

Systematic Review

Factors Associated with Respiratory Health and Function in Duchenne Muscular Dystrophy: A Systematic Review and Evidence Grading

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Abstract.

Background: Despite advances in the medical management of the disease, respiratory involvement remains a significant source of morbidity and mortality in children and adults with Duchenne muscular dystrophy (DMD).

Objective: The objective of this systematic literature review was to synthesize and grade published evidence of factors associated with respiratory health and function in DMD.

Methods: We searched MEDLINE, Embase, and the Cochrane Library for records of studies published from January 1, 2000 (to ensure relevance to current care practices), up until and including December 31, 2022, reporting evidence of prognostic indicators and predictors of disease progression in DMD. The quality of evidence (i.e., very low to high) was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.

Results: The bibliographic search strategy resulted in the inclusion of 29 articles. In total, evidence of 10 factors associated with respiratory health and function in patients with DMD was identified: glucocorticoid exposure high- to very low-quality

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evidence), DMD mutations (low-quality evidence), DMD genetic modifiers (low-quality evidence), other pharmacological interventions (i.e., ataluren, eteplirsen, idebenone, and tamoxifen) (moderate- to very low-quality evidence), body mass index and weight (low-quality evidence), and functional ability (low-quality evidence).

Conclusions: In conclusion, we identified a total of 10 factors associated with respiratory health in function in DMD, encompassing both pharmacological therapies, genetic mutations and modifiers, and patient clinical characteristics. Yet, more research is needed to further delineate sources of respiratory heterogeneity, in particular the genotype-phenotype association and the impact of novel DMD therapies in a real-world setting. Our synthesis and grading should be helpful to inform clinical practice and future research of this heavily burdened patient population.

Keywords: Muscular dystrophy, Duchenne, lung diseases, pulmonary ventilation, practice guideline, GRADE approach

INTRODUCTION

In recent decades, improvements to the standard of care of Duchenne muscular dystrophy (DMD), a rare, X-linked neuromuscular disease characterized by progressive muscle degeneration, has significantly transformed prognosis of affected patients [1]. In addition to glucocorticoid therapy and proactive cardiac intervention, one key contributor to this development is improved respiratory management, in particular the routine use of mechanical ventilatory support in adults. Yet, despite these significant advances in care, respiratory involvement remains a significant source of morbidity and mortality in children and adults with DMD. Common complications include respiratory muscle fatigue, mucus plugging, atelectasis, pneumonia, and respiratory failure. In the absence of intervention (e.g., lung volume recruitment, assisted coughing, and assisted ventilation), patients are at risk of severe dyspnoea, atelectasis or pneumonia, and death due to respiratory arrest or respiratory-induced cardiac arrhythmias [2]. Moreover, in part due to limitations with current measures of functional ability (e.g., the six-minute walk test) due to non-trivial inter- and intra-patient variability, endpoints in randomized controlled trials (RCTs) are increasingly also defined in terms of respiratory outcomes [3, 4].

In spite of their importance for clinical practice and research, there is currently no up-to-date synthesis of factors significantly impacting respiratory health and function in children and adults with DMD. Indeed, in addition to informing respiratory care, counselling, and prognosis, such data would be expected to also help facilitate selection of patients to research (e.g., at different levels of risks of respiratory outcomes), as well as comparative analysis and contextualization of treatment efficacy as observed in single-arm trials [5]. To bridge this evidence gap, the objective of this study was to review, synthesize, and grade published

evidence of factors associated with respiratory health and function in DMD.

MATERIALS AND METHODS

We conducted this systematic literature review according to the guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6].

Search strategy

We implemented the bibliographic searches analogously to the strategy employed in our previously published scoping review of prognostic indicators of disease progression in DMD [7], revised for the review topic and updated to present date. Specifically, we searched MEDLINE (via Ovid), Embase (via Ovid), and the Cochrane Library (via the Wiley online platform) for records of studies published from January 1, 2000 (to ensure relevance to current care practices), up until and including December 31, 2022, reporting evidence of prognostic indicators and predictors of disease progression in DMD. The search string contained “Duchenne muscular dystrophy” as a Medical Subject Heading term or free text term, in combination with variations of the term “predictor” and “prognostic indicator” (full search strings are provided in the supplemental material online).

Inclusion criteria

We employed eligibility criteria for study inclusion based on the Population, Intervention, Comparison, Outcomes and Study design (PICOS) framework identical to those specified in our previous scoping review [7] amended for the review topic (Table 1). We did not consider editorial letters or conference abstracts (as they lack details essential for meaningful synthesis and grading) and did not formally

Table 1
PICOS eligibility criteria for study inclusion

	Inclusion	Exclusion
Population	Patients diagnosed with DMD	None
Intervention	Any	None
Comparators	Any	None
Outcome	Prognostic indicator/predictor of respiratory health and function	None
Study design	Any	Systematic literature reviews were not formally included, but screened for relevant references

Note: Population, Intervention, Comparison, Outcomes and Study design (PICOS). Duchenne muscular dystrophy (DMD).

include identified systematic reviews (but screened their reference lists for potential publications).

Screening and data extraction

One investigator (EL) initially screened article titles and abstracts for eligibility, and subsequently reviewed full-text versions of selected records. The reason for exclusion was recorded and confirmed by a second investigator (SA). For all articles that met the inclusion criteria upon full-text review, the following information was extracted into a pre-specified data extraction form: Author; title; study year; geographical setting(s); study design; site(s)/data source(s); study period; sample population characteristics; case ascertainment; pharmacological interventions (incl. number of exposed, dose, and duration of exposure); outcome measures(s); method of analysis; and outcome results. For the purpose of this review, we only considered statistically significant factors of respiratory health and function (as reported in the included studies). Per previous research, we considered commonly used respiratory interventions, such as lung volume recruitment, cough assists, and assisted ventilation, to be milestones or outcomes indicative of increasing deterioration in respiratory function [2, 8–10] and did therefore not collate evidence pertaining to the effects of such devices and procedures. Finally, due to the progressive nature of DMD, we did not consider age a predictor of interest.

Upon identification of the relevant literature, two investigators (EL and SA) systematically screened reference lists of all included publications with the aim to identify additional records of interest not captured by the employed search strategy.

Level of evidence

The quality of the identified evidence of factors associated with respiratory health and function in

DMD was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework [11]. GRADE rates the overall quality of evidence based on design limitations, risk of bias, consistency of the results across available studies, the precision of the results, directness, and likelihood of publication. The tool comprises of four levels of evidence, also known as certainty in evidence or quality of evidence: (1) very low (i.e., the true effect is probably markedly different from the estimated effect), (2) low (i.e., the true effect might be markedly different from the estimated effect), (3) moderate (i.e., the authors believe that the true effect is probably close to the estimated effect), and (4) high (i.e., the authors have a lot of confidence that the true effect is similar to the estimated effect). Per the GRADE manual, two investigators (EL and AA) independently provided an initial rating of all included records. Next, the quality of evidence at the outcome level was rated down for issues or limitations pertaining to study limitations, inconsistency of results, imprecision, indirectness of evidence, and publication bias, and/or rated up in case of a large magnitude of effect, a dose response, or if confounders are likely to minimize the effect. Finally, each investigator independently provided an overall GRADE quality rating of each outcome and study [11]. All GRADE ratings were subsequently reviewed and confirmed by HL and RMQ.

RESULTS

The bibliographic search strategy resulted in the identification of 29 articles [8, 9, 12–38] (Table 2). Identified studies included patients with DMD from 10 countries (i.e., Australia, Belgium, Canada, France, Germany, India, Italy, the Netherlands, the United Kingdom [UK], and the United States of America [USA]). However, 38% (11 of 29) were

Table 2
Characteristics of included studies

Author (year) [country]	Study design	Data source(s)/site(s)	Study period	Sample, n (age) [†]	Case ascertainment	Pharmacological intervention(s)	n (%) exposed [†]	Dose, mean	Duration of exposure, mean (SD)
Angliss et al. (2020) [AU] [12]	Retrospective cohort study	Children's Health Queensland (Brisbane, AU)	2008–2018	29 patients with DMD (median age: 15 years, IQR: 10–18 years)	NR	Glucocorticoids (DFZ and/or PRED)	21 (72%)	<ul style="list-style-type: none"> ● DFZ: NR ● PRED: 0.25 mg/kg/day 	1–5 years
						ACE inhibitors (agents NR)	21 (72%)	NR	NR
						Spinal surgery	7 (24%)	NR	NR
Balaban et al. (2005) [NR] [13]	Retrospective cohort study	NR	NR	49 patients with DMD (mean age: 14 years, range: 12–15 years)	Muscle biopsy, dystrophin genotyping studies, and EMG	Glucocorticoids (DFZ and/or PDN)	30 (61%)	<ul style="list-style-type: none"> ● DFZ: 0.9 mg/kg/day ● PDN: 0.75 mg/kg/day 	<ul style="list-style-type: none"> ● DFZ: 5.85 (1.5) years ● PDN: 5.49 (1.98) years
Bello et al. (2020) [IT] [14]	Retrospective cohort study	Italian DMD Network (IT, multi-centre)	1990–2018	327 patients with DMD (mean age: 12 years, range: 4–45 years)	Genetic testing; or dystrophin levels and/or overt muscle weakness by 5 years of age; or loss of ambulation by 13 years of age without glucocorticoid treatment or by 16 years of age with glucocorticoid treatment	Glucocorticoids (agents NR)	134 (41%)	NR	4.5 (3.9) years
						NIV	87 (27%)	NA	NR

