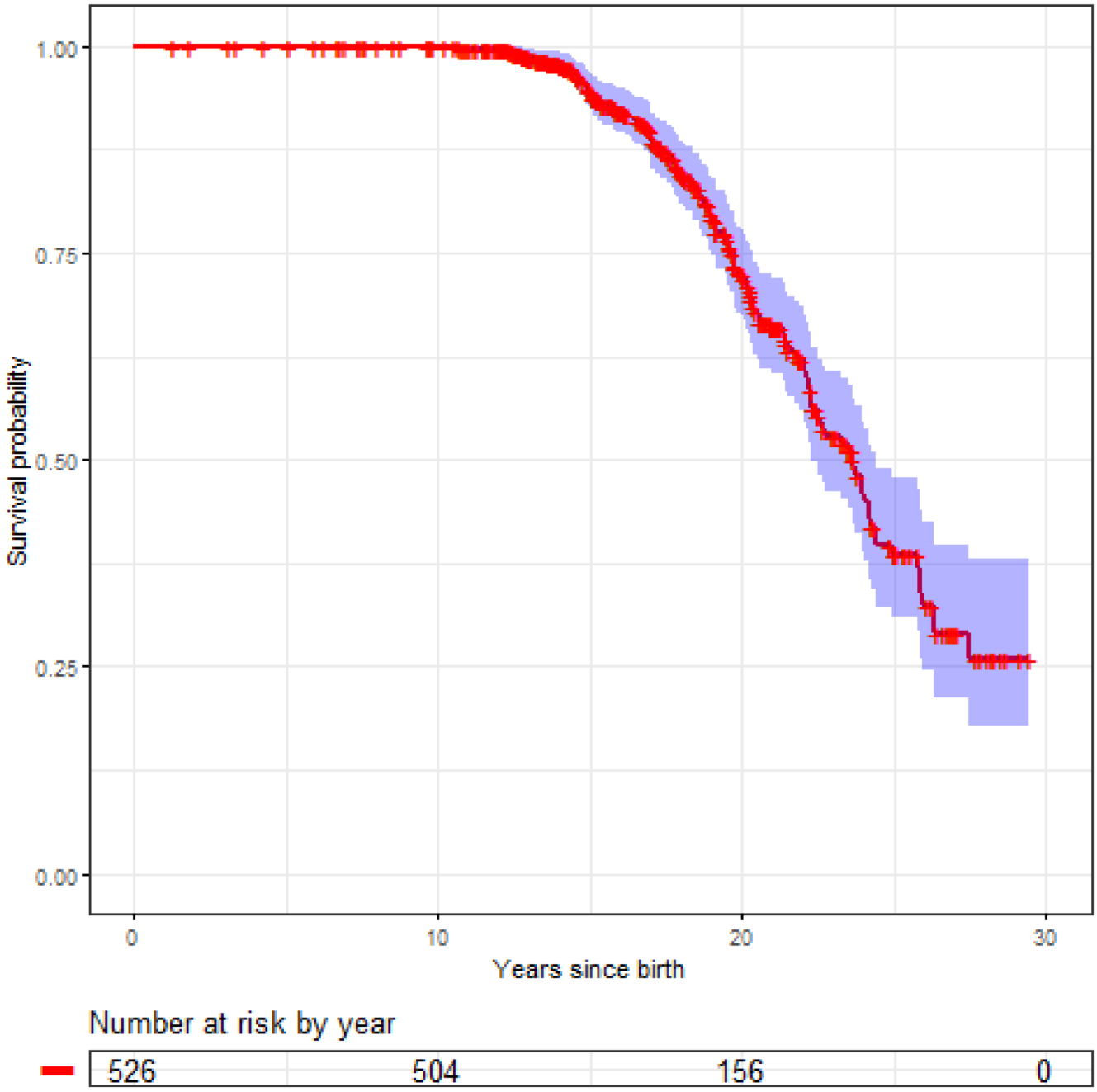

Figure 2.

Kaplan- Meier Survival Curve from Birth, Muscular Dystrophy Surveillance, Tracking, and Research Network, 1982-2011. Red line is the overall estimated survival probability from birth with red plus signs representing censored individuals and blue shade region the 95% confidence interval.

