

A Systematic Review and Meta-analysis on the Epidemiology of the Muscular Dystrophies

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ABSTRACT: *Background:* The muscular dystrophies are a heterogeneous group of genetic muscle diseases with variable distribution of weakness and mode of inheritance. *Methods:* We previously performed a systematic review of worldwide population-based studies on Duchenne and Becker muscular dystrophies; the current study focused on the epidemiology of other muscular dystrophies using Medline and EMBASE databases. Two reviewers independently reviewed all abstracts, full-text articles, and abstracted data from 1985 to 2011. Pooling of prevalence estimates was performed using random-effect models. *Results:* A total of 1104 abstracts and 167 full-text articles were reviewed. Thirty-one studies met all eligibility criteria and were included in the final analysis. The overall pooled prevalence of combined muscular dystrophies was 16.14 (confidence interval [CI], 11.21-23.23) per 100,000. The prevalence estimates per 100,000 were 8.26 (CI, 4.99-13.68) for myotonic dystrophy, 3.95 (CI, 2.89-5.40) for facioscapulohumeral dystrophy, 1.63 (CI, 0.94-2.81) for limb girdle muscular dystrophy, and 0.99 (CI, 0.62-1.57) for congenital muscular dystrophies. *Conclusions:* The studies differed widely in their approaches to case ascertainment, and substantial gaps remain in the global estimates of many other types of muscular dystrophies. Additional epidemiological studies using standardized diagnostic criteria as well as multiple sources of case ascertainment will help address the economic impact and health care burden of muscular dystrophies worldwide.

RÉSUMÉ: *Revue systématique et méta-analyse de l'épidémiologie des dystrophies musculaires.* *Contexte:* Les dystrophies musculaires constituent un groupe hétérogène de maladies musculaires génétiques ayant une distribution de la faiblesse et une hérédité variables. *Méthode:* Nous avons effectué antérieurement une revue systématique des études populationnelles du monde entier sur la dystrophie musculaire de Duchenne et celle de Becker. Cette étude, effectuée dans les bases de données Medline et EMBASE, cible l'épidémiologie d'autres dystrophies musculaires. Deux examinateurs indépendants ont revu tous les résumés, le texte intégral des articles et les données publiées de 1985 à 2011. Le regroupement des estimés de prévalence a été effectué au moyen de modèles à effets aléatoires. *Résultats:* En tout, 1104 résumés et 167 articles en texte intégral ont été revus. Trente et une études rencontraient tous les critères d'éligibilité et ont été incluses dans l'analyse finale. La prévalence globale des dystrophies musculaires combinées était de 16,14 (intervalle de confiance [IC] de 11,21 à 23,23) par 100,000 de population. Les estimés de prévalence par 100,000 étaient de 8,26 (IC : 4,99 à 13,68) pour la dystrophie myotonique, 3,95 (IC : 2,89 à 5,40) pour la myopathie facio-scapulo-humérale, 1,63 (IC : 0,94 à 2,81) pour la myopathie scapulo-humérale et 0,99 (IC : 0,62 à 1,57) pour les dystrophies musculaires congénitales. *Conclusions:* Les études utilisaient des approches sensiblement différentes pour l'identification des cas et il existe des écarts considérables dans les estimés globaux de plusieurs autres types de dystrophies musculaires. D'autres études épidémiologiques utilisant des critères diagnostiques standardisés ainsi que de multiples sources d'identification des cas aideront à faire face à l'impact économique et au fardeau des soins de santé engendrés par les dystrophies musculaires à l'échelle mondiale.

Keywords: Epidemiology, muscular dystrophies, population-based, prevalence systematic review

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The muscular dystrophies are a group of hereditary degenerative disorders associated with progressive muscle weakness. They can be transmitted as autosomal dominant, autosomal recessive, or X-linked traits; sporadic cases may also arise as a result of de novo mutation. Early presentation during childhood is generally associated with a more severe phenotype. Traditionally, the diagnosis is based on clinical and pathological features; more recently, the majority of muscular dystrophies have been classified based on molecular genetic confirmation.¹ Research toward effective therapies is ongoing. Regional population-based prevalence estimates for the muscular dystrophies exist, but more precise pooled estimates representing the global burden of

disease are unavailable. Robust pooled estimates are essential to facilitate the interpretation of clinical studies on molecular epidemiology, natural history, and impact of potential treatments.

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In addition, analysis of economic impact and health care burden are contingent upon precise prevalence estimates. We previously reported on the epidemiology of Duchenne and Becker muscular dystrophies.² The purpose of this study is to systematically evaluate the worldwide incidence and prevalence of other muscular dystrophies including myotonic dystrophy, facioscapulohumeral dystrophy, limb girdle muscular dystrophy, and congenital muscular dystrophy.

Myotonic dystrophy is an autosomal dominant disorder associated with clinical myotonia, progressive muscular weakness, and extramuscular manifestations such as cardiac arrhythmia and endocrine dysfunction. It is classified based on molecular genetic testing showing an expansion of trinucleotide (CTG) repeats on chromosome 19q13.3 for type 1 and tetranucleotide (CCTG) repeats on chromosome 3q21.3 for type 2 disease.^{3,4} Myotonic dystrophy type 1 can be subdivided into several clinical phenotypes depending on the age of presentation, including congenital, early childhood, adult, and late-onset forms. Congenital myotonic dystrophy type 1 is associated with multiple joint contractures, severe hypotonia, and generalized weakness; dysphagia and respiratory insufficiency leads to increased mortality during the neonatal period.⁵

Facioscapulohumeral dystrophy is an autosomal dominant disorder resulting from deletions within the D4Z4 repeat region located on chromosome 4q35 for type 1; mutations of *SMCHD1* on chromosome 18p11.32 in association with a permission chromosome 4 allele account for the majority of type 2 disease.^{6,7} It results in progressive atrophy and, frequently, asymmetrical weakness in a descending pattern. Early-onset facioscapulohumeral dystrophy is associated with more severe weakness as well as central nervous system involvement such as mental retardation, epilepsy, retinal vasculopathy, and sensorineural hearing loss.⁸

Limb girdle muscular dystrophy refers to a heterogeneous group of autosomal muscular dystrophies with progressive weakness affecting predominantly the hip and shoulder girdles. It is further classified as either type 1 (dominant) or type 2 (recessive) disease based on the mode of inheritance, and labeled consecutively by letters of the alphabet according to the sequence of genes identified. It is related to mutations involving extracellular matrix or external membrane proteins, enzymes or proteins with putative enzymatic function, sarcolemma-associated proteins, nuclear membrane proteins, sarcomeric proteins, and other as-yet unspecified disorders.⁹

Congenital muscular dystrophy refers to a heterogeneous group of early-onset muscular dystrophies. Affected children are usually symptomatic at birth or before their first 6 months of life. The salient features include hypotonia, muscle weakness, and reduced deep tendon reflexes, with or without joint contractures. Feeding and respiratory insufficiency are common; additional features may include microcephaly, eye anomalies, cerebral malformation, joint laxity, muscle atrophy, or hypertrophy. It is further subdivided into disorders involving: (1) the basal lamina or extracellular matrix proteins; (2) alpha-dystroglycanopathy; (3) sarcoplasmic reticulum calcium release channel; (4) endoplasmic reticulum proteins; (5) nuclear envelope proteins; (5) mitochondrial membrane proteins; and (6) other unspecified dystrophies.¹⁰

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METHODS

Search Strategy

The search strategy was developed by the study authors with expertise in neurology and epidemiology and in consultation with a research librarian with systematic review expertise. The comprehensive systematic review was conducted on January 28, 2011, using Medline and EMBASE databases to identify worldwide population-based studies on the incidence and prevalence of muscular dystrophies. References were exported and managed using EndNote X5.