Biggar et al. (2001) [CA] [15]	Retrospective cohort study	The Bloorview MacMillan Children's Center (Toronto, CA)	1993–1999	54 patients with DMD (mean age: 12 years, range: 7–15 years)	Age at onset of symptoms (<5 years of age), male sex, proximal muscle weakness, increased serum creatine kinase levels, and muscle biopsy and/or genetic testing	Glucocorticoids (DFZ)	30 (56%)	<i>Initial dose</i> • 0.9 mg/kg/day <i>At 10 years of age</i> • 0.76 (0.19) mg/kg/day <i>At 15 years of age</i> • 0.61 (0.20) mg/kg/day	3.2 (1.3) years
Biggar et al. (2006) [CA] [16]	Retrospective cohort study	The Bloorview MacMillan Children's Center (Toronto, CA)	1990–2004	74 patients with DMD (mean age: 15 years, range: 10–18 years)	Age at onset of symptoms (<5 years of age), male sex, proximal muscle weakness, increased serum creatine kinase levels, and muscle biopsy and/or genetic testing	Glucocorticoids (DFZ)	40 (54%)	<i>Initial dose</i> • 0.9 mg/kg/day <i>At 10 years of age</i> • 0.8 (0.18) mg/kg/day <i>At 15 years of age</i> • 0.55 (0.09) mg/kg/day <i>At 18 years of age</i> • 0.5 (0.2) mg/kg/day	5.5 years
Buyse et al. (2011) [BE] [17]	RCT	NR	2005–2007	21 patients with DMD (mean age: 12 years, range: 8–16 years)	NR	Idebenone	13 (62%)	450 mg/day	52 weeks
Daftary et al. (2007) [US] [18]	Case-control study	Cincinnati Children's Hospital Medical Center (Ohio, US)	NR	35 patients with DMD (mean age: 12 years, range: 8–17 years)	Genetic testing or muscle biopsy	Glucocorticoids (DFZ and/or PDN)	10 (29%)	<i>Initial dose</i> • DFZ: 0.9 mg/kg/day • PDN: 0.75 mg/kg/day	8.2 (range: 1–14) years

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Table 2
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Author (year) [country]	Study design	Data source(s)/site(s)	Study period	Sample, n (age) [†]	Case ascertainment	Pharmacological intervention(s)	n (%) exposed [†]	Dose, mean	Duration of exposure, mean (SD)
Escolar et al. (2011) [US] [19]	RCT	12 institutions in the CINRG network (names and locations NR)	NR	64 patients with DMD (mean age: 7 years, range: 4–10 years)	NR	Glucocorticoids (PDN)	64 (100%)	<i>Daily dose</i> • 0.75 mg/kg/day <i>Weekend dose</i> • 10 mg/kg/week	12 months
Fayssol et al. (2021) [FR] [20]	Retrospective cohort study	Neuromuscular clinic (name and location NR)	2015–2018	74 patients with DMD (median age: 22 years, range: 19–25 years)	NR	Glucocorticoids (DFZ or PDN)	14 (19%)	• DFZ: NR • PDN: 0.75 mg/kg/day	NR
Henricson et al. (2013) [*] [21]	Prospective cohort study	Multi-country, multi-centre (CINRG DNHS)	2005–2009	340 patients with DMD (mean age: NR, range: 2–28 years)	Clinical presentation, family history of DMD, and molecular diagnostic characterization of DMD-associated dystrophinopathy	Glucocorticoids (agents NR)	210 (62%)	NR	NR
Houde et al. (2008) [CA] [22]	Retrospective cohort study	The multidisciplinary Neuromuscular Clinic of the Marie-Enfant Rehabilitation Centre (Montreal, CA)	NR	29 patients with DMD (mean age: NR, range: NR)	Muscle biopsy and/or genetic testing	Glucocorticoids (DFZ)	8 (28%)	<i>Initial dose</i> • 0.9 mg/kg per day (adjusted according to evolution or side effects to a maximum of 1 mg/kg)	NR
						ACE inhibitors (agents NR)	NR	NR	NR

Humbertclaude et al. (2012) [FR] [8]	Retrospective cohort study	The French dys-trophinopathy database (UMD–DMD France) (FR, multi-centre)	NR	262 patients with DMD (mean age: 11 years; range: NR)	Genetic testing and loss of ambulation before 13 years of age	Glucocorticoids (agents NA)	0 (0%)	NA	NA
Iff et al. (2022) [*] [23]	Indirect treatment comparison study	<ul style="list-style-type: none"> • Study 204 (open-label study; US, multi-centre [NCT02286947]) • Study 301 (open-label study; US, multi-centre [NCT0225552]) • CINRG DNHS (prospective cohort study; multi-country, multi-centre [NCT00468832]) 	<ul style="list-style-type: none"> • Study 204 : 2014–2018 • Study 301 : 2014–2019 • CINRG-DNHS: 2006–2016 	<p><i>Study 204</i></p> <ul style="list-style-type: none"> • 20 patients with DMD (mean age: 13 years; range: 10–17 years) <p><i>Study 301</i></p> <ul style="list-style-type: none"> • 52 patients with DMD (mean age: 11 years; range: 10–16 years) <p><i>CINRG DNHS</i></p> <ul style="list-style-type: none"> • 20 patients with DMD (mean age: 12 years; range: 10–18 years) 	<ul style="list-style-type: none"> • Study 204: NR^a • Study 301: NR^a • CINRG DNHS: NR^a 	Eteplirsen	<ul style="list-style-type: none"> • Study 204 : 20 (100%) • Study 301 : 52 (100%) • CINRG DNHS: 0 (0%) 	NR	Specific to each study (see article for details)
			Glucocorticoids (agents NR)	<ul style="list-style-type: none"> • Study 204 : 20 (100%) • Study 301 : 52 (100%) • CINRG DNHS: 20 (100%) • DEMAND III: 11 (100%) 	NR	NR			
Kelley et al. (2019) [*] [25]	Retrospective cohort study	CINRG DNHS (multi-country, multi-centre)	NR	175 patients with DMD (mean age: 12 years, range: 3–25 years)	NR ^a	Glucocorticoids (agents NR)	NR	NR	3.40 (SE: 0.31) years
Kelley et al. (2022) [*] [24]	Retrospective cohort study	CINRG DNHS (multi-country, multi-centre)	NR	169 patients with DMD (mean age: 12 years, range: 5–25 years)	NR ^a	Glucocorticoids (agents NR)	NR	NR	3.40 (SE: 0.31) years

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Table 2
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Author (year) [country]	Study design	Data source(s)/site(s)	Study period	Sample, n (age) [†]	Case ascertainment	Pharmacological intervention(s)	n (%) exposed [†]	Dose, mean	Duration of exposure, mean (SD)
Khan et al. (2019) [*] [26]	Indirect treatment comparison study	<ul style="list-style-type: none"> • Study 201 (RCT; US; single-centre [NCT01396239]) • Study 202 (open label, multiple dose extension study; US, multi-centre [NCT01540409]) • Study 204 (open-label study; US, multi-centre [NCT02286947]) • Study 301 (open-label study; US, multi-centre [NCT02255552]) • CINRG DNHS (prospective cohort study; multi-country, multi-centre [NCT00468832]) 	<ul style="list-style-type: none"> • Study 201/202: NR • Study 204: NR • Study 301: NR • CINRG DNHS: NR 	<i>Study 201/202</i> <ul style="list-style-type: none"> • 12 patients with DMD (mean age: 10 years; range: 10–11 years) 	<ul style="list-style-type: none"> • Study 201/202: NR^a • Study 204: NR^a • Study 301: NR^a • CINRG DNHS: NR^a 	Eteplirsen	<ul style="list-style-type: none"> • Study 201/202: 12 (100%) • Study 204: 20 (100%) • Study 301: 42 (100%) • CINRG DNHS: 0 (0%) 	<ul style="list-style-type: none"> • Study 201/202: 30 or 50 mg/kg/week • Study 204: 30 mg/kg/week • Study 301: 30 mg/kg/week 	Specific to each study (see article for details)
				<i>Study 204</i> <ul style="list-style-type: none"> • 20 patients with DMD (mean age: 13 years; range: 10–17 years) 		<i>Study 301</i> <ul style="list-style-type: none"> • 42 patients with DMD (mean age: 11 years; range: 10–16 years) 			

Kim et al. (2017) [US] [27]	Retrospective cohort study	MD STARnet (US, multi-centre)	NR	660 patients with DMD (mean age: NR, range: NR)	Clinical presentation, genetic testing, muscle biopsy, and/or elevated creatine kinase levels, X-linked pedigree, and family history of DMD (based on genetic testing or muscle biopsy)	Glucocorticoids (DFZ, PDN, or PRED)	<ul style="list-style-type: none"> • Early treatment (mean age: 4 years): 59 (9%) • Late treatment (mean age: 8 years): 259 (39%) 	NR	5.9–6.4 years
Koeks et al. (2017) [*] [28]	Retrospective cohort study	The TREAT-NMD global DMD database (multi-national, multi-centre)	2007–2013	5,345 patients with DMD (mean age: NR, range: NR)	Genetic testing	Glucocorticoids (DFZ, PDN, or PRED)	<i>Current use</i> <ul style="list-style-type: none"> • 2,658 (50%) <i>Past use</i> <ul style="list-style-type: none"> • 522 (10%) 	NR	NR
Lee et al. (2016) [US] [29]	Cross-sectional	The Comprehensive Neuromuscular Center at Cincinnati Children's Hospital Medical Center (Cincinnati, US)	2013	43 patients with DMD (mean age: 16 years, range: 10–30 years)	Clinical presentation, elevated creatine kinase levels, and positive family history of DMD, or muscle biopsy and/or genetic testing	Glucocorticoids (DFZ or PDN)	43 (100%)	NR	8.9 (SD: 3.1) years
LoMauro et al. (2018) [IT] [30]	Retrospective cohort study	Istituto di Ricovero e Cura a Carattere Scientifico (San Giovanni Rotondo, IT)	NR	115 patients with DMD (mean age: NR, range: 6–24 years)	NR	Glucocorticoids (agents NR)	NR	NR	NR

(Continued)

Table 2
(Continued)

Author (year) [country]	Study design	Data source(s)/site(s)	Study period	Sample, n (age) [†]	Case ascertainment	Pharmacological intervention(s)	n (%) exposed [†]	Dose, mean	Duration of exposure, mean (SD)
Mayer et al. (2017) [*] [31]	Post-hoc RCT analysis study	Multi-country, multi-centre	2009–2012	64 patients with DMD (mean age: NR, range: 10–19 years)	NR	Idebenone	31 (48%)	900 mg/day	52 weeks
						Glucocorticoids (agents NA)	0 (0%)	NA	NA
McDonald et al. (2018) [*] [9]	Prospective cohort study	CINRG DNHS (multi-country, multi-centre)	2006–2009; 2012–2016	397 patients with DMD (mean: 11 years, range: 2–28 years)	Clinical and molecular diagnostic picture consistent with typical DMD (see article for details)	Glucocorticoids (DFZ, PDN, and/or PRED)	335 (81%)	NR	4.7–8.9 years
McDonald et al. (2022) [*] [32]	Indirect treatment comparison study	<ul style="list-style-type: none"> • Study 019 (open-label study; multi-country, multi-centre [NCT01557400]) • CINRG DNHS (prospective cohort study; multi-country, multi-centre [NCT00468832]) 	<ul style="list-style-type: none"> • Study 019: NR • CINRG DNHS: 2006–2016 	<i>Study 019</i> <ul style="list-style-type: none"> • 45 patients with DMD (mean age: NR, range: NR) 	<ul style="list-style-type: none"> • Study 019: NR^a • CINRG DNHS: NR^a 	Ataluren	45 (50%)	40 mg/kg/day	NR ^b
				<i>CINRG DNHS</i> <ul style="list-style-type: none"> • 45 patients with DMD (mean age: NR, range: NR) 		Glucocorticoids (DFZ, PDN, and/or PRED)	NR	NR	NR