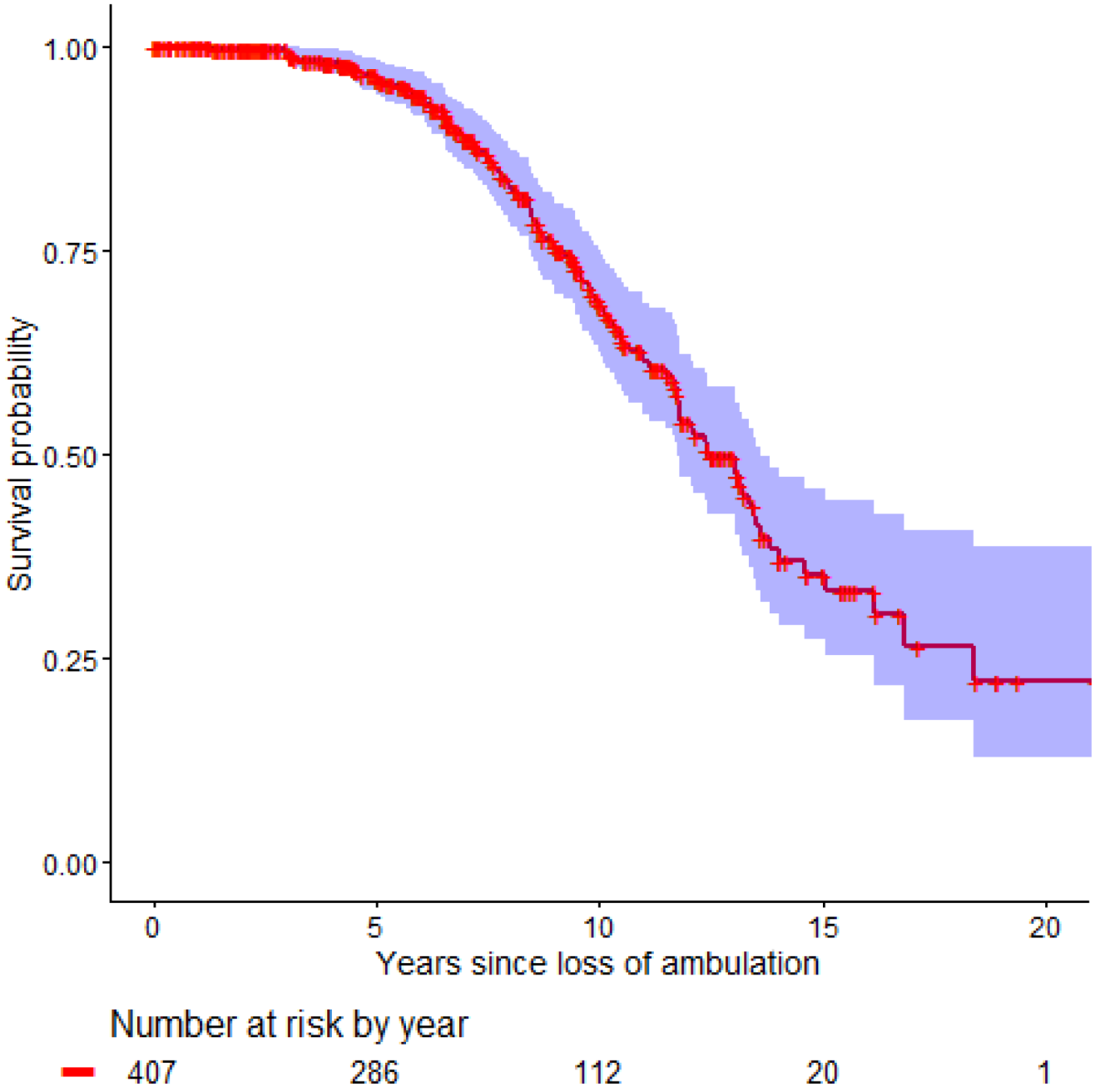

Figure 3.

Kaplan-Meier Survival Curve from Loss of Ambulation, Muscular Dystrophy Surveillance, Tracking, and Research Network, 1982-2011. Red line is the overall estimated survival probability from loss of ambulation with red plus signs representing censored individuals and blue shade region the 95% confidence interval.

