

# Life Expectancy in Duchenne Muscular Dystrophy

## Reproduced Individual Patient Data Meta-analysis

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## Abstract

### Background and Objectives

Duchenne muscular dystrophy (DMD) is a rare progressive disease that is often diagnosed in early childhood and leads to considerably reduced life expectancy; because of its rarity, research literature and patient numbers are limited. To fully characterize the natural history, it is crucial to obtain appropriate estimates of the life expectancy and mortality rates of patients with DMD.

### Methods

A systematic review of the published literature on mortality in DMD up to July 2020 was undertaken, specifically focusing on publications in which Kaplan-Meier (KM) survival curves with age as a timescale were presented. These were digitized, and individual patient data (IPD) were reconstructed. The pooled IPD were analyzed with the KM estimator and parametric survival analysis models. Estimates were also stratified by birth cohort.

### Results

Of 1,177 articles identified, 14 publications met the inclusion criteria and provided data on 2,283 patients, of whom 1,049 had died. Median life expectancy was 22.0 years (95% confidence interval [CI] 21.2, 22.4). Analyses stratified by 3 time periods in which patients were born showed markedly increased life expectancy in more recent patient populations; patients born after 1990 have a median life expectancy of 28.1 years (95% CI 25.1, 30.3).

### Discussion

This article presents a full overview of mortality across the lifetime of a patient with DMD and highlights recent improvements in survival. In the absence of large-scale prospective cohort studies or trials reporting mortality data for patients with DMD, extraction of IPD from the literature provides a viable alternative to estimating life expectancy for this patient population.

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## Glossary

CI = confidence interval; DMD = Duchenne muscular dystrophy; IPD = individual patient data; JBI = Joanna Briggs Institute; KM = Kaplan-Meier.

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Duchenne muscular dystrophy (DMD) is an X-linked, muscle degeneration disease affecting males nearly exclusively. It is a rare disease with a global prevalence of 1 in 3,500 to 5,000 male births.<sup>1</sup> Although corticosteroids are the mainstay treatment, there is currently no cure. To be reimbursed by health agencies, companies that develop new treatments need to show cost-effectiveness, which requires accurate modeling of the natural history of the disease, including mortality.

DMD mortality has been published in isolation across different countries, sources, and time periods, typically representing the experience of a single practice or selective population. Previous estimates of life expectancy have been reported in the literature as 25 years,<sup>2,3</sup> while in more recent years, this has increased to 31.7 (95% confidence interval [CI] 27.4, 36.0).<sup>4</sup> Many studies report trends of increasing life expectancy with time.<sup>1,5-7</sup>

A systematic review was recently conducted and obtained a single estimate of life expectancy of 29.9 years (95% CI 26.5, 30.8) in ventilated patients with DMD.<sup>8</sup> While the review provides an excellent summary of the published literature, survival across the whole disease pathway, rather than just the median, is needed to appropriately characterize a natural history model.

This article therefore aims to extend beyond these single summary estimates of life expectancy and provide comprehensive survival probabilities/mortality rates at different ages. This was achieved by performing a systematic review of the published literature on DMD life expectancy, reconstructing individual patient data (IPD) and calculating pooled estimates. These can be used in future natural history or economic modeling of DMD.

## Methods

### Systematic Review

A systematic review was performed on PubMed on July 31, 2020, and publications on DMD mortality before this date were identified. The following search terms were used: (1) Duchenne muscular dystrophy or DMD; (2) survival or mortality or death or life expectancy; and (3) 1 and 2.

The citations of a subset of the results, which represented systematic reviews and meta-analyses, were also reviewed for inclusion. The additional search terms included for this review were (4) systematic review or meta-analysis and (5) 3 and 4.

Searches 3 and 5 were used to conduct the review. There were no exclusions based on region, language, or time. Only full texts that were freely available to the Universities of Leicester and

Sheffield were included in the review. The publications were required to report at least 1 Kaplan-Meier (KM) curve for survival in patients with DMD, which was generally confirmed by articles reporting genetic diagnosis. The KM curve had to be calculated as all-cause survival, with age as a timescale. Last, the reported KM curve had to be able to be digitized, requiring the number of patients at risk to be reported and the curve to be of suitable digital quality. When KM curves were stratified by a covariate, the number of patients in each stratum had to be reported because these curves must be digitized separately.

The review was restricted to all-cause mortality to ensure that the outcome was comparable across studies, and it was assumed that most deaths in these patients would be related to DMD. Age was chosen as the timescale because this provided clinically meaningful survival estimates and, for example, did not require knowledge of age at diagnosis.

If multiple KM curves were presented in a single article relating to the same DMD population, all were digitized for comparison, and a joint decision was made by the authors as to which data to include in the analysis, prioritizing curves including the highest number of patients and curves of higher digital quality.

The review was carried out according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for conducting a systematic review.<sup>9</sup> Two authors conducted the review separately and discussed any discrepancies. The quality of the articles included was assessed with the Joanna Briggs Institute (JBI) Critical Appraisal tool for case series because the population consists exclusively of patients with DMD<sup>10</sup>; if studies were assessed by the tool as being at risk of bias, the methods were repeated with these studies excluded as a sensitivity analysis.