Mitelman et al. (2022) [*] [33]	Indirect treatment comparison study	<ul style="list-style-type: none"> • Study 201 (RCT; US; single-centre [NCT01396239]) • Study 202 (open label, multiple dose extension study; US, multi-centre [NCT01540409]) • Study 405 (retrospective cohort study; US, multi-centre) • CINRG DNHS (prospective cohort study; multi-country, multi-centre [NCT00468832]) 	NR ^a	<p><i>Study 201/202/405</i></p> <ul style="list-style-type: none"> • 12 patients with DMD (mean age: 9 years; range: 7–11 years) <p><i>CINRG DNHS</i></p> <ul style="list-style-type: none"> • 20 patients with DMD (mean age: NR; range: NR) 	<ul style="list-style-type: none"> • Study 201/202: NR^a • Study 405: NR^a • CINRG DNHS: NR^a 	<p>Eteplirsen 12 (14%)</p> <hr/> <p>Glucocorticoids (DFZ or PDN) 27 (100%)</p>	<p>30 or 40 mg/kg/week</p> <hr/> <p>NR</p>	<p>5.72 (SD: 0.90) (range: 4.13–6.88)</p> <hr/> <p>NR</p>
Pradhan et al. (2006) [IN] [34]	Retrospective cohort study	NR	NR	34 patients with DMD (mean age: 9 years, range: NR)	Clinical presentation (e.g., difficulty rising from the floor and walking, calf hypertrophy, and positive Gower's sign), increased creatine kinase levels, myogenic pattern on EMG, and deletion of the dystrophin gene	Glucocorticoids (PRED) 15 (44%)	0.75 mg/kg/day	NR

(Continued)

Table 2
(Continued)

Author (year) [country]	Study design	Data source(s)/site(s)	Study period	Sample, n (age) [†]	Case ascertainment	Pharmacological intervention(s)	n (%) exposed [†]	Dose, mean	Duration of exposure, mean (SD)
Schara et al. (2001) [DE] [35]	Retrospective cohort study	NR	NR	26 patients with DMD (mean: NR, range: NR)	NR	Glucocorticoids (DFZ)	13 (50%)	0.9 mg/kg/day	NR
Silversides et al. (2003) [CA] [36]	Retrospective cohort study	The Bloorview MacMillan Children's Center (Toronto, CA)	1998–2002	33 patients with DMD (mean age: 15 years, range: 10–18 years)	Age at onset of symptoms (<5 years of age), male sex, proximal muscle weakness, increased serum creatine kinase levels, and muscle biopsy and/or genetic testing	Glucocorticoids (DFZ)	21 (64%)	<i>Initial dose</i> • 0.9 mg/kg/day <i>At 10 years of age</i> • 0.76 (0.19) mg/kg/day <i>At 15 years of age</i> • 0.61 (0.20) mg/kg/day <i>At 18 years of age</i> • 0.59 (0.15) mg/kg/day	5.1 (SD: 2.4) years
						ACE inhibitors (agents NR)	6 (18%)	NR	NR
						Cardiotonic agents (digoxin)	3 (9%)	NR	NR

Trucco et al. (2022) [NL/FR/UK] [37]	Retrospective cohort study	The UK NorthStar Network (multi-site, UK) and the Association Française contre les Myopathies (AFM) Network (multi-site, FR)	2003–2020	142 patents with DMD (mean age: 9 years, range: 5–NR)	NR	Glucocorticoids (agents NR)	142 (100%)	NR	NR
Tsabari et al. (2021) [IL] [38]	Prospective cohort study	Hadassah University Hospital (Jerusalem, IL) and the Duchenne Muscular Dystrophy Regulatory Science Consortium (D-RSC) Data Platform (country NR)	2016–2019	97 patents with DMD ^d (mean age: 9 years, range: 6–14 years)	NR	Tamoxifen Glucocorticoids (agents NR)	9 (9%) ^d 88 (100%) ^d	20 mg/day NR	≤3 years NR

Note: Australia (AUS). Belgium (BE). Canada (CAN). Confidence interval (CI). Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS). Deflazacort (DFZ). Duchenne muscular dystrophy (DMD). Electromyography (EMG). France (FR). India (IN). Inter-quartile range (IQR). Israel (IL). Italy (IT). Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). Neuromuscular Reference Center (NMRC). Not applicable (NA). Not reported (NR). Prednisolone (PRED). Prednisone (PDN). Standard deviation (SD). Standard error (SE). The Netherlands (NL). United Kingdom (UK). United States of America (US). [†]Details for the sample analysed with respect to outcomes of respiratory health and function. *Multi-national (see article for details). ^aCase ascertainment details not reported but provided in referenced publications. ^bDistribution across categories of duration of treatment reported in the article. ^cMean age in treated patients: 9 years (range: 7–11 years). ^d13–88 untreated patients (depending on the assay).

based on multi-national cohorts and/or did not disclose patients' country of residence. Additionally, several sets of studies were based on identical, or very similar, samples. In total, 10% (3 of 29) of articles described results from randomized research, 10% (3 of 29) from prospective cohort studies, 59% (17 of 29) from retrospective cohort studies, 14% (4 of 29) from indirect treatment comparison studies, 3% (1 of 29) from case-control studies, and 3% (1 of 29) from cross-sectional studies.

Factors associated with respiratory health and function in DMD

We identified evidence of 10 factors associated with respiratory health and function in patients with DMD, namely glucocorticoid exposure, DMD mutations, DMD genetic modifiers, other pharmacological interventions (i.e., ataluren, eteplirsén, idebenone, and tamoxifen), body mass index (BMI) and weight, and functional ability.

Glucocorticoid exposure

We identified one RCT reporting evidence of benefits of glucocorticoids on respiratory outcomes (Table 3). Specifically, Escolar et al. [19] compared the efficacy and safety of daily versus weekend prednisone among 64 US patients with DMD recruited via the Cooperative International Neuromuscular Research Group (CINRG). After 12 months of follow-up, although equivalence was met for the primary outcomes (i.e., muscle testing), patients receiving a weekend regimen had significantly higher predicted forced vital capacity (FVC) than those treated with a daily regimen (mean difference in change: 4.6%, 95% CI: -9.8 to 19.1). A weekend regimen was also associated with higher predicted forced expiratory volume in one second (FEV₁) (mean difference in change vs. daily regimen: 6.1%, 95% CI: -9.1% to 20.4%).

We identified 13 observational studies reporting evidence of benefits of glucocorticoids on FVC in patients with DMD (Table 3). Compared with no treatment, significant improvements in predicted FVC were reported by Angliss et al. [12] in their study of 21 Australian patients receiving deflazacort and/or prednisolone (total $n=29$) (mean annual rate of decline: -6.60% vs. -7.39%, $p<0.001$ [random-effects model]); Bello et al. [14] in 134 Italian patients treated with glucocorticoids (agents not reported [NR]) (total $n=327$) (estimated coefficient [β]: 14.5, SE: 2.1, $p<0.0001$ [generalized estimating equation

[GEE] model]); Biggar et al. [15] in 30 Canadian patients receiving deflazacort (total $n=54$) (mean at 15 years of age: 88% vs. 39%, $p<0.001$); Biggar et al. [16] in 40 Canadian patients treated with deflazacort (total $n=74$) (mean at 18 years of age: 81% vs. 34%, $p<0.05$); Henricson et al. [21] in a multi-national prospective cohort study (CINRG Duchenne Natural History Study [CINRG DNHS]) comprising of 210 patients treated with glucocorticoids (agents NR) (total $n=340$) (mean for patients > 18 years of age: 32% vs. 22%, $p<0.05$); Houde et al. [22] in 8 Canadian patients treated with deflazacort (total $n=29$) (mean at 16 years of age: 66% vs. 48%, $p<0.007$); Kelley et al. [24] in a multi-national sample comprising of 169 patients from the CINRG DNHS (based on regression analysis of duration of exposure; $p<0.001$); LoMauro et al. [30] in Italian patients with DMD treated with glucocorticoids ($n=NR$, agents NR) (total $n=115$) (predicted FVC was significantly higher among treated patients compared with untreated and previously treated patients, respectively, in the age range 15.1–21.3 years (p -value NR); McDonald et al. [9] in a multi-national cohort comprising of 335 patients from CINRG DNHS receiving either deflazacort, prednisone, and/or prednisolone (total $n=397$) (mean annual change in patients 7 to 18 years of age: β : -6.06, $p<0.001$ [mixed-effects model]); Schara et al. [35] in 13 German patients treated with deflazacort (total $n=26$) (median across follow-up: 86.8% vs. and 55%, $p=0.0173$); and Silversides et al. [36] in 21 Canadian patients treated with deflazacort (total $n=33$) (mean at end of follow-up: 83% vs. 41%, $p<0.001$). Moreover, in the retrospective cohort study by Balaban et al. [13], involving 49 patients with DMD (country NR), the mean change in FVC was significantly higher in those treated with deflazacort or prednisone compared with no treatment (0.75 litres [deflazacort] vs. 0.13 litres [no treatment], $p=0.02$; and 0.46 litres [prednisone] vs. 0.13 litres [no treatment], $p=0.046$). Kim et al. [27] found that late treatment with deflazacort, prednisone, or prednisolone was associated with improved FVC compared with early treatment (β : -0.39, $p<0.01$ [generalized estimating equation model]), as well as no treatment (β : -0.21, $p=0.04$ [generalized estimating equation model]), among 660 US patients with DMD. Angliss et al. [12] reported of a significantly reduced decline in FVC in patients treated with deflazacort and/or prednisolone compared with untreated patients (0.003 litres [95% CI: -0.03 to 0.30] vs. -0.09 litres [95% CI: -0.12 to -0.06], $p<0.001$). Finally, Silversides et al. [36] also

Table 3
GRADE assessment of studies of factors associated with respiratory outcomes in DMD

Author (year) [country]	Predictor(s)/ indicator(s)	Outcome measure(s)	Method of analysis	Outcome results	Initial GRADE	Outcome GRADE modifi- cation	Overall GRADE
Angliss et al. (2020) [AU] [12]	Glucocorticoids (DFZ and/or PRED)	Maximum TcCO ₂ (mm Hg)	Descriptive (Mann-Whitney <i>U</i> test)	<i>Mean (SD) across follow-up</i> ● 49.0 (5.0) mm Hg (treated) vs. 56.0 (3.7) mm Hg (untreated), <i>p</i> = 0.03.	Low	–	Low
		Maximum REM TcCO ₂ (mm Hg)		<i>Mean (SD) across follow-up</i> ● 47.7 (6.3) mm Hg (treated) vs. 56.0 (3.7) mm Hg (untreated), <i>p</i> = 0.02.			
		FEV ₁ (litres)	Regression analysis (random-effects model)	<i>Mean (95% CI) annual rate of decline</i> ● –0.005 (–0.32 to –0.02) litres (treated) vs. –0.07 (–0.11 to –0.04) litres (untreated), <i>p</i> < 0.01.			
		FEV ₁ (Z-score)		<i>Mean (95% CI) annual rate of decline</i> ● –0.52 (–0.60 to 0.43) (treated) vs. –0.57 (–0.66 to –0.49) (untreated), <i>p</i> < 0.001.			
		FEV ₁ (% predicted)		<i>Mean (95% CI) annual rate of decline</i> ● –6.55% (–7.57% to –5.54%) (treated) vs. –7.67% (–8.73% to –6.62%) (untreated), <i>p</i> < 0.001.			
		FVC (litres)		<i>Mean (95% CI) annual rate of decline</i> ● 0.003 (–0.03 to 0.30) litres (treated) vs. –0.09 (–0.12 to –0.06) litres (untreated), <i>p</i> < 0.001.			
		FVC (Z-score)		<i>Mean (95% CI) annual rate of decline</i> ● –0.58 (–0.67 to –0.50) (treated) vs. 0.68 (–0.75 to –0.60) (untreated), <i>p</i> < 0.001.			
		FVC (% predicted)		<i>Mean (95% CI) annual rate of decline</i> ● –6.60% (–7.55% to –5.65%) (treated) vs. –7.39% (–8.23% to –6.54%) (untreated), <i>p</i> < 0.001.			
Balaban et al. (2005) [NR] [13]	Glucocorticoids (DFZ and/or PDN)	FVC (litres)	Descriptive (Mann-Whitney <i>U</i> test)	<i>Mean (SD) FVC change between the ages of 7 and 15 years</i> ● 0.75 (0.62) litres (DFZ) vs. 0.13 (0.35) litres (no treatment), <i>p</i> = 0.020. ● 0.46 (0.50) litres (PDN) vs. 0.13 (0.35) litres (no treatment), <i>p</i> = 0.046.	Low	–	Low

(Continued)

Table 3
(Continued)

Author (year) [country]	Predictor(s)/ indicator(s)	Outcome measure(s)	Method of analysis	Outcome results	Initial GRADE	Outcome GRADE modifi- cation	Overall GRADE
Bello et al. (2020) [IT] [14]	Glucocorticoids (agents NR)	FVC (% predicted)	Regression analysis (GEE model)	• β : 14.5, SE: 2.1, $p < 0.0001$.	Low	–	Low
		FEV ₁ (% predicted)		• β : 15.1, SE: 2.0, $p < 0.0001$.	–	–	
		PEF (% predicted)		• β : 14.2, SE: 1.9, $p < 0.0001$.	–	–	
		Mutation 3' of exon 44		FVC (% predicted)	• β : –6.1, SE: 2.3, $p = 0.008$.	–	–
		Mutation type: skip 8		FVC (% predicted)	• β : 13.8, SE: 8.3, $p = 0.049$. ^a	–	–
		Mutation type: skip 44		FVC (% predicted)	• β : 7.1, SE: 3.3, $p = 0.016$. ^a	–	–
		Mutation type: skip 51		FVC (% predicted)	• β : –5.7, SE: 2.3, $p = 0.007$. ^a	–	–
		Mutation type: skip 53		FVC (% predicted)	• β : –10.3, SE: 2.7, $p < 0.0001$. ^a	–	–
		Splice site		FVC (% predicted)	• β : 13.9, SE: 7.0, $p < 0.023$.	–	–
		Mutation 3' of exon 44		FEV ₁ (% predicted)	• β : 6.3, SE: 2.5, $p = 0.011$.	–	–
		Mutation type: skip 8		FEV ₁ (% predicted)	• β : 15.3, SE: 7.9, $p = 0.027$. ^a	–	–
		Mutation type: skip 51		FEV ₁ (% predicted)	• β : –7.5, SE: 4.3, $p = 0.042$.	–	–
		Mutation type: skip 53		FEV ₁ (% predicted)	• β : –6.6, SE: 3.2, $p = 0.021$. ^a	–	–
		Nonsense		FEV ₁ (% predicted)	• β : –7.1, SE: 4.3, $p = 0.048$. ^b	–	–
		Splice site		FEV ₁ (% predicted)	• β : 11.6, SE: 5.1, $p = 0.011$. ^a	–	–
		Mutation 3' of exon 44		PEF (% predicted)	• β : –5.8, SE: 2.3, $p = 0.010$.	–	–

	Mutation type: skip 8	PEF (% predicted)		• β : 23.0, SE: 4.2, $p < 0.0001$.		–	
	Mutation type: skip 51	PEF (% predicted)		• β : –5.7, SE: 3.4, $p = 0.048$.		–	
	Mutation type: skip 53	PEF (% predicted)		• β : –5.9, SE: 2.7, $p = 0.014$. ^a		–	
	SNP modifier rs28357094 (dominant)	FVC (% predicted)		• β : –4.5, SE: 2.5, $p = 0.020$. ^a		–	
	SNP modifier rs1883832 (additive)	FVC (% predicted)		• β : –6.1, SE: 2.2, $p = 0.005$. ^b		–	
	SNP modifier rs1883832 (additive)	FEV ₁ (% predicted)		• β : –4.8, SE: 2.2, $p = 0.030$. ^b		–	
	SNP modifier rs28357094 (dominant)	PEF (% predicted)		• β : –8.7, SE: 3.1, $p = 0.005$. ^b		–	
	SNP modifier rs1883832 (additive)	PEF (% predicted)		• β : –4.1, SE: 1.8, $p = 0.024$. ^a		–	
	CD40 rs1883832 (additive)	NIV	Regression analysis (Cox proportional hazards model)	• HR: 1.71, 95% CI: 1.01 to 2.88, $p = 0.044$. ^b		–	
Biggar et al. (2001) [CA] [15]	Glucocorticoids (DFZ)	FVC (% predicted)	Descriptive (Student's <i>t</i> -test)	<p><i>Mean (SD) at 13 years of age</i></p> <ul style="list-style-type: none"> • 82.5% (14%) (treated) vs. 43.2% (9%) (untreated), $p < 0.002$. <p><i>Mean (SD) at 15 years of age</i></p> <ul style="list-style-type: none"> • 88% (18%) (treated) vs. 39% (20%) (untreated), $p < 0.001$. 	Low	–	Low
Biggar et al. (2006) [CA] [16]	Glucocorticoid (DFZ)	FVC (% predicted)	Descriptive (Student's <i>t</i> -test)	<p><i>Mean (SD) at 10 years of age</i></p> <ul style="list-style-type: none"> • 95% (14%) (treated) vs. 65% (13%) (untreated), $p < 0.05$. <p><i>Mean (SD) at 15 years of age</i></p> <ul style="list-style-type: none"> • 88% (12%) (treated) vs. 47% (19%) (untreated), $p < 0.05$. <p><i>Mean (SD) at 18 years of age</i></p> <ul style="list-style-type: none"> • 81% (13%) (treated) vs. 34% (10%) (untreated), $p < 0.05$. 	Low	–	Low
		NIV	Descriptive (Fisher's exact test)	<p><i>Prevalence at 18 years of age</i></p> <ul style="list-style-type: none"> • 0% (treated) vs. 46% (untreated), $p < 0.05$. 		–	

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Table 3
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Author (year) [country]	Predictor(s)/ indicator(s)	Outcome measure(s)	Method of analysis	Outcome results	Initial GRADE	Outcome GRADE modifi- cation	Overall GRADE
Buyse et al. (2011) [BE] [17]	Idebenone	PEF (litre/min)	Descriptive (Student's <i>t</i> -test)	<i>Mean (SD) change across follow-up (from baseline to 52 weeks)</i> ● 30.8 (54.4) litre/min (treated) vs. -13.8 (51.0) litre/min (untreated), $p=0.039$.	High	Moderate (small sample size)	Moderate
		PEF (% predicated)		<i>Mean (SD) change across follow-up (from baseline to 52 weeks)</i> ● 2.8% (13.8%) (treated) vs. -8.5% (13.8%) (untreated), $p=0.042$.			
Daftary et al. (2007) [US] [18]	Glucocorticoids (DFZ and/or PDN)	PCF	Regression analysis (linear model)	● β : 27.3, SE: 12.1, t: 2.26, $p<0.0328$.	Low	Very low (small sample size)	Very low
Escolar et al. (2011) [US] [19]	Glucocorticoid (PDN) regimen (weekend and daily)	FVC (% predicted)	Descriptive (Student's <i>t</i> -test)	<i>Mean (95% CI) difference in change (weekend vs. daily regimen) across follow-up (from baseline to 12 months)</i> ● 4.6% (-9.8% to 19.1%), p -value (lower)=0.03, p -value (upper)=0.23.	High	-	High
		FEV ₁ (% predicted)		<i>Mean (95% CI) difference in change (weekend vs. daily regimen) across follow-up (from baseline to 12 months)</i> ● 6.1% (-9.1% to 20.4%), p -value (lower)=0.02, p -value (upper)=0.31.			
Fayssoil et al. (2021) [FR] [20]	Functional ability (the GMW Scale)	Right diaphragm TF (%)	Correlation analysis (Spearman's Rho [r])	● $r=-0.45$, $p=0.012$.	Low	-	Low
		Left diaphragm TF (%)		● $r=-0.75$, $p=0.001$.			
		Right diaphragm motion (mm)		● $r=-0.53$, $p<0.0001$.			
		Left diaphragm motion (mm)		● $r=-0.59$, $p<0.0001$.			
		BMI		Right diaphragm motion (mm)			
	Left diaphragm motion (mm)	● $r=0.41$, $p=0.016$					

Henricson et al. (2013) [*] [21]	Glucocorticoids (agents NR)	Invasive ventilation	Descriptive (χ^2 test) ^c	Prevalence in patient > 18 years of age ● 0% (treated) vs. 13% (untreated), $p < 0.001$.	Low	–	Low
		NIV		Prevalence in patient > 18 years of age ● 32% (treated) vs. 56% (untreated), $p < 0.001$.		–	
		FVC (% predicted)	Descriptive (Kruskal-Wallis H test)	Mean for patients 10–12 years of age ● 78% (treated [current user]) vs. 63% (untreated [naive]), $p < 0.05$. Mean for patients 13–15 years of age ● 70% (treated [current user]) vs. 40% (untreated [naive]), $p < 0.05$. Mean for patients 16–18 years of age ● 44% (treated [current user]) vs. 35% (untreated [naive]), $p < 0.05$. Mean for patients > 18 years of age ● 32% (treated [current user]) vs. 22% (untreated [naive]), $p < 0.05$.		–	
Houde et al. (2008) [CA] [22]	Glucocorticoids (DFZ)	FVC (% predicted)	Descriptive (Student's t -test)	Mean (SD) at 16 years of age ● 66% (14%) (treated) vs. 48% (22%) (untreated), $p < 0.007$.	Low	Very low (small sample size)	Very low
Humbertclaude et al. (2012) [FR] [8]	Age at loss of ambulation: < 8 years (Group A), ≥ 8 and < 11 years (Group B), and ≥ 11 years (Group C)	FVC (% predicted)	Descriptive (Student's t -test or Mann-Whitney U test)	Maximum (SD) value ● 74.67% (13.71) (Group A) vs. 83.66% (14.15) years (Group B) vs. 85.01% (14.82) years (Group C), $p = 0.005$. Mean (SD) age at maximum value ● 8.55 (1.83) years (Group A) vs. 9.81 (2.65) years (Group B) vs. 11.67 (2.63) years (Group C), $p < 0.001$. Mean (SD) change per year (descending phase) ● 8.83% (6.37) (Group A) vs. 7.52% (4.22) (Group B) vs. 6.03% (2.94) (Group C), $p = 0.003$. Mean (SD) age at minimum value (descending phase) ● 12.96 (4.06) years (Group A) vs. 16.19 (4.76) years (Group B) vs. 19.90 (6.68) years (Group C), $p < 0.001$.	Low	–	Low

(Continued)

Table 3
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Author (year) [country]	Predictor(s)/ indicator(s)	Outcome measure(s)	Method of analysis	Outcome results	Initial GRADE	Outcome GRADE modifi- cation	Overall GRADE
		FVC (litres)		<p><i>Maximum (SD) value</i></p> <ul style="list-style-type: none"> 1.596 (0.395) litres (Group A) vs. 1.971 (0.536) litres (Group B) vs. 2.569 (0.776) litres (Group C), $p < 0.001$. <p><i>Mean (SD) age at maximum value</i></p> <ul style="list-style-type: none"> 10.26 (1.71) years (Group A) vs. 12.45 (2.04) years (Group B) vs. 14.58 (2.25) years (Group C), $p < 0.001$. <p><i>Minimum (SD) value (descending phase)</i></p> <ul style="list-style-type: none"> 0.680 (0.401) litres (Group A) vs. 1.119 (0.599) litres (Group B) vs. 1.644 (0.943) litres (Group C), $p < 0.001$. <p><i>Mean (SD) age at minimum value (descending phase)</i></p> <ul style="list-style-type: none"> 15.35 (3.37) years (Group A) vs. 17.89 (4.26) years (Group B) vs. 21.05 (6.76) years (Group C), $p < 0.001$. 		–	
		Moderate respiratory insufficiency (FVC < 50%)		<p><i>Mean (SD) age at first occurrence</i></p> <ul style="list-style-type: none"> 12.79 (2.32) years (Group A) vs. 15.12 (3.30) years (Group B) vs. 18.91 (4.61) years (Group C), $p < 0.0001$. 		–	
			Correlation analysis (Spearman's Rho [r])	$r = 0.54, p < 0.0001$.		–	
		Severe respiratory insufficiency (FVC < 30%)		<p><i>Mean (SD) age at first occurrence</i></p> <ul style="list-style-type: none"> 14.72 (1.89) years (Group A) vs. 18.11 (2.62) years (Group B) vs. 22.12 (5.72) years (Group C), $p < 0.0001$. 		–	
			Correlation analysis (Spearman's Rho [r])	$r = 0.67, p < 0.0001$.		–	
		Death due to respiratory failure	Survival analysis (Gray's test)	<p><i>Cumulative incidence proportion at 20 years of age</i></p> <ul style="list-style-type: none"> 19% (Group A) vs. 4.3% (Group B) vs. 1.7% (Group C), $p = 0.03$. 		–	

Iff et al. (2022) [*] [23]	Eteplirsen	FVC (% predicted)	Regression analysis (mixed-effects model)	Mean annual change across follow-up ● -3.47% (treated) vs. -5.95% (untreated), $p = 0.0001$.	Low	–	Low	
Kelley et al. (2019) [*] [25]	ADRB2 genotype variant (Gly16 and ARG16)	Nocturnal ventilation	Kaplan-Meier (log-rank test)	Mean (SE) (95% CI) age at first initiation ● 21.80 (0.59) (20.86 to 23.42) years (Gly16) vs. 25.91 (1.31) (23.35 to 28.49) years (Arg16), $p < 0.05$. Median (SE) (95% CI) age at first initiation ● 22.17 (0.40) (21.38 to 22.96) years (Gly16) vs. 28.30 (4.14) (20.19 to 36.41) years (Arg16), $p < 0.05$.	Low	–	Low	
		Nocturnal ventilation	Regression analysis (Cox proportional hazards model)	HR (Gly16 vs. Arg16): 6.52, SE: 0.71, 95% CI: 1.64 to 25.99, $p < 0.05$.		–		
		Ambulatory	Nocturnal ventilation		HR (ambulatory vs. non-ambulatory): 0.05, SE: 0.79, 95% CI: 0.01–0.23, $p < 0.05$.		–	
		Weight	Nocturnal ventilation		HR (per kg): 1.02, SE: 0.01, 95% CI: 1.00–1.04, $p < 0.05$.		–	
Kelley et al. (2022) [*] [24]	ADRB2 genotype variant (Gly16 vs. Arg16)	FVC (% predicted)	Regression analysis (GAMM)	Coefficient (Gly16 vs. Arg16): -5.80, SE: 1.32, T-value: -4.41, $p < 0.001$.	Low	–	Low	
		FVC (litre)		Patients expressing the Gly16 polymorphism demonstrated higher absolute FVC between the ages of 5.0 and 12.8 years, and lower FVC between the ages of 15.9 and 25.0 years, compared with patients expressing the Arg16 polymorphism ($p < 0.001$) (GAMM coefficients NR).		–		
		Ambulatory	FVC (% predicted)		Coefficient (ambulatory vs. non-ambulatory): -15.11, SE: 1.68, T-value: -9.01, $p < 0.001$.		–	
		Glucocorticoids (agents NR)	FVC (% predicted)		Coefficient (duration in years; first-order smooths): 2.29, SE: 9.00, T-value: 39.28, $p < 0.001$.		–	

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Table 3
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Author (year) [country]	Predictor(s)/ indicator(s)	Outcome measure(s)	Method of analysis	Outcome results	Initial GRADE	Outcome GRADE modifi- cation	Overall GRADE
Khan et al. (2019) [*] [26]	Eteplirsen	FVC (% predicted)	Regression analysis (linear mixed-effects model)	<p><i>Mean (SE) (95% CI) difference in annual change across follow-up treated vs. untreated (10-18 years of age) (exon 51 CINRG DNHS natural history cohort)</i></p> <ul style="list-style-type: none"> • Study 201/202 : 3.80% (0.819%) (2.19% to 5.42%), $p < 0.001$. • Study 204 : 2.34% (0.793%) (0.77% to 3.90%), $p = 0.004$. • Study 301 : 2.21% (0.919%) (0.40% to 4.02%), $p < 0.017$. <p><i>Mean (SE) (95% CI) difference in annual change across follow-up treated vs. untreated (10-18 years of age) (genotyped CINRG DNHS natural history cohort)</i></p> <ul style="list-style-type: none"> • Study 201/202 : 3.48% (0.735%) (2.03% to 4.92%), $p < 0.001$. • Study 204 : 2.01% (0.706%) (0.62% to 3.40%), $p = 0.005$. • Study 301 : 1.89% (0.845%) (0.23% to 3.54%), $p = 0.026$. <p><i>Mean (SE) (95% CI) difference in annual change across follow-up treated vs. untreated (10-18 years of age) (total CINRG DNHS natural history cohort)</i></p> <ul style="list-style-type: none"> • Study 201/202 : 3.37% (0.733%) (1.93% to 4.80%), $p < 0.001$. • Study 204 : 1.90% (0.703%) (0.52% to 3.28%), $p = 0.007$. • Study 301 : 1.77% (0.843%) (0.12% to 3.43%), $p = 0.036$. 	Low	Very low (incon- sis- tency of results)	Very low

Kim et al. (2017) [US] [27]	Timing of initiation of glucocorticoids (DFZ, PDN, or PRED) (early treatment [age ≤ 5 years] vs. late treatment [> 5 years]) Late initiation (i.e., age > 5 years) of glucocorticoids (DFZ, PDN, or PRED)	FVC (litre)	Regression analysis (GEE model)	β (early treatment [age ≤ 5 years] vs. late treatment [> 5 years]): -0.39, SE: 0.12, <i>p</i> < 0.01. β (late treatment [> 5 years] vs. no treatment): -0.21, SE: 0.10, <i>p</i> = 0.04.	Low	-	Low
Koeks et al. (2017) [*] [28]	Glucocorticoids (DFZ, PDN, or PRED)	Ventilation support	Descriptive (χ^2 test)	<i>Prevalence of ventilation support at end of follow-up in patients ≥ 20 years of age</i> • 28% (treated), 58% (previously treated), and 70% (never treated), <i>p</i> = 0.0001.	Low	-	Low
Lee et al. (2016) [US] [29]	The Performance of the Upper Limb (PUL) score	FVC (% predicted) MIP (% predicted) MIP (cmH ₂ O) MEP (% predicted) MEP (cmH ₂ O) PCF (L/min)	Correlation analysis (Pearson's correlation coefficient [r])	$r = 0.70, p \leq 0.0001$. r = 0.52, <i>p</i> = 0.0042. r = 0.72, <i>p</i> = 0.0052. r = 0.73, <i>p</i> < 0.0001. r = 0.81, <i>p</i> = 0.0008. r = 0.46, <i>p</i> = 0.0020.	Low	-	Low
LoMauro et al. (2018) [IT] [30]	Glucocorticoids (agents NR)	FVC (% predicted)	Regression analysis (see article for details)	Predicted FVC was higher among treated patients compared with untreated and previously treated patients, respectively, in the age range 15.1–21.3 years (<i>p</i> < 0.05).	Low	-	Low

(Continued)

Table 3
(Continued)

Author (year) [country]	Predictor(s)/ indicator(s)	Outcome measure(s)	Method of analysis	Outcome results	Initial GRADE	Outcome GRADE modifi- cation	Overall GRADE
Mayer et al. (2017) [*] [31]	Idebenone	FVC (ml)	Regression analysis (random coefficient model)	<p><i>Mean (95% CI) difference in change (treated vs. placebo) across follow-up (from week 13 to week 52)</i></p> <ul style="list-style-type: none"> ● 136 (50 to 223) ml, $p=0.003$. 	Low	—	Low
		FVC (litre)	Regression analysis (Cox proportional hazards model)	<p><i>Patients with persistent decline by any margin across follow-up (from baseline to week 52)</i></p> <ul style="list-style-type: none"> ● HR (idebenone vs. placebo): 0.36 (95% CI: 0.19 to 0.67), $p=0.002$. <p><i>Patients with any relative decline of $\geq 10\%$ across follow-up (from baseline to week 52)</i></p> <ul style="list-style-type: none"> ● HR (idebenone vs. placebo): 0.35 (0.16 to 0.77), $p=0.009$. <p><i>Patients with a persistent relative decline of $\geq 10\%$ across follow-up (from baseline to week 52)</i></p> <ul style="list-style-type: none"> ● HR (idebenone vs. placebo): 0.39 (0.16 to 0.95), $p=0.039$. 		—	
		FVC (% predicted)	Regression analysis (random coefficient model)	<p><i>Mean (95% CI) difference in change (treated vs. placebo) across follow-up (from week 13 to week 52)</i></p> <ul style="list-style-type: none"> ● 4.06% (1.28% to 6.84%), $p=0.005$. 		—	
			Regression analysis (Cox proportional hazards model)	<p><i>Patients with persistent decline by any margin across follow-up (from baseline to week 52)</i></p> <ul style="list-style-type: none"> ● HR (idebenone vs. placebo): 0.43 (95% CI: 0.24 to 0.75), $p=0.003$. <p><i>Patients with any relative decline of $\geq 10\%$ across follow-up (from baseline to week 52)</i></p> <ul style="list-style-type: none"> ● HR (idebenone vs. placebo): 0.46 (0.26 to 0.81), $p=0.008$. <p><i>Patients with a persistent relative decline of $\geq 10\%$ across follow-up (from baseline to week 52)</i></p> <ul style="list-style-type: none"> ● HR (idebenone vs. placebo): 0.54 (0.30 to 1.00), $p=0.048$. 		—	

McDonald et al. (2018) [*] [9]	Brooke Scale	FVC (% predicted)	Descriptive (test NR)	<p><i>Mean (SD) at Brooke Scale scores</i></p> <ul style="list-style-type: none"> • 85.2% (19.1%) at Brooke score 1, 73.3% (18.5%) at Brooke score 2, 57.3% (16.7%) at Brooke score 3, 50.3% (17.7%) at Brooke score 4, 30.9% (18.0%) at Brooke score 5, and 19.1% (13.5%) at Brooke score 6, $p < 0.0001$. 	Low	–	Low
	Glucocorticoids (DFZ, PDN, and/or PRED)		Regression analysis (mixed-effects model)	<p><i>Mean annual change in patients 7 to 18 years of age</i></p> <ul style="list-style-type: none"> • β: -6.06, $p < 0.001$. 		–	
McDonald et al. (2022) [*] [32]	Ataluren	FVC (% predicted)	Kaplan-Meier (log-rank test)	<p><i>Median age at predicted FVC < 60%</i></p> <ul style="list-style-type: none"> • 18.1 years (treated) vs. 15.1 years (untreated), $p = 0.0004$. <p><i>Survival functions (treated vs. untreated): $p = 0.0039$.</i></p>	Low	–	Low
		FVC < 1 litre				–	
Mitelman et al. (2022) [*] [33]	Eteplirsen	FVC (% predicted)	Regression analysis (mixed-effects model)	<p><i>Mean annual change across follow-up</i></p> <ul style="list-style-type: none"> • -3.3% (treated) vs. -6.0% (untreated), $p < 0.0001$. 	Low	Very low (small sample size)	Very low
Pradhan et al. (2006) [IN] [34]	Glucocorticoids (PRED)	PEF (litre/sec)	Descriptive (Student's t -test)	Changes between groups were significant between months 0–2 ($p = 0.002$) and months 2–4 ($p = 0.023$) (data NR).	Low	Very low (small sample size)	Very low
Schara et al. (2001) [DE] [35]	Glucocorticoids (DFZ)	FVC (% predicted)	Descriptive (Mann-Whitney U test)	<p><i>Median (range) across follow-up</i></p> <ul style="list-style-type: none"> • 86.8% (62% to 122%) (treated) and 55% (10% to 105%) (untreated), $p = 0.0173$. 	Low	Very low (small sample size)	Very low
Silversides et al. (2003) [CA] [36]	Glucocorticoids (DFZ)	FVC (litres)	Descriptive (Student's t -test)	<p><i>Mean (SD) at end of follow-up</i></p> <ul style="list-style-type: none"> • 2.0 (0.4) litres (treated) and 1.4 (0.5) litres (untreated), $p = 0.001$. 	Low	–	Low
		FVC (% predicted)		<p><i>Mean (SD) at end of follow-up</i></p> <ul style="list-style-type: none"> • 83% (12%) (treated) and 41% (19%) (untreated), $p < 0.001$. 		–	

(Continued)

Table 3
(Continued)

Author (year) [country]	Predictor(s)/ indicator(s)	Outcome measure(s)	Method of analysis	Outcome results	Initial GRADE	Outcome GRADE modifi- cation	Overall GRADE
Trucco et al. (2022) [NL/FR/UK] [37]	<i>DMD</i> mutations amenable to skipping of exons 44, 45, 51, and 53	FVC (% predicted)	Regression analysis (mixed-effects model)	<i>Mean annual change across follow-up (after 9 years of age)</i> <ul style="list-style-type: none"> ● Exon 44: -2.7%, 95% CI: -4.5 to -1.0, $p < 0.01$. ● Exon 45: -3.4%, 95% CI: -5.1 to -1.8, $p < 0.01$. ● Exon 51: -5.9%, 95% CI: -7.1 to -4.8, $p < 0.01$. ● Exon 53: -4.5%, 95% CI: -6.1 to -3.0, $p < 0.01$. 	Low	–	Low
Tsabari et al. (2021) [IL] [38]	Tamoxifen	FVC (% predicted)	Descriptive	<i>Mean change after 12 months</i> <ul style="list-style-type: none"> ● 5.7% ($p = \text{NS}$) (treated) and -8.6% ($p < 0.05$) (untreated). 	Low	Very low (small sample size)	Very low

Note: Australia (AUS). Belgium (BE). Body mass index (BMI). Canada (CAN). Confidence interval (CI). Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS). Deflazacort (DFZ). Duchenne muscular dystrophy (DMD). Forced expiratory volume in one second (FEV₁). Forced vital capacity (FVC). France (FR). Generalized additive mixed model (GAMM). Gardner Medwin Walton (GMW). Generalized estimating equation (GEE). Hazard ratio (HR). India (IN). Israel (IL). Italy (IT). Maximal voluntary ventilation (MVV). Maximum inspiratory pressure (MIP). Non-invasive ventilation (NIV). Not applicable (NA). Not reported (NR). Not significant (NS). Peak cough flow (PCF). Peak expiratory flow (PEF). Prednisolone (PRED). Prednisone (PDN). Rapid eye movement (REM). Standard deviation (SD). Standard error (SE). The Netherlands (NL). Thickening fraction (TF). Transcutaneous carbon dioxide (TcCO₂). United Kingdom (UK). United States of America (US). ^aIn treated and untreated patients (i.e., meta-analysis cohort). ^bIn untreated patients (i.e., the CINRG DNHS cohort). ^cDerived p -value (based on data reported in the article).

found that the mean FVC was higher in patients treated with deflazacort compared with no treatment (2.0 litres [treated] and 1.4 litres [untreated], $p=0.001$).

Further benefits of glucocorticoids in DMD include improved FEV₁ [12, 14]; maximum transcutaneous carbon dioxide (TcCO₂) and rapid eye movement (REM) TcCO₂ [12]; peak cough flow (PCF) [18]; predicted peak expiratory flow (PEF) [14, 34]; and lower prevalence of ventilation support [16, 21, 28].

DMD mutations and genetic modifiers

We identified four observational studies reporting evidence of effects of *DMD* mutations or genetic modifiers on respiratory health and function in DMD (Table 3). Specifically, in a retrospective cohort study encompassing 327 patients with DMD, Bello et al. [14] investigated the association between mutations and genetic modifiers and predicted FVC, predicted FEV₁, predicted PEF, and use of non-invasive ventilation (NIV), respectively. Mutations situated 3' of *DMD* intron 44 were associated with lower FVC, FEV₁, and PEF, deletions amenable to skipping of exons 51 and 53 with lower FVC and PEF, and deletions amenable to skipping of exon 8 and exon 44 were associated with higher FVC, FEV₁, and PEF. The SPP1 rs28357094 and CD40 rs1883832 minor alleles were found to be associated with lower FVC, FEV₁, and PEF, and CD40 rs1883832 was associated with an increased risk of use of NIV (HR: 1.71 [95% CI: 1.01 to 2.88], $p=0.044$). Moreover, based on data collected as part of the CINRG DNHS, Kelley et al. [25] found that patients with the ADRB2 genotype variant Gly16 required nocturnal ventilation at an earlier mean age than those with the Arg16 variant (21.80 years [95% CI: 20.86 to 23.42] vs. 25.91 years [95% CI: 23.35 to 28.49], $p<0.05$). This corresponded to a higher average risk of nocturnal ventilation across follow-up (HR: 6.52 [95% CI: 1.64 to 25.99], $p<0.05$). In a subsequent study based on the same data source [24], patients expressing the Gly16 polymorphism were reported to demonstrate systematically lower predicted FVC at any given age compared with patients expressing the Arg16 polymorphism ($p<0.01$). Finally, in their retrospective cohort study comprising of 142 UK and French patients, Trucco et al. [37] estimated the mean annual change in predicted FVC across follow-up (after 9 years of age) at -2.7% for exon 44, -3.4% for exon 45, -5.9% for exon 51, and -4.5% for exon 53 (all $p<0.01$).

Other pharmacological interventions

We identified three indirect treatment comparison studies that investigated the effect of eteplirsen on respiratory outcomes, all based on similar sample populations (Table 3). Specifically, Iff et al. [23] included 20 US patients from Study 204 (phase II; open-label), 52 US patients from Study 301 (phase III; open-label), as well as 20 untreated patients from the multi-country CINRG DNHS prospective cohort. Khan et al. [26] included 12, 20, and 42 patients from Study 201/202 (phase II RCT and open-label extension), Study 204, and Study 301, respectively, as well as 172 patients from CINRG DNHS. Finally, Mitelman et al. [33] included 12 patients from Study 201/202 and Study 405 (retrospective cohort study), as well as 20 patients from CINRG DNHS. Iff et al. [23] reported the mean annual change in predicted FVC across the (study-specific) follow-up at -3.47% for patients treated with eteplirsen and -5.95% for those not treated ($p=0.0001$). Corresponding results by Mitelman et al. [33] were reported at -3.3% and -6.0% , respectively ($p<0.0001$). Finally, Khan et al. [26] reported mean differences (treated vs. untreated) in annual changes in predicted FVC across follow-up by study (i.e., 201/202, 204, and 301) in relation to three comparator samples: (1) glucocorticoid-treated patients amenable to exon 51 skipping (exon 51 CINRG DNHS), (2) glucocorticoid-treated and genotyped patients (genotyped CINRG DNHS), and (3) all glucocorticoid-treated patients (total CINRG DNHS). Across the three studies (i.e., 201/202, 204, and 301), the mean difference in annual change (treated vs. untreated) was reported at between 2.21% and 3.80% in relation to the exon 51 CINRG DNHS cohort, 1.89% and 3.48% in relation to the genotyped CINRG DNHS cohort, and 1.77% and 3.37% in relation to the total CINRG DNHS cohort.

We identified two RCTs investigating the effect of idebenone on respiratory outcomes in patients with DMD. Specifically, in the RCT conducted by Buyse et al. [17], involving 21 Belgian patients followed for 12 months, there was a significant difference in the change in mean PEF (litre/min) from baseline to end of follow-up between patients treated with idebenone and untreated patients (30.8 vs. -13.8 , $p=0.039$). Additionally, Buyse et al. [17] estimated the mean change in predicted PEF across the 12-month follow-up at 2.8 and -8.5 for treated and untreated patients, respectively ($p=0.042$). The RCT by Mayer et al. [31] included a multi-national sample of 64 patients with DMD followed for 52 weeks and found that patients treated with idebenone had signifi-

cantly higher FVC at end of follow-up compared with placebo (mean difference in change: 136 ml [95% CI: 50 to 223], $p=0.003$). Idebenone was also associated with lower risk of decline in FVC (decline by any margin, any relative decline of $\geq 10\%$, and persistent relative decline of $\geq 10\%$, all $p \leq 0.039$). Additionally, Mayer et al. [31] estimated the mean difference in change (idebenone vs. placebo) in predicted FVC across follow-up at 4.06 (95% CI: 1.28 to 6.84, $p=0.005$). Idebenone was also associated with lower risk of decline in predicted FVC.

We identified one indirect treatment comparison study, McDonald et al. [32], examining benefits of ataluren in terms of predicted FVC. Specifically, in this study, encompassing 45 patients with DMD from a phase III open-label study (Study 019) and 45 from the CINRG DNHS prospective cohort, the median age at predicted FVC < 60% (indicative of increasing deterioration in respiratory function and an elevated risk of hypoventilation [32]) was estimated at 18.1 years among patients treated with ataluren and 15.1 years in the natural history cohort ($p=0.0004$). Additionally, there was a significant difference between ataluren and controls in the cumulative incidence proportion of patients reaching FVC < 1 litre (predictive of mortality within three years [32]) ($p=0.0039$).

We identified one prospective observational study reporting of effects of tamoxifen on predicted FVC. Among 97 Israeli DMD patients, Tsabari et al. [38] reported that the mean change in predicted FVC after 12 months was not significantly different from zero in those treated with tamoxifen and -8.6% in untreated patients ($p < 0.05$).

Body mass index (BMI) and weight

We identified two retrospective cohort studies describing effects of BMI/weight on respiratory outcomes in DMD. Specifically, Fayssoil et al. [20] reported of a significant relationship between BMI and right diaphragm motion ($r=0.38$, $p=0.002$) and left diaphragm motion ($r=0.41$, $p=0.016$) among 74 French DMD patients. Additionally, Kelley et al. [25] found an increased risk of nocturnal ventilation in heavier patients (HR [per kg]: 1.02 [95% CI: 1.00–1.04], $p < 0.05$).

Functional ability

We identified four observational studies describing effects of functional ability on respiratory outcomes in DMD. Specifically, Fayssoil et al. [20] found the Gardner Medwin Walton scale (a single-item, generic measure of functional disability, with levels ranging

from normal [0] to bedridden [10]) to be significantly associated with right diaphragm thickening fraction (TF) ($r=-0.45$, $p=0.012$), left diaphragm TF ($r=-0.75$, $p=0.001$), right diaphragm motion ($r=-0.53$, $p < 0.0001$), and left diaphragm motion ($r=-0.59$, $p < 0.0001$). Additionally, McDonald et al. [9] estimated mean predicted FVC across categories of Brooke scale scores among 397 patients from CINRG DNHS. Estimates ranged from 82.5% among patients with a Brooke score of 1 (“Starting with arms at the sides, the patient can abduct the arms in a full circle until they touch above the head”) to 19.1% in those with a score of 6 (“Cannot raise hands to the mouth and has no useful function of hands”). Lee et al. [29] investigated the association between the Performance of the Upper Limb (PUL) score and respiratory outcomes in 43 US patients with DMD. Pearson’s correlation coefficient for predicted FVC was estimated at 0.70 ($p \leq 0.0001$). Finally, in two retrospective cohort studies based on data from CINRG DNHS, Kelley et al. [24, 25] found that ambulatory patients had a lower risk of requiring nocturnal ventilation compared with their non-ambulatory counterparts (HR: 0.05 [95% CI: 0.01 to 0.23], $p < 0.05$), as well as better FVC ($p < 0.001$).

Rating of the quality of the evidence

Per the manual of GRADE, we initially attributed included RCTs a high rating and observational studies a low rating. Next, we downgraded the rating for Buyse et al. [17], Daftary et al. [18], Houde et al. [22], Mitelman et al. [33], Pradhan et al. [34], and Schara et al. [35], and Tsabari et al. [38] due to a small sample size; and Khan et al. [26] due to inconsistency of results. Finally, we provided an overall rating of the quality of the evidence of each study (Table 3).

DISCUSSION

As a result of the pathophysiology of the disease, children with DMD typically experience the first signs and symptoms of compromised respiratory health and function – including difficulties with airway clearance and ventilation due to respiratory muscle degeneration and loss of chest wall – around the time at which they start becoming more fully dependent on wheelchairs for mobility. Yet, the trajectory of respiratory impairment over time varies greatly between, as well as within, patients [2]. Indeed, further insights into the sources of this heterogeneity would be expected to not only help improve

respiratory disease management in general, including the specification of patient-centric therapies, but also inform counselling initiatives and discussions of prognosis with affected children and their families, as well as planning of future studies. To that end, in this systematic review, encompassing a total of 29 studies involving children and adults with DMD from 10 countries, we synthesized and graded the body of evidence of factors associated with respiratory health and function in DMD. In summary, our analysis identified 10 sets of predictors:

- Glucocorticoid exposure (high- to very low-quality evidence);
- *DMD* mutations (low-quality evidence);
- DMD genetic modifiers (low-quality evidence);
- Other pharmacological interventions (i.e., ataluren, eteplirsen, idebenone, and tamoxifen) (moderate- to very low-quality evidence);
- BMI and weight (low-quality evidence); and
- Functional ability (low-quality evidence).

There is a considerable body of evidence demonstrating significant effects of glucocorticoids on respiratory health and function in DMD. In particular, compared with no treatment, patients receiving glucocorticoids have been found to have markedly greater FVC as measured at a range of different ages, including 15 years of age (88% vs. 39% [15]), 16 years of age (66% vs. 48% [22]), 18 years of age (81% vs. 34% [16]), and > 18 years of age (32% vs. 22% [21]). However, it is important to note that these estimates were derived from samples with varying demographic and clinical characteristics, as well as different glucocorticoid exposure profiles (e.g., criteria for exposure initiation, duration of exposure, dose, and regimen), and are therefore not directly comparable. Although we found few estimates pertaining to specific glucocorticoid agents or regimens, we did identify one retrospective cohort study [27] comparing late treatment initiation (i.e., at an age > 5 years) with deflazacort, prednisone, or prednisolone with early treatment (i.e., at an age ≤ 5 years) and no treatment, respectively. Interestingly, late treatment was found to be associated with improved FVC compared with the other strata (and detrimental effects of early treatment were also reported for cardiomyopathy fracture risks). The authors note that the lower FVC observed in patients treated early could potentially reflect greater total body growth suppression from longer and/or early glucocorticoid treatment, but more research is needed to understand the mechanisms behind these results. Additionally,

we identified one RCT [19] assessing the equivalence of daily versus weekend prednisone. Although the authors conclude that both regimens are equally safe and effective in preserving muscle strength and preventing BMI increases, a significantly higher predicted FVC was reported for children receiving the weekend regimen (mean difference in annual change: 4.6%).

We found evidence that mutations situated 3' of DMD intron 44, deletions amenable to skipping of exons 51 and 53, the SPP1 rs28357094 and CD40 rs1883832 minor alleles, and the ADRB2 genotype variant Gly16 are associated with weaker muscle leading to worse respiratory outcomes [14, 24, 25] in DMD. In contrast, deletions amenable to skipping of exon 8 and exon 44 have been reported to be associated with better respiratory health and function [14]. That being said, in many studies, the causal effect of specific *DMD* mutations and/or genetic modifiers are not easily quantified due to concurrent exposure to pharmacological interventions, predominantly glucocorticoids. More research is thus needed to further establish the genotype-phenotype association in terms of respiratory health and function in DMD to inform treatment strategies, as well as the selection of patients to research.

Ataluren is an orally administered, small-molecule compound for nonsense mutation DMD promoting readthrough of an in-frame premature stop codon to enable the production of full-length dystrophin. We found one indirect treatment comparison study [32] quantifying the benefits of this therapy in terms of respiratory outcomes in relation to natural history controls from CINRG DNHS. Specifically, based on propensity score matching, ataluren was shown to be associated with a three-year delay in predicted FVC decreasing to < 60%, as well as significant improvements in the cumulative incidence proportion of reaching an absolute FVC < 1 litre [9, 10].

We found three indirect treatment comparison studies [23, 26, 33] quantifying the effects of eteplirsen, a phosphorodiamidate morpholino oligomer promoting dystrophin production by restoring the translational reading frame of the *DMD* gene in patients with gene mutations amenable to exon 51 skipping. Specifically, by pooling treated patients from phase II and III clinical trials, as well as a retrospective cohort study, with natural history controls from CINRG DNHS, eteplirsen was shown to result in a significantly reduced annual decline in predicted FVC compared with standard of care (e.g., -3.47% vs. -5.95% [23] and -3.3% vs. -6.0% [33]).

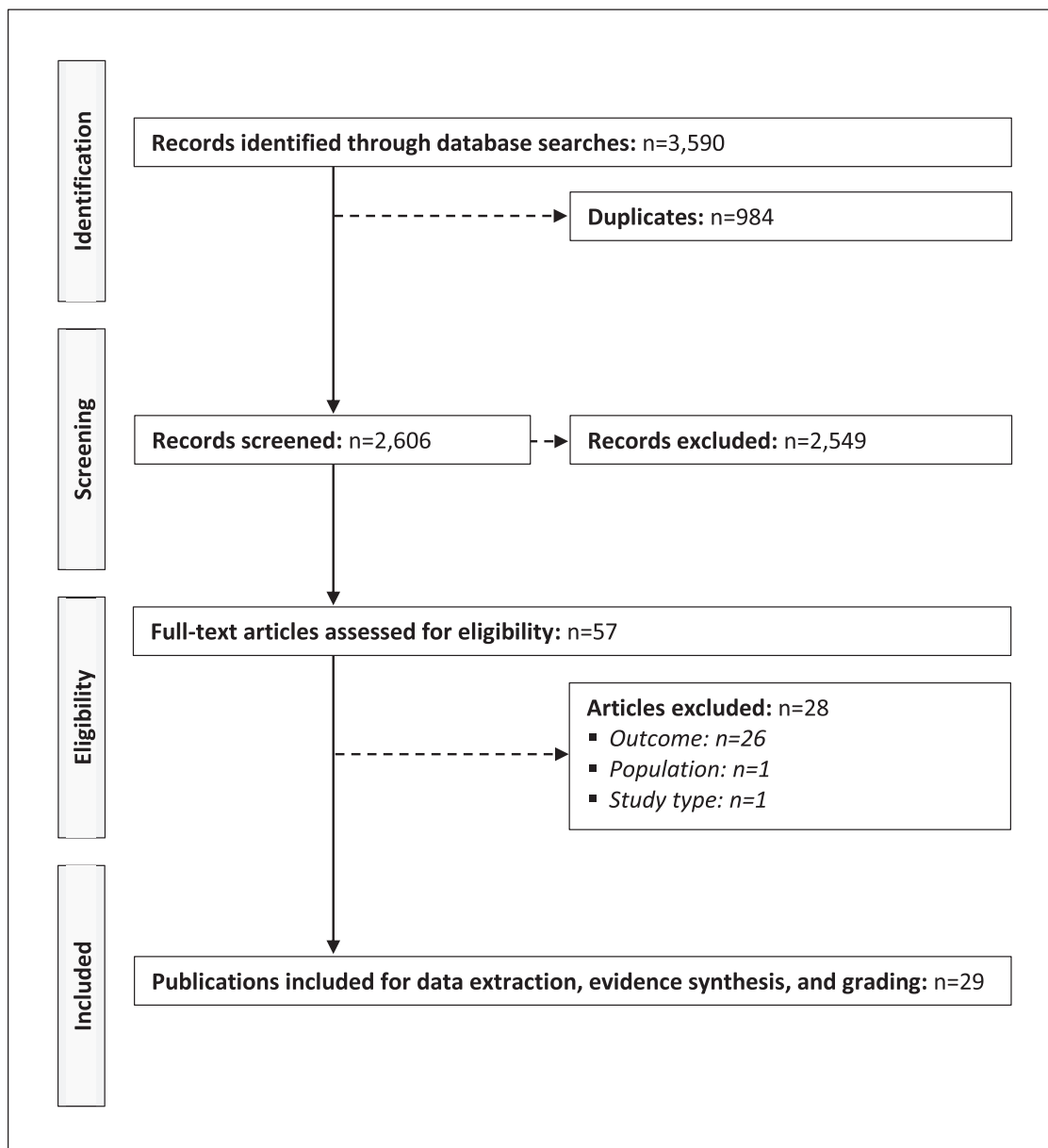


Fig. 1. PRISMA diagram of the selection process of the included publications.

We found two RCTs [17, 31] investigating the effect of idebenone – a short-chain benzoquinone with anti-oxidant properties – on FVC or PEF in children and adults with DMD, both of which demonstrated significant treatment effects versus no treatment. However, it is important to mention that subsequent clinical trials [39, 40] were terminated due to lack of efficacy and that idebenone currently is not approved nor recommended for use in patients with DMD [2].

We found one prospective observational study, Tsabari et al. [38], examining the effects of tamoxifen – a selective estrogen receptor modulator – on respiratory health and function in DMD. Although the mean annual change in predicted FVC was not statistically significant from zero in the exposed cohort, untreated patients experienced a significant decline of 8.6% ($p < 0.05$). Despite these data, analogous to idebenone, tamoxifen is currently not approved nor recommended for the treatment of DMD [2, 41].

We found two observational studies reporting of significant effects of BMI or weight on respiratory outcomes in DMD. Interestingly, Fayssol et al. [20] described a positive association between BMI and right and left diaphragm motion, whereas Kelley et al. [25] found a negative association between weight and risk of requiring nocturnal ventilation support. More research is needed to further establish the impact of these factors, in particular considering the typical distribution of weight over time in DMD, where younger children commonly struggle with obesity due to glucocorticoid exposure and reduced physical activity and many adolescents and adults often become underweight due to functional impairment and feeding problems.

Functional ability, quantified by the Gardner Medwin Walton scale [20], the Brooke scale [9], and current ambulatory status [24, 25], was found to be significantly associated with several respiratory outcomes in DMD, including right and left diaphragm thickening fraction and motion, predicted FVC, and nocturnal ventilation. Similarly, Lee et al. [29] reported upper extremity functioning measured using the PUL to be significantly associated with predicted FVC (among other measures). Yet, little is known of the comparative ability of the above-mentioned scales, or other measures of functional ability, to accurately predict respiratory health and function in DMD and more research is needed to further establish the relationship between degeneration and wasting of different muscle groups and respiratory health and function in DMD.

Strengths of our review include the unrestricted search strategy, as well as the comprehensive evidence grading. Concerning limitations, we were unable to perform a formal meta-analysis, including assessment of, for example, heterogeneity and publications bias, due to the wide range of respiratory outcomes identified. Additionally, we limited the search strategy to include only studies published after calendar year 2000, and we did not pursue grey literature, which means that data pertaining to the impact of some interventions might not have been fully identified. Finally, due to the observational nature of most of the synthesized evidence, conclusions regarding causality should be made with some caution.

In conclusion, we identified a total of 10 factors associated with respiratory health in function in DMD, encompassing both pharmacological therapies, genetic mutations and modifiers, and patient clinical characteristics. Yet, more research is needed to further delineate sources of respiratory heterogene-

ity, in particular the genotype-phenotype association and the impact of novel DMD therapies in a real-world setting. Our synthesis and grading should be helpful to inform clinical practice and future research of this heavily burdened patient population.

DECLARATIONS

FUNDING

This study was funded by PTC Therapeutics.

CONFLICTS OF INTEREST

Dr Alemán reports being sub-investigator of clinical trials in DMD sponsored by Pfizer and Reveragen, and receiving a research grant from PTC. Ms Zhang, Dr Werner, and Dr Tomazos are employees of PTC Therapeutics and may own stock/options in the company. Professor Lochmüller reports being principal investigator of clinical trials in DMD sponsored by Pfizer, PTC Therapeutics, Santhera, Sarepta, and Reveragen. Professor Quinlivan reports having received honoraria for teaching, consultancy, and iDMC membership from PTC therapeutics, Sanofi-Genzyme, Santhera, Sarepta, TRiNDS, and Astellas, as well as research and trial funding from PTC therapeutics, Santhera, and MDUK. The remaining authors have no conflicts of interest.

DATASETS/DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available within the article and/or its supplementary material.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JND-230094>.

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