Table 1a.

Frequency of Select Demographic and Clinical Factors, Muscular Dystrophy Surveillance, Tracking, and Research Network, 1982-2011

Variable	Time since age 10 [a] N=504 n(%)	Time since loss of ambulation [a] N=407 n(%)
Birth Year		
1982-1984	51 (10.1%)	46 (11.3%)
1985-1989	141 (28.0%)	128 (31.5%)
1990-1994	147 (29.2%)	120 (29.5%)
1995-1999	165 (32.7%)	113 (27.8%)
Race/Ethnicity		
White, Non-Hispanic	292 (57.9%)	229 (56.3%)
Black, Non-Hispanic	39 (7.7%)	34 (8.4%)
Hispanic	113 (22.4%)	101 (24.8%)
Others [b]	60 (11.9%)	43 (10.6%)
Surveillance Site		
Arizona	130 (25.8%)	110 (27.0%)
Colorado	117 (23.2%)	94 (23.1%)
Georgia	129 (25.6%)	103 (25.3%)
Iowa	67 (13.3%)	52 (12.8%)
Western New York	61 (12.1%)	48 (11.8%)
Age of First Signs and Symptoms		
<1.5 Years	116 (23.0%)	92 (22.6%)
1.5 – < 3.0 Years	143 (28.4%)	115 (28.3%)
3.0 – <5.0 Years	111 (22.0%)	92 (22.6%)
5.0+ years	134 (26.6%)	108 (26.5%)
Ever Used Cardiac Medications	262 (52.0%)	225 (55.3%)
Ever Used Cough Assist Machine	148 (29.4%)	130 (31.9%)
Ever Had Scoliosis Surgery	176 (34.9%)	161 (39.6%)
Ever Used BiPAP Machine [c]	191 (37.9%)	166 (40.8%)
Glucocorticoid Use During Follow-up	220 (43.7%)	153 (37.6%)
Died	136 (27.0%)	113 (27.8%)
Censored	368 (73.0%)	294 (72.2%)

[a] Time since age 10 models and time since loss of ambulation models are not mutually exclusive, 404 individuals are in both models.

[b] Other category includes individuals who were Asian, Native Hawaiian, Pacific Islander, Native American, Alaskan Native, of multiple races or whose race and ethnicity was not documented.

[c] Bilevel positive airway pressure

Table 1b.

Distribution of age at loss of ambulation, age at death, and follow-up time, Muscular Dystrophy Surveillance, Tracking, and Research Network, 1982-2011

Variable	Time since age 10 [a]	Time since loss of ambulation [a]
Age at Loss of Ambulation in Years	n/a	
Mean (Standard Deviation)		10.8 (2.0)
Median		10.6
25th Percentile, 75th Percentile		9.2, 12.4
Minimum, Maximum		5.5, 16.0
Age at Death in Years		
Mean (Standard Deviation)	19.0 (3.6)	19.4 (3.6)
Median	19.0	19.5
25th Percentile, 75th Percentile	16.4, 21.8	16.8, 22.1
Minimum, Maximum	10.7, 27.5	11.7, 27.5
Follow-Up Time in Years Among Censored		
Mean (Standard Deviation)	7.5 (4.3)	7.0 (4.4)
Median	6.9	6.5
25th Percentile, 75th Percentile	3.9, 10.4	3.6, 9.9
Minimum, Maximum	0.2, 19.4	0.01, 21.2

[a]Time since age 10 models and time since loss of ambulation models are not mutually exclusive, 404 individuals are in both models.

Table 2.

Hazard Ratios from Cox Regression Models with Time Since Age 10 years, Muscular Dystrophy Surveillance, Tracking, and Research Network, 1982-2011