### IPD Extraction

The KM curves for each strata were digitized with Web-PlotDigitizer.<sup>11</sup> The IPD were reconstructed using the approach of Guyot et al,<sup>12</sup> which was developed and implemented with the `ipdfc` command<sup>13</sup> in Stata. Many studies reported KM curves split by levels of a discrete covariate. In these instances, each curve was digitized separately and the data from the curves were pooled. Digitization of curves was also conducted by 2 authors, with summary statistics (medians or earlier quantiles if not reached and survival probabilities) and reproduced graphs being compared to the original study graph to ensure a suitable degree of accuracy. If the digitized number of patients or deaths was greater or less than the original number by 10% for both authors, the study was deemed insufficiently digitized and excluded from analysis.

## Pooled Data Analysis

Two approaches to the data analysis were adopted: a non-parametric overview of DMD mortality and a parametric calculation of mortality rates. The data were analyzed first as a combined cohort and second by stratifying the pooled IPD into 3 cohorts based on the period of birth for each study: before 1970, 1970 to 1990, and after 1990. If period of birth for each group of patients was not explicitly reported, then it was approximated as the average age at recruitment subtracted from the midpoint of the period of recruitment. The birth cohorts were defined to evenly split patients and to investigate trends in life expectancy over time. The most recent birth cohort is likely to contain only steroid-using patients because steroid use has been the mainstay of treatment since the 1990s. The cohort analysis is also likely to represent a comparison of ventilated and nonventilated patients because ventilation was introduced in many clinical settings only in the 1990s.<sup>8</sup>

A nonparametric KM curve was used to summarize the survival estimates of the pooled sources. Median survival was compared in the pooled dataset and across birth cohorts.

A parametric survival model with a piecewise-constant hazard function was estimated with cut points first every 5 years and then every year from age 0 to the maximum observed death. This covered follow-up from possible diagnosis at birth to a time horizon of the oldest observed death in the dataset. This model assumes that the rate of death of patients is the same for all ages within a time period while allowing rates of death to differ across time periods. Because the rate of death in young patients is likely to be very different from the rate of death in older patients, this model choice is preferred to, for example, an exponential model that assumes the same rate of death across all ages. Rates for patients >40 years of age were grouped and averaged because patient numbers were small after this time. A normally distributed frailty term for study was incorporated into the model on the log-hazard scale to account for potential between-study variability.<sup>14</sup> The frailty term allows the precise estimates of mortality within each study to differ by introducing unobserved variation between studies. It is included because the studies cover a range of global populations with follow-up over different calendar periods. The choice of parametric model enables smoother results with interval-specific mortality, which are directly applicable to health economic analysis. Proportional hazards were assumed in secondary analysis between birth cohorts; the assumption was assessed with log-log plots of survival in each cohort against log time. Stata 16 was used for statistical analysis.

## Data Availability

The data used in this review are reconstructed IPD and thus do not directly correspond to real patients. The full reconstructed dataset is available on request.

## Standard Protocol Approvals, Registrations, and Patient Consents

No protocol or ethics approval was required for this work because the data are already anonymized and in the public domain.

## Results

### Systematic Review

The flowchart of the systematic review is shown in Figure 1. Of 1,177 results from the initial search described in Systematic Review in Methods, 21 articles contained at least 1 appropriate KM curve. Two were excluded for not being able to be digitized. Two more were excluded for a potential overlap of patients; in both instances, a larger study was conducted by the same authors in the same location that was eligible for inclusion, so the smaller study was excluded. Thus, 17 articles remained eligible for digitization. After the supplementary review of references in systematic reviews of DMD mortality, a further article was identified as appropriate for inclusion from the Landfeldt et al.<sup>8</sup> review. This brought the final total number of articles to 18.

Eighteen articles were eligible for digitizing,<sup>1-7,15-25</sup> contributing 3,131 total patients and 1,250 total deaths. Table 1 contains the key details of these articles. The studies were performed worldwide, including Europe, the United States, Chile, and Japan, and covered a range of birth, clinic admittance, and death cohorts, with the earliest being born in 1954 and the latest in the late 2000s. Table 2 details how studies were assigned to each birth cohort.

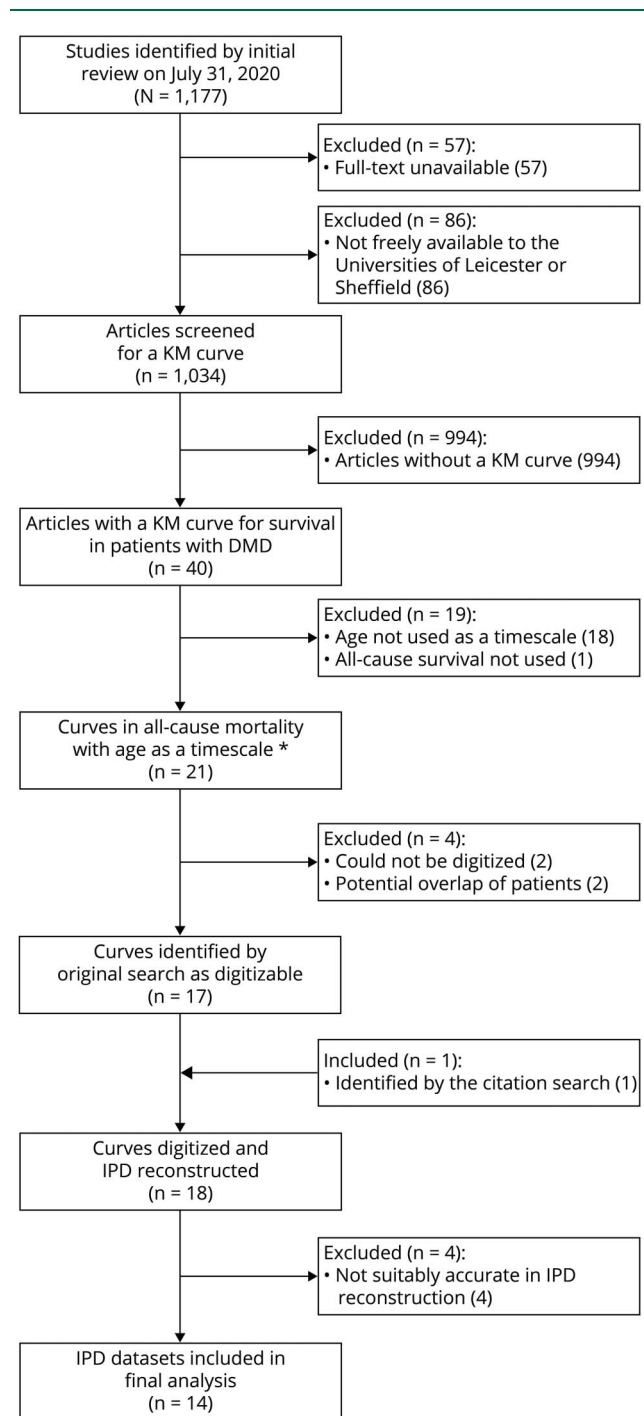
The results of the JBI tool are displayed in Table 3. Overall, articles were of fairly high quality; the most common issue was with exclusion criteria (criteria C5). Two articles performed slightly more poorly than the rest, 1 due to poor reporting of methods of diagnosis and analysis<sup>19</sup> and the other to the article being an editorial and providing insufficient detail.<sup>25</sup>

### IPD Extraction

Of the KM curves from the 18 articles, 4 were not adequately reproduced by either of the 2 authors.<sup>2,6,15,20</sup> The reason was that the number of deaths in each level of the curve was not reported, so the algorithm was much less accurate in data reconstruction. These studies were excluded from the analysis. In addition, 1 article contained only information on the number of deaths for some of the covariate levels<sup>17</sup>; IPD from these curves were included, but not from the other curves in this articles because deaths were again overestimated by both authors.

The digitized data from the remaining 14 studies yielded 2,283 patients and 1,050 deaths (compared to 1,049 in the original; 1 article produced 1 more digitized death than was reported<sup>16</sup>). The digitized data gave KM curves broadly very similar to those presented in the publications. The algorithm

**Figure 1** Flow of Identified DMD Mortality Articles on PubMed



DMD = Duchenne muscular dystrophy; IPD = individual patient data; KM = Kaplan-Meier. \*The KM curve in 1 article did not use age as a timescale, but the age of patients could be calculated.

is least accurate when reproducing ages at death at the end of follow-up, so KM curve replication was poorest in the tails of some studies.<sup>1,5,22</sup> In these studies, a small percentage of deaths were observed at late follow-up. Median survival was also compared between original and reproduced curves and was consistently reproduced and is presented in Table 4.

## Pooled Data Analysis

The total follow-up time was 40,274 patient-years with a maximum age of 44.4 years. Median survival age, calculated with the KM estimator, was 22.0 years (95% CI 21.2, 22.4). Survival probabilities at 10, 20, 30, and 40 years were 99.8% (95% CI 99.4%, 99.9%), 59.5% (95% CI 56.9%, 61.9%), 26.1% (95% CI 23.5%, 28.8%), and 13.3% (95% CI 9.8%, 17.3%), respectively. Figure 2A illustrates the survival probabilities from the digitized data. The at-risk table shows the number of patients at risk at the beginning of the interval, and the number in parentheses is the number of deaths that occurred within the interval.

Secondary analysis suggested an improvement in life expectancy over time. The median survival age from the pre-1970 birth cohort was 18.3 years (95% CI 18.0, 18.9) compared to 24.0 years in the 1970 to 1990 birth cohort (95% CI 22.8, 25.0) and 28.1 years in the post-1990 birth cohort (95% CI 25.1, 30.3). Survival split by birth cohort is presented in Figure 2B. Log-log plots of survival in each cohort were approximately parallel, indicating that proportional hazards was an appropriate assumption.

The 5-year mortality rates per 1,000 person-years with CIs from the piecewise exponential model are given in Table 5, adjusted for between-study variability by including a shared frailty term. Mortality is averaged over patients >40 years of age because data are sparse.

Mortality is very low in patients with DMD between 0 and 10 years of age and increases with age. In the combined analysis, it was estimated that for every 1,000 patients 20 to 25 years of age, 86 would die each year, increasing to 336 each year for those >40 years of age. Uncertainty increases as patients age; more patients die or are censored, so there are fewer patients from which to estimate mortality rates. Mortality rates were much higher in the birth cohort from before 1970 compared to the later cohorts; 265 of every 1,000 patients with DMD 25 to 30 years of age who were born before 1970 died every year compared to just 27.6 a year for every 1,000 born after 1990.

As a sensitivity analysis, the studies that performed more poorly in the JBI tool<sup>19,25</sup> were removed, and the non-parametric analysis was rerun. This yielded an overall median survival of 21.4 years (95% CI 20.8, 22.2) and median survival estimates of 18.1 years (95% CI 17.8, 18.7), 22.9 years (95% CI 22.0, 24.0), and 28.1 years (95% CI 25.1, 30.3) for patients born before 1970, between 1970 and 1990, and after 1990, respectively. These estimates are very similar to the original analysis.

## Discussion

Our work has provided a set of accessible age-specific all-cause mortality rates that can be incorporated into the natural history modeling of DMD. This is particularly important for



**Table 1** Description of the 18 Studies Eligible for Digitization

Authors	Year	Region	Time period	No. Deaths, n	Covariate(s)	Birth cohort
Wittlieb-Weber et al. <sup>15,a</sup>	2020	US and Canada	Admitted 2005–2015	407 27	None	After 1990
San Martin et al. <sup>1</sup>	2018	Santiago, Chile	Admitted 1993–2013	462 166	None; admittance period; socioeconomic status	After 1990
Wang et al. <sup>4</sup>	2018	Greater Cleveland, OH	Visited clinic 2003–2015	57 27	Genetic mutation	After 1990
van den Bergen et al. <sup>5</sup>	2014	Netherlands	Born 1961–2006	629 139	Birth cohort	Before 1970, After 1990
Kieny et al. <sup>6,a</sup>	2012	Nantes, France	Visited clinic 1981–2011	119 55	Ventilation; birth cohort	Before 1970, 1970–1990
Rall and Grimm <sup>16</sup>	2012	Wuerzburg, Germany	Born 1970–1980	66 45	Ventilation	1970–1990
Matsumura et al. <sup>17,b</sup>	2011	Osaka, Japan	Visited clinic 1977–2010	286 177	Period/ventilation	Before 1970, 1970–1990, after 1990
Fraser et al. <sup>18</sup>	2011	Leeds, UK	Visited clinic 1987–2010	192 93	None	1970–1990
Bach and Martinez <sup>19</sup>	2011	New Jersey	Visited clinic 2002–2011	101 45	None	1970–1990
Gordon et al. <sup>20,a</sup>	2011	Nova Scotia, Canada	Visited clinic 1977–2006	44 13	Bisphosphonate use	Before 1970, 1970–1990
Ishikawa et al. <sup>7</sup>	2010	Yakumo, Japan	Visited clinic 1964–2010	187 113	Period/ventilation	Before 1970, 1970–1990, after 1990
Kohler et al. <sup>21</sup>	2009	Zurich, Switzerland	Enrolled 1999–2006	43 3	None	1970–1990
Mochizuki et al. <sup>2,*</sup>	2008	Hasuda, Japan	Admitted 1995–2007	74 11	Mental difficulty	1970–1990
Eagle et al. <sup>3</sup>	2002	Newcastle, UK	Visited clinic 1967–2002	183 168	Period/ventilation	Before 1970, 1970–1990
Gomez-Merino et al. <sup>22</sup>	2002	New Jersey	Visited clinic 1983–2002	91 34	Protocol access	1970–1990
Phillips et al. <sup>23</sup>	2001	Liverpool, UK	Visited clinic 1986–1999	58 37	None	1970–1990
Boland et al. <sup>24</sup>	1996	Minnesota	Born 1953–1983	33 17	None	Before 1970
Yasuma et al. <sup>25</sup>	1996	Suzuka, Japan	Visited clinic 1980–1995	99 80	Ventilation	Before 1970, 1970–1990

<sup>a</sup> Study was entirely excluded from final analysis for insufficiently accurate individual patient data.

<sup>b</sup> Study was partly excluded from final analysis for insufficiently accurate individual patient data.

economic decision modeling evaluating future health technologies/treatments not just in DMD but also as a framework for other rare diseases.<sup>26</sup> Natural history models rely on reliable estimates of mortality throughout the disease pathway, and while the analysis is not without limitation, the only previous meta-analytic work of this nature provides a median estimate of survival,<sup>8</sup> which, while useful, is not sufficiently granular for natural history modeling.

Early mortality is negligible both in the overall dataset and in each birth cohort. Median survival in the overall dataset was 22.0 years (95% CI 21.2, 22.4), but survival rates have

increased over time, with a median survival of 28.1 years (95% CI 25.1, 30.3) in patients born after 1990. These results are consistent with other recent work.<sup>8</sup> Moreover, these estimates may slightly underestimate median survival in more recently diagnosed patients because some of the articles that were excluded from the final analysis at the data reconstruction phase had KM curves of patients who either had not reached median survival by 30 years of age<sup>15</sup> or had median estimates >30 years of age.<sup>6,17</sup>

Our work is comparable to the Landfeldt et al.<sup>8</sup> review. The search terms were almost identical, and all articles included in

**Table 2** Assignment of KM Curves to Birth Cohorts

Study	Year	Covariate	Birth period	Recruitment period	Recruitment age, y	Birth cohort
Wittlieb-Weber et al. <sup>15,a</sup>	2020	—	Not reported	2005–2015	Mean 10.2	After 1990
San Martin et al. <sup>1</sup>	2018	—	Not reported	1993–2013	Mean 6.1	After 1990
Wang et al. <sup>4</sup>	2018	Pooled	Not reported	2003–2015	Mean 18.1	Before 1990
van den Bergen et al. <sup>5</sup>	2014	Birth 1	1961–1974			Before 1970
		Birth 2	1980–2006			Before 1990
Kieny et al. <sup>6 a</sup>	2012	Birth 1	1955–1970			Before 1970
		Birth 2	1970–1994			1970–1990
Rall et al. <sup>16</sup>	2012	Pooled	1970–1980			1970–1990
Matsumura et al. <sup>17</sup>	2011	No vent 1	Not reported	1977–1984	Not reported	Before 1970
		No vent 2	Not reported	1984–2010	Not reported	1970–1990
		Vent 1 <sup>a</sup>	Not reported	1984–1993	Not reported	1970–1990
		Vent 2 <sup>a</sup>	Not reported	1994–2003	Not reported	1970–1990
		Vent 3 <sup>a</sup>	Not reported	2004–2010	Not reported	Post 1990
Fraser et al. <sup>18</sup>	2011	—	Not reported	1987–2010	Mean 11.8	1970–1990
Bach and Martinez et al. <sup>19</sup>	2011	—	Not reported	2002–2011	Not reported	1970–1990
Gordon et al. <sup>20,a</sup>	2011	No bisphos	Not reported	1977–1997	Not reported	1970–1990
		Bisphos	Not reported	1997–2007	Median 12	After 1990
Ishikawa et al. <sup>7</sup>	2010	NIV	Not reported	1991–2010	Not reported	After 1990
		Tracheotomy	Not reported	1984–1991	Not reported	970–1990
		No vent 1	Not reported	1991–2010	Not reported	1970–1990
		No vent 2	Not reported	1984–1991	Not reported	Before 1970
		No vent 3	Not reported	1964–1984	Not reported	Before 1970
Kohler et al. <sup>21</sup>	2009	—	Not reported	1999–2006	Mean 15.3	1970–1990
Mochizuki et al. <sup>2,a</sup>	2008	Pooled	Not reported	1995–2007	Not reported	1970–1990
Eagle et al. <sup>3</sup>	2002	Ventilation	Not reported	1990–2002	Not reported	1970–1990
		No vent 1	Not reported	1990–2002	Not reported	1970–1990
		No vent 2	Not reported	1980–1989	Not reported	Before 1970
		No vent 3	Not reported	1970–1979	Not reported	Before 1970
		No vent 4	Not reported	1960–1969	Not reported	Before 1970
Gomez-Merino and Bach <sup>22</sup>	2002	Pooled	Not reported	1983–2002	Not reported	1970–1990
Phillips et al. <sup>23</sup>	2001	—	Not reported	1986–1999	Mean 12	1970–1990
Boland et al. <sup>24</sup>	1996	—	1954–1982			Before 1970
Yasuma et al. <sup>25</sup>	1996	No vent	Not reported	1980–1987	Not reported	Before 1970
		CR vent	Not reported	1987–1991	Not reported	Before 1970
		NIPPV	Not reported	1992–1995	Not reported	1970–1990

Abbreviations: bisphos = bisphosphonate; CR = cuirass respirator; KM = Kaplan-Meier; NIPPV = noninvasive positive pressure ventilation; NIV = noninvasive; vent = ventilation

<sup>a</sup> Study or curve was excluded from final analysis for insufficiently accurate individual patient data.

**Table 3** Results From the JBI Tool for Assessing Bias

Article	Year	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Wittlieb-Weber et al. <sup>15,a</sup>	2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
San Martin et al. <sup>1</sup>	2018	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang et al. <sup>4</sup>	2018	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
van den Bergen et al. <sup>5</sup>	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kieny et al. <sup>6,a</sup>	2012	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Rall and Grimm <sup>16</sup>	2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Matsumura et al. <sup>17,b</sup>	2011	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Fraser et al. <sup>18</sup>	2011	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bach and Matinez <sup>19</sup>	2011	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Yes	No
Gordon et al. <sup>20,a</sup>	2011	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Ishikawa et al. <sup>7</sup>	2010	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Kohler et al. <sup>21</sup>	2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mochizuki et al. <sup>2,a</sup>	2008	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
Eagle et al. <sup>3</sup>	2002	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Gomez-Merino et al. <sup>22</sup>	2002	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Phillips et al. <sup>23</sup>	2001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Boland et al. <sup>24</sup>	1996	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Yasuma et al. <sup>25</sup>	1996	Yes	Unclear	Unclear	Yes	Yes	No	No	Yes	No	Yes

Abbreviations: C = criterion; JBI = Joanna Briggs Institute.

<sup>a</sup> Study was entirely excluded from final analysis for insufficiently accurate individual patient data.

<sup>b</sup> Study was partly excluded from final analysis for insufficiently accurate individual patient data.

C1: were there clear criteria for inclusion in the case series? C2: was the condition measured in a standard, reliable way for all participants included in the case series? C3: were valid methods used for identification of the condition for all participants included in the case series? C4: did the case series have consecutive inclusion of participants? C5: did the case series have complete inclusion of participants? C6: was there clear reporting of the demographics of the participants in the study? C7: was there clear reporting of clinical information of the participants? C8: were the outcomes or follow up results of cases clearly reported? C9: was there clear reporting of the presenting site(s)/clinic(s) demographic information? C10: was statistical analysis appropriate?

their study were identified by our search. However, 6 of our 18 articles identified by the systematic review were not included in their review, which could be due to slightly differing search terms<sup>2</sup> or differing exclusion criteria of DMD diagnosis.<sup>18</sup> While our article relied only on a clinical, rather than genetic, diagnosis, the 2 studies produced very similar results, as did a subanalysis of our cohort excluding studies that were not included in the Landfeldt et al.<sup>8</sup> review. Median survival was comparable between the reviews, with both identifying a marked improvement in life expectancy over time. However, our work also provides age-specific estimates of survival and mortality rates over the whole trajectory of a patient with DMD, allowing natural history models to incorporate mortality representative of the global population of patients with DMD.

This study highlights the importance of making the most of available data, an issue particularly pertinent to rare diseases such as DMD. Appropriate estimates of life expectancies are also important for other reasons; for instance, a better

understanding of life expectancies and estimates of age-specific mortality for patients with DMD could help with disease management and planning of service provision, as well as counseling for parents and caregivers.

However, there are limitations with our work. First, access to the full IPD in the studies would be most desirable to avoid unnecessary study exclusion caused by a lack of knowledge of strata sample sizes and to eliminate any errors caused by data extraction. This study does provide generalizable methodology for situations when IPD are unavailable. We were also limited by restricted literature access and could not review 86 of the 1,177 identified articles. In addition, the assignment of patients to birth cohorts was not always straightforward, and knowledge of the exact period of birth of patients in each study would have been preferable.

A further complication from the lack of IPD is that all patients are assumed to have been followed up from birth. This introduces the possibility of immortal time bias in studies

**Table 4** Original and Reproduced Statistics From Each Study

Study	Year	Covariate	No. (deaths, n)		Median		S(20)	
			Original	Reproduced	Original	Reproduced	Original	Reproduced
Wittlieb-Weber et al. <sup>15,a</sup>	2020	—	407 (28)	406 (39)	27.065 <sup>b</sup>	27.037 <sup>b</sup>	0.887	0.908
San Martin et al. <sup>1</sup>	2018	—	462 (166)	462 (166)	20.271	20.278	0.518	0.519
Wang et al. <sup>4</sup>	2018	Deletion exon 14	9 (3)	9 (3)	24.029 <sup>b</sup>	24.283 <sup>b</sup>	0.918	0.889
		Other mutation	48 (24)	48 (24)	31.919	32.083	0.892	0.948
van den Bergen et al. <sup>5</sup>	2014	Born 1961–1974	293 (98)	293 (98)	17.969	18.087	0.181	0.177
		Born 1980–2006	336 (41)	336 (41)	29.008	29.070	0.832	0.831
Kieny et al. <sup>6,a</sup>	2012	Born 1955–1970	119 (55)	119 (84)	25.753	25.743	0.930	0.930
		Born 1970–1994			40.964	40.964	1.000	1.000
Rall and Grimm <sup>16</sup>	2012	No ventilation	66 (45)	66 (46)	18.943	19.051	0.272	0.273
		Ventilation			26.943	20.057	0.819	0.886
Matsumura et al. <sup>17</sup>	2011	No vent, 1977–1984	33 (33)	33 (33)	17.501	17.575	0.396	0.394
		No vent, 1984–2010	49 (49)	49 (49)	19.261	19.319	0.396	0.408
		Vent, 1984–1993 <sup>a</sup>	204 (95)	204 (148)	32.175	32.343	0.894	0.895
		Vent, 1994–2003 <sup>a</sup>			32.846	33.052	0.949	0.949
		Vent, 2004–2010 <sup>a</sup>			27.458 <sup>b</sup>	27.575 <sup>b</sup>	0.966	0.971
Fraser et al. <sup>18</sup>	2011	—	192 (93)	192 (93)	21.443	21.550	0.593	0.607
Bach and Martinez <sup>19</sup>	2011	—	101 (45)	101 (45)	28.000	28.094	0.894	0.895
Gordon et al. <sup>20,a</sup>	2011	No bisphosphonates	44 (13)	39 (39)	20.948	20.996	0.608	0.607
		Bisphosphonates			26.942	24.013	0.850	0.818
Ishikawa et al. <sup>7</sup>	2010	NIV, 1991–2010	88 (17)	88 (17)	39.603	39.561	0.972	0.966
		Tracheo, 1984–1991	24 (21)	24 (21)	28.808	29.693	0.834	0.826
		No vent, 1991–2010	8 (8)	8 (8)	21.939	20.132	0.665	0.625
		No vent, 1984–1991	11 (11)	11 (11)	17.173	17.149	0.352	0.357
		No vent, 1964–1984	56 (56)	56 (56)	18.084	18.036	0.088	0.091
Kohler et al. <sup>21</sup>	2009	—	43 (3)	43 (3)	35.044	35.010	1.000	1.000
Mochizuki et al. <sup>2a</sup>	2008	Mental retardation	74 (11)	74 (22)	25.925	25.877	0.915	0.913
		No retardation			32.870 <sup>c</sup>	32.913 <sup>c</sup>	1.000	1.000
Eagle et al. <sup>3</sup>	2002	Vent, 1990–2002	24 (9)	24 (9)	26.206	26.165	0.892	0.830
		No vent, 1990–2002	33 (33)	33 (33)	19.025	18.961	0.338	0.333
		No vent, 1980–1989	68 (68)	68 (68)	18.678	18.710	0.385	0.382
		No vent, 1970–1979	49 (49)	49 (49)	17.983	17.849	0.216	0.245
		No vent, 1960–1969	9 (9)	9 (9)	14.334	14.337	0.000	0.000
Gomez-Merino et al. <sup>22</sup>	2002	No protocol access	57 (31)	57 (31)	24.729 <sup>c</sup>	25.002 <sup>c</sup>	1.000	1.000
		Access to protocol	34 (3)	34 (3)	28.778	28.912	0.802	0.803
Phillips et al. <sup>23</sup>	2001	—	58 (37)	58 (37)	21.500	21.454	0.727	0.732
Boland et al. <sup>24</sup>	1996	—	33 (17)	33 (17)	22.698	22.573	0.515	0.546

Continued



**Table 4** Original and Reproduced Statistics From Each Study (continued)

Study	Year	Covariate	No. (deaths, n)		Median		S(20)	
			Original	Reproduced	Original	Reproduced	Original	Reproduced
Yasuma et al. <sup>25</sup>	1996	No vent, 1980–1987	65 (65)	65 (65)	20.092	20.122	0.507	0.508
		CR, 1987–1991	7 (7)	7 (7)	21.034	21.007	0.710	0.714
		NIPPV, 1992–1995	27 (8)	27 (8)	30.422	30.478	0.916	0.944

Abbreviations: CR = cuirass respirator; NIPPV, noninvasive positive pressure ventilation; NIV = noninvasive; Tracheo, tracheostomy; vent = ventilation.

<sup>a</sup> Study or curve was excluded from final analysis for insufficiently accurate individual patient data.

<sup>b</sup> Median was not reached, so we compared p(25).

<sup>c</sup> Median and p(25) were not reached, so we compared p(10).

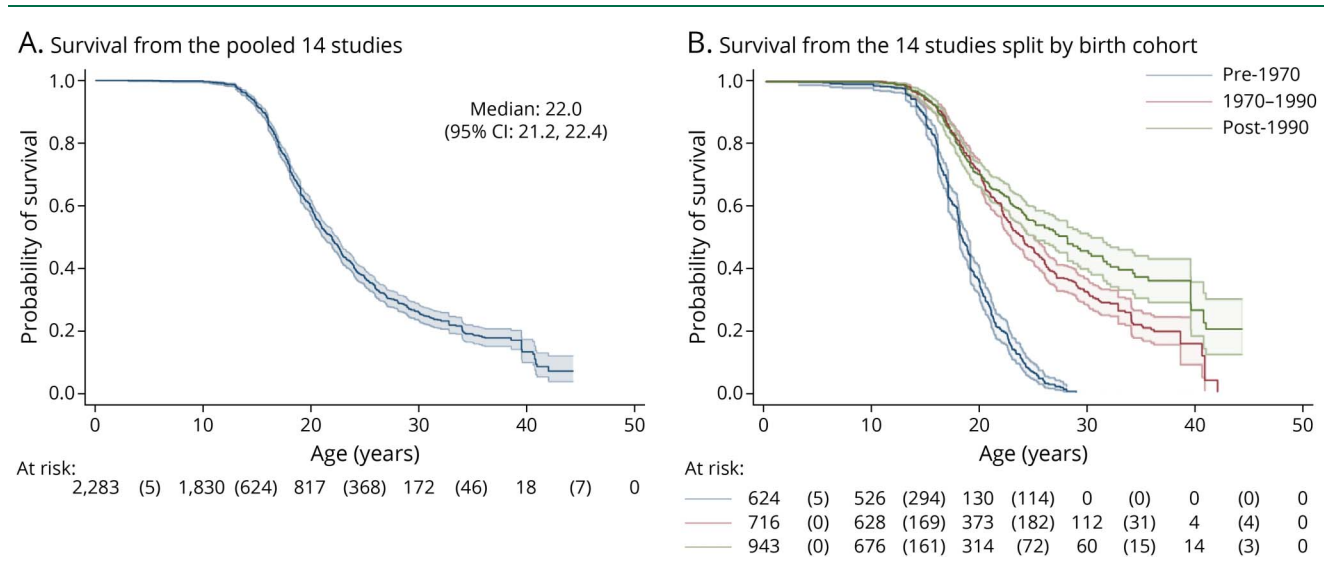
because it is an unintentional condition to survive beyond a certain point to be included in these studies. In other words, the sickest patients who die before being recruited to a study are ignored, so the population analyzed may be slightly healthier than the true underlying DMD population. The impact of this is probably minimal because studies that did report average ages at recruitment generally reported fairly young (<10 years of age) recruitment ages, but it is difficult to assess what impact, if any, this possible bias may have on the final results.

Further work could be undertaken investigating the impact of other covariates such as geographic location (which could affect standard of care), information on steroid treatment (such as type and duration of treatment, age at initiation), and ventilator use. Although these are interesting and pertinent questions, this would require a high level of harmonization between studies. Our birth cohort assignment should stratify between patient populations before and after steroid use became mainstay (after the publication of a number of trials in the late 1980s and early 1990s reporting beneficial effects of

corticosteroid therapy<sup>27</sup>), but this obviously does not guarantee a clear comparison of steroid and nonsteroid users. The study populations vary globally and ethnically, with studies from North America, South America, Europe, and Asia. While an in-depth subanalysis by region would be desirable, it is a reflection of the rarity of the disease that these sources must be pooled together to obtain more precise estimates of survival rates and probabilities.

Extensions of the work could be to supplement and compare with results from the Cooperative International Neuromuscular Research Group. This group has conducted an international natural history study on 440 patients.<sup>28</sup> This study included prospectively collected mortality data,<sup>29</sup> but to date, no mortality analysis has been published. Comparison with this study would enable validation of these results in a US population because only 5 of the 14 included studies contained patients from the United States. Similar work could be completed in the United Kingdom by linking to large-scale population-linked electronic health record data, for example, the Clinical Practice Research Datalink. This would have the

**Figure 2** Kaplan-Meier Estimates, (A) Pooled and (B) Split by Birth Cohort, From the Digitized Data



**Table 5** Five-Year Mortality Rates per 1,000 Patient-Years, Combined and Stratified (95% CIs)

Age, y	Combined	Before 1970	1970–1990	After 1990
0–5	0.07	0.141	0.061	0.0148
	(0.00955, 0.513)	(0.019, 1.05)	(0.00814, 0.449)	(0.00195, 0.111)
5–10	0.324	0.649	0.278	0.0678
	(0.115, 0.918)	(0.223, 1.89)	(0.0956, 0.808)	(0.0226, 0.203)
10–15	11.9	24.2	10.4	2.53
	8.09, 17.6	(15.4, 38.2)	(6.57, 16.4)	(1.50, 4.26)
15–20	66.9	148	63.4	15.5
	(46.7, 95.9)	(96.2, 228)	(41.2, 97.5)	(9.43, 25.4)
20–25	85.5	232	99.5	24.3
	(59.3, 123)	(149, 362)	(64.4, 154)	(14.9, 39.6)
25–30	87.7	275	118	28.7
	(58.7, 131)	(171, 444)	(74.2, 187)	(17.2, 48.0)
30–35	84.4	265	113	27.6
	(51.9, 137)	(152, 459)	(66.2, 194)	(15.4, 49.4)
35–40	71	244	104	25.5
	(35.5, 142)	(116, 514)	(50.3, 217)	(11.9, 54.7)
≥40	336	1,250	536	131
	(146, 773)	(518, 3,020)	(225, 1,280)	(53.4, 318)

Abbreviation: CI = confidence interval. Variance between studies = 0.442 (95% CI 0.180, 0.991) in combined analysis. Variance between studies = 0.557 (95% CI 0.246, 1.35) in stratified analysis.

additional advantage of minimizing selection effects due to cohorts often being established at specialist centers.

We make several recommendations on the basis of our findings. This work highlights improvements in survival for patients with DMD over time; standards of care have improved. We emphasize the need for mortality collection to be considered in the design stage, especially in natural history/registry studies. We strongly advocate the need to include mortality data in any natural history mode, to accurately represent the whole natural history, regardless of whether IPD are available. When they are not available, we recommend using the DMD mortality statistics provided here or obtaining them through other means (such as a review of relevant records or similar systematic review of mortality rates).

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<b>Micki Hill, MSc</b>	Department of Health Sciences, University of Leicester, UK	Joint first author of manuscript; conducted the systematic review and data reconstruction, and analysis and data interpretation
<b>Michela Guglieri, MD</b>	Institute of Human Genetics, Newcastle University, UK	Reviewed and edited final manuscript

Continued

## Appendix (continued)

Name	Location	Contribution
<b>Michael Crowther, PhD</b>	Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden	Contributed to analysis and data interpretation; reviewed and edited final manuscript
<b>Keith Abrams, CStat</b>	Centre for Health Economics, University of York, UK	Contributed to analysis and data interpretation; reviewed and edited final manuscript

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