Study Selection

Two independent reviewers screened abstracts to determine eligibility for full-text review. Abstracts and titles of all references were screened independently, in duplicate, to identify original research articles reporting on the prevalence or incidence of muscular dystrophies, including congenital muscular dystrophy, myotonic dystrophy, facioscapulohumeral muscular dystrophy, limb girdle muscular dystrophy, Emery-Dreifuss muscular dystrophy, oculopharyngeal muscular dystrophy, severe childhood autosomal recessive muscular dystrophy, Duchenne muscular dystrophy, or Becker muscular dystrophy. Articles were included if they met the following criteria: (1) original research, (2) population-based, (3) reported an incidence or prevalence estimate of any muscular dystrophy, and (4) published in English or French. Studies were considered population-based if they used a sampling method meant to be representative of the entire population and/or were completed in a defined geographic area of known population size. Studies were excluded if they were clearly not population-based, did not provide an estimate of incidence or prevalence, reported non-original data (i.e. reviews, letters, editorials), or if the study data were collected before 1985. The decision to include publications from 1985 onward was based on the advent of molecular genetic testing as well as magnetic resonance imaging studies after 1985. The reference lists of excluded non-original data studies and the studies that were included in the review were manually searched for additional articles.

Data Abstraction

Two reviewers independently screened the full-text articles of abstracts identified in the first phase. Demographic data including age characteristics, race, sex, and geographic location were recorded. Diagnostic data were also collected, as were the sources of those data and the definitions/diagnostic criteria for muscular dystrophy. Incidence and prevalence estimates of muscular dystrophy from each study were recorded, along with any stratification by age or gender, if provided. Agreement at the abstract review stage was calculated using the Kappa statistic (see <http://www.cochrane.org/handbook/726-measuring-agreement>). Disagreements between reviewers during abstract screening, full-text review, and/or data extraction were resolved by consensus and the use of a third reviewer as required.

Study Quality

Two reviewers independently completed a quality review for each study using a modified existing quality assessment tool.¹² Quality scores were determined from eight key questions pertaining to sample representativeness, condition assessment, and

statistical methods. Each study was given a quality score of 0 to 8 based on fulfillment of the quality criteria, as previously described.²

Statistical Analysis

Estimates of point and period prevalence can vary widely depending on the natural history of a disease; in the current study, both forms of prevalence were considered together because of the irreversible nature of muscular dystrophy. The pooled prevalence of combined dystrophies including Duchenne, Becker, congenital, facioscapulohumeral, limb girdle, myotonic overall and myotonic, facioscapulohumeral, limb girdle, Emery-Dreifuss, and congenital muscular dystrophies by age group per 100,000 were calculated where appropriate. Estimates using total population (males and females) as the denominator were considered separately from those including only children in the denominator.

To be included in the meta-analysis, studies needed to report the number of cases and sample size, the estimate with accompanying confidence intervals, or the information required to calculate the missing values. To assess for significant between-study heterogeneity, the Cochrane Q statistic was calculated and I^2 was used to quantify the magnitude of between-study heterogeneity. An a priori decision was made to use a random effects model

because of the heterogeneous nature of the condition. Publication bias was investigated visually using funnel plots and statistically using Begg's and Egger's tests. For all tests, a p value less than 0.05 was deemed to be statistically significant. All statistical analyses were carried out in R (version 2.14)¹³; the *meta* package (version 1.6-1.2010) was used to produce the stratified analyses and forest plots.¹⁴ The *metafor* package was used to produce the pooled estimates using restricted maximum likelihood estimation.¹⁵

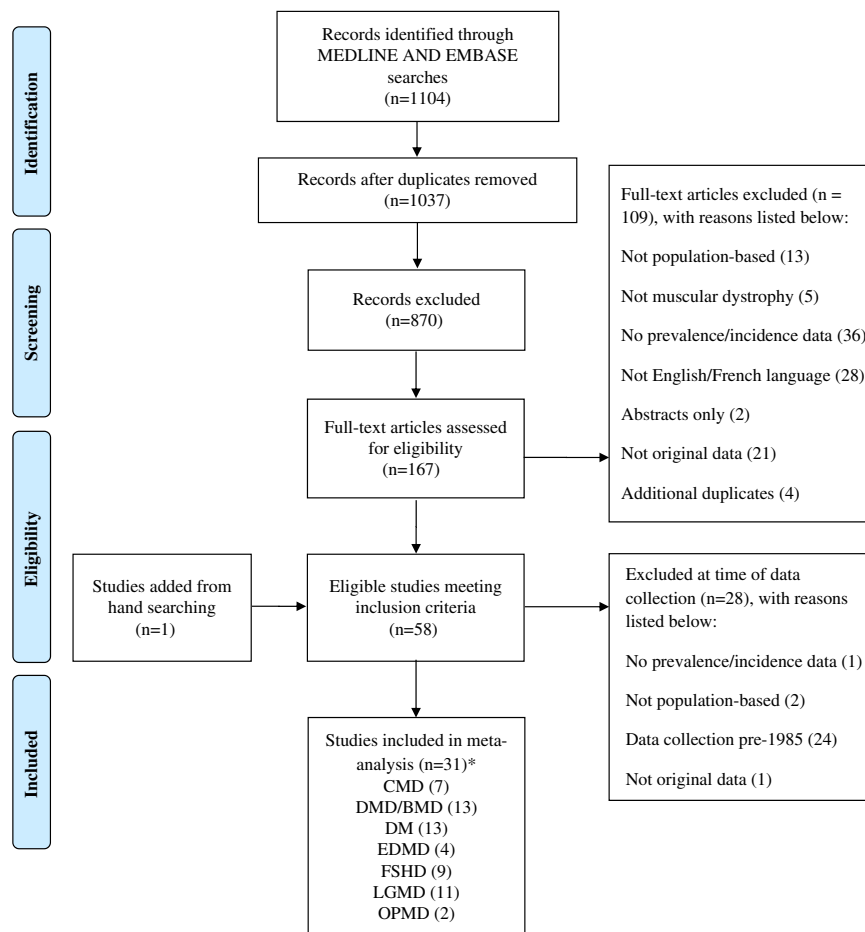
RESULTS

Identification and Description of Studies

The results of the combined search strategy yielded a total of 1104 citations; 167 articles met the criteria for full-text review. Thirty-one studies met all eligibility criteria and were included in the systematic review (Figure 1). Twenty-four studies were related to other muscular dystrophies apart from Duchenne and Becker muscular dystrophies.

Systematic Review of Muscular Dystrophies

Sixteen of the studies were conducted in Europe, including Darin and Tulinius,¹⁶ De Munain et al,¹⁷ Fanin et al,^{18,19}



DMD = Duchenne muscular dystrophy, BMD = Becker muscular dystrophy, DM = myotonic dystrophy, FSHD = facioscapulohumeral muscular dystrophy, LGMD = limb girdle muscular dystrophy, EDMD = Emery-Dreifuss muscular dystrophy, CMD = congenital muscular dystrophy. *several publications reported data on multiple types of muscular dystrophies.

Figure 1: Flow chart of study selection.

Table 1: Prevalence studies on myotonic dystrophy listed by study population and year of publication

First author, publication year, country, reference number	Age (years)	Reference for diagnostic criteria	Data source	Diagnosis established by	Prevalence date	Population size (i.e. denominator)	Number of cases	Prevalence (95% CI) per 100,000
Chung, 2003, China ³⁵	Children <19	Emery, 1991; World Federation of Neurology Research Group, 1988	Hospital/clinic chart review	Medical chart review, muscle biopsy, serum creatine kinase	2001	1,335,469	5	0.37
Darin, 2000, Sweden ¹⁶	Children <16	Emery, 1997	Mailed survey, hospital/clinic chart review, administrative databases	Clinical examination, serum creatine kinase, \pm family history, \pm muscle biopsy, \pm EMG, \pm genetic test	1995	359,676	18	5.00 (2.97-7.91)
De Munain, 1993, Spain ¹⁷	All	Harper, 1989	Mailed survey, hospital/clinic chart review, family history	Medical chart review, \pm genetic test	1991	689,836	183	26.53
Ford, 2006, New Zealand ³⁸	All, 16-74	Unspecified	Hospital/clinic chart review, Patient registry, Family History	Clinical examination, medical chart review, \pm genetic test for DM1 in 10/21 individuals	2001	181,539	21	11.57
Hsiao, 2003, Taiwan ³⁶	All, 1-80	Unspecified	Hospital/clinic chart review, family history	Medical chart review, \pm genetic test for DM1 in 59/96 individuals	2001	21,172,626	96	0.45
Hughes, 1996, Ireland ²⁰	All, 0.3-84	Emery, 1994; World Federation of Neurology Research Group, 1988	Mailed survey, hospital/clinic chart review, administrative databases, patient registry	Clinical examination, medical chart review	1994	1,573,282	134	8.52
Magee, 1999, Ireland ²¹	All	Harper; 1973; Griggs and Wood, 1989; Harley et al 1993	Mailed survey, hospital/clinic chart review, administrative databases, family history	Medical chart review, \pm DM1 genetic test in 110/311 at risk individuals	1991	1,500,000	185	12.33
Medica, 1997, Croatia ²²	All	Griggs and Woods, 1989	Hospital/clinic chart review, patient registry, relatives	Clinical examination, medical chart review, \pm DM1 genetic test in 27/33 cases	1989	204,646	33	16.13
Mladenovic, 2006, Serbia ²³	All, 1-60	Walton and Natrass, 1954; Gennarelli et al, 1999	Hospital/clinic chart review, patient registry	Medical chart review, Genetic test	2002	1,602,226	101	6.30 (5.13-7.66)
Nakagawa, 1991, Japan ³⁷	All	Griggs et al, 1989	Hospital/clinic chart review	Clinical examination, muscle biopsy, serum creatine kinase	1989	1,225,496	112	9.14
Norwood, 2009, England ²⁶	All	Emery, 1998; Kaplan, 2009	Hospital/clinic chart review, administrative database, relatives, patient registry	Clinical exam, medical chart review, genetic test, muscle biopsy	2007	2,990,000	316 DM1 = 311 DM2 = 5	10.57 10.40 0.17
Segel, 2003, Israel ³⁴ (Jewish population)	All	Harper, 1989	Hospital/clinic chart review, family history	Clinical examination, medical chart review, \pm DM1 genetic test in 307/416 cases	1994	4,441,000	416	9.37
Siciliano, 2001, Italy ²⁷	All, 6-86	Novelli et al, 1993; Walton and Natrass, 1954	Mailed survey, hospital/clinic chart review, patient registry, relatives	Medical chart review, \pm DM1 genetic test in 176/199 cases	1999	2,138,101	199	9.31

\pm = with or without; CI = confidence interval; DM1 = myotonic dystrophy type 1; DM2 = myotonic dystrophy type 2; EMG = electromyography.

Table 2: Prevalence studies on facioscapulohumeral dystrophy listed by study population and year of publication

First author, year, country, reference	Age (years)	Reference for diagnostic criteria	Data source	Diagnosis established by:	Prevalence date	Population size	Number of cases	Prevalence (95% CI) per 100,000
Darin, 2000, Sweden ¹⁶	Children <16	Emery, 1997	Mailed survey, hospital/clinic chart review, administrative databases	Clinical examination, serum creatine kinase, \pm family history, \pm muscle biopsy, \pm EMG, \pm genetic test	1995	359,676	3	0.83 (0.17-2.44)
Chung, 2003, China ³⁵	Children <19	Emery, 1991; World Federation of Neurology Research Group, 1988	Hospital/clinic chart review	Medical chart review, muscle biopsy, serum creatine kinase	2001	1,335,469	1	0.07
El-Tallawy, 2005, Egypt ³³	All	Padberg, 1991	Door-to-door survey	Clinical examination, serum creatine kinase, \pm muscle biopsy, \pm EMG	1997	52,203	1	1.92
Flanigan, 2001, United States ³⁹	All	Not specified	Hospital/clinic chart review, family history	Clinical examination, medical chart review, genetic test	Undefined	3,070,886	208	6.77
Hughes, 1996, Ireland ²⁰	All, 0.3-84	Emery, 1994; World Federation of Neurology Research Group, 1988	Mailed survey, hospital/clinic chart review, administrative databases, patient association	Clinical examination, medical chart review	1994	1,573,282	50	3.18
Mostacciolo, 2009, Italy ²⁵	All, 26-87	Emery, 1997	Hospital/clinic chart review	Clinical examination, medical chart review, serum creatine kinase, genetic test, muscle biopsy	2004	871,190	40	4.59
Nakagawa, 1991, Japan ³⁷	All	Walton and Nattrass, 1954	Hospital/clinic chart review	Clinical examination, Muscle biopsy, Serum creatine kinase	1989	1,225,496	25	2.04
Norwood, 2009, England ²⁶	All	Emery, 1998; Kaplan, 2009	Hospital/clinic chart review, administrative database, relatives, patient database	Clinical examination, Medical chart review, genetic test, muscle biopsy	2007	2,990,000	118	3.95 (3.27-4.73)
Sposito, 2005, Italy ²⁸	All, 12-81	Tawil et al, 1994	Hospital/clinic chart review, administrative database, relatives	Clinical examination, medical chart review, genetic test	2004	1,259,400	58	4.61

\pm = with or without; CI = confidence interval; EMG = electromyography.

Table 3: Prevalence studies on limb girdle muscular dystrophy listed by study population and year of publication

