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# Sleep apnoea and hypoventilation in patients with five major types of muscular dystrophy

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### ABSTRACT

**Background** The characteristics of and relationship between sleep apnoea and hypoventilation in patients with muscular dystrophy (MD) remain to be fully understood.

**Methods** We analysed 104 in-laboratory sleep studies of 73 patients with MD with five common types (DMD— Duchenne, Becker MD, CMD—congenital, LGMD—limb-girdle and DM—myotonic dystrophy). We used generalised estimating equations to examine differences among these types for outcomes.

**Results** Patients in all five types had high risk of sleep apnoea with 53 of the 73 patients (73%) meeting the diagnostic criteria in at least one study. Patients with DM had higher risk of sleep apnoea compared with patients with LGMD (OR=5.15, 95% CI 1.47 to 18.0; p=0.003). Forty-three per cent of patients had hypoventilation with observed prevalence higher in CMD (67%), DMD (48%) and DM (44%). Hypoventilation and sleep apnoea were associated in those patients (unadjusted OR=2.75, 95% CI 1.15 to 6.60; p=0.03), but the association weakened after adjustment (OR=2.32, 95% CI 0.92 to 5.81; p=0.08). In-sleep average heart rate was about 10 beats/min higher in patients with CMD and DMD compared with patients with DM (p=0.0006 and p=0.02, respectively, adjusted for multiple testing).

**Conclusion** Sleep-disordered breathing is common in patients with MD but each type has its unique features. Hypoventilation was only weakly associated with sleep apnoea; thus, high clinical suspicion is needed for diagnosing hypoventilation. Identifying the window when respiratory muscle weakness begins to cause hypoventilation is important for patients with MD; it enables early intervention with non-invasive ventilation—a therapy that should both lengthen the expected life of these patients and improve its quality.Cite Now

### INTRODUCTION

Muscular dystrophy disorders are a heterogeneous group of inherited genetic diseases characterised by progressive skeletal muscle weakness including diaphragm weakness and cardiomyopathy and wasting.[1–4] Respiratory insufficiency and cardiomyopathy are two major causes for mortality and morbidity in those patients. Chronic respiratory insufficiency results in alveolar hypoventilation and

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### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sleep apnoea and hypoventilation are common in patients with muscular dystrophy (MD); however, the characteristics of sleep-disordered breathing among patients with the five types are less known. This study looks into five major types of MD (Duchenne MD, Becker MD, congenital MD, LGMD—limb-girdle and DM—myotonic dystrophy).

### WHAT THIS STUDY ADDS

⇒ Not all types of MD have the same degree and characteristics of sleep-disordered breathing. Importantly, hypoventilation was only weakly associated with sleep apnoea in patients with MD. Moreover, we found that patients with DM had significantly higher risk of sleep apnoea compared with patients with LGMD.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Specific attention should be paid to each type of MD. Because of the weak association between sleep apnoea and hypoventilation, high clinical suspicion is needed so that hypoventilation can be diagnosed early to allow for timely intervention with non-invasive ventilation and thus better outcome.

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hypercapnia,[5] both are common in patients with muscular dystrophy.[6–8] Early treatment of cardiomyopathy improves outcomes.

The major types of muscular dystrophy include: Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), limb-girdle muscular dystrophy (LGMD), congenital muscular dystrophy (CMD) and myotonic dystrophy (DM, Greek name 'dystrophia myotonica'). DMD[9 10] is a degenerative X linked recessive muscle disease often caused by out-of-frame mutations in the *DMD* gene resulting in a complete loss of the functional dystrophin protein. BMD,[11] also due to a defective *DMD* gene resulting in a partial loss of dystrophin function, presents a milder clinical spectrum compared with DMD. LGMDs[12 13] are a heterogeneous group

of diseases caused often by mutations (repeat expansions) in genes coding for proteins involving muscle structure formation, functions, and/or repair. DM[14] is characterised by progressive muscle weakness, wasting and complex extramuscular manifestations including those in the cardiac and central nervous systems; its two principal subtypes are caused by mutations in two different genes: the *DMPK* gene for DM1 and the *CNBP* gene for DM2. CMD[15 16] refers to a heterogeneous group of often severe muscular dystrophies that become apparent at or near birth.

Sleep-disordered breathing (sleep apnoea and hypoventilation) is common in patients with muscular dystrophy.[17–22] Sleep apnoea occurs when normal breathing during sleep is interrupted.[23] Sleep-related hypoventilation refers to breathing that is too slow or shallow during sleep resulting in impaired gas exchange as evidenced by an increase in partial arterial carbon dioxide ($CO_2$) pressure.[24] Possible differences in characteristics of sleep-disordered breathing among patients with the five major types are less well understood. Moreover, little is known about the relationship between sleep apnoea and hypoventilation in those patients. In this report, we analysed baseline and sleep variables obtained from 104 in-laboratory polysomnography (PSG) studies on 73 patients diagnosed with one of the five major types of muscular dystrophy. Our goals were: (1) to compare average values of selected clinical variables among muscular dystrophy types; (2) to examine the association of hypoventilation and sleep apnoea with clinical variables and types; and (3) to characterise the association between hypoventilation and sleep apnoea in these patients.

## METHODS
### Subjects and study protocol
A retrospective in-laboratory PSG data review was conducted for studies carried out between January 2004 and December 2021 in an American Academy of Sleep Medicine (AASM)-accredited sleep laboratory at the University of North Carolina at Chapel Hill (UNC-CH) on patients with a diagnosis of muscular dystrophy.

### In-laboratory PSG study
Routine level 1 in-laboratory PSG studies were carried out at UNC-CH hospitals. Each in-laboratory PSG included at least six channel electroencephalograms, two electrooculograms, submental and bilateral tibialis surface electromyograms and an ECG. Additional recordings included airflow from nasal pressure and nasal/oral thermocouple, chest and abdominal movement via respiratory impedance plethysmography belts, end-tidal $CO_2$ via a BCI capnograph sampled through a nasal cannula and arterial blood oxygen via a finger probe. Transcutaneous $CO_2$ was used when end-tidal $CO_2$ measurement was not feasible in selected patient groups such as the very young. Time-locked digital video was recorded with the PSG. The

multichannel polysomnogram was recorded digitally and stored using a Stellate Systems polygraph, Grass Systems polygraph, and Natus polygraph between 2004 and 2012, between 2013 and 2018, and 2019 and 2021, respectively.

Studies before 2007 were scored using the guidelines from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association.[25] Studies from September 2007 until June 2016 were scored with the 2007 guidelines from the AASM scoring manuals. Subsequent studies were scored with the 2016 guidelines.[26] For all three periods, respiratory events were required to be a minimum of two breaths in duration. Hypopnoeas were required to be associated with at least 3% desaturation or arousal or 4% desaturation if the patient was on certain insurance such as Medicare. Diagnoses of obstructive sleep apnoea (OSA) and hypoventilation were based on the criteria by International Classification of Sleep Disorders-3.[27] Briefly, mild, moderate and severe sleep apnoea were defined based on the apnoea–hypopnoea index (AHI) but, by convention, with different ranges depending on the patient's age at PSG.[28 29] For those younger than 13 years old, mild, moderate and severe were defined, respectively, by the following ranges: $1.5 \leq AHI < 5$, $5 \leq AHI < 10$ and $AHI \geq 10$; for those at or above 18 years old, the corresponding ranges were: $5 \leq AHI < 15$, $15 \leq AHI < 30$ and $AHI \geq 30$. For teenagers between the ages of 13 and 18 years, criteria were chosen at the discretion of the reading physician. Hypoventilation was also defined differently depending on the patient's age. For those under the age of 18 years, hypoventilation was defined as having greater than 25% of time in sleep spent with partial pressure of $CO_2$ ($pCO_2$) or surrogate measurements >50 mm Hg and a more than 10 mm Hg increase in $pCO_2$ in sleep in comparison with awake. For those 18 years and older, hypoventilation required having greater than 10 min with $pCO_2$ or surrogate measurements >55 mm Hg.[8] Each sleep study was initially scored by an AASM board-certified sleep technologist and finalised by an AASM-certified physician. Paediatric studies were all scored by AASM board-certified sleep physicians specialised in children. Additional information can be found in the online supplemental materials.

### Data
We included 96 diagnostic PSG studies and 8 split-night sleep studies. For a split-night study, we used data only from the diagnostic portion of the study.

We extracted patient details from electronic medical records including data on arterial blood gases (ABGs), maximal inspiratory/expiratory pressure (MIP/MEP) as measures of respiratory muscle strength, echocardiogram, Epworth Sleepiness Scale score, beta-blocker prescription, whether the patients were on ventilator at the time of study, status of tracheostomy and other relevant information (online supplemental table 1). For inclusion, these variables had to be measured within ±6 months of the sleep study. Specifically, we looked at the

date of the sleep study and then at the closest clinical record before or after that date within 6 months.

From the sleep study records, we extracted the basic variables: sex, age (years), weight (kg), height (cm), body mass index (BMI) and muscular dystrophy type, as well as PSG-specific variables. These included baseline variables: oxygen saturation (%), end-tidal $CO_2$ (mm Hg), heart rate (beats/min) and respiratory rate (breaths/min), as well as variables measured during sleep: average and peak heart rate, average and peak end-tidal $CO_2$ and overall AHI. Some PSG studies did not record all these variables, so our data have sporadic missing values.

## Statistical analysis

We computed the age-adjusted and gender-adjusted BMI z-scores using weight (kg) and height (cm) according to the method proposed by Centers for Disease Control and Prevention.[30] We then categorised these z-scores into three groups: z-score <−2, −2≤ z-score ≤2 and z-score >2. For some statistical analyses, we transformed continuous variables like age (by the base-2 logarithm) to improve model fit. Using the criteria delineated earlier, we also created binary (present or absent) variables for hypoventilation and sleep apnoea.

We used generalised estimating equations (GEE) with an exchangeable correlation structure[31] when examining associations. Model specification differed somewhat for different response variables. For binary responses, such as apnoea or hypoventilation, our GEE models used a binomial distribution with the logistic link function; for continuous responses, such as heart rate, our GEE models used a normal distribution with the identity link function.

Although we have a reasonably large collection of patients with muscular dystrophy with PSG data, our sample, containing approximately 100 PSG studies, supports only small numbers of predictors in individual statistical models and limits statistical power. Consequently, we examined associations between response variable and individual predictor variables including adjustment for a few selected covariates. In general, we report p values without accounting for multiple testing although we employ the Tukey-Kramer procedure[32] for pairwise comparisons among types. For model fitting, we used PROC GENMOD in SAS (V.9.4) (details in online supplemental materials).

## Patient and public involvement

Neither patients nor the public had any involvement with planning, conducting or reporting this research.

## RESULTS

We identified 104 PSG studies from 73 unique patients with confirmed diagnosis of one of the five major types of muscular dystrophy (table 1). The most frequently represented among the major types were DMD (37% of patients) and DM (33% of patients); BMD, CMD and LGMD made up approximately 7%, 10% and 14% of patients, respectively. Of the 73 patients, 57 (78%) contributed one study, 7 (10%) had two studies, 7 (10%) had three studies and 1 (1%) had four studies. One patient (1%) with congenital DM had eight studies (online supplemental table 2). At least one patient of each type had more than one study. The patient who had eight studies was diagnosed with congenital DM type 1. Of the 31 consecutive pairs of studies from patients with multiple studies, their separation in time ranged from 0 to 10 years, with 17 (55%) within 2 years of the previous study. The patients' pulmonologists or neurologists ordered all PSGs. All patients with DMD and BMD were male, consistent with these types being X linked recessive diseases. All patients with CMD except one were also male. Approximately half of the patients with LGMD and the DM were male.

## Brief summary of the clinical variables

We sought certain both PSG and non-PSG-related clinical variables from patient medical records within ±6 months of each PSG study. These included ABGs, beta-blocker prescription, echocardiogram, MIP/MEP, vital status, tracheostomy status, Epworth Sleepiness Scale, ventilator status at PSG study, among others (table 1 and online supplemental table 1). For many subjects, some variables were not recorded during the 6-month window around the PSG. For example, MIP/MEP was recorded for 29, marked as 'unable' for 8 and unrecorded for 67 of 104 PSG studies; these factors were not routinely assessed by their pulmonologists for patients with DM and for the young because of small nostrils and other constraints. Among the 49 studies with ABG ($pCO_2$) measurements, 35 (71%) had borderline to elevated levels ($pCO_2$ ≥45 mm Hg or bicarb >30 mEq/L). Among the 27 studies with MIP measurements, 26 (96%) had reduced pressures. Similarly, among the 27 with MEP measurements, 22 (81%) had reduced pressures. Eight of the 67 studies (12%) with echocardiograms showed reduced left ventricular ejection fraction. Five patients (three DM, one CMD and one DMD) had tracheostomy. Among the 73 patients, 14 (1 BMD, 2 CMD, 3 DM, 6 DMD and 2 LGMD) are known to have died, 1 has unknown vital status; the remainder are alive. Among the 14 deaths, the median and average age at death were 21 and 25 years old.

## Age and BMI in the patients under study

Based on all 104 studies, patients with DMD and CMD had the youngest median ages (13 and 14 years, respectively); whereas patients with DM, LGMD and BMD had older median ages (22, 23 and 18 years, respectively) (table 2 and online supplemental table 3).

Based on 103 studies (information on BMI was missing for one study), the median BMI z-score for patients with BMD or DMD either approached or exceeded the 90th

**Table 1** Summary of clinical data for the 73 patients with muscular dystrophy from 104 PSG studies

| Variables | All types N (%) | BMD N (%) | CMD N (%) | DM N (%) | DMD N (%) | LGMD N (%) |
|---|---|---|---|---|---|---|
| Total patients | 73 (100) | 5 (100) | 7 (100) | 24 (100) | 27 (100) | 10 (100) |
| Male | 55 (75) | 5 (100) | 6 (86) | 10 (42) | 27 (100) | 7 (70) |
| Female | 18 (25) | 0 (0) | 1 (14) | 14 (58) | 0 (0) | 3 (30) |
| Vital status as of January 2023* | | | | | | |
| Alive | 58 (79) | 4 (80) | 5 (71) | 20 (83) | 21 (78) | 8 (80) |
| Deceased | 14 (19) | 1 (20) | 2 (29) | 3 (13) | 6 (22) | 2 (20) |
| Unknown | 1 (1) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 0 (0) |
| Tracheostomy* | | | | | | |
| Yes | 5 (7) | 0 (0) | 1 (14) | 3 (13) | 1 (4) | 0 (0) |
| No | 68 (93) | 5 (100) | 6 (86) | 21 (87) | 26 (96) | 10 (100) |
| Total studies† | 104 (100) | 7 (100) | 9 (100) | 37 (100) | 38 (100) | 13 (100) |
| Male | 76 (73) | 7 (100) | 8 (89) | 16 (43) | 38 (100) | 7 (54) |
| Female | 28 (27) | 0 (0) | 1 (11) | 21 (57) | 0 (0) | 6 (46) |
| Daytime hypoventilation (ABG) (pCO$_2$ >45 mm Hg or bicarb >30 mEq/L)† | | | | | | |
| Present | 14 (13) | 0 (0) | 2 (22) | 7 (19) | 2 (5) | 3 (23) |
| Absent | 35 (34) | 3 (43) | 3 (33) | 8 (22) | 17 (45) | 4 (31) |
| Not recorded | 55 (53) | 4 (57) | 4 (44) | 22 (59) | 19 (40) | 6 (46) |
| Maximal inspiratory pressure† | | | | | | |
| Normal | 1 (1) | 0 (0) | 1 (11) | 0 (0) | 0 (0) | 0 (0) |
| Reduced (<75 cm H$_2$O) | 27 (26) | 0 (0) | 4 (44) | 4 (11) | 14 (37) | 5 (38) |
| Not recorded | 76 (73) | 7 (100) | 4 (44) | 33 (89) | 24 (63) | 8 (62) |
| Maximal expiratory pressure† | | | | | | |
| Normal | 5 (5) | 0 (0) | 1 (11) | 1 (3) | 1 (3) | 2 (15) |
| Reduced (<60 cm H$_2$O) | 23 (22) | 0 (0) | 4 (44) | 3 (8) | 13 (34) | 3 (23) |
| Not recorded | 76 (73) | 7 (100) | 4 (44) | 33 (89) | 24 (63) | 8 (62) |
| Echocardiogram† | | | | | | |
| Normal | 59 (57) | 4 (57) | 6 (67) | 14 (38) | 24 (63) | 11 (85) |
| Reduced (<50 NL LVEF) | 8 (8) | 1 (14) | 0 (0) | 0 (0) | 7 (18) | 0 (0) |
| Not recorded | 37 (36) | 2 (29) | 3 (33) | 23 (62) | 7 (18) | 2 (15) |

Clinical data were recorded within ±6 months of the corresponding PSG studies. Vital status was assessed up to January 2023. Clinical data for each patient nearest each PSG study are presented in online supplemental table 1.
*Percentages for all types use total number of patients (73) as the denominator; percentages for specific types use the number of patients in the total patients row for that specific type as the denominator. Percentages may not sum to 100 due to rounding.
†Percentages for all types use total number of PSG studies (104) as the denominator; percentages for specific types use the number of PSG studies in the total studies row for that specific type as the denominator. Percentages may not sum to 100 due to rounding.
ABG, arterial blood gas; BMD, Becker muscular dystrophy; CMD, congenital muscular dystrophy; DM, myotonic dystrophy; DMD, Duchenne muscular dystrophy; LGMD, limb-girdle muscular dystrophy; NL LVEF, normal left ventricular ejection fraction; pCO$_2$, partial pressure of carbon dioxide; PSG, polysomnography.

percentile (z=1.28) in the general population (table 2). BMI z-score for patients with CMD was below the average z-score (z=0) in the general population in over 75% of the studies. Some patients showed signs of malnourishment at the time of study with BMI z-scores less than −2. Eleven of the 72 patients had at least one study with a BMI z-score greater than 2, indicative of overweight; eight of these were patients with DMD.

**Table 2** Summary statistics of age and BMI z-score among all PSG studies of patients with each type of muscular dystrophy

| Type | N* | Minimum | 1st quartile | Median | Average | 3rd quartile | Maximum |
|---|---|---|---|---|---|---|---|
| **Age (years)** | | | | | | | |
| BMD | 7 | 3.4 | 3.4 | 18 | 30.1 | 54.4 | 58.5 |
| CMD | 9 | 4.4 | 11.5 | 14.2 | 13.6 | 14.3 | 19.3 |
| DM | 37 | 0.3 | 7.3 | 22 | 23.7 | 31.7 | 69.2 |
| DMD | 38 | 2.8 | 10.5 | 13.4 | 14 | 16.9 | 25.4 |
| LGMD | 13 | 9.8 | 12.8 | 23.1 | 28.5 | 34 | 68.8 |
| All types | 104 | 0.3 | 10.5 | 14.4 | 20.3 | 25.4 | 69.2 |
| **BMI (kg/cm$^2$)** | | | | | | | |
| BMD | 7 | 16.5 | 16.5 | 29 | 26.9 | 31.3 | 33.6 |
| CMD | 8 | 10.8 | 16.5 | 17.7 | 17.4 | 19.5 | 20.4 |
| DM | 37 | 13.3 | 16.1 | 19.5 | 21.7 | 24.2 | 38.4 |
| DMD | 38 | 13.8 | 16.9 | 23.6 | 24 | 27.3 | 45.2 |
| LGMD | 13 | 15.4 | 17.1 | 22.3 | 24.1 | 26.4 | 49.7 |
| All types | 103 | 10.8 | 16.8 | 21.1 | 22.9 | 27.8 | 49.7 |
| **BMI z-score** | | | | | | | |
| BMD | 7 | 0.74 | 0.74 | 1.46 | 1.57 | 1.95 | 2.31 |
| CMD | 8 | −9.56 | −1.61 | −0.73 | −1.64 | −0.45 | 0.58 |
| DM | 37 | −2.09 | −0.98 | 0.58 | 0.26 | 0.99 | 2.46 |
| DMD | 38 | −6.32 | −0.53 | 1.18 | 0.63 | 1.86 | 2.82 |
| LGMD | 13 | −2.87 | −1.28 | 0.21 | 0.19 | 1.2 | 2.87 |
| All types | 103 | −9.56 | −0.62 | 0.74 | 0.33 | 1.53 | 2.87 |

*Number of PSG studies.
BMD, Becker muscular dystrophy; BMI, body mass index; CMD, congenital muscular dystrophy; DM, myotonic dystrophy; DMD, Duchenne muscular dystrophy; LGMD, limb-girdle muscular dystrophy; PSG, polysomnography.

## Sleep apnoeas and AHI in patients with muscular dystrophy

Fifty-three of the 73 patients (73%) were diagnosed with sleep apnoea (table 3). Four of the five patients with BMD exhibited severe primary OSA.

We examined differences in the prevalence of sleep apnoea among the types by fitting a logistic regression model adjusted for age, sex and three categories of BMI z-score using GEE. Although sleep apnoea prevalence tended to increase with age, the evidence was inconclusive (OR 1.03 per year, 95% CI 0.99 to 1.06; p=0.08). Neither were extremely high BMI z-scores (>2) associated with apnoea compared with scores between −2 and 2 (OR

**Table 3** Number (%) of patients of each type ever diagnosed with hypoventilation and with mild, moderate or severe apnoea

| Type | Total patients | Hypoventilation | Level of sleep apnoea severity | | | |
|---|---|---|---|---|---|---|
| | | | None | Mild | Moderate | Severe |
| BMD | 5 | 0 (0)* | 1 (20) | 0 (0) | 0 (0) | 4 (80) |
| CMD | 7 | 4 (57) | 2 (29) | 4 (57) | 0 (0) | 1 (14) |
| DM | 24 | 10 (42) | 6 (25) | 11 (46) | 5 (21) | 2 (8) |
| DMD | 27 | 14 (52) | 7 (26) | 11 (41) | 7 (26) | 2 (7) |
| LGMD† | 10 | 2 (22) | 4 (40) | 4 (40) | 2 (20) | 0 (0) |
| Overall | 73 | 30 (42) | 20 (27) | 30 (41) | 14 (19) | 9 (12) |

Patients with multiple studies were assigned their highest observed apnoea severity level.
*Percentages use the type-specific total number of patients (column 2) as the denominator. Apnoea percentages may not sum to 100 due to rounding.
†One of 10 patients with LGMD was missing hypoventilation status; thus, the denominator for hypoventilation was 9 for LGMD and 72 overall.
BMD, Becker muscular dystrophy; CMD, congenital muscular dystrophy; DM, myotonic dystrophy; DMD, Duchenne muscular dystrophy; LGMD, limb-girdle muscular dystrophy.

0.71, 95% CI 0.19 to 2.67; p=0.61); however, extremely low BMI z-scores were associated with lower prevalence of apnoea (OR 0.19, 95% CI 0.04 to 0.91; p=0.04). Female patients had lower prevalence of sleep apnoea (OR 0.41, 95% CI 0.15 to 1.08; p=0.07) compared with male patients, though not significantly. Adjusted estimates of the odds of sleep apnoea differed across muscular dystrophy types with DM exhibiting the highest odds and LGMD the lowest, but estimates were imprecise (online supplemental table 4A). In comparisons among all possible pairs of types, only the OR comparing DM with LGMD was statistically significant after adjustment for multiple testing (OR=5.15, 95% CI 1.47 to 18.0; p=0.003) (online supplemental table 4B).

We also examined differences in mean AHI among muscular dystrophy types by fitting a regression model using GEE adjusting for age, sex and category of BMI z-score. Based on this model, each 10-year age increase was associated with a slight increase in AHI (1.5 events/hour, 95% CI 0.5 to 2.4; p=0.002). Female patients had about the same AHI on average as male patients (mean difference=−1.3 events/hour, 95% CI −4.5 to 2.3; p=0.52). Although patients with extremely low BMI z-scores (<−2) tended to have lower AHI than the reference group (−2≤ z-score ≤2), the difference was not statistically significant (mean difference=−3.3 events/hour, 95% CI −7.5 to 0.5; p=0.08). For those with extremely high BMI z-scores (>2), mean AHI was similar to the reference group (mean difference=1.1 events/hour, 95% CI −5.5 to 7.7; p=0.74). Mean AHI appeared to differ among muscular dystrophy types. Patients with BMD had the highest observed mean AHI, over 10 events/hour higher than any other type, and patients with CMD and LGMD had the lowest (online supplemental table 3). The same relationship held after adjustment for these covariates, but confidence limits were broad (online supplemental table 5A). In comparisons of all possible pairs of types, only the BMD versus LGMD difference was statistically significant after correction for multiple testing (online supplemental table 5B).

### Hypoventilation in patients with muscular dystrophy
Among the 104 PSG studies, 54 and 89 had recordings for average end-tidal $CO_2$ (mean 44.3 mm Hg, range 26.4–62.0 mm Hg) and peak end-tidal $CO_2$ (mean 51.7, range 35.2–90 mm Hg) during sleep, respectively (online supplemental table 3). Correlation between age and average $CO_2$ or peak $CO_2$ was small (Spearman correlation coefficient 0.13 and 0.03, respectively). Among the 72 patients with hypoventilation status, 30 (42%) were diagnosed with hypoventilation at least once. Patients with CMD were most likely to be diagnosed with hypoventilation (table 3), consistent with the finding that patients with CMD showed the highest mean end-tidal $CO_2$ levels at baseline and during sleep (online supplemental table 3). Hypoventilation was common in the following types: 57% of CMD, 52% of DMD and 42% of DM. Patients with BMD and LGMD were the least likely to exhibit

hypoventilation (table 3); in fact, none of the seven PSG studies on five patients with BMD yielded a diagnosis of hypoventilation.

We examined differences in the prevalence of hypoventilation among muscular dystrophy types by fitting a logistic regression model adjusted for age, sex and three categories of BMI z-score using GEE. The prevalence of hypoventilation was constant with age (OR 1.00 per year, 95% CI 0.98 to 1.03; p=0.86). Those with extreme BMI z-scores (<−2 or >2) had similar prevalence of hypoventilation compared with those with intermediate scores (z-score <−2: OR 0.40, 95% CI 0.06 to 2.79; p=0.35 and z-score >2: OR 1.31, 95% CI 0.34 to 4.97; p=0.69). Adjusted estimates of the odds of hypoventilation differed across muscular dystrophy types with CMD exhibiting the highest odds and LGMD the lowest, but estimates were imprecise (online supplemental table 6A). In comparisons among all possible pairs of types, none of the pairwise differences were statistically significant after adjustment for multiple comparisons (online supplemental table 6B).

### Association of hypoventilation and sleep apnoea or AHI in patients with muscular dystrophy
We examined the relationship between sleep apnoea and hypoventilation among the 102 studies encompassing 71 patients where both were recorded with BMI available. We considered the association first without adjusting for any covariates and again after simultaneously adjusting for age, sex, three categories of BMI z-score and muscular dystrophy type by fitting logistic models using GEE. Among 68 PSG studies where the patient exhibited sleep apnoea, the patient also exhibited hypoventilation in 28 of them; whereas in the 34 PSG studies where the patient did not have sleep apnoea, only 7 had hypoventilation (GEE unadjusted OR 2.75, 95% CI 1.15 to 6.60; p=0.03). After adjustment for covariates, the association weakened slightly (adjusted OR 2.31, 95% CI 0.92 to 5.81; p=0.08).

We also examined the relationship between AHI and hypoventilation by replacing sleep apnoea with AHI in the GEE logistic model. The odds of hypoventilation were estimated to increase slightly with increasing AHI, but the association was not statistically significant (adjusted OR for a 5 events/hour increase in AHI: 1.02, 95% CI 0.79 to 1.31; p=0.89). A plot of AHI against age with points coded by hypoventilation status and type failed to show a clear relationship of hypoventilation status or type to AHI (figure 1).

### Heart rates in patients with muscular dystrophy
Mean baseline heart rates were 79, 96, 85, 98 and 84 beats/min (overall mean 90 beats/min) for patients with BMD, CMD, DM, DMD and LGMD, respectively (online supplemental table 3). Likewise, during sleep, the mean heart rates were 67, 90, 77, 93 and 79 beats/min (overall mean 83 beats/min), and mean peak heart rates were 113, 126, 115, 126 and 112 beats/min (overall mean 119
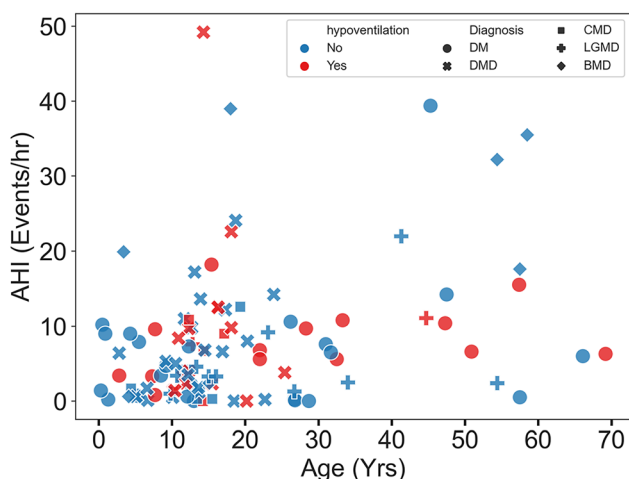
**Figure 1** Scatter plot of age versus AHI for the 104 PSG studies on patients with muscular dystrophy. Plotting symbols of different shapes indicate muscular dystrophy type (list the shapes and give the type for each). Plotting symbols in different colours indicate hypoventilation status (red symbols, present; blue symbols, absent). AHI, apnoea–hypopnoea index; BMD, Becker muscular dystrophy; CMD, congenital muscular dystrophy; DM, myotonic dystrophy; DMD, Duchenne muscular dystrophy; LGMD, limb-girdle muscular dystrophy; PSG, polysomnography.

beats/min), respectively. Patients with DMD had significantly higher baseline heart rate and average and peak heart rates during sleep by about 10 beats/min (online supplemental table 7A), than those of patients with DM (p=0.003, p<0.0001 and p=0.02, respectively) (online supplemental table 7B and figure 2). Similarly, patients with CMD had significantly higher baseline heart rate and average and peak heart rates during sleep than those of patients with DM, again with mean differences near 10 beats/min (p=0.03, p<0.0001 and p=0.0006, respectively).
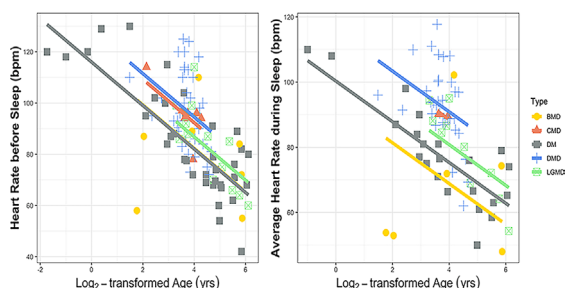


**Figure 2** Differences among muscular dystrophy types in mean heart rates after adjusting for age using regression fit by GEE methods (top: baseline heart rate; bottom: average heart rate during sleep). BMD, Becker muscular dystrophy; bpm, beats per minute; CMD, congenital muscular dystrophy; DM, myotonic dystrophy; DMD, Duchenne muscular dystrophy; GEE, generalised estimating equations; LGMD, limb-girdle muscular dystrophy.

## DISCUSSION

Our finding is consistent with sleep-disordered breathing being common in patients with muscular dystrophy.[18–21 24 33] Among the five common muscular dystrophy types, sleep apnoea tended to be mild for patients with LGMD and severe for patients with BMD, an observation based on very few subjects of each type. Hypoventilation is also a major concern for patients with muscular dystrophy. Patients with CMD had the highest prevalence of hypoventilation, but it was also common in patients with DMD and DM; patients with LGMD had the lowest prevalence though differences in hypoventilation prevalence among types were not statistically significant. In a recent study of patients with DMD in their early teens,[34] ~34% had hypoventilation; this proportion is somewhat lower than in our patients with DMD. Hypoventilation in patients with muscular dystrophy is usually most severe in rapid eye movement sleep.[18]

Unlike conditions related to skeletal muscle weakness, hypoventilation due to respiratory muscle weakness can be treated with non-invasive ventilation such as bilevel positive airway pressure. Our results support the importance of nocturnal hypoventilation monitoring for patients with muscular dystrophy as part of disease management,[35] because of the high prevalence of hypoventilation and progressive nature of the diseases in patients with muscular dystrophy. Non-invasive mechanical ventilation can be a valuable modality for patients with muscular dystrophy for more favourable outcomes and better survival.[8 18 24 36–38]

Our analysis also revealed that sleep apnoeic events and hypoventilation events in patients with muscular dystrophy were mildly associated, though of borderline statistical significance. This finding has important clinical implications. Unlike obese hypoventilation, which is strongly associated with OSA,[24 39] hypoventilation in patients with muscular dystrophy is only marginally associated with OSA. Thus, for patients with muscular dystrophy, treating OSA may not provide equal relief for hypoventilation and vice versa; both conditions may need to be managed concomitantly. Hypoventilation commonly occurs alongside sleep apnoea especially for those with obesity. Chronic hypoventilation in patients with muscular dystrophy is likely related to the underlying aetiology of the disease rather than to other conditions such as obesity, though we did see a tendency toward higher prevalence of hypoventilation among the most obese patients. Chronic weakening of respiratory muscles including diaphragm in patients with muscular dystrophy is likely the major contributor of hypoventilation in those patients.[1 8 18 19 21 24 40–42] Monitoring and diagnosing early muscle weakness in those patients are important for appropriate early intervention.[35] Once sleep-disordered breathing has developed, both sleep apnoeas and hypoventilation may need to be monitored and managed alongside.

Consistent with our findings, patients with CMD and DMD had high heart rate during sleep.[43–45] For patients

with muscular dystrophy, routine cardiology follow-up for the risk of cardiomyopathy and early pharmacological intervention may be needed especially for those with DMD and CMD.

Lastly, not all types of muscular dystrophy have the same degree and characteristics of sleep-disordered breathing or the same clinical manifestations. Specific attention should be paid to each type. For instance, patients with CMD tend to have severe muscle weakness. As a result, those patients had the lowest average BMI z-scores and the highest risk of hypoventilation compared with patients with other types. Mean AHI appeared to differ among muscular dystrophy types. DM had statistically significant higher odds of sleep apnoea compared with LGMD. Patients with BMD exhibited the severest primary OSA compared with all other types. Hypoventilation was common in the following types: 57% of CMD, 52% of DMD and 42% of DM. Patients with DMD had significantly, or nearly significantly, higher baseline heart rate and average and peak heart rates during sleep than those of patients with DM. Similarly, patients with CMD had significantly higher average and peak heart rates during sleep than those of patients with DM.

This study has several limitations. Despite having one of the largest collections of diagnostic PSG studies of patients with muscular dystrophy ever reported, our small sample size limited our ability to probe associations; consequently, CIs were wide and statistical power was restricted. BMD, CMD and LGMD had especially small samples. Our sample size was too small to probe some questions of interest such as whether the association of hypoventilation and sleep apnoea differed among the types. Further, our tertiary data collection may skew our sample of patients toward the more severe spectrum; how well the patients in our study represent the disease population is difficult to assess. Our analysis included PSG studies spanning 17 years during which different PSG technologies and scoring criteria were used. The changes in scoring criteria during the study period may have influenced scoring of hypopnoea events. We did not attempt to rescore all original studies using a single scoring criterion. Our analysis also did not consider medication use and other potential clinical confounders.

## CONCLUSIONS

Sleep-disordered breathing is common among the patients with muscular dystrophy. Not all types of muscular dystrophy have the same degree and characteristics of sleep-disordered breathing or the same clinical manifestations. Specific attention should be paid to each type. Patients with DM had the highest odds of sleep apnoea, significantly higher than patients with LGMD who had the lowest odds. Patients with DMD had the highest proportion with moderate to severe OSA. Patients with CMD had the highest odds of hypoventilation followed by DMD. Hypoventilation was mildly associated with sleep apnoea after adjusting for age, sex, BMI and type,

although the statistical significance of the association was borderline. Thus, $CO_2$ retention may be an independent process from upper airway obstructive breathing. Early diagnosis of muscle weakness is critical for early intervention with non-invasive ventilation and will have a positive effect on the quality of care of a patient with muscular dystrophy and, thus, life expectancy.[46]

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ONLINE DATA SUPPLEMENT

**Sleep Apnoea and Hypoventilation in Patients with Five Major Types of Muscular Dystrophy**

Leping Li, David M. Umbach, Yuanyuan Li, Pallav Hallani, Min Shi, Mihye Ahn, Deryck Yeung,

Bradley Vaugh, and Zheng Fan

**Statistical Methods**

*General Considerations*

Our data involves results of 104 PSG studies conducted on 73 different patients. In analyzing such data, application of appropriate statistical techniques is important for valid results. The differences in muscular dystrophy types that we are interested are inherently questions about patients, but some of the associations that we probe involve patent characteristics that can change from PSG study to PSG study. Consequently, repeated studies on a single patient can aid in inference about muscular dystrophy types. Results from repeated studies on a single patient are generally more similar than results from the same number of studies on different patients. This within-patient correlation means that the amount of additional information provided by including a second PSG on a patient is less than that provided by including a new patient to the data set. A statistical approach known as Generalized Estimating Equations (GEE) [2] was developed to address within-patient correlations for data structured like ours. Heuristically, this approach can be thought of as estimating the within-patient correlation and using it to appropriately weigh responses from multiple PSGs on the same patients vis-à-vis responses from single PSGs from other patients.

We used the GEE approach with an exchangeable correlation structure [2] when examining associations. For responses modeled as continuous, such as heart rate or AHI, our GEE models used a normal distribution with the identity link function. For binary responses, such as apnoea or hypoventilation, our GEE models used a binomial distribution with the logistic link function.

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Although we have a reasonably large collection of muscular dystrophy patients with PSG data,
we have more limited data on each individual muscular dystrophy type. With only 104 PSG
studies and 73 patients altogether, our data set supports only small numbers of predictors in
individual statistical models and limits statistical power. Consequently, we examined
associations between response variable and individual predictor variables including limited
adjustment for selected covariates like age, sex, and categorical BMI z-score. In general, we
report p values without accounting for multiple testing although we employ the Tukey-Kramer
procedure [3] for pairwise comparisons among types. For model fitting , we used PROC
GENMOD in SAS (version 9.4).

When fitting models to continuous outcomes with the goal of comparing muscular dystrophy
types and adjusting for covariates, we report mean values for each type or mean differences
between pairs of types as estimated by the fitted model. The estimated means are associated
with a specified set of covariate values but, under the models we used, the mean differences
are not. We chose a set that we regarded as a reference baseline: male sex, normal BMI (a
category with $-2 \leq$ BMI z-score $\leq 2$), and age 15 yrs (a convenient integer value between the
mean and median age of patients at the time of their PSG study). When fitting models to
binary outcomes, we proceeded in the same way, but the quantities estimated are odds and
odds ratios instead of means and mean differences, respectively.

*Analysis of Heart Rates*

We used the same statistical modelling approach for all three heart rate variables: initial heart
rate (before sleep onset); average heart rate during sleep; and peak heart during sleep. Using
GEE, we fit a regression modal with heart rate as the dependent variable; the model included
muscular dystrophy type and $\log_2$(age in yrs) as predictors. We use $\log_2$(age) instead of age
itself because the relationship between heart rate and $\log_2$(age) exhibited a linear, rather than
curved, relationship. We examined residual plots for deviations from model assumptions. If
we detected possible outliers with any heart rate, we conducted a sensitivity analysis by
removing those outlying data points and refitting the model on the reduced data set. In every

instance, the original analysis and the sensitivity analysis reached similar conclusions. We report the analysis based on the full data set.

*Analysis of AHI*

Using GEE, we fit a regression model with AHI as the dependent variable; the model included muscular dystrophy type, age, sex, and categorical BMI z-score (described in the main text) as predictors. Because of some evidence of skewness in residuals from this model, we conducted a sensitivity analysis by transforming AHI to the square root of AHI and refitting the model. Because we reached similar conclusions with both models, we report the analysis using AHI (without transformation) as providing estimates in customary units (events/hr).

*Separate Analyses of Sleep Apnoea and of Hypoventilation*

Because sleep apnoea and hypoventilation are each binary variables (present/absent), we fit logistic regression models with either sleep apnoea or hypoventilation as the dependent variable using GEE. The model for sleep apnoea included five-category muscular dystrophy type, age, sex, and categorical BMI z-score as predictors. The model for hypoventilation included the same covariates except the categorization of muscular dystrophy type was modified because no patients with BMD exhibited hypoventilation. Consequently, we opted to combine BMD and DMD, two types with a closely related genetic origin, into a single type so the model for hypoventilation included a four-category muscular dystrophy type.

*Joint Analysis of Hypoventilation and Sleep Apnoea*

Using GEE, we assessed the association of hypoventilation with sleep apnoea using logistic regression models with hypoventilation as the dependent variable. In the first model where the only predictor was sleep apnoea, we assessed the association without adjustment for any other factors. In the second model, in addition to sleep apnoea, we included the four-category muscular dystrophy type (BMD and DMD combined), age, sex, and categorical BMI z-score. In sensitivity analyses, we interchanged the roles of sleep apnoea and hypoventilation – making sleep apnoea the dependent variable and hypoventilation the predictor – and fitting the same

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two models. This sensitivity analysis did not modify conclusions about the association of hypoventilation and sleep apnoea, so we report results from models with hypoventilation as the dependent variable.

*Joint Analysis of Hypoventilation and AHI*

For this analysis, we used GEE and fit a logistic regression model with hypoventilation as the dependent variable. Predictors included four-category muscular dystrophy type, age, sex, categorical BMI-z-score, and AHI. In a sensitivity analysis, we replaced AHI as a predictor in the model with the square root of AHI, but conclusions were unchanged.

**Supplementary results**

*Heart rates in patients with muscular dystrophy*

Three PSG studies failed to record baseline heart rate; 31 failed to record average and peak heart rate during sleep, leaving 101 and 73 studies representing 72 and 53 patients with data on baseline and in-sleep heart rates, respectively. Correlations of baseline heart rate measurements with in-sleep average and peak heart rate measurements were both high (0.83 and 0.73, respectively, p<0.0001 for each). The correlation of average and peak heart rates during sleep was also high (0.76, p<0.0001).

We compared the mean baseline heart rate and the mean average and peak heart rates during sleep among muscular dystrophy types after regression adjustment for log-transformed age (see supplementary statistical methods). Age-adjusted mean heart rates, whether measured at baseline or during sleep, varied among types (Table S7A) with DMD patients tending to have among the highest rates and DM patients among the lowest. Patients with DMD had significantly, or nearly significantly, higher baseline heart rate and average and peak heart rates during sleep than those of patients with DM; (p=0.003, p<0.0001, and p=0.02, respectively); mean differences were approximately 10 bpm (Table S7B). Similarly, patients with CMD had significantly higher average and peak heart rates during sleep than those of DM patients again with mean differences near 10 bpm (p=0.03, p<0.0001 and p=0.0006, respectively). Differences

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in heart rate among other pairs of muscular dystrophy types were generally smaller and not

statistically significant.

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**Table S1**. Clinic characteristics of the 73 muscular dystrophy patients with 104 reports.

| Patient | DM Type | Age(yr) | Sex | Echo. | Beta blocker | ABG (PCO$_2$/bicarb) | MIP/MEP | Trach. | On Ventil. | Snore | Epwo. | Hypo. | AHI | Vital Status | Age at death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | BMD | 3.4 | M | NL LVEF | - | /19(v) | unable | - | - | - | n/d | 0 | 19.9 | alive | n/a |
| 3 | BMD | 4.1 | M | NL LVEF | - | /19(v) | unable | - | - | - | 12 | 0 | 0.6 | alive | n/a |
| 55 | BMD | 18.0 | M | 38% LVEF | + | 47/26(v) | n/d | - | - | - | 4 | 0 | 39.0 | deceased | 18 |
| 58 | BMD | 15.1 | M | NL LVEF | - | n/d | n/d | - | - | - | 21 | 0 | 2.4 | alive | n/a |
| 60 | BMD | 58.5 | M | NL LVEF | + | n/d | n/d | - | - | - | 4 | 0 | 35.5 | alive | n/a |
| 66 | BMD | 54.4 | M | n/d | - | n/d | n/d | - | - | - | 10 | 0 | 32.2 | alive | n/a |
| 66 | BMD | 57.5 | M | n/d | - | n/d | n/d | - | - | - | 9 | 0 | 17.6 | alive | n/a |
| 6 | CMD | 11.5 | M | n/d | - | n/d | n/d | - | - | - | n/d | 0 | 4.2 | alive | n/a |
| 6 | CMD | 13.4 | M | n/d | - | n/d | n/d | - | - | - | n/d | 0 | 0.3 | alive | n/a |
| 6 | CMD | 14.3 | M | NL LVEF | - | 32/25 | 22/25(23%/15%) | - | - | - | n/d | 1 | 6.7 | alive | n/a |
| 7 | CMD | 17.1 | M | NL LVEF | - | n/d | 27/45(28%/26%) | - | - | - | n/d | 1 | 9.0 | alive | n/a |
| 13 | CMD | 15.5 | M | NL LVEF | - | 45/24 | 25/15(26%/9%) | - | - | - | 2 | 0 | 0.3 | alive | n/a |
| 29 | CMD | 12.3 | M | NL LVEF | - | n/d | 85/57 | - | - | - | n/d | 1 | 10.9 | alive | n/a |
| 35 | CMD | 4.4 | M | n/d | - | 52/24 | unable | + | - | - | n/d | 0 | 1.7 | deceased | 6 |
| 43 | CMD | 14.2 | M | NL LVEF | - | 45/26 | 55/60(57%/35%) | - | - | - | n/d | 1 | 0.0 | alive | n/a |
| 69 | CMD | 19.3 | F | NL LVEF | + | 62/33 | n/d | - | - | - | n/d | 0 | 12.6 | deceased | 21 |
| 2 | DM | 69.2 | F | NL LVEF | - | /30(v) | 14/23 | - | - | - | 5 | 1 | 6.3 | alive | n/a |
| 9 | DM | 28.7 | F | n/d | - | n/d | n/d | - | - | - | 11 | 0 | 0.0 | alive | n/a |
| 12 | DM | 47.5 | M | n/d | - | n/d | n/d | - | - | - | n/d | 0 | 14.2 | n/d | n/a |
| 12 | DM | 50.9 | M | n/d | - | n/d | n/d | - | - | - | n/d | 1 | 6.6 | alive | n/a |
| 15 | DM | 13.0 | F | n/d | - | n/d | n/d | + | + | - | n/d | 0 | 0.0 | deceased | 28 |
| 16 | DM | 57.4 | M | NL LVEF | - | /29(v) | n/d | - | - | - | n/d | 1 | 15.5 | alive | n/a |
| 17 | DM | 26.8 | F | n/d | - | /27(v) | n/d | - | - | - | 9 | 0 | 0.1 | alive | n/a |
| 18 | DM | 57.5 | M | NL LVEF | - | /25(v) | n/d | - | - | - | 5 | 0 | 0.5 | alive | n/a |
| 19 | DM | 22.0 | M | n/d | - | n/d | n/d | - | - | - | n/d | 1 | 5.6 | alive | n/a |
| 19 | DM | 22.0 | M | n/d | - | n/d | n/d | - | - | - | n/d | 1 | 6.8 | alive | n/a |
| 19 | DM | 31.7 | M | NL LVEF | - | /33(v) | n/d | - | - | - | 12 | 0 | 6.5 | alive | n/a |
| 24 | DM | 12.6 | F | NL LVEF | - | 50/23 | n/d | + | - | - | 0 | 0 | 2.2 | alive | n/a |
| 24 | DM | 1.3 | F | n/d | - | n/d | n/d | + | - | - | n/d | 0 | 0.2 | alive | n/a |
| 24 | DM | 15.4 | F | NL LVEF | - | /29(v) | n/d | + | - | - | n/d | 1 | 18.2 | alive | n/a |
| 24 | DM | 2.8 | F | n/d | - | n/d | n/d | - | - | - | n/d | 1 | 3.4 | alive | n/a |
| 24 | DM | 5.3 | F | n/d | - | n/d | n/d | + | - | - | n/d | 0 | 0.7 | alive | n/a |

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| 24 | DM | 7.3 | F | n/d | - | n/d | n/d | + | - | - | 4 | 1 | 3.3 | alive | n/a |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 24 | DM | 7.7 | F | n/d | - | n/d | n/d | + | - | - | n/d | 1 | 0.8 | alive | n/a |
| 24 | DM | 8.5 | F | n/d | - | n/d | n/d | + | - | - | 4 | 0 | 3.4 | alive | n/a |
| 25 | DM | 12.3 | M | n/d | - | n/d | 12/23 | - | - | - | 0 | 0 | 7.3 | alive | n/a |
| 26 | DM | 47.3 | M | NL LVEF | - | 75/40 | unable | - | - | - | 14 | 1 | 10.4 | deceased | 51 |
| 30 | DM | 32.5 | F | NL LVEF | - | 37/26 | n/d | - | - | + | n/d | 1 | 5.6 | alive | n/a |
| 32 | DM | 12.1 | M | n/d | - | n/d | n/d | - | - | - | n/d | 0 | 0.6 | alive | n/a |
| 42 | DM | 9.2 | F | NL LVEF | - | /29(v) | n/d | - | - | - | n/d | 0 | 4.7 | alive | n/a |
| 45 | DM | 26.7 | F | n/d | - | n/d | n/d | - | - | - | 6 | 0 | 0.2 | n/d | n/a |
| 47 | DM | 0.3 | M | NL LVEF | - | n/d | n/d | - | - | - | n/d | 0 | 1.4 | alive | n/a |
| 47 | DM | 0.5 | M | n/d | - | 41/18 | n/d | - | - | - | 0 | 0 | 10.2 | alive | n/a |
| 47 | DM | 0.9 | M | n/d | - | n/d | n/d | - | - | - | 8 | 0 | 9.0 | alive | n/a |
| 52 | DM | 5.5 | M | n/d | - | /30(v) | n/d | + | - | - | n/d | 0 | 7.9 | alive | n/a |
| 52 | DM | 7.7 | M | NL LVEF | - | /34(v) | n/d | + | - | - | 11 | 1 | 9.6 | alive | n/a |
| 54 | DM | 45.3 | F | NL LVEF | - | /27(v) | n/d | - | - | - | 9 | 0 | 39.4 | alive | n/a |
| 56 | DM | 4.3 | M | NL LVEF | - | n/d | n/d | - | - | - | n/d | 0 | 9.0 | alive | n/a |
| 57 | DM | 66.1 | F | NL LVEF | + | n/d | 49/68 | - | - | - | n/d | 0 | 6.0 | alive | n/a |
| 64 | DM | 31.0 | F | n/d | - | n/d | 38/43 | - | - | - | n/d | 0 | 7.6 | alive | n/a |
| 68 | DM | 28.3 | F | n/d | - | n/d | n/d | - | - | - | n/d | 1 | 9.7 | alive | n/a |
| 70 | DM | 26.2 | F | n/d | - | 34/21 | n/d | - | - | - | n/d | 0 | 10.6 | deceased | 27 |
| 73 | DM | 33.3 | F | n/d | - | n/d | n/d | - | - | + | 15 | 1 | 10.8 | alive | n/a |
| 1 | DMD | 2.8 | M | NL LVEF | - | /26(v) | unable | + | - | - | n/d | 0 | 6.4 | alive | n/a |
| 5 | DMD | 12.2 | M | low LVEF | - | /25(v) | n/d | - | - | - | n/d | 0 | 3.5 | alive | n/a |
| 8 | DMD | 23.9 | M | NL LVEF | + | n/d | n/d | - | - | - | 0 | 0 | 14.2 | alive | n/a |
| 8 | DMD | 25.4 | M | NL LVEF | - | 44/30 | 43/28 | - | - | - | 0 | 1 | 3.8 | alive | n/a |
| 10 | DMD | 13.9 | M | low LVEF | - | n/d | n/d | - | - | - | 4 | 0 | 13.6 | deceased | 15 |
| 11 | DMD | 13.7 | M | 35-40% LVEF | - | n/d | 8/28(8%/16%) | - | - | - | 4 | 0 | 1.2 | deceased | 17 |
| 14 | DMD | 20.3 | M | NL LVEF | - | n/d | 32/33 | - | - | - | 2 | 0 | 8.0 | deceased | 26 |
| 20 | DMD | 14.3 | M | NL LVEF | - | n/d | n/d | - | - | - | n/d | 1 | 49.2 | deceased | 21 |
| 21 | DMD | 11.5 | M | 33% LVEF | - | /28(v) | n/d | - | - | - | n/d | 1 | 3.3 | deceased | 15 |
| 22 | DMD | 12.7 | M | 48% LVEF | - | /28(v) | 35/45(36%/26%) | - | - | - | 17 | 0 | 9.8 | alive | n/a |
| 23 | DMD | 16.3 | M | NL LVEF | - | 35/24 | n/d | - | - | - | n/d | 1 | 12.5 | alive | n/a |
| 27 | DMD | 12.3 | M | NL LVEF | - | 35/20 | 40/53 | - | - | - | 8 | 1 | 9.7 | alive | n/a |
| 27 | DMD | 18.7 | M | NL LVEF | - | /22(v) | 43/ | - | - | - | 7 | 0 | 24.1 | alive | n/a |
| 28 | DMD | 12.3 | M | 48% LVEF | - | n/d | unable | - | - | - | n/d | 1 | 4.0 | alive | n/a |
| 28 | DMD | 13.6 | M | 52% LVEF | - | n/d | n/d | - | - | - | 8 | 0 | 1.8 | alive | n/a |

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| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 28 | DMD | 14.5 | M | 53% LVEF | - | /27(v) | n/d | - | - | - | 0 | 0 | 6.8 | alive | n/a |
| 31 | DMD | 17.3 | M | 59% LVEF | - | /27(v) | n/d | - | - | - | 8 | 0 | 12.2 | alive | n/a |
| 36 | DMD | 6.7 | M | NL LVEF | - | /22(v) | n/d | - | - | - | n/d | 0 | 0.1 | alive | n/a |
| 37 | DMD | 11.9 | M | NL LVEF | - | n/d | n/d | - | - | - | 8 | 1 | 2.4 | alive | n/a |
| 38 | DMD | 22.7 | M | 32% LVEF | + | n/d | n/d | - | - | - | 8 | 0 | 0.2 | alive | n/a |
| 39 | DMD | 10.1 | M | n/d | - | /27(v) | n/d | - | - | - | n/d | 0 | 0.5 | alive | n/a |
| 44 | DMD | 11.7 | M | 55% LVEF | - | n/d | 55/73 | - | - | - | 0 | 0 | 11.0 | alive | n/a |
| 46 | DMD | 10.2 | M | NL LVEF | - | /30(v) | 71/35(79%/26%) | - | - | - | n/d | 1 | 1.4 | alive | n/a |
| 48 | DMD | 16.9 | M | 56% LVEF | - | n/d | 64/51(67%/30%) | - | - | - | n/d | 0 | 6.6 | alive | n/a |
| 48 | DMD | 18.5 | M | 49% LVEF | - | n/d | 61/41 | - | - | - | 1 | 0 | 0.0 | alive | n/a |
| 48 | DMD | 20.2 | M | n/d | - | /27(v) | 51/43 | - | - | - | 0 | 1 | 0.0 | alive | n/a |
| 49 | DMD | 10.4 | M | NL LVEF | - | n/d | 31/30(35%/36%) | - | - | - | 7 | 1 | 1.4 | alive | n/a |
| 50 | DMD | 10.5 | M | NL LVEF | - | n/d | n/d | - | - | + | 20 | 0 | 5.0 | alive | n/a |
| 50 | DMD | 6.6 | M | NL LVEF | - | n/d | n/d | - | - | - | n/d | 0 | 1.7 | alive | n/a |
| 50 | DMD | 9.2 | M | NL LVEF | - | n/d | n/d | - | - | - | n/d | 0 | 5.3 | alive | n/a |
| 51 | DMD | 10.9 | M | NL LVEF | - | 34/21 | n/d | - | - | - | 11 | 1 | 8.4 | alive | n/a |
| 53 | DMD | 5.1 | M | NL LVEF | - | n/d | unable | - | - | - | 12 | 0 | 0.6 | alive | n/a |
| 59 | DMD | 12.2 | M | NL LVEF | - | /25(v) | n/d | - | - | - | 7 | 0 | 3.3 | alive | n/a |
| 59 | DMD | 15.5 | M | low LVEF | - | n/d | 47/51(49%/30%) | - | - | - | n/d | 1 | 2.3 | alive | n/a |
| 59 | DMD | 18.1 | M | 41% LVEF | - | /29(v) | 45/48 | - | - | - | n/d | 1 | 9.8 | alive | n/a |
| 71 | DMD | 18.1 | M | n/d | - | 58/29 | unable | - | - | - | n/d | 1 | 22.6 | deceased | 19 |
| 72 | DMD | 13.1 | M | NL LVEF | - | 40/27(v) | 35%/26% | - | - | - | n/d | 0 | 17.2 | alive | n/a |
| 72 | DMD | 16.3 | M | n/d | - | n/d | n/d | - | - | - | 1 | 1 | 12.6 | alive | n/a |
| 4 | LGMD | 68.8 | M | NL LVEF | + | /28(v) | n/d | - | - | + | 7 | -99 | 6.0 | alive | n/a |
| 33 | LGMD | 26.7 | M | NL LVEF | + | 59/24 | n/d | - | - | - | 3 | 0 | 1.3 | alive | n/a |
| 34 | LGMD | 10.7 | F | NL LVEF | - | n/d | 71/47 | - | - | - | 10 | 0 | 3.4 | alive | n/a |
| 34 | LGMD | 13.3 | F | NL LVEF | - | n/d | 36/72 | - | - | - | 11 | 0 | 4.6 | alive | n/a |
| 34 | LGMD | 15.0 | F | NL LVEF | - | n/d | 71/62 | - | - | - | 13 | 0 | 3.3 | alive | n/a |
| 34 | LGMD | 16.0 | F | NL LVEF | - | /26(v) | n/d | - | - | - | 14 | 0 | 3.3 | alive | n/a |
| 40 | LGMD | 23.1 | M | NL LVEF | - | /27(v) | n/d | - | - | - | 7 | 0 | 9.2 | alive | n/a |
| 41 | LGMD | 12.8 | M | n/d | - | /27(v) | n/d | - | - | - | n/d | 1 | 7.6 | alive | n/a |
| 61 | LGMD | 44.7 | M | n/d | - | n/d | n/d | - | - | - | 9 | 1 | 11.1 | alive | n/a |
| 62 | LGMD | 54.4 | F | NL LVEF | - | n/d | n/d | - | - | - | 3 | 0 | 2.4 | alive | n/a |
| 63 | LGMD | 9.8 | F | NL LVEF | - | /30(v) | 42/40 | - | - | - | 2 | 0 | 1.0 | alive | n/a |
| 65 | LGMD | 34.0 | M | 50% LVEF | - | /30(v) | 43/37 | - | - | - | 11 | 0 | 2.5 | deceased | 47 |
| 67 | LGMD | 41.3 | M | NL LVEF | - | n/d | n/d | - | - | + | n/d | 0 | 22.0 | deceased | 45 |

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Only clinical reports within ± 6 months of the sleep study are included.

BMD: Becker muscular dystrophy; CMD: congenital muscular dystrophy; DM: myotonic dystrophy; DMD: Duchenne muscular dystrophy; LGMD: Limb-Girdle muscular dystrophy. +: yes; -: no; n/d: no data; n/a: not applicable; Echo: echocardiogram; NL LVEF: normal left ventricular ejection fraction; v: venous chemistry; M: male; F: female; echo: echocardiogram; ABG: arterial blood gases; $PCO_2$: partial pressure of carbon dioxide; trach.: tracheostomy; ventil.: ventilation; Epwo.: Epworth; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; AHI: apnea hypopnea index.

Echocardiogram is reported as normal (NL) LVEF or percentage of the normal value of LVEF.

ABG($PCO_2$/bicarb) is presented as either both $PCO_2$ and bicarbonate separated by '/' or bicarbonate after '/' from venous chemistry only.

MIP/MEP is presented as original values and percentages of the normal values, when available.

On ventilation refers to the time of the sleep study.

For the eight patients on beta blocker, all were on metoprolol except one patient (pID=60) who was on bisoprolol.

Vital status assessed as of January 2023.

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**Table S2.** Muscular dystrophy patients with multiple PSG studies: 73 patients and 104 total studies.

| Number of studies | Number of Patients | Percentage of Patients |
|:---:|:---:|:---:|
| 1 | 57 | 78.1 |
| 2 | 7 | 9.6 |
| 3 | 7 | 9.6 |
| 4 | 1 | 1.4 |
| 5 | 0 | 0.0 |
| 6 | 0 | 0.0 |
| 7 | 0 | 0.0 |
| 8 | 1 | 1.4 |

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**Table S3**. Summary statistics of age, BMI, and heart rate for available studies.

| Type | N | Min. | 1st Quantile | Median | Average | 3rd Quantile | Max. |
|---|---|---|---|---|---|---|---|
| | | | | Age (yrs) | | | |
| BMD | 7 | 3.4 | 3.4 | 18.0 | 30.1 | 54.4 | 58.5 |
| CMD | 9 | 4.4 | 11.5 | 14.2 | 13.6 | 14.3 | 19.3 |
| DM | 37 | 0.3 | 7.3 | 22.0 | 23.7 | 31.7 | 69.2 |
| DMD | 38 | 2.8 | 10.5 | 13.4 | 14.0 | 16.9 | 25.4 |
| LGMD | 13 | 9.8 | 12.8 | 23.1 | 28.5 | 34.0 | 68.8 |
| All Types | 104 | 0.3 | 10.5 | 14.4 | 20.3 | 25.4 | 69.2 |
| | | | | BMI ($kg/m^2$) | | | |
| BMD | 7 | 16.5 | 16.5 | 29.0 | 26.9 | 31.3 | 33.6 |
| CMD | 8 | 10.8 | 16.5 | 17.7 | 17.4 | 19.5 | 20.4 |
| DM | 37 | 13.3 | 16.1 | 19.5 | 21.7 | 24.2 | 38.4 |
| DMD | 38 | 13.8 | 16.9 | 23.6 | 24.0 | 27.3 | 45.2 |
| LGMD | 13 | 15.4 | 17.1 | 22.3 | 24.1 | 26.4 | 49.7 |
| All Types | 103 | 10.8 | 16.8 | 21.1 | 22.9 | 27.8 | 49.7 |
| | | | | Baseline Heart Rate (bpm) | | | |
| BMD | 7 | 55.0 | 55.0 | 84.0 | 79.3 | 87.0 | 110.0 |
| CMD | 7 | 78.0 | 78.0 | 96.0 | 95.6 | 96.0 | 114.0 |
| DM | 36 | 42.0 | 69.0 | 79.5 | 84.9 | 95.0 | 130.0 |
| DMD | 38 | 72.0 | 85.0 | 96.0 | 97.6 | 110.0 | 125.0 |
| LGMD | 13 | 60.0 | 66.0 | 86.0 | 83.5 | 88.0 | 114.0 |
| All Types | 101 | 42.0 | 75.0 | 89.0 | 89.9 | 100.0 | 130.0 |
| | | | | Sleep Average Heart Rate (bpm) | | | |
| BMD | 6 | 48.0 | 48.0 | 62.8 | 67.2 | 71.9 | 102.2 |
| CMD | 1 | 90.1 | 90.1 | 90.1 | 90.1 | 90.1 | 90.1 |
| DM | 22 | 50.0 | 65.3 | 76.2 | 77.2 | 81.0 | 110.0 |
| DMD | 28 | 62.0 | 86.9 | 93.9 | 93.1 | 100.0 | 117.7 |
| LGMD | 10 | 54.3 | 64.2 | 82.3 | 78.8 | 86.6 | 95.0 |
| All Types | 67 | 48.0 | 71.0 | 85.3 | 83.4 | 94.4 | 117.7 |
| | | | | Sleep Peak Heart Rate (bpm) | | | |
| BMD | 6 | 80.0 | 80.0 | 111.5 | 112.7 | 116.0 | 154.0 |
| CMD | 2 | 123.0 | 123.0 | 125.5 | 125.5 | 128.0 | 128.0 |
| DM | 22 | 79.0 | 90.0 | 111.0 | 114.7 | 128.0 | 197.0 |
| DMD | 33 | 89.0 | 120.0 | 126.0 | 125.5 | 135.0 | 140.0 |
| LGMD | 10 | 68.0 | 93.0 | 116.0 | 112.0 | 121.0 | 129.0 |
| All Types | 73 | 68.0 | 109.0 | 121.0 | 119.3 | 129.0 | 197.0 |
| | | | | Baseline $CO_2$ (mm Hg) | | | |
| BMD | 7 | 22.0 | 22.0 | 38.0 | 36.9 | 41.0 | 43.0 |
| CMD | 7 | 36.0 | 36.0 | 47.0 | 45.9 | 48.0 | 58.0 |
| DM | 34 | 27.0 | 38.0 | 40.5 | 42.1 | 46.0 | 59.0 |
| DMD | 37 | 29.0 | 36.0 | 40.0 | 39.9 | 43.0 | 52.0 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| LGMD | 12 | 34.0 | 37.0 | 40.0 | 40.2 | 41.0 | 48.0 |
| All Types | 97 | 22.0 | 37.0 | 40.0 | 40.9 | 45.0 | 59.0 |

Sleep Average $CO_2$ (mm Hg)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| BMD | 5 | 35.1 | 35.1 | 40.7 | 40.1 | 40.7 | 47.0 |
| CMD | 6 | 37.0 | 37.0 | 49.8 | 49.5 | 50.0 | 62.0 |
| DM | 4 | 38.0 | 38.0 | 40.5 | 43.6 | 41.0 | 55.4 |
| DMD | 29 | 26.4 | 41.7 | 44.0 | 44.0 | 47.6 | 55.2 |
| LGMD | 10 | 38.6 | 38.9 | 44.8 | 44.4 | 46.0 | 49.0 |
| All Types | 54 | 26.4 | 41.0 | 44.1 | 44.3 | 47.7 | 62.0 |

Sleep Peak $CO_2$ (mm Hg)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| BMD | 5 | 40.1 | 40.1 | 46.0 | 47.8 | 46.0 | 55.0 |
| CMD | 8 | 44.0 | 45.0 | 55.0 | 58.0 | 61.0 | 90.0 |
| DM | 29 | 40.0 | 48.6 | 52.0 | 53.4 | 56.0 | 77.0 |
| DMD | 38 | 35.2 | 46.0 | 50.2 | 50.2 | 54.0 | 65.0 |
| LGMD | 9 | 47.0 | 47.0 | 49.0 | 49.6 | 51.0 | 53.2 |
| All Types | 89 | 35.2 | 47.0 | 51.0 | 51.7 | 54.9 | 90.0 |

AHI (events/hr)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| BMD | 7 | 0.60 | 0.60 | 19.90 | 21.03 | 32.20 | 39.00 |
| CMD | 9 | 0.00 | 0.30 | 4.20 | 5.08 | 6.70 | 12.60 |
| DM | 37 | 0.00 | 0.80 | 6.30 | 6.87 | 9.00 | 39.40 |
| DMD | 38 | 0.00 | 1.40 | 5.15 | 7.80 | 9.80 | 49.20 |
| LGMD | 13 | 1.00 | 2.40 | 3.40 | 5.98 | 6.00 | 22.00 |
| All Types | 104 | 0.00 | 1.70 | 5.80 | 7.90 | 10.20 | 49.20 |

**Table S4**. Odds of sleep apnoea among muscular dystrophy types estimated by fitting logistic regression models adjusted for age, sex, and category of BMI z-score using GEE. (**A**) Adjusted odds of sleep apnoea by muscular dystrophy type for a male patient aged 15 years with BMI z-score between -2 and 2; and (**B**) Pairwise adjusted odds ratios (ORs) comparing risk of sleep apnoea between muscular dystrophy types.  This analysis used 103 PSG studies and 73 patients (one subject with only one PSG was missing).

| **A.** Estimated adjusted odds of sleep apnoea prevalence by muscular dystrophy type for a male patient aged 15 years with BMI z-score between -2 and 2. [a] | | |
|---|---|---|
| Type | Estimated Odds | 95% Confidence Limits |
| BMD | 0.68 | 0.17 | 2.69 |
| CMD | 0.76 | 0.21 | 2.67 |
| DM | 1.68 | 0.77 | 3.85 |
| DMD | 0.91 | 0.38 | 2.21 |
| LGMD | 0.33 | 0.11 | 0.98 |

[a] We chose 15 years as an integer-valued age between the mean and median of the entire sample.  Though estimated odds of sleep apnoea would differ at other ages and for females or patients having extreme BMI z-scores, the regression model used implies that odds ratios between muscular dystrophy types adjusted to this

| B.  Pairwise adjusted odds ratios (ORs) comparing prevalence of sleep apnoea between muscular dystrophy types. | | | | |
|---|---|---|---|---|
| Contrast | OR | Simultaneous 95% Confidence Limits[a] | | p value[a] |
| BMD - CMD | 0.89 | 0.11 | 7.24 | 1.00 |
| BMD - DM | 0.40 | 0.05 | 3.31 | 0.76 |
| BMD - DMD | 0.74 | 0.12 | 4.66 | 0.99 |
| BMD - LGMD | 2.07 | 0.25 | 16.98 | 0.88 |
| CMD - DM | 0.45 | 0.07 | 2.97 | 0.78 |
| CMD - DMD | 0.83 | 0.15 | 4.67 | 1.00 |
| CMD - LGMD | 2.32 | 0.33 | 16.37 | 0.77 |
| DM - DMD | 1.84 | 0.33 | 10.35 | 0.87 |
| DM - LGMD | 5.15 | 1.47 | 18.03 | 0.003 |
| DMD - LGMD | 2.80 | 0.45 | 17.57 | 0.54 |

particular set of covariate values match corresponding odds ratios estimated at other sets of values.

[a] The p values and confidence limits were adjusted via the Kramer-Tukey method to control the error rate simultaneously for all ten pairwise comparisons at $\alpha = 0.05$.

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**Table S5**. AHI means and mean differences among muscular dystrophy types estimated by fitting regression models adjusted for age, sex, and category of BMI z-score using GEE. (**A**) Adjusted mean AHI by muscular dystrophy type for a male patient aged 15 years with BMI z-score between -2 and 2; and (**B**) Pairwise adjusted mean difference comparing risk of sleep apnoea between muscular dystrophy types. This analysis used 103 PSG studies and 72 patients (one subject with only one PSG was missing BMI).

| **A.** Estimated mean AHI (events/hr) by muscular dystrophy type for a male patient aged 15 years with BMI z-score between -2 and 2. [a] | | |
|---|---|---|
| Type | Estimated mean | 95% Confidence Limits |
| BMD | 17.8 | 8.7 | 27.0 |
| CMD | 5.6 | 0.9 | 10.4 |
| DM | 5.8 | 2.2 | 9.3 |
| DMD | 7.5 | 3.7 | 11.2 |
| LGMD | 4.2 | 1.0 | 7.3 |

[a] We chose 15 years as an integer-valued age between the mean and median of the entire sample. Though estimated mean AHI would differ at other ages and for females or patients having extreme BMI z-scores, the regression model used implies that mean differences between muscular dystrophy types adjusted to this particular set of covariate values match corresponding mean differences estimated at other sets of values.

| B. Pairwise adjusted mean difference in AHI (events/hr) between muscular dystrophy types. | | | | | | |
|---|---|---|---|---|---|---|
| Contrast | Estimated Mean Difference | Standard Error | z value | p value[a] | Simultaneous 95% Confidence Limits[a] | |
| BMD - CMD | 12.2 | 5.1850 | 2.36 | 0.13 | 26.36 | -1.93 |
| BMD - DM | 12.1 | 4.8200 | 2.50 | 0.09 | 25.21 | -1.08 |
| BMD - DMD | 10.4 | 5.0484 | 2.05 | 0.24 | 24.13 | -3.41 |
| BMD - LGMD | 13.6 | 4.7873 | 2.85 | 0.04 | 26.71 | 0.59 |
| CMD - DM | -0.1 | 1.9761 | -0.07 | 1.00 | -5.54 | 5.24 |
| CMD - DMD | -1. 9 | 2.3880 | -0.78 | 0.94 | -8.37 | 4.66 |
| CMD - LGMD | 1.4 | 2.4528 | 0.59 | 0.98 | -5.26 | 8.13 |
| DM - DMD | -1.7 | 2.1171 | -0.81 | 0.93 | -7.48 | 4.07 |
| DM - LGMD | 1.6 | 1.7363 | 0.91 | 0.89 | -3.15 | 6.32 |
| DMD - LGMD | 3.3 | 2.4360 | 1.35 | 0.66 | -3.35 | 9.94 |

[a] The p values and confidence limits were adjusted via the Kramer-Tukey method to control the error rate simultaneously for all ten pairwise comparisons at $\alpha = 0.05$.

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**Table S6**. Odds of hypoventilation among muscular dystrophy types estimated by fitting logistic regression models adjusted for age, sex, and category of BMI z-score using GEE. (**A**) Adjusted odds of hypoventilation by muscular dystrophy type for a male patient aged 15 years with BMI z-score between -2 and 2; and (**B**) Pairwise adjusted odds ratios (ORs) comparing risk of hypoventilation between muscular dystrophy types.  Because no BMD subjects exhibited hypoventilation, we combined types BMD and DMD, which each carry mutations in the same gene, into a single combined type "B_DMD" for this analysis.  This analysis used 102 PSG studies and 71 patients (one subject missing BMI had only one PSG; another subject missing hypoventilation status also had only one PSG).

| **A.** Estimated adjusted odds of hypoventilation prevalence by muscular dystrophy type for a male patient aged 15 years with BMI z-score between -2 and 2. [a] | | | |
|---|---|---|---|
| Type | Estimated Odds | 95% Confidence Limits | |
| B_DMD | 0.40 | 0.14 | 1.12 |
| CMD | 0.83 | 0.22 | 3.23 |
| DM | 0.69 | 0.28 | 1.72 |
| LGMD | 0.13 | 0.02 | 0.91 |

[a] We chose 15 years as an integer-valued age between the mean and median of the entire sample.  Though estimated odds of hypoventilation would differ at other ages and for females or patients having extreme BMI z-scores, the regression model used implies that odds ratios between muscular dystrophy types adjusted to this particular set of covariate values match corresponding odds ratios estimated at other sets of values.

| B.  Pairwise adjusted odds ratios (ORs) comparing prevalence of hypoventilation  between muscular dystrophy types. | | | | |
|---|---|---|---|---|
| Contrast | OR | Simultaneous 95% Confidence Limits[a] | | p value[a] |
| B_DMD - CMD | 0.48 | 0.09 | 2.68 | 0.69 |
| B_DMD - DM | 0.58 | 0.12 | 2.80 | 0.81 |
| B_DMD - LGMD | 3.06 | 0.18 | 50.76 | 0.74 |
| CMD - DM | 1.20 | 0.18 | 7.97 | 0.99 |
| CMD - LGMD | 6.40 | 0.34 | 119.76 | 0.36 |
| DM - LGMD | 5.31 | 0.53 | 53.76 | 0.25 |

[a] The p values and confidence limits were adjusted via the Kramer-Tukey method to control the error rate simultaneously for all six pairwise comparisons at $\alpha$ = 0.05.

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**Table S7**. Age-adjusted heart rate estimated by GEE for each type of muscular dystrophy. (**A**) Adjusted mean heart rate (bpm) at age 15 years with 95% confidence limits; and (**B**) Pairwise differences in adjusted mean heart rate between muscular dystrophy types.

**A**.   Estimated mean heart rate (bpm) at age 15 years[a]

| Type | Mean | 95% Confidence Limits | |
|---|---|---|---|
| Baseline heart rate (101 studies, 72 patients) | | | |
| BMD | 83.1 | 65.0 | 101.3 |
| CMD | 93.0 | 87.8 | 98.3 |
| DM | 82.8 | 78.5 | 87.1 |
| DMD | 95.3 | 90.2 | 100.4 |
| LGMD | 87.6 | 82.4 | 92.7 |
| In-sleep average heart rate (73 studies, 53 patients) | | | |
| BMD | 69.7 | 48.5 | 90.9 |
| CMD | 89.0 | 88.0 | 90.1 |
| DM | 75.9 | 72.3 | 79.4 |
| DMD | 91.4 | 87.1 | 95.7 |
| LGMD | 81.3 | 75.4 | 87.2 |
| In-sleep peak heart rate (73 studies, 53 patients) | | | |
| BMD | 114.4 | 94.6 | 134.1 |
| CMD | 123.9 | 123.4 | 124.3 |
| DM | 112.4 | 106.9 | 117.9 |
| DMD | 122.6 | 119.0 | 126.3 |
| LGMD | 120.1 | 114.1 | 126.1 |

[a] We chose 15 years as an integer-valued age between the mean and median of the entire sample. Though estimates at other ages would differ since heart rate tended to decrease with increasing age, differences between types are the same at all ages under the regression model used for estimation.

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**Table S7 continued**

| **B.** Pairwise differences in adjusted mean heart rate between types | | | | | | |
|---|---|---|---|---|---|---|
| Contrast | Estimated Mean Difference | Standard Error | z value | p value[a] | Simultaneous 95% Confidence Limits[a] | |
| Baseline heart rate | | | | | | |
| BMD - CMD | -9.94 | 9.7906 | -1.01 | 0.85 | -36.64 | 16.77 |
| BMD - DM | 0.28 | 9.3756 | 0.03 | 1.00 | -25.29 | 25.86 |
| BMD - DMD | -12.18 | 9.7509 | -1.25 | 0.72 | -38.78 | 14.42 |
| BMD - LGMD | -4.47 | 9.2128 | -0.48 | 0.99 | -29.60 | 20.67 |
| CMD - DM | 10.22 | 3.5241 | 2.90 | 0.03 | 0.60 | 19.83 |
| CMD - DMD | -2.24 | 3.6990 | -0.61 | 0.97 | -12.33 | 7.85 |
| CMD - LGMD | 5.47 | 3.8826 | 1.41 | 0.62 | -5.12 | 16.06 |
| DM - DMD | -12.46 | 3.4611 | -3.60 | 0.003 | -21.90 | -3.02 |
| DM - LGMD | -4.75 | 3.2909 | -1.44 | 0.60 | -13.72 | 4.23 |
| DMD - LGMD | 7.71 | 3.8261 | 2.02 | 0.26 | -2.72 | 18.15 |
| In-sleep average heart rate | | | | | | |
| BMD - CMD | -19.36 | 10.8988 | -1.78 | 0.39 | -49.09 | 10.37 |
| BMD - DM | -6.17 | 10.9500 | -0.56 | 0.98 | -36.04 | 23.70 |
| BMD - DMD | -21.71 | 11.1750 | -1.94 | 0.30 | -52.19 | 8.77 |
| BMD - LGMD | -11.60 | 10.7134 | -1.08 | 0.82 | -40.82 | 17.62 |
| CMD - DM | 13.19 | 1.8518 | 7.12 | <0.0001 | 8.13 | 18.24 |
| CMD - DMD | -2.35 | 2.2402 | -1.05 | 0.83 | -8.46 | 3.76 |
| CMD - LGMD | 7.76 | 3.0920 | 2.51 | 0.09 | -0.68 | 16.19 |
| DM - DMD | -15.54 | 2.8120 | -5.53 | <0.0001 | -23.21 | -7.87 |
| DM - LGMD | -5.43 | 3.6049 | -1.51 | 0.56 | -15.26 | 4.41 |
| DMD - LGMD | 10.11 | 3.8492 | 2.63 | 0.07 | -0.39 | 20.61 |
| In-sleep peak heart rate | | | | | | |
| BMD - CMD | -9.48 | 10.1502 | -0.93 | 0.88 | -37.16 | 18.21 |
| BMD - DM | 1.97 | 10.4681 | 0.19 | 1.00 | -26.59 | 30.52 |
| BMD - DMD | -8.26 | 10.3622 | -0.80 | 0.93 | -36.53 | 20.01 |
| BMD - LGMD | -5.72 | 10.2058 | -0.56 | 0.98 | -33.56 | 22.11 |
| CMD - DM | 11.44 | 2.8482 | 4.02 | 0.0006 | 3.67 | 19.21 |
| CMD - DMD | 1.21 | 1.8377 | 0.66 | 0.96 | -3.80 | 6.23 |
| CMD - LGMD | 3.75 | 3.1176 | 1.20 | 0.75 | -4.75 | 12.26 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| DM - DMD | -10.23 | 3.4160 | -2.99 | 0.02 | -19.55 | -0.91 |
| DM - LGMD | -7.69 | 4.0058 | -1.92 | 0.31 | -18.62 | 3.24 |
| DMD - LGMD | 2.54 | 3.6505 | 0.69 | 0.96 | -7.42 | 12.49 |

[a] The p values and confidence limits were adjusted via the Kramer-Tukey method to control the error rate simultaneously for all ten pairwise comparisons for a given response at $\alpha = 0.05$.

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