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Review: Limb-girdle muscular dystrophies (LGMDs) existing registries and natural history studies: Where do we stand?

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Abstract

Introduction: Limb-Girdle Muscular Dystrophies (LGMDs) are heterogeneous inherited disorders with no cure, including 29 recessive (LGMDR) and 5 dominant forms (LGMDD), characterized by proximal muscle weakness. Finding a cure for LGMD is difficult due to the their slow evolution for which comprehensive data collection through registries, network, and natural history studies is pivotal.

Methods: We conducted a review following PRISMA guidelines searching in PubMed, Scopus, and Web of Science for articles published between 2000–2025, focusing on LGMD registries, networks, and natural history studies. We included observational studies, cohort designs, and registry-based studies.

Results: Among 443 records, 38 studies were included, 10 registries, 4 networks, and 17 natural history studies respectively. Registries varied in scope, with many focused on specific LGMD subtypes. Natural history studies were predominantly subtype-specific, poorly linked to registries. Only 12 studies were connected to registries or networks, and most performed in Europe and North America.

Discussion: Registries, networks, and natural history studies showed considerable design variability, leading to challenges with data interoperability and underscoring the need for standardization. Despite regional coverage, low-income countries are underrepresented in the data. The limited linkage between natural history studies and registries presents a missed opportunity to leverage well-characterized cohorts. Many registries and networks remain unpublished, limiting available data for global research.

Conclusion: Registries are crucial, benefiting patients, clinicians, researchers, and industries. The scarcity of natural history studies hinders the development of centralized datasets. Standardizing registry design, improving data interoperability, and enhancing patient diversity are critical to boost LGMD research.

Keywords

limb girdle muscular dystrophy LGMD, registries, natural history studies, data collection

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Introduction

Limb-Girdle Muscular Dystrophies (LGMDs) are a heterogeneous group of inherited myopathies[1,2] characterized by progressive weakness and wasting of hip and shoulder muscles. The clinical course of LGMDs exhibits marked variability, ranging from mild, slowly progressive forms to debilitating variants that significantly impair mobility.[3] Onset typically occurs after the age of two years, and serum creatine kinase levels are often elevated[3] due to the degeneration of myofibers.[4] To date, 25 distinct LGMDs are recognized, categorized into 5 autosomal dominant (LGMD D), and 29 autosomal recessive (LGMDR).[5,6] LGMDs present challenges in diagnosis, disease monitoring, and disease trajectory identification due to their rarity and clinical variability.[7] The emerging development of effective treatment strategies necessitates the establishment of reliable outcome measures that accurately reflect disease progression and therapeutic efficacy. Networks play a crucial role in developing patient registries by connecting research institutions, clinicians, and patient advocacy groups to facilitate multi-center studies and standardized data collection. They provide infrastructure, harmonized protocols, and funding to enhance data interoperability and foster international collaborations. Although networks typically do not collect primary patient data, they coordinate efforts between existing registries and clinical research initiatives, ensuring streamlined collaboration and efficient resource utilization.[8] Medical registries have emerged over the past century as a crucial tool to improve knowledge of diverse pathologies and provide access to quality, non-biased data.[9] These registries systematically collect health and demographic data for specific public health purposes. Registries have evolved from simply calculating basic epidemiological data to supporting applications in disease prevention, diagnosis, treatment, and healthcare planning.[10] The implementation and maintenance of effective registries, which require substantial effort and a robust organizational framework, are instrumental in supporting various types of research, including epidemiological analyses and natural history studies, contributing to a deeper understanding of disease mechanisms and progression. Furthermore, they provide a foundation for clinical trials, ensuring the efficient recruitment of well-characterized patient populations.[11]

However, the definition of the natural history of LGMD subtypes and assess potential treatment effects have historically been limited by the lack of large, well-characterized patient cohorts.

Here we performed a comprehensive analysis of the literature on LGMD registries and natural history studies published within the period from January 2000 to May 2025. This analysis evaluates their contributions to research and clinical trial development, discusses the broader implications of registries in natural history studies, their benefits for patients, clinicians, researchers, and the pharmaceutical industry, and the challenges related to data interoperability and the inclusion of underrepresented populations.

Methods

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[12] To ensure relevance and quality, specific inclusion and exclusion criteria were applied.

Studies were considered eligible if they met the following criteria: (i) involvement of patients diagnosed with LGMD, confirmed through genetic or clinical testing, (ii) registries or database studies, (iii) observational or cohort study design, (iv) natural history study, (iv) cross-sectional studies based on registries or natural history studies. Only articles published in English or French between January 2000 and May 2025, indexed in PubMed, Scopus, or Web of Science, with at least abstract or full-text access available, were included.

Studies were excluded if they met one of the following criteria: (i) focus on neuromuscular diseases unrelated to LGMD according to the classification proposed at the 229th ENMC International Workshop,[6] (ii) reliance on animal models or in vitro research, (iii) classification as clinical trials, interventional studies, epidemiological trial articles, conference abstracts, letters to the editor, or editorials without original data, and (iv) retrospective study design.

The literature search was performed using specific search strings tailored to each database. In PubMed, the query included (LGMD OR limb girdle muscular dystroph* OR limb girdle muscular dystroph*) AND (registr* OR databas* OR multicent* OR natural history). In Scopus, the search was conducted using TITLE-ABS-KEY ((LGMD OR limb AND girdle AND muscular AND dystrophy) AND (registr* OR databas* OR multicent* OR natural AND history)).

The initial stage of study selection leveraged Rayyan, a digital workspace designed for collaborative reviews.[13] Two independent reviewers (Author 1, Author 2) performed a preliminary assessment of titles and abstracts. Supplementary searches of reference lists from pertinent articles were conducted to ensure comprehensive identification of relevant literature. Any disagreements encountered during this process were resolved through discussion, or by engaging a third reviewer (Corresponding Author) for arbitration.

Utilizing a standardized protocol, two independent reviewers (Author 1, Author 2) extracted pertinent data from each included study. The data extracted consisted of the year the study began, the type of governance, the study design, the inclusion criteria, the number of participants, the data that was collected, the main findings, and the problems that occurred during the research.

A descriptive synthesis of the included studies was undertaken, focusing on their characteristics and principal findings. The resulting data are presented in both narrative and tabular formats.