First author, year, country, reference	Age (years)	References for the diagnostic criteria	Data source	Diagnosis established by:	Prevalence date	Population size	Number of cases	Prevalence (95% CI) per 100,000
Darin, 2000, Sweden ¹⁶	Children <16	Emery, 1997	Mailed survey, hospital/clinic chart review, administrative databases	Clinical examination, serum creatine kinase, \pm family history, \pm muscle biopsy, \pm EMG	1995	359,676	3	0.83 (0.17-2.44)
Chung, 2003, China ³⁵	Children <19	Emery, 1991; World Federation of Neurology, 1988	Hospital/clinic chart review	Medical chart review, muscle biopsy, serum creatine kinase, EMG	2001	1,335,469	4	0.30
El-Tallawy, 2005, Egypt ³³	All	Bushby, 1995	Door-to-door survey	Clinical examination, serum creatine kinase, \pm muscle biopsy, \pm EMG	1997	52,203	3	5.75
Fanin, 1997, Italy ¹⁸	All, 2-44	Unspecified	Hospital/clinic chart review	Clinical examination, genetic test, medical chart review, muscle biopsy, serum creatine kinase	1996	2,319,147	18	0.56
Fanin, 2005, Italy ¹⁹	All	Unspecified	Hospital/clinic chart review	Clinical examination, Serum creatine kinase, Muscle biopsy, Genetic test	2001	3,801,045	36	0.95
Hughes, 1996, Ireland ²⁰	All, 0-84	Emery, 1994; World Federation of Neurology, 1988	Mailed survey, hospital/clinic chart review, administrative databases, patient registry	Clinical examination, medical chart review	1994	1,573,282	18	1.14
Nakagawa, 1991, Japan ³⁷	All	Walton and Nattrass, 1954	Hospital/clinic chart review	Clinical examination, muscle biopsy, serum creatine kinase	1989	1,225,496	19	1.55
Norwood, 2009, England ²⁶	All	Emery, 1998; Kaplan, 2009	Hospital/clinic chart review, administrative database, relatives, patient database	Clinical examination, medical chart review, genetic test, muscle biopsy	2007	2,990,000	68	2.27 (1.77-2.88)
Stensland, 2011, Norway ²⁹	All	Undefined	Hospital/clinic chart review, relatives	Medical chart review, questionnaire, genetic test	2008	Undefined	88	1.85
Urtasun, 1998, Spain ³⁰	All, 16-71	Bushby and Beckman, 1995	Hospital/clinic chart review, registry	Clinical examination, medical chart review, genetic test, muscle biopsy, serum creatine kinase	1997	695,750	48	6.90
van der Kooi, 1996, Netherlands ³¹	All, 3-69	Unspecified	Hospital/clinic chart review, relatives	Clinical examination, medical chart review, genetic test, muscle biopsy, serum creatine kinase	1993	15,239,182	105	0.69

\pm = with or without; CI = confidence interval; EMG = electromyography.

Table 4: Prevalence studies on Emery-Dreifuss muscular dystrophy listed by study population and year of publication

First author, year, country, reference	Age (years)	References for diagnostic criteria	Data source	Diagnosis established by:	Prevalence date	Population size	Number of cases	Prevalence (95% CI) per 100,000
Chung, 2003, China ³⁵	Children <19	Emery, 1991; World Federation of Neurology, 1988	Hospital/clinic chart review	Medical chart review, muscle biopsy, serum creatine kinase	2001	1,335,469	3	0.22
El-Tallawy, 2005, Egypt ³³	All ages	Undefined	Door-to-door survey	Clinical examination, serum creatine kinase, \pm muscle biopsy, \pm EMG	1997	52,203	1	1.92
Hughes, 1996, Ireland ²⁰	All ages, 0.3-84	Emery, 1994; World Federation of Neurology, 1988	Mailed survey, hospital/clinic chart review, administrative databases, patient registry	Clinical examination, medical chart review	1994	1,573,282	7	0.44
Norwood, 2009, England ²⁶	All	Emery, 1998; Kaplan, 2009	Hospital/clinic chart review, administrative database, relatives, patient database	Clinical examination, medical chart review, genetic test, muscle biopsy	2007	2,990,000	4	0.13 (0.04-0.34)

\pm = with or without; CI = confidence interval; EMG = electromyography.

Table 5: Prevalence studies on congenital muscular dystrophy listed by study population and year of publication

First author, year, country, reference	Age (years)	References for the diagnostic criteria	Data source	Diagnosis established by:	Prevalence date	Population Size	Number of cases	Prevalence (95% CI) per 100,000
All ages								
Hughes, 1996, Ireland ²⁰	All ages, 0.3-84	Emery, 1994; World Federation of Neurology, 1988	Mailed survey, hospital/clinic chart review, administrative data, registry	Clinical examination, chart review	1994	1,573,282	9	0.57
El-Tallawy, 2005, Egypt ³³	All ages	Not specified	Door-to-door community survey	Clinical examination, serum creatine kinase, \pm muscle biopsy, \pm EMG	1997	52,203	2	3.83
Nakagawa, 1991, Japan ³⁷	All ages	Fukuyama, 1960	Hospital/clinic chart review	Clinical examination, serum creatine kinase, muscle biopsy	1989	1,225,496	14	1.14
Norwood, 2009, England ²⁶	All ages	Emery, 1998; Kaplan, 2009	Hospital/clinic chart review, administrative database, relatives, registry	Clinical examination, serum creatine kinase, muscle biopsy, genetic testing	2007	2,999,000	27	0.90
Children only								
Chung, 2003, China ³⁵	Children <19 yrs	Emery, 1991; World Federation of Neurology, 1988	Hospital/clinic chart review	Clinical examination, serum creatine kinase, muscle biopsy, EMG	2001	1,335,469	4	0.30
Darin, 2000, Sweden ¹⁶	Children <16	Emery, 1997	Mailed survey, hospital/clinic chart review, Administrative databases	Clinical examination, serum creatine kinase, \pm family history, \pm muscle biopsy, \pm EMG	1995	359,676	9	2.50 (1.14-4.75)
Mostacciolo, 1996, Italy ²⁴	Children <21	International Consortium on CMD	Hospital/clinic chart review, Relatives, Registry	Clinical examination, serum creatine kinase, muscle biopsy	1993	2,586,830	17	0.66

\pm = with or without; CI = confidence interval; EMG = electromyography.

Table 6: Prevalence studies on oculopharyngeal muscular dystrophy listed by study population and year of publication

First author, year, country, reference	Age	References for the diagnostic criteria	Data source	Diagnosis established by:	Prevalence date	Population size	Number of cases	Prevalence (95% CI) per 100,000
Blumen, 1997, Israel ³²	All	Not specified	Hospital/clinic chart review, neighborhood and community surveys	Clinical examination, medical chart review	Undefined	70,000	117	167.14
Norwood, 2009, England ²⁶	All	Emery, 1998; Kaplan, 2009	Hospital/clinic chart review, administrative database, relatives, patient database	Clinical examination, medical chart review, genetic test, muscle biopsy	2007	2,990,000	4	0.13 (0.04-0.34)

CI = confidence interval.

Hughes et al,²⁰ Magee and Nevin,²¹ Medica et al,²² Mladenovic et al,²³ Mostacciolo et al,^{24,25} Norwood et al,²⁶ Siciliano et al,²⁸ Sposito et al; Stensland et al,²⁹ Urtasun et al,³⁰ and van der Kooi et al.³¹ Three studies were from the Middle East, including Blumen et al,³² El-Tallawy et al,³³ and Segel et al³⁴; three studies were from Asia, including Chung et al,³⁵ Hsiao et al,³⁶ and Nakagawa et al³⁷; one study by Ford et al was from New Zealand³⁸; and one study by Flanigan et al was from North America.³⁹ All 24 studies reported on the prevalence of muscular dystrophy; no studies reported on its incidence. The studies were hospital- or clinic-based estimates of the prevalence of muscular dystrophies, with the exception of one door-to-door home-based survey by El-Tallawy et al in 2005.³³

The diagnostic criteria for muscular dystrophies were based on predefined criteria including the age of onset and distribution of muscle weakness, associated symptoms, rate of disease progression, family history, serum creatine kinase, and histological studies, with or without neurophysiology tests such as electromyography and nerve conduction studies (Tables 1-6). Genetic data were not specified in earlier studies by Hughes et al,²⁰ Darin and Tulinius,¹⁶ Chung et al,³⁵ El-Tallawy et al,³³ Mostacciolo et al,²⁴ Nakagawa et al,³⁷ van der Kooi et al,³¹ and Blumen et al.³² Molecular genetic testing was used for diagnosis in some but not all patients in other studies by De Munain et al,¹⁷ Ford et al,³⁸ Hsiao et al,³⁶ Magee & Nevin,²¹ Medica et al,²² Segel et al,³⁴ Siciliano et al,²⁷ and Urtasun et al.³⁰ Genetic confirmation in most or all patients was reported by Norwood et al,²⁶ Mladenovic et al,²³ Fanin et al,¹⁸ Fanin et al,¹⁹ Stensland et al,²⁹ Sposito et al,²⁸ and Mostacciolo et al.²⁵

Myotonic Dystrophy

Thirteen studies reported on the prevalence of myotonic dystrophy, and all were included in the meta-analysis. The majority of the studies did not distinguish between types 1 and 2 diseases. Eleven studies focused on all age groups, including De Munain et al,¹⁷ Ford et al,³⁸ Hsiao et al,³⁶ Hughes et al,²⁰ Magee and Nevin,²¹ Medica et al,²² Mladenovic et al,²³ Nakagawa et al,³⁷ Norwood et al,²⁶ Segel et al,³⁴ and Siciliano et al.²⁷ Studies by Darin and Tulinius¹⁶ and Chung et al³⁵ involved children only (Figure 2). The pooled prevalence of myotonic dystrophy in all age groups was 8.26 per 100,000 (95% confidence interval [CI], 4.99-13.68), and 1.41 per 100,000 (95% CI, 0.11-17.85) in children alone. Significant heterogeneity existed among studies of all age groups ($I^2 = 99.1\%$, $p < 0.0001$) and between the two pediatric studies ($I^2 = 96.2\%$, $p < 0.0001$).

Facioscapulothoracic Dystrophy

Nine studies reported on the prevalence of facioscapulothoracic dystrophy and all were included in the meta-analysis. Seven studies reported on all age groups, including El-Tallawy et al,³³ Flanigan et al,³⁹ Hughes et al,²⁰ Mostacciolo et al,²⁵ Nakagawa et al,³⁷ Norwood et al,²⁶ and Sposito et al.²⁸ Two studies by Darin and Tulinius¹⁶ and Chung et al³⁵ focused on children only (Figure 3). The pooled prevalence of facioscapulothoracic dystrophy in all age groups was 3.95 per 100,000 (95% CI, 2.89-5.40). The pooled prevalence in children only was 0.29 per 100,000 (95% CI, 0.03-3.00). Significant heterogeneity was present for both groups ($I^2 = 89.5\%$, $p < 0.0001$ for all ages, and $I^2 = 77.1\%$, $p = 0.04$ for children only).

Limb Girdle Muscular Dystrophy

Eleven studies reported on the prevalence of limb girdle muscular dystrophy and were included in the meta-analysis: nine reported on all age groups, including El-Tallawy et al,³³ Fanin et al,^{18,19} Hughes et al,²⁰ Nakagawa et al,³⁷ Norwood et al,²⁶ Stensland et al,²⁹ Urtasun et al,³⁰ and van der Kooi et al.³¹ Two studies by Darin and Tulinius¹⁶ and Chung et al³⁵ focused on children alone (Figure 4). Among studies including all age groups, the pooled prevalence of limb girdle muscular dystrophy was 1.63 per 100,000 (95% CI, 0.94-2.81). In children alone, the pooled prevalence was 0.48 per 100,000 (95% CI, 0.18-1.31). Significant heterogeneity was present for studies reporting on all age groups ($I^2 = 96.3\%$, $p < 0.0001$), but not for those including children only ($I^2 = 44.4\%$, $p = 0.18$).

Emery-Dreifuss Muscular Dystrophy

Four studies reported on the prevalence of Emery-Dreifuss muscular dystrophy. Three studies reported on all age groups and were included in the meta-analysis, including El-Tallawy et al,³³ Hughes et al,²⁰ and Norwood et al.²⁶ Chung et al³⁵ was the only pediatric study, with a prevalence of 0.22 per 100,000 children. The pooled prevalence of Emery-Dreifuss muscular dystrophy in all age groups was 0.39 per 100,000 (95% CI, 0.12-1.30; Figure 5), with significant heterogeneity among the estimates ($I^2 = 71.3\%$, $p = 0.03$).

Congenital Muscular Dystrophy

Four studies reported on the prevalence of congenital muscular dystrophy in all age groups, including El-Tallawy et al,³³ Hughes et al,²⁰ Nakagawa et al,³⁷ and Norwood et al.²⁶ Three studies

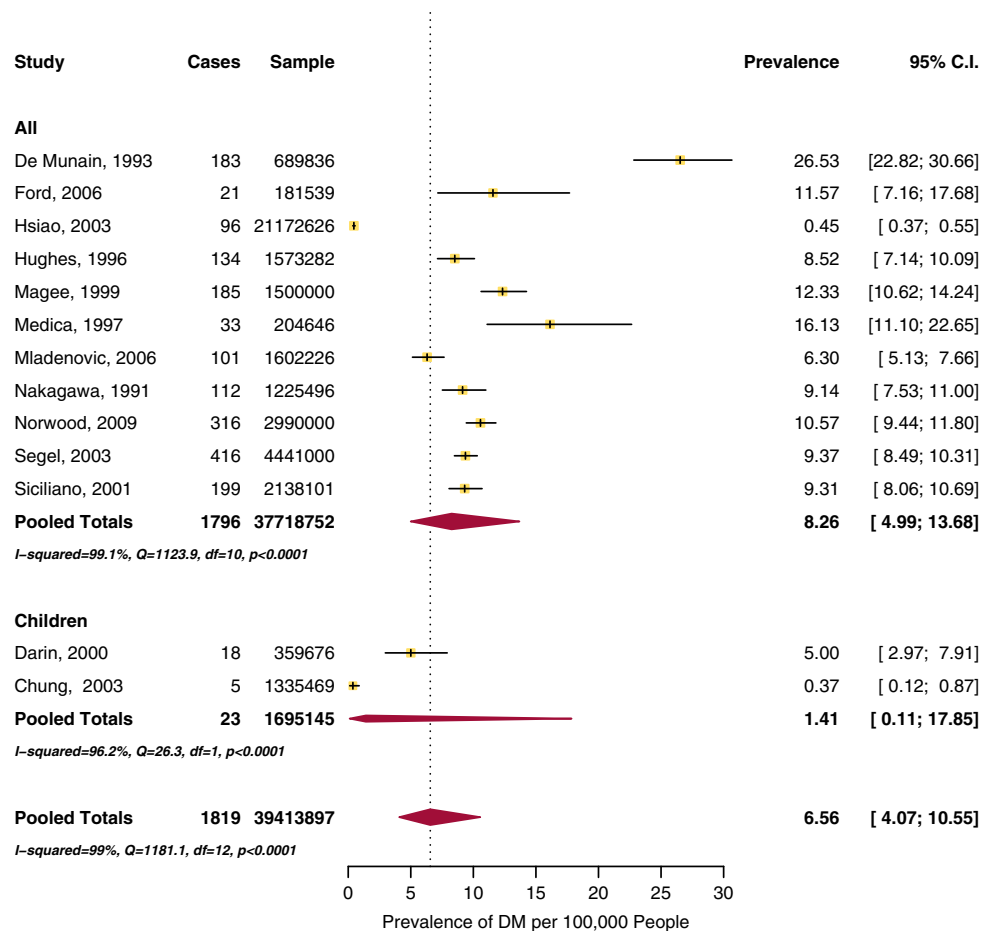


Figure 2: Forest plots of individual studies and pooled prevalence estimates of myotonic dystrophy (DM).

reported on the prevalence in children alone, including Darin and Tulinus,¹⁶ Chung et al,³⁵ and Mostacciolo et al²⁴ (Figure 6). The pooled prevalence of congenital muscular dystrophy in all age groups was 0.99 per 100,000 (95% CI, 0.62-1.57), and 0.82 per 100,000 (95% CI, 0.27-2.47) in children only. Significant heterogeneity was present among the pediatric studies ($I^2 = 87.4%$, $p = 0.0003$) but not for studies reporting on all age groups ($I^2 = 55.5%$, $p = 0.08$).

Oculopharyngeal Muscular Dystrophy

Two studies described the prevalence of oculopharyngeal muscular dystrophy in all age groups, including Blumen et al³² and Norwood et al.²⁶ A pooled analysis was not performed because of the limited number of studies.

Combined Muscular Dystrophies

Five studies reported on the overall prevalence of combined muscular dystrophies, including Duchenne muscular dystrophy, Becker muscular dystrophy, congenital muscular dystrophy, facioscapulohumeral dystrophy, limb girdle muscular dystrophy, and myotonic dystrophy by Chung et al,³⁵ Darin and Tulinus,¹⁶ Hughes et al,²⁰ Nakagawa et al,³⁷ and Norwood et al.²⁶ The overall pooled prevalence of combined muscular dystrophies was

16.14 per 100,000 (95% CI, 11.21-23.23). Random effects model showed significant heterogeneity, with $I^2 = 97.5%$, $p < 0.0001$ (Figure 7).

Publication Bias

Using both Begg's and Egger's tests, no evidence of publication bias was found for the muscular dystrophies ($p > 0.05$), apart from facioscapulohumeral dystrophy. There was evidence of publication bias based on Egger's test for facioscapulohumeral dystrophy ($p = 0.008$), but not Begg's ($p = 0.13$); visual inspection of the funnel plot revealed an asymmetry, suggesting the potential of missing studies with a lower prevalence.

Study Quality

As indicated in Table 7, there were notable differences in research methodology as well as study quality. The median study quality score for studies reporting on the prevalence of muscular dystrophies was 7 of 8 (range, 4-8). All 31 articles described the target population in detail and 27 of 31 studies sampled either the entire population or used probability sampling. Of those studies necessitating a response rate, 26 reported a response rate greater than 70% and described the nonresponders adequately. The majority of studies reported on whether their sample was

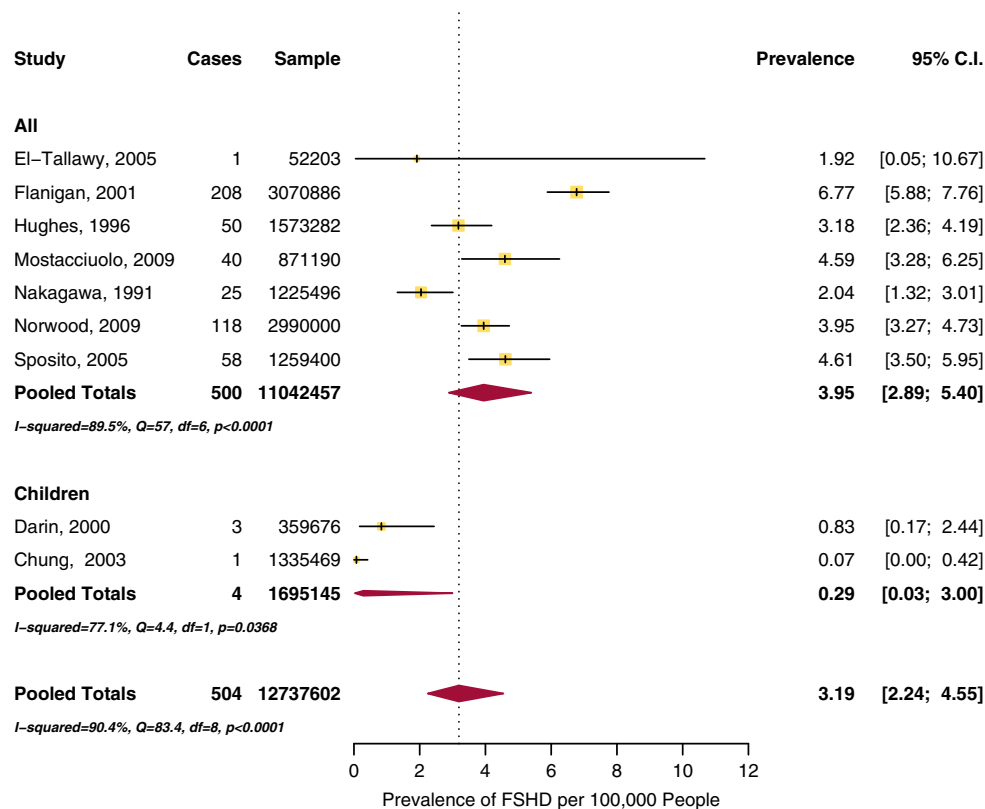


Figure 3: Forest plots of individual studies and pooled prevalence estimates of facioscapulohumeral muscular dystrophy (FSHD).

representative of the target population. All studies used standardized data collection methods and most used validated criteria to assess for the presence of muscular dystrophies. Only five studies reported estimates with their accompanying confidence intervals or by subgroups.

DISCUSSION

According to Emery's report in 1991, the prevalence of inherited neuromuscular disorders including Duchenne and Becker muscular dystrophies, spinal muscular atrophy, myotonic dystrophy, congenital myotonias, hereditary motor and sensory neuropathies, familial motor neuron disease, and familial myasthenia gravis was estimated to be around 28.6 per 100,000, or 1 in 3500.⁴⁰ In the current systematic review, the overall worldwide prevalence of combined muscular dystrophies is estimated to be 16.14 per 100,000, or 1 in 6200. The reports of muscular dystrophies prevalence included in this systematic review were all population-based, used appropriate methodology, and were of good quality. However, several outlier estimates were observed. The overall prevalence estimates for facioscapulohumeral dystrophy in Egypt was high, likely as a result of the relatively small population sampled, the door-to-door survey methodology, and the number of cases identified.³³ Also, the overall prevalence estimate for myotonic dystrophy type 1 in Spain of 26.53 per 100,000 is higher than in the other included studies without any clear methodological differences, possibly related to a founder effect.¹⁷ In contrast, a lower prevalence

estimate of myotonic dystrophy was observed in China and Taiwan (0.37 and 0.46 per 100,000, respectively); this may be attributed to variation in the availability of genetic testing for confirmation of diagnosis and restriction of the sample population to those younger than 19 years of age.^{35,36} Similarly, lower prevalence estimates were found in other systematic reviews of neurological conditions such as Huntington or Parkinson diseases in Asia.^{41,42} However, Darin and Tulinius also restricted their sample population to those younger than 16 years of age and demonstrated a more typical prevalence estimate of myotonic dystrophy at 5.0 per 100,000.¹⁶ Therefore, the variation may also be related to genetic differences and/or the influence of migration on the prevalence of the inherited muscular dystrophies.

Comparison of pooled estimates demonstrates that myotonic dystrophy type 1 is the most prevalent muscular dystrophy in childhood and in the overall population, with a pooled prevalence of 8.26 (95% CI, 7.99-13.68) per 100,000. Emery estimated an overall prevalence of 5.0 per 100,000 in adults.⁴⁰ Much higher prevalence of myotonic dystrophy type 1 had been reported because of founder effect and geographical isolation. A prevalence of 158 per 100,000 was recently reported by Mathieu et al in 2012 at the Saguenay-Lac-Saint-Jean region in Northern Quebec, Canada; the prevalence has progressively declined over the past two decades because of reduced fertility rate.⁴³ Facioscapulohumeral dystrophy is the second most prevalent muscular dystrophy; the pooled prevalence in all age groups from this study was 3.95 (95% CI, 2.89-5.40) per 100,000, which is about twice as high as the estimate of 2 per 100,000 by Emery in 2001.⁴⁰

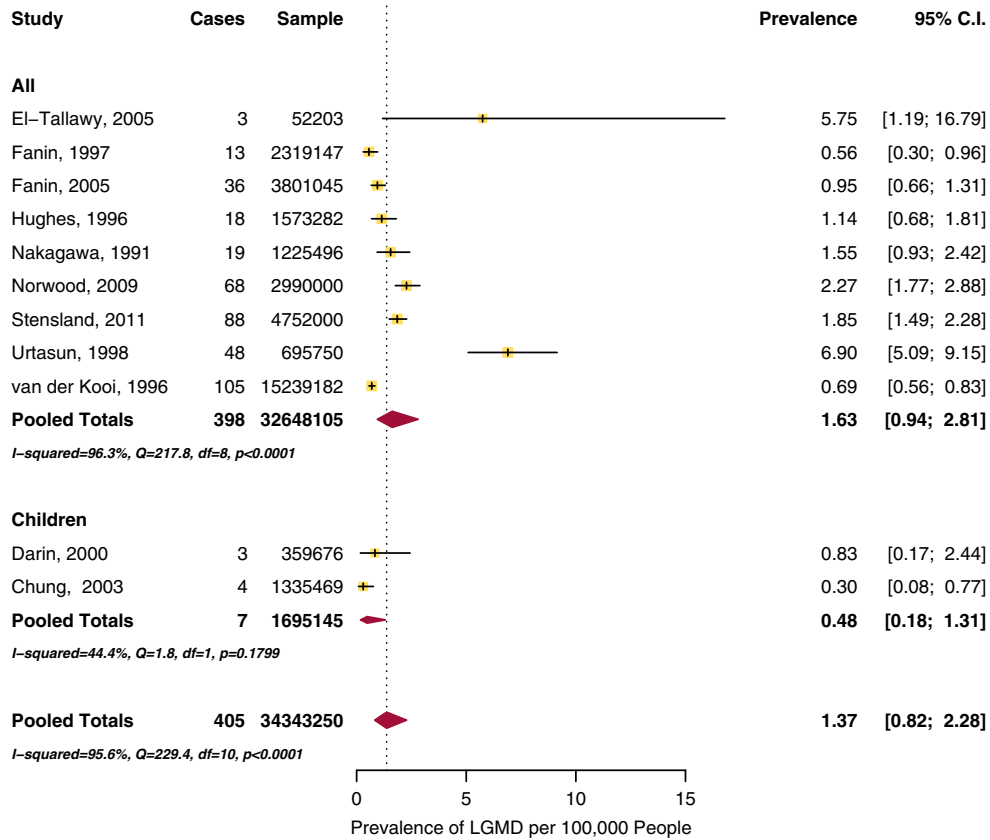


Figure 4: Forest plots of individual studies and pooled prevalence estimates of limb girdle muscular dystrophy (LGMD).

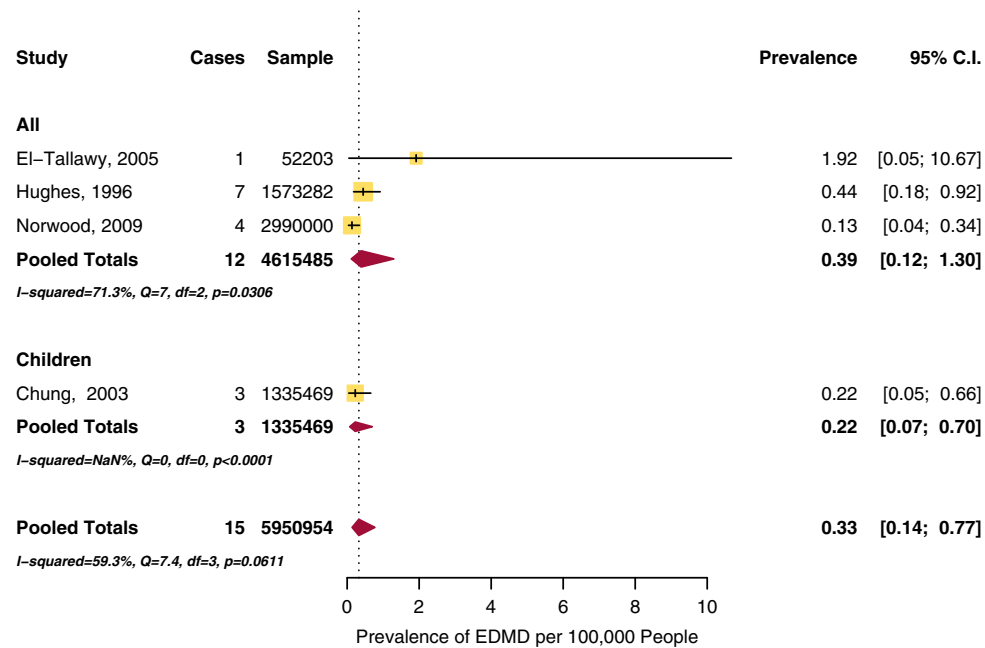


Figure 5: Forest plots of individual studies and pooled prevalence estimates of Emery-Dreifuss muscular dystrophy (EDMD).

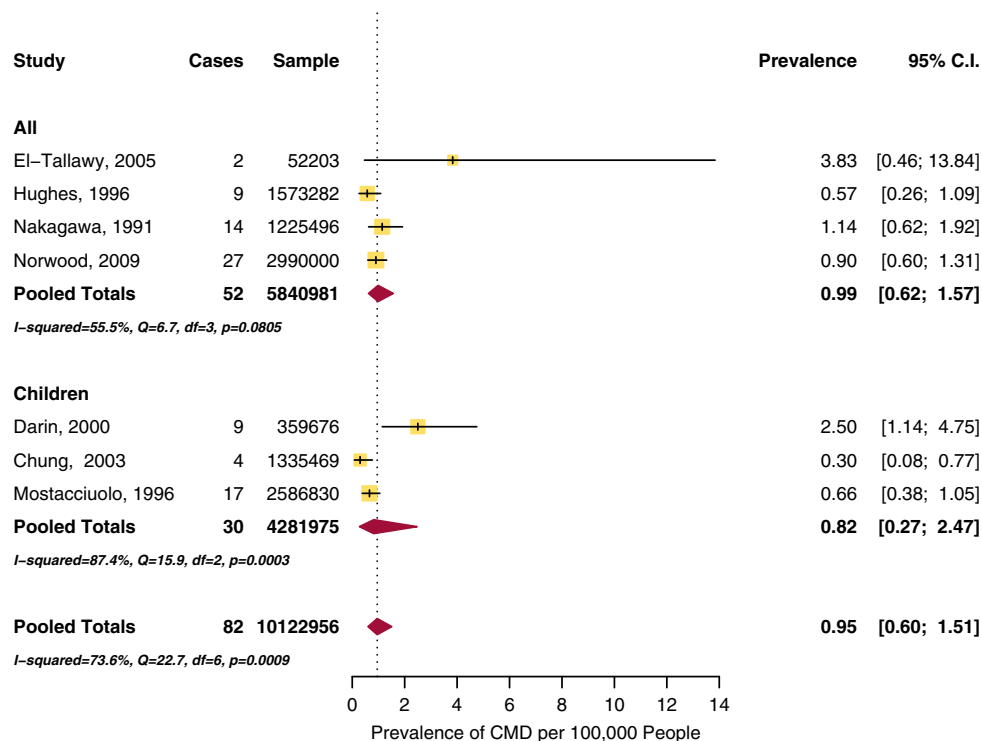


Figure 6: Forest plots of individual studies and pooled prevalence estimates of congenital muscular dystrophy (CMD).

Duchenne muscular dystrophy remains the most prevalent muscular dystrophy of childhood in boys. The estimated prevalence of Duchenne and Becker muscular dystrophies according to Emery was 6.3 and 2.4 per 100,000, respectively, which is similar to our recent estimates of 4.78 (95% CI, 1.94-11.81) and 1.53 (95% CI: 0.26-8.94) per 100,000.²

Variation in the reported prevalence of muscular dystrophies could be related to genetic variations between populations or ethnic groups as well as differences in available molecular diagnostic tools for accurate diagnosis.^{35,36} Furthermore, neuromuscular disorders are relatively uncommon in the general population, and one must often resort to hospital charts and other

sources of medical information in the community for the number of diagnosed cases. The availability of such information varies among countries and within regions. As well, some affected individuals may not seek medical attention; undiagnosed cases therefore may lead to an underestimation of the true prevalence of muscular dystrophies. On the other hand, advances in research activity may generate an increased awareness in a region for a particular group of disorders, as may be seen by Norwood et al within the United Kingdom.²⁶ Comparatively fewer cases of muscular dystrophy were diagnosed during the first 4 years of life, as indicated in a recent study on congenital myotonic dystrophy⁴⁴; diagnostic difficulties may contribute to the lower prevalence of

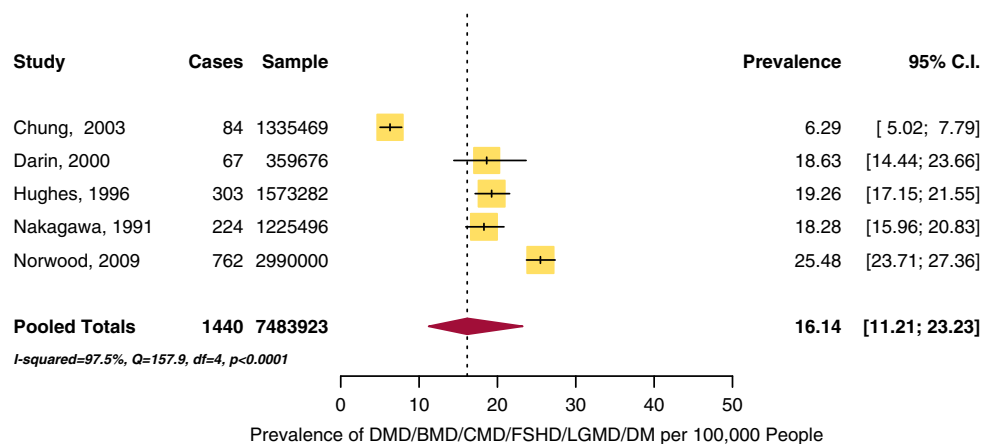


Figure 7: Forest plots of individual studies and pooled prevalence estimates of the combined muscular dystrophies (MDs).

Table 7: Quality scores of studies included in the muscular dystrophies systemic review

Study, date	Is the target population clearly defined?	Was either of the following ascertainment method used?	Is the response rate $\geq 70\%$?	Are nonresponders clearly described?	Is the sample representative of the target population?	Were data collection methods standardized?	Were validated criteria used to assess for the presence/absence of the disease?	Are the estimates of prevalence and incidence given with confidence intervals and in detail by subgroup (if applicable)?	Total quality score
Ballo, 1994	Yes	No	Not reported	No	Yes	Yes	Yes	No	4
Blumen, 1997	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Bushby, 1991	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Chung, 2003	Yes	No	Yes	Yes	Unclear	Yes	Yes	No	5
Darin, 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
De Munain, 1993	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
El-Tallawy, 2005	Yes	Yes	Not reported	Not reported	Yes	Yes	Yes	No	5
Fanin, 1997	Yes	No	Yes	Yes	Yes	Yes	Yes	No	6
Fanin, 2005	Yes	Yes	Yes	Yes	No	Yes	Yes	No	7
Flanigan, 2001	Yes	No	Not reported	Not reported	Yes	Yes	No	No	3
Ford, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Greenberg, 1988	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Hsiao, 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Hughes, 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Jeppesen, 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Magee, 1999	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Medica, 1997	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Mladenovic, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
MMWR, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Mostacciolo, 1996	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Mostacciolo, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Nakagawa, 1991	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	No	5
Norwood, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Segel, 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Siciliano, 1999	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Siciliano, 2001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Sposito, 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Stensland, 2011	Yes	No	Yes	Yes	No	Yes	Yes	No	5
Talkop, 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Urtasun, 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Van der Kooi, 1996	Yes	yes	Yes	Yes	Yes	Yes	Yes	No	7

muscular dystrophies as reported in early childhood. Prevalence figures in school-aged children are therefore likely to give a better estimate of the true childhood prevalence of neuromuscular disorders.¹⁶

As previously mentioned,² limitations of this systematic review include variability in methodology, nonrandom geographic distribution, and the lack of validated international classification of disease codes for the muscular dystrophies among the studies.⁴⁵ The lack of genetic testing in earlier studies may also lead to an imprecise estimation of the true prevalence of the muscular dystrophies. It was not possible to calculate a pooled estimate of myotonic dystrophy type 2 as several of the epidemiologic studies were conducted prior to the discovery of the gene for type 2 disease.⁴ There was evidence of publication bias, but only for facioscapulohumeral dystrophy. Flanigan et al reported a high prevalence of disease in a geographically and genetically restricted population³⁹; there may be other studies with a lower prevalence of facioscapulohumeral dystrophy that were not identified in our search. Despite great efforts to ensure the search strategy to be as comprehensive as possible, we did not include abstracts, gray literature, or articles written in languages apart from English or French. Application of these results must be made in light of these limitations. Multiple sources of case ascertainment beyond clinical-based settings such as national registries, genetic databases, and patient organizations should be considered for future incidence or prevalence studies of the muscular dystrophies.

CONCLUSION

This is a meta-analysis of the minimum prevalence estimates for myotonic dystrophy, facioscapulohumeral dystrophy, limb girdle muscular dystrophies, congenital muscular dystrophies, and combined muscular dystrophies derived from studies around the world. Population-based registries for the muscular dystrophies were limited to parts of Europe, Asia, and North America only. Substantial gaps exist with no available data from many other continents, limiting the generalization of the reports. In the United States, the reported national costs of illness for Duchenne muscular dystrophy, myotonic dystrophy, and other progressive neuromuscular diseases has been estimated to exceed more than \$1 billion per year.⁴⁶ Our pooled estimates are useful for calculating projections of expected case numbers in regions without accurate prevalence data facilitating estimation of health care burden, economic impact, and clinical resource requirements. Clinical research must continue to be anchored to epidemiological understanding to enable interpretation of relevance to, and effect of, the overall patient population.

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DISCLOSURES

TP has served as a consultant for and received consulting fees from Teva Canada; received an unrestricted grant from Shire Canada; and been a meeting attendee and received support to attend meetings for Allergan Canada. NJ has received a research grant and research support paid to the university from the Public Health Agency of Canada; been an award recipient and received a salary award paid to the university from the Canada Research Chair Program; and received a salary award paid to the university from Albert Innovates Health Solutions. JM, KF, JD, LD, and LK have nothing to disclose.

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