Variable	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted [a] Hazard Ratio (95% Confidence Interval)
Race/Ethnicity		
White, Non-Hispanic	Referent	Referent
Black, Non-Hispanic	1.81 (1.02 – 3.21)	2.09 (1.11 – 3.92)
Hispanic	1.03 (0.68 – 1.55)	0.96 (0.61 – 1.51)
Others [b]	0.63 (0.34 – 1.16)	0.49 (0.26 – 0.92)
Surveillance Site		
Arizona	Referent	Referent
Colorado	0.95 (0.60 – 1.51)	0.86 (0.53 – 1.40)
Georgia	1.07 (0.65 – 1.77)	0.80 (0.45 – 1.40)
Iowa	1.01 (0.59 – 1.71)	1.38 (0.77 – 2.49)
Western New York [c]	0.74 (0.41 – 1.36)	0.78 (0.41 – 1.49)
Age of First Signs and Symptoms		
<1.5 years	Referent	Referent
1.5 - < 3.0 years	0.80 (0.48 – 1.35)	0.72 (0.42 – 1.23)
3.0 - <5.0 years	1.41 (0.86 – 2.31)	1.67 (1.01 – 2.78)
5.0+ years	0.95 (0.58 – 1.57)	0.87 (0.52 – 1.46)
Ever Used Cardiac Medications [d]	0.84 (0.58 – 1.21)	1.12 (0.74 – 1.71)
Ever Used Cough Assist Machine [d]	0.55 (0.35 – 0.88)	0.55 (0.32 – 0.93)
Ever Had Scoliosis Surgery [d]	0.82 (0.58 – 1.18)	0.58 (0.39 – 0.86)
Ever Used BiPAP Machine [d,e]	0.84 (0.58 – 1.23)	1.12 (0.72 – 1.73)
Current Glucocorticoid Use [d]	0.23 (0.11 – 0.48)	0.17 (0.08 – 0.38)

[a] Adjusted for all variables listed.

[b] Other category includes individuals who were Asian, Native Hawaiian, Pacific Islander, Native American, Alaskan Native, of multiple races or whose race and ethnicity was not documented

[c] Western New York surveillance site included 12 counties

[d] Treatment variables were included as time-varying covariates in one-year increments

[e] Bilevel positive airway pressure

Table 3.

Hazard Ratios from Cox Regression Models with Time Since Loss of Ambulation, Muscular Dystrophy Surveillance, Tracking, and Research Network, 1982-2011

Variable	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted [a] Hazard Ratio (95% Confidence Interval)
Race/Ethnicity		
White, Non-Hispanic	Referent	Referent
Black, Non-Hispanic	1.68 (0.86 – 3.29)	1.76 (0.84 – 3.67)
Hispanic	0.98 (0.63 – 1.52)	1.03 (0.63 – 1.67)
Others [b]	0.81 (0.41 – 1.58)	0.64 (0.31 – 1.31)
Surveillance Site		
Arizona	Referent	Referent
Colorado	1.01 (0.60 – 1.70)	0.97 (0.56 – 1.68)
Georgia	1.45 (0.85 – 2.49)	1.07 (0.58 – 1.98)
Iowa	1.08 (0.59 – 1.96)	1.43 (0.73 – 2.81)
Western New York [c]	1.21 (0.65 – 2.25)	1.33 (0.68 – 2.63)
Age of First Signs and Symptoms		
<1.5 years	Referent	Referent
1.5 - < 3.0 years	0.79 (0.45 – 1.37)	0.68 (0.38 – 1.22)
3.0 - <5.0 years	1.42 (0.83 – 2.45)	1.40 (0.80 – 2.45)
5.0+ years	0.92 (0.53 – 1.62)	0.82 (0.45 – 1.48)
Ever Used Cardiac Medications [d]	0.77 (0.52 – 1.16)	1.04 (0.66 – 1.62)
Ever Used Cough Assist Machine [d]	0.46 (0.28 – 0.75)	0.46 (0.26 – 0.80)
Ever Had Scoliosis Surgery [d]	0.60 (0.41 – 0.88)	0.47 (0.31 – 0.72)
Ever Used BiPAP Machine [d,e]	0.76 (0.50 – 1.14)	1.15 (0.71 – 1.86)
Current Glucocorticoid Use [d]	0.28 (0.11 – 0.69)	0.23 (0.09 – 0.57)

[a] Adjusted models were adjusted for all variables listed.

[b] Other category includes individuals who were Asian, Native Hawaiian, Pacific Islander, Native American, Alaskan Native, of multiple races or whose race and ethnicity was not documented

[c] Western New York surveillance site included 12 counties

[d] Treatment variables were included as time-varying covariates in one-year increments

[e] Bilevel positive airway pressure