Results

The systematic literature search identified 443 records, with the addition of 3 papers studies found through reference list examination (Figure 1). After removing duplicates, 270 publications underwent title and abstract screening, leading to the selection of 72 articles for full-text evaluation. Two independent reviewers (Author 1, Author 2) ultimately included 38 studies that met the predefined criteria for this systematic review (Tables 1–3).

At least three main categories were identified among the analyzed papers: (I) Registries or Networks; (II) Natural History studies; (III) Cross-sectional studies based on natural history research (Figure 2(a)).

Registries and networks

The systematic review identified 10 LGMD registries and 4 networks across 18 papers, with the earliest publication dating back to 2012[14] (Figure 2(b)).

Two are global and the rest are national, spanning nine countries: four in Europe, two in North America, and two global registries (Figure 3(a)).

Four major networks were identified (Table 1), playing key roles in research and clinical trials for neuromuscular diseases (NMDs). Two focus broadly on NMDs, two specifically on LGMDs:

- The Muscular Dystrophy Clinical Trial Network (MDCTN), launched in Japan in 2012, was the first national NMD clinical trial network in Asia. It enrolled over 5500 patients, standardized assessments, used the TREAT-NMD dataset,[15] and supported Phase I–IV trials, notably for Duchenne, FSHD, myotonic dystrophy, and LGMD. Key challenges remain: access to genetic diagnostics and limited international trial inclusion.[15]
- GRASP-LGMD, created in 2019, validates clinical outcomes across LGMD subtypes, including LGMDR9, with sites in the US and Europe.[16]
- MOVR (MDA's NeuroMuscular Observational Research Data Hub), started in 2019, includes over 3800 patients (109 with LGMD) from 50 US Care Centers. It provides longitudinal data on disease progression, genetics, and functional status. Limitations include underrepresentation of minorities and limited access to genetic testing. Integration of patient-reported outcomes and global collaboration are ongoing goals.[17]
- The TREAT-NMD LGMD Registry Network, launched in 2020, harmonizes LGMD registry data worldwide.[18] A core dataset, created by consensus, was piloted in 10 registries. It aims to improve trial recruitment and translational research. Main barriers are regional implementation and global data consistency.[19]

Registries differ in scope—some target LGMD only, others include broader NMD populations (Table 1):

- The New Zealand NMD Patient Registry (NZNMD), established in 2011, enrolled 1000 + patients across 70+ NMDs including LGMD, contributing anonymized data to international research.[20]
- The Belgian NMD Registry (BNMDR), started in 2008, covers 62 NMD subtypes via Neuromuscular Reference Centers, including LGMD. It supports both epidemiology and trial feasibility through integration into TREAT-NMD and national research frameworks.[21]
- The Canadian NMD Registry (CNDR), founded in 2011, includes pediatric and adult LGMD patients and is part of TREAT-NMD.[18] It supports trial recruitment but faces limited adult enrollment and genetic data gaps. CNDR explores direct-to-patient recruitment to improve coverage.[8,22]
- The IBIC-NMDs Database (Japan, 2015) focuses on muscle imaging in classified and unclassified LGMD, helping with diagnostics and follow-up.[23]

Three registries cover all LGMD subtypes:

- The Italian LGMD Registry, first published in 2014,[24] includes data on 599 patients and was among the earliest to encompass all subtypes. It highlighted the need for cardiac/respiratory monitoring in some forms and identified LGMDR1, R2, and sarcoglycanopathies as most prevalent. It faced challenges related to genetic diversity and biomarker scarcity.[25]
- The Saudi Arabian LGMD Cohort, launched in 2000, collected data on 112 families, including 34 LGMDR1 patients. It investigated consanguinity, disease progression, gender-related differences, and novel mutations.[26]
- The Dutch LGMD Registry, initiated in 2022, enrolled 111 patients and used the TREAT-NMD LGMD dataset.[27] It tracked symptoms, milestones, and treatments from both clinician and patient perspectives. Main challenges were patient retention and data consistency.[28]

Three registries target specific LGMD subtypes:

- UMD-DYSF (France, 1998) focuses on dysferlinopathies (LGMD2B and Miyoshi). With 152 LGMD2B and 154 Miyoshi patients, it explores

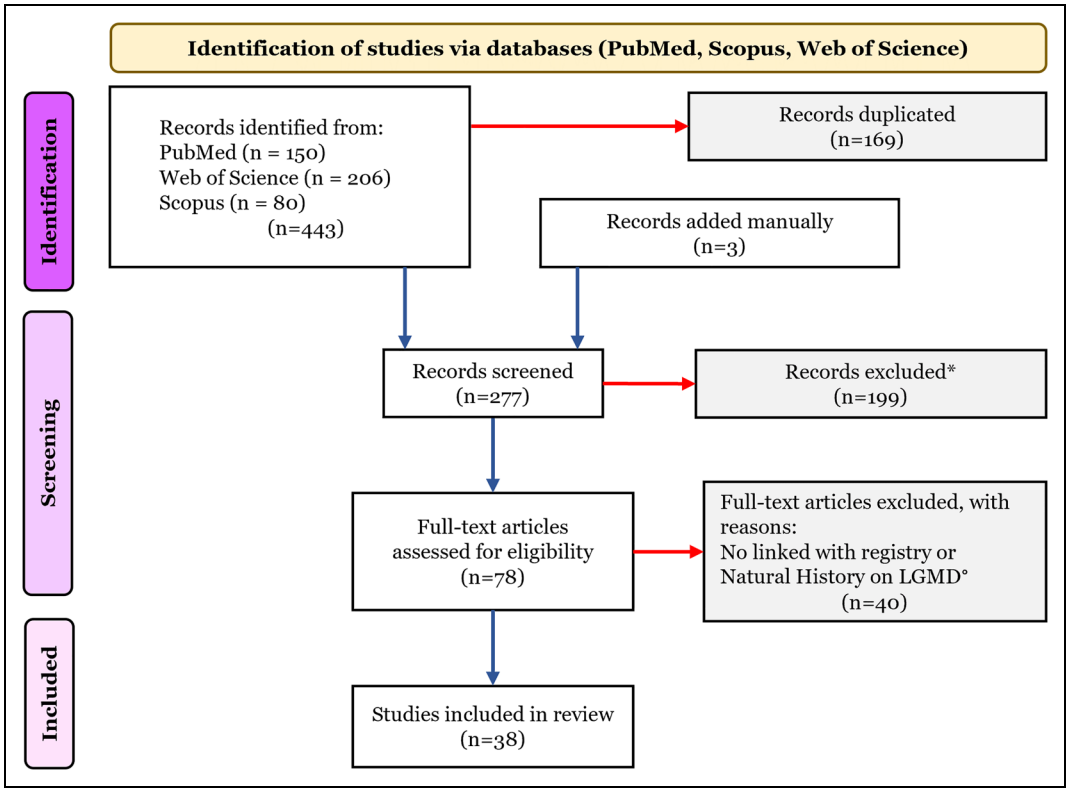

Figure 1. PRISMA flow diagram of the literature search.[12] *all records excluded were screened manually by a human reviewer. °According to the classification proposed at the 229th ENMC International Workshop.[6]

DYSF genotype-phenotype correlations. Key difficulties involve novel variant classification and phenotype refinement.[14]

- The Global FKRP Registry (2011) includes data from 23 countries on LGMDR9. Patients self-enroll and data is provided via questionnaires and clinicians. In 2024, it adopted the TREAT-NMD LGMD core dataset[27] and the NSAD motor scale,[23] improving rare disease data coordination. It identified the FKRP variant c.826C > A (p.Leu276Ile) (NM_024301.5) as linked to milder phenotypes. Ongoing work includes integration of MRI biomarkers.[30,33]
- The French National Registry of Calpainopathy (2021) is including and follows EURO-NMD standards.[35] It gathers data on genetically confirmed calpainopathy (LGMDR1 or LGMDD4) from 23 FILNEMUS centers,[40] with a focus on epidemiology and myopathology.[36] Updates are shared through newsletters on the FILNEMUS and AFM-Téléthon platforms.

Data collection strategies. All registries collected genetic and clinical data, while functional assessments were documented in six out of nine. Evaluations of ambulation, including walking speed, distance, and assistive device use, were common. Functional assessments also included motor function measurements, covering muscle strength, coordination, and daily activity performance. Standardized scales such as the Motor Function Measure (MFM), Vignos scale, 6-Minute Walk Test (6MWT), 10-Meter Walk Test (10MWT), and NSAD were frequently employed. Given that loss of ambulation is a critical milestone in many muscular dystrophies, assessing walking ability remains central to functional evaluations.

Quality of life was assessed in 2 out of 10 registries using patient-reported questionnaires[8,28] with one also employing the McGill Pain Questionnaire.[28] Muscle imaging, most frequently using MRI, was included as a recorded parameter in five registries,[14,21,23,24] with one registry dedicated entirely to imaging[21] emphasizing its relevance in disease characterization and progression monitoring. While most registries extensively documented cardiorespiratory function, incorporating both instrumental examinations and patient-reported data, there were notable exceptions. Specifically, TREAT-NMD, UMD-DYSF, and IBIC-NMDs did not include cardiorespiratory assessments due to their less clinical focus. Furthermore, the CNDR differed in its approach by recording only patient-reported ventilation status, rather than utilizing instrumental examinations. Additionally, three registries[8,14,28] tracked patient participation in clinical trials, reinforcing the role of registries in facilitating research and potential therapeutic interventions.

Several common challenges were identified within the registry. One challenge involved maintaining comprehensive

Table 1. Registries and networks. Overview of the 10 registries and 4 networks identified in this systematic review, including their corresponding publications, year of establishment, geographic scope, and the specific LGMD subtypes they cover. The table also details the countries involved, the number of LGMD patients enrolled, and the types of data collected, such as genetic, clinical, and functional assessments. *Only abstract available. °article discussed also Natural History or cross-sectional part, as both are addressed. **In bold we represent the 100% patient-driven registries.**

Networks and Registry

Name	Ref.	Year	Conditions	Setting	Numbers	Collected Data
NMD Networks						
Muscular dystrophy clinical trial network (MDCTN)	Shimizu et al. 2016[14]	2012	NMDs	Japan	614 LGMD patients	Genetic, clinical, functional, imaging, participation in clinical trials
NeuroMuscular ObserVational Research Data Hub (MOVR)	Kilroy et al. 2023[15]	2019	NMDs	USA	109 LGMD patients (93 genetically confirmed)	Genetic, clinical, functional assessment
LGMD Networks						
Genetic Resolution and Assesment Solving Phenotypes in LGMD (GRASP-LGMD) consortium	Alfano et al. 2025[16]° Doody et al. 2024[7]°	2019	LGMDs	USA and Europe	188 LGMD patients	Genetic, clinical, functional assessments, imaging data
TREAT-NMD LGMD global registry network	Segovia et al. 2021[17]*	2020	LGMDs	Global	LGMD patient in existing registries	Standardized LGMD dataset, including clinical characterization, natural history, and trial readiness
NMD Registries						
The New Zealand Neuromuscular Disease Patient (NZNMD) Registry	**Rodrigues et al. 2017[18]**	**2011**	**NMDs**	**New Zealand**	**28 LGMD patients**	**Genetic, clinical, participation in clinical trials**
The Belgian Neuromuscular Disease Registry (BNMDR)	Roy et al. 2017[19]	2008	NMDs	Belgium	58 LGMD patients (28 genetically confirmed)	Genetic, clinical, participation in clinical trials
The Canadian Neuromuscular Disease Registry (CNDR)	Wei et al. 2018[20] Hodgkinson et al. 2021[8]	2011	NMDs	Canada	257 LGMD patients (56 genetically confirmed)	Genetic, quality of life data, participation in clinical trials
Integrative Brain Imaging Center (IBIC)-NMDs database	Nakayama et al. 2016[21]*	2015	NMDs	Japan	100 LGMD patients	Genetic, clinical, imaging
LGMD Registries						
The Italian Registry of LGMD	Magri et al. 2014[22] * Magri et al. 2017[23]	Not mentioned	LGMDs	Italy	599 LGMD patients (370 genetically confirmed)	Genetic, clinical, functional, and imaging
The National Saudi Arabian LGMD cohort database	Alharbi et al. 2021[24]	2000	LGMDs	Saudi Arabia	112 LGMD families (of them 34 LGMDR1 patients)	Genetic, clinical, functional assessment, respiratory and cardiac involvement, imaging data
The Dutch LGMD registry	Schrama et al. 2024[25]*	2022	LGMDs	Netherlands	111 LGMD patients	Genetic, clinical, respiratory and cardiac involvement, patient-reported questionnaires
LGMD subtype Registries						

(continued)

Table 1. Continued.

Networks and Registry						
Name	Ref.	Year	Conditions	Setting	Numbers	Collected Data
Universal Mutation Database for Dysferlin (UMD-DYSF)	Blading et al. 2012[26]	1998	Dysferlinopathies	France	558 patients diagnosed in 2011 with primary dysferlinopathy	Genetic, clinical
Global FKRP Registry	**Murphy et al. 2020[27] 2011 McDonald et al. 2024[28]***		**FKRP-related muscular dystrophies**	**23 countries (German, USA, UK, Denmark)**	**305 LGMDR9 patients**	**Genetic, muscle strength, functional performance, respiratory and cardiac involvement, quality of life, participation in clinical trials**
The French National Registry of Calpainopathy	Richard et al. 2022[29]	2021	Calpainopathy	France	LGMDR1/D4 Recruitment ongoing	Genetic, clinical, myopathological, quality of life data

data entry and ensuring consistent long-term follow-up across geographically diverse sites. Another significant issue was that a substantial portion of the registries included patients with a clinical diagnosis of LGMDs, resulting in a large portion of the cohort without a specific LGMD subtype diagnosis, leading to reduced cohort specificity. Conversely, patient selection based on genetic data presented a potential obstacle. Limited access to genetic testing in certain regions potentially resulted in the underrepresentation of diverse ethnic groups. For instance, the Global FKRP Registry,[27] which required genetic diagnosis as an inclusion criterion, predominantly enrolled patients from European and North American cohorts.

Natural history studies

This systematic review analyzed 17 natural history studies on muscular dystrophies, the first published in 2008.[30] One study overlapped with the registry section, as it presented both network and natural history data. Two studies specifically focused on all forms of LGMD[7,30] while one included a broader spectrum of conditions, notably Duchenne muscular dystrophy (DMD).[33] The remaining studies examined LGMD subtype-specific: Laminin alpha-2 (LAMA2)-related muscular dystrophies (n = 1[35]), LGMDD1 (n = 1[40]), LGMDR12 (n = 1[36]), sarcoglycanopathies (n = 1[49]), LGMDR4 (n = 1[38]), calpainopathy (n = 2[32,46]), dysferlinopathy (n = 2[39,43]) and LGMDR9 (n = 5[31,34,37,41,44]) (Table 2) (Figure 2(b)).

Geographically, the studies were conducted across eleven countries, with a concentration in Europe (France, including Réunion Island; Spanish Basque Country; Italy; Denmark; the United Kingdom (UK); and Belgium; n = 7). Additional studies originated from the United States of America (USA), China, India, and South Africa (n = 4) (Figure 3(b)). All studies mandated a confirmed genetic diagnosis as an inclusion criterion. The mean number of LGMD patients evaluated per study was 58 (range: 18–188), with a mean observation period of 4 years (range: 1–17).

MMT was the most frequently used strength assessment (5/18 studies). Functional assessments were also prevalent, often employing standardized tests. Notably, the NSAD and North Star Assessments for ambulatory function (NSAA) were introduced in 2022[39] and utilized in six studies. Upper limb function was first assessed in 2023[42] using the Performance of Upper Limb (PUL/PUL 2.0) scale in four studies. Common timed functional tests included the 6MWT (n = 4), 10MWT (n = 6), Timed Up and Go (TUG) test (n = 3), and Stair Climb Tests (n = 3). Quality of life was evaluated in four studies using patient-reported questionnaires such as the Activity Limitations Measure (ACTIVLIM) (n = 2), Patient-Reported Outcomes Measurement Information System – 57 items (PROMIS-57) (n = 3), and LGMD Health Inventory (LGMDHI) (n = 1). Cardiac and respiratory evaluations were conducted in 9 and

Table 2. Natural history studies. Overview of natural history studies identified in this systematic review. It details the specific muscular dystrophy conditions investigated, the clinical or research settings in which the studies were conducted, the number of LGMD patients involved, and, where specified, the particular LGMD subtypes examined. Additionally, the table highlights the primary focus of each study, whether on disease progression, natural history, instrumental biomarkers, or genotype-phenotype correlations. NA: not available in the text. *Only abstract available. °article discussed also in the Registries and Networks part, as both are addressed.

Natural History Studies

Ref.	Conditions	Setting	Number	Time of observation	Focus
Stübgen et al. 2008[30]	LGMD	South Africa	18 LGMD patients	17 years	Natural history, disease progression
Willis et al. 2013[31]	LGMDR9	UK, Denmark, and France	32 LGMDR9 patients	1 year	Imaging biomarkers, disease progression
Richard et al. 2014[32]	Calpainopathy	France (Basque country, Reunion Island)	85 LGMDR1 patients	4 years (up to)	Natural history, clinical trial endpoints
Miller et al. 2019[33]*	LGMD, DMD	USA	5 LGMD patients	2 years	Wearable devices measuring in activity level
Murphy et al. 2019[34]	LGMDR9	UK, Denmark, France	23 LGMDR9 patients	6 years	Natural history, Imaging biomarkers, disease progression
Tan et al. 2021[35]	LAMA2-related muscular dystrophy	China	14 LGMDR23 patients	8.2 years (median; range 3.2–27.0 years)	Natural history, genotype-phenotype correlations
De Wel et al. 2022[36]	LGMDR12	Belgium	24 LGMDR12 patients	2 years	Natural history, Imaging biomarkers, disease progression
Reyngoudt, et al. 2022[37]* Rauh et al. 2025[38]	LGMDR9	France, UK, Denmark	52 LGMDR9 patients (18 enrolled at the French clinical site)	2 years	Imaging biomarkers, disease progression
Reyngoudt et al. 2022[39]	Dysferlinopathy	UK, France	75 LGMDR2/MM patients	4 years	Imaging biomarkers, disease progression
Findlay et al. 2022[40]	LGMDD1	Multicenter (14 countries)	122 LGMDD1 patients (96 from a systematic review of 22 articles, 36 patients from retrospective chart review, 30 patients from SCTIVLIM/LGMDD1 questionnaire – only 23 underwent to clinical assessment)	NA	Natural history, genotype-phenotype correlation
Jensen et al. 2023[41]	LGMDR9	Norway	101 LGMDR9 patients	NA	Natural history, genotype-phenotype correlations
Lowes et al. 2023[42]*	Sarcoglycanopathies	Multicenter	64 LGMDR3/R4/R5 patients	3 years	Natural history, disease progression
Nashi et al. 2023[43]	Dysferlinopathy	India	124 LGMDR2/MM patients	5 years (median, range 1–24)	Natural history, genotype-phenotype correlations
Vissing et al. 2023[44]*	LGMDR9	Denmark, France, UK	52 LGMDR9 patients	1 year	Natural history, disease progression
Doody et al. 2024[7]°	LGMD	USA, UK, Denmark	188 LGMDR1/R2/R3/R4/R5/R6/R12/D1 patients	1 year	Clinical outcome measures, disease progression
Iammarino et al. 2025[45]	LGMDR4	USA	46 LGMDR4 patients	3 years	Natural history, Clinical outcome measures, disease progression
Hunn et al. 2025[46]	LGMDR1	USA, UK	42 LGMDR1 patients	1 year	Natural history, Clinical outcome measures

Table 3. Cross-sectional studies based on natural history studies or databases. Cross-sectional studies from natural history or database research in this systematic review, detailing the specific muscular dystrophy conditions, study settings, number of LGMD patients, and the primary focus (disease progression, natural history, biomarkers, or genotype-phenotype correlations). *Only abstract available. °article discussed also in the Registries and Networks part, as both are addressed.

Cross-sectional studies based on natural history studies or database				
Reference	Conditions	Setting	Number	Focus
Iwabuchi et al. 2016[47]*	LGMDR1	Japan	19 LGMDR1 patients	MRI muscle involvement pattern linked to clinical severity
Hagedorn et al. 2023[48]	LGMDR9	USA	8 LGMDR9 patients	Retinal biomarkers, disease characterization
Lowes et al. 2024[49]*	Sarcoglycanopathies	Multicenter	137 LGMDR3/R4/R5 patients	Clinical and functional assessment
Alfano et al. 2025[16]°	LGMDR9	USA, Denmark	101 LGMDR9 patients	Functional outcome measure

7 studies, respectively. Cardiac evaluations involved electrocardiography (ECG) and echocardiography. Spirometry was the sole method employed to assess respiratory function in the study. Among the measured parameters, forced vital capacity (FVC) was the most utilized, serving as the primary indicator of pulmonary performance. Additional parameters included forced expiratory volume in one second (FEV1), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP), which provided further insights into respiratory muscle strength and ventilatory capacity.

In five studies, muscle MRI of the lower limbs, predominantly imaging the thighs and calves, was conducted. Only one of these studies uses a whole-body protocol.[36] Across these studies, both conventional sequences (T1, T2, FLAIR, STIR) and advanced Dixon imaging (three- to six-point methods) were used to quantify muscle fat fraction. Cardiac MRI was systematically used in only one study, focusing on LGMDR9.[37] The initial reported use of wearable devices in LGMDs was in 2019, utilizing consumer-grade devices (Fitbit Flex 2®). This device was employed to collect daily activity levels, including step counts, intraday variability, and seasonal impacts, alongside traditional motor function measures assessed every six months. Findings revealed that patients with Duchenne muscular dystrophy (DMD) and LGMD took statistically significantly fewer steps than controls, exhibited notable intraday variability in activity levels, and showed decreased activity during winter months.[33]

All studies documented progressive muscle weakness with distinct distribution patterns. LGMDs consistently presented with proximal muscle weakness, predominantly affecting the lower limbs, while hand function remained relatively preserved. LGMDR9 exhibited significant phenotypic and genotypic heterogeneity, including gender-specific differences in disease manifestations and progression rates, alongside consistent observations of progressive muscle fat replacement, heterogeneous progression rates, and frequent cardiac complications, such as cardiomyopathy and arrhythmias. Dysferlinopathy (LGMD R2) was characterized by predominant posterior thigh and leg muscle involvement, leading to progressive ambulatory decline and, in many cases, wheelchair dependency.

These natural history studies, while valuable, face several key challenges. The variability in disease progression, particularly the slow progression observed in some subtypes, complicates endpoint selection for clinical trials. Conventional functional assessments often lack the sensitivity required to accurately track changes in these slow-progressing cases. There is a critical need for standardized and validated imaging biomarkers, such as muscle MRI protocols, to provide objective measures of disease progression. The identification of high-risk patients, particularly those susceptible to cardiac complications, is essential for early intervention. These studies underscore the overarching need for well-defined outcome measures to address the variability in disease presentation and facilitate effective clinical trial design.

Cross-sectional studies based on natural history studies

This systematic review identified four cross-sectional studies: three based on natural history studies on LGMDs and one utilizing an LGMD database. One study overlapped with the registry section, as it presented both network and cross sectional. These studies focused on specific LGMD subtypes: LGMDR1, sarcoglycanopathy, and two on LGMDR9 (Table 3). The studies were conducted in various locations, including Italy, Japan, USA, and Denmark, including one multicenter study (Figure 3(b)). Sample sizes varied widely, from 8 participants in *Hagedorn* et al.[48] to 137 in *Lowes* et al.[49]

Despite differences in disease focus and methodology, all studies employed genetic confirmation for diagnosis, ensuring accurate patient selection. *Lowes* et al.[49] described the baseline characteristics of *the JOURNEY natural*

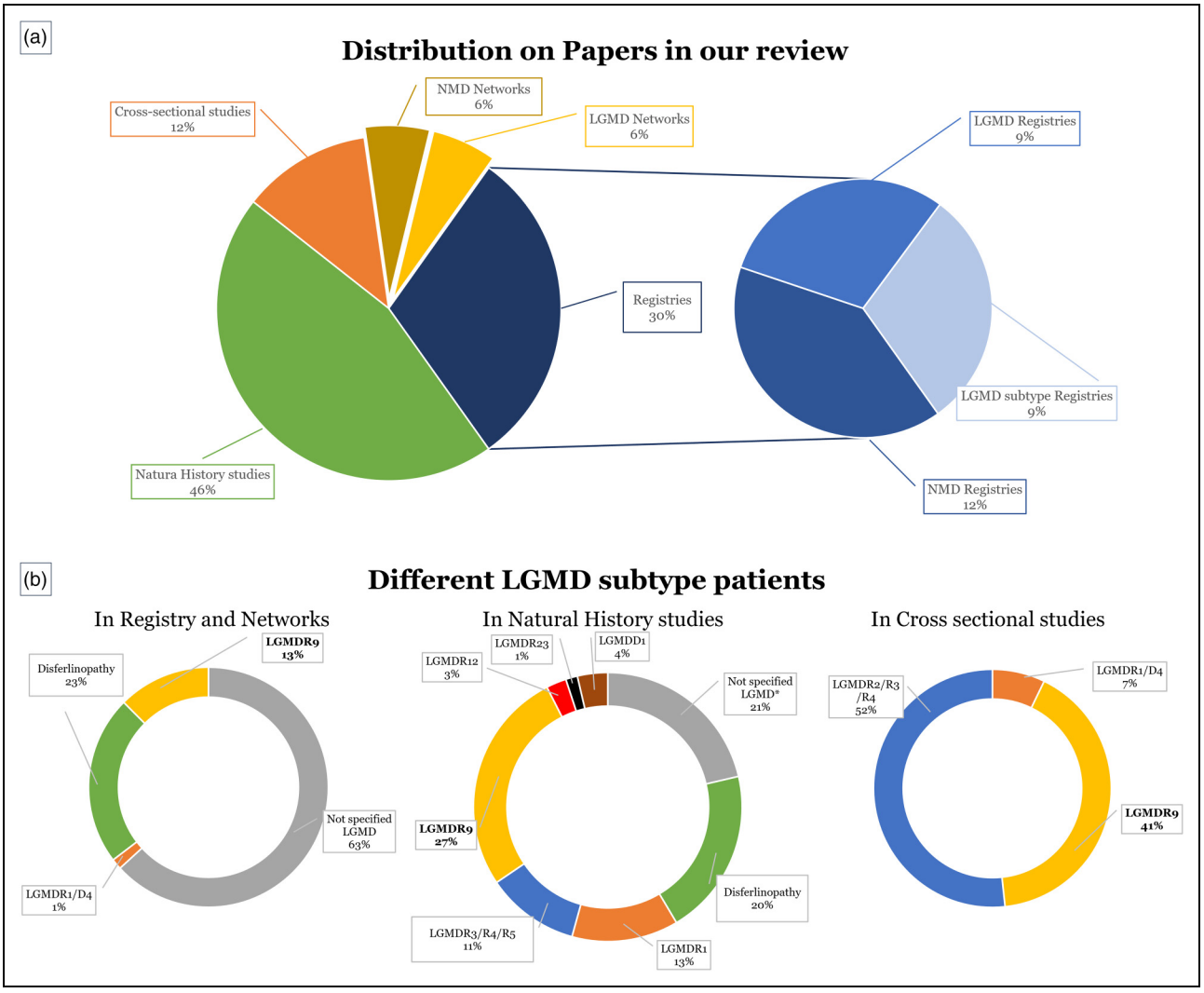

Figure 2. Distribution of studies and LGMD subtypes in the systematic review. (a) Pie charts show the distribution of included papers by study type: natural history studies (50%), registries (27%), cross-sectional studies (11%), NMD networks (6%), and LGMD networks (6%). Registries are further divided into LGMD registries (8%), LGMD subtype registries (8%), and NMD registries (11%). (b) Donut charts display the distribution of LGMD subtypes among patients in registries and networks, natural history studies, and cross-sectional studies included in the review. Most patients in registries are "not specified LGMD" (63%), while LGMD R9 is the most represented subtype in natural history (27%) and cross-sectional studies (41%).

history study (NCT04475926)[50] on sarcoglycanopathies, evaluating patients using NSAD, PUL, timed tests, cardio-respiratory assessments, and ambulatory status records. *Hagedorn* et al. (2023)[48] focused on LGMDR9 patients enrolled in the natural history studies on dystroglycanopathies (NCT00313677)[51] characterizing their electroretinogram findings and identifying abnormal ON/OFF bipolar cell responses and sawtooth 30 Hz flicker waveforms on full-field electroretinogram as a potential new LGMD subtype-specific feature. *Alfano* et al.[16] examined LGMDR9 patients from the *GRASP natural history study* (NCT04202627)[52] aiming to identify reliable outcome measures. They found NSAD and PUL to be highly reliable measures of disease severity, observed significant correlations between the 100-meter test and 10MWT with disease progression, and noted the prevalence of patient-reported fatigue and pain impacting quality of life.

We also wanted to highlight *Iwabuchi* et al. *2016*[47] article, even though it is not based on Natural History. It serves as a valuable example of how registries can be utilized for research. Using the IBIC-NMDs database, filtered for LGMDR1 patients, the study aimed to correlate MRI muscle involvement patterns with clinical severity, as assessed by ambulation status.

Registries, networks and natural history

Our systematic review identified a crucial dependency of natural history studies on registries and networks in advancing clinical research. Registries serve as essential data

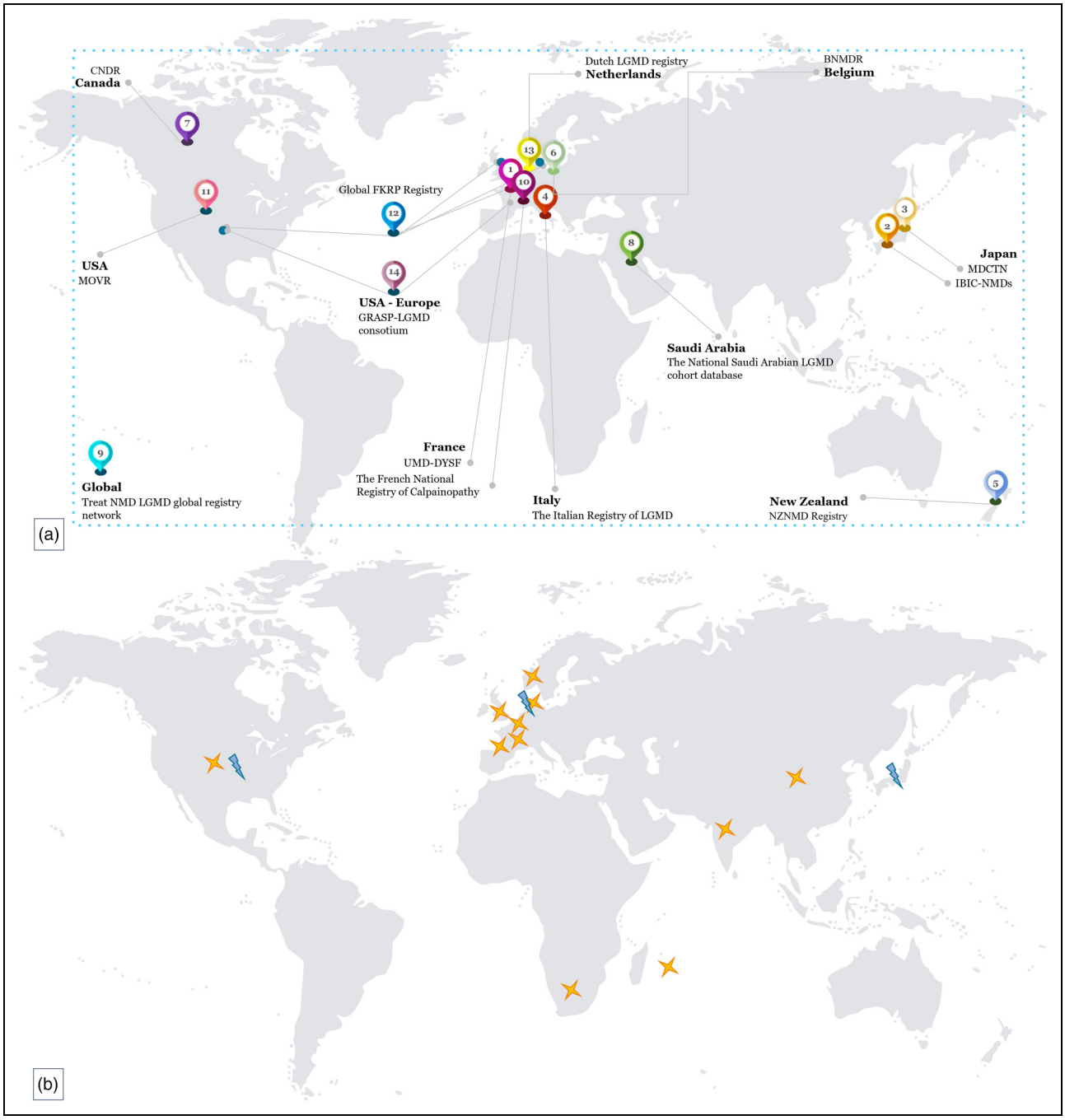

Figure 3. Global distribution of registries and networks related to LGMDs. (A) Map showing geographical coverage of included registries and networks. (B) Country-level distribution of natural history studies (represented by yellow stars) and cross-sectional studies (represented by blue lightning bolts).

sources, providing the longitudinal patient information necessary for natural history studies, while networks act as facilitators, supporting registry development and promoting large-scale research integration. This interconnected system enhances disease modeling, biomarker discovery, and therapeutic advancements by ensuring comprehensive and structured data collection. However, only three registries and two networks from our selection resulted in published natural history studies (Figure 3).

Among the registries, the *Global FKRP Registry* contributed to three studies,[27,28,53] the Italian Limb Girdle Muscular Dystrophy Registry to two,[22,23] and the CNDR also to two.[8,53]

Regarding research networks, the Muscular Dystrophy Clinical Trial Network (MDCTN) contributed to two

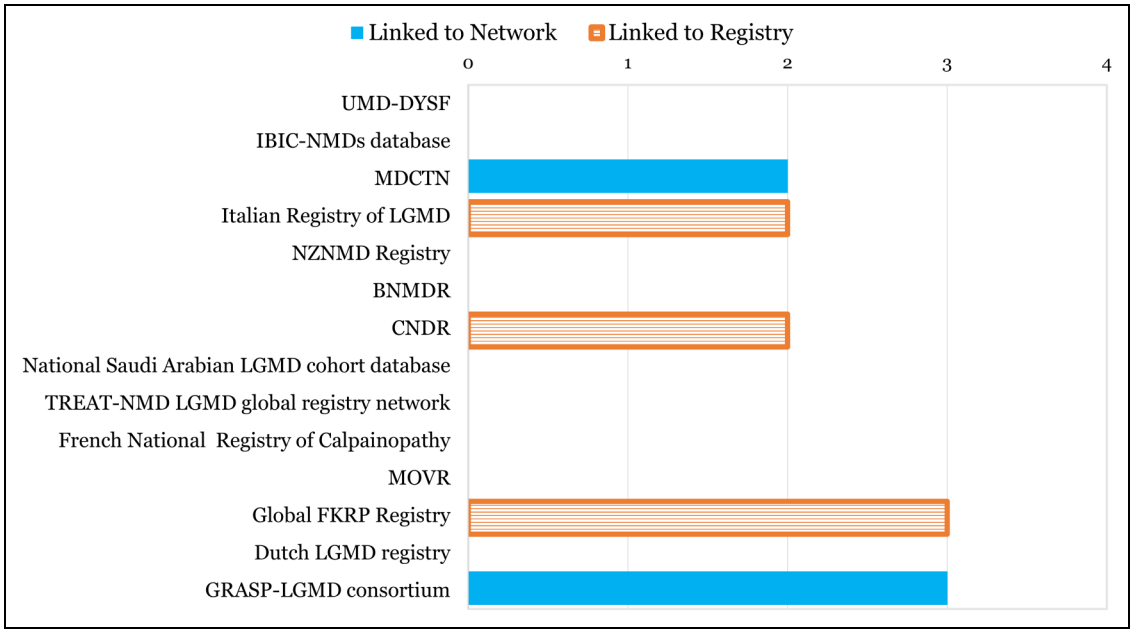

Figure 4. Number of natural history studies associated with registries and networks in LGMD research. Each entry on the y-axis represents a patient registry or research network identified through the systematic review. Horizontal bars indicate the number of natural history studies linked to registries (orange striped bars) or networks (blue solid bars).

publications,[21,47] while the GRASP-LGMD study, as part of the GRASP-LGMD consortium, was also associated with three publications[7,16,46] (Figure 4).

Discussion

Scope and distribution of LGMD registries and networks

The results of this review identified 18 papers, published from 2000–2025, discussing 10 registries and 4 networks linked to LGMDs. Among this, four registries and two networks focus broadly on NMDs, with LGMDs representing only a subset, while three registry and two networks cover all LGMDs in general. Three registries are dedicated to specific LGMD subtypes, such as dysferlinopathies, calpainopathy and FKRP-related muscular dystrophies.

In contrast, 18 papers on natural history studies were identified. Among them, 13 are subtype-specific for LGMDs, focusing on calpainopathy, LAMA2-related muscular dystrophies, LGMDD1, LGMDR12, sarcoglycanopathies, dysferlinopathy, and LGMDR9. Four cross-sectional studies based on natural history or database studies were found, focusing only on specific LGMD subtypes: LGMDR1, sarcoglycanopathy, and two on LGMDR9. LGMDR9 is the most extensively studied LGMD subtype, with one dedicated registry, five natural history studies, and two cross-sectional studies, encompassing a total of 659 patients (range per study: 8–305). This body of research was significantly accelerated by the launch of major gene therapy clinical trials. Given the rarity and clinical heterogeneity of LGMDR9, a detailed understanding of its natural history and phenotypic spectrum was essential to define appropriate clinical endpoints and to identify eligible participants for therapeutic interventions. The need for such foundational data is exemplified by two ongoing gene therapy trials, AskBio's AB-1003 (NCT05230459) in the United States,[54] and Atamyo's GNT0006 (NCT05224505) in Europe,[55] both of which have shown early positive trends.

Geographic distribution and global reach

Another interesting finding is that all but one of the registries were designed as national initiatives, primarily concentrated in Europe and North America (6/10). Networks were a mix of national, international, and global, but the most represented country was the USA, with one national and one international network focused on patients from both the USA and Europe. In contrast, the majority of natural history studies were conducted as international studies (9/17), yet they remained largely focused on the same regions. Only two papers—the Global FKRP Registry[28] and the JOURNEY Natural History Study (NCT04475926)[50]—were designed as truly global initiatives. The Global FKRP Registry includes 23 countries, with most sites in Europe and North America, while the JOURNEY Natural History Study involved 26 sites, with 24 in these regions and 2 outside (Brazil and Turkey). TREAT-NMD LGMD is the only

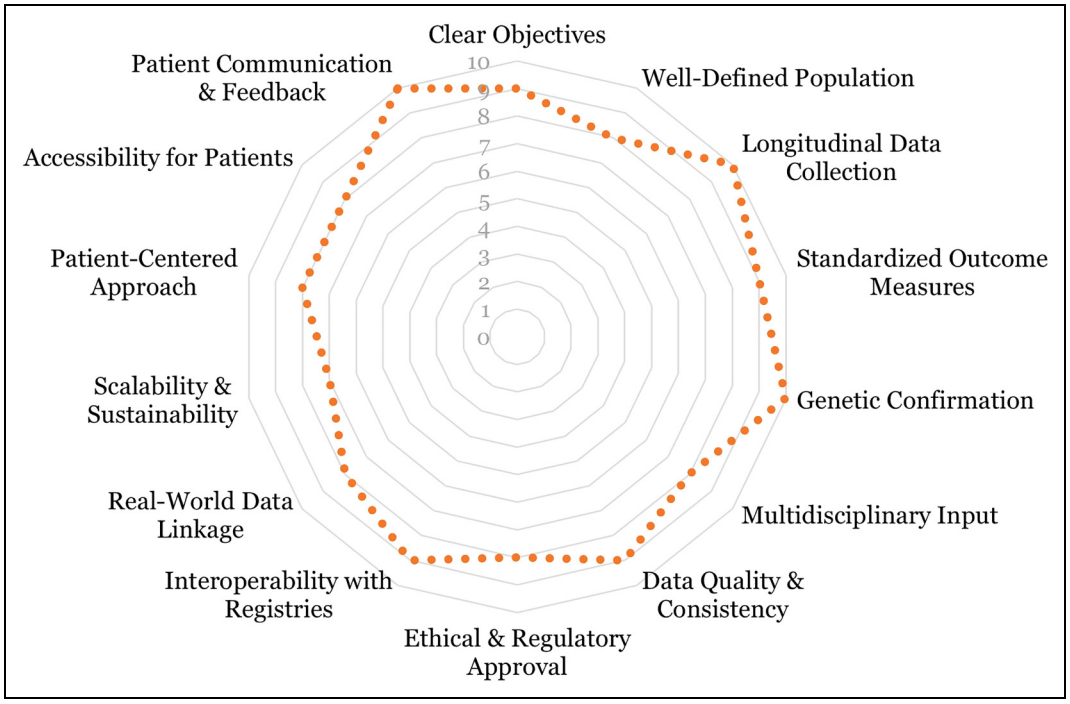

Figure 5. Key criteria for designing and conducting natural history studies this figure illustrates the essential criteria for designing and conducting high-quality natural history studies. These include scientific rigor, robust methodology, and patient-centered approaches. Together, they ensure comprehensive and standardized data collection, long-term follow-up, and clinically meaningful outcomes. Adhering to these principles enhances our understanding of disease progression, supports clinical trial readiness, and contributes to the development of improved therapeutic strategies and patient care.

network created as a global initiative, proposing a common dataset to share with existing LGMD registries to improve data exchange through national databases and create a worldwide network.

Governance and patient involvement

While all networks are, by definition, clinician-led, many collaborate with patient associations to improve data collection and ensure relevance to the patient community. However, the majority of existing registries remain primarily operator-led—designed and managed by clinical or research institutions—with limited patient involvement in governance, priority setting, or data access. This structure often prioritizes regulatory or scientific outcomes over the lived experiences of patients, resulting in several limitations from the patient perspective.

Patient-reported outcomes such as fatigue, pain, and emotional burden are frequently underrepresented, and the communication strategy is typically oriented toward academic audiences, offering little meaningful feedback to patients (Figure 5). Moreover, the rigid design and slow data collection cycles of these registries may fail to capture the day-to-day variability and real-life impact of disease progression.

To address these gaps, a shift toward more inclusive and patient-centered registry frameworks is essential. This involves integrating patient voices into the governance process, ensuring transparency, improving access to individual data, and broadening the scope of outcomes to better reflect the realities of living with the disease (Figure 5).

Data collection trends and methodological limitations

By refining the research, data collection across the selected studies revealed several common trends. Clinical and genetic data were consistently prioritized, followed by functional assessments—typically including ambulation status, strength tests, and NMD-specific standardized scales such as the NSAD or PUL. These standardized scales have only been introduced in the past decade, as they were previously unavailable. A major issue that emerges is the lack of outcome measures specifically designed for LGMD, and particularly ones that are adaptable to the wide spectrum of LGMD subtypes. This is especially relevant for forms like LGMDR1, which demonstrate a slow and nonlinear progression, making it difficult to pinpoint disease onset and to establish sensitive and reliable outcome measures.

Cardiorespiratory function tracking was also frequently included. Muscle MRI was widely used in the selected

Table 4. Existing registries that have not been published and their associated pathologies. **In bold we represent the 100% patient-driven registries.** ▲ Collaborative registry: Operated jointly by patient organizations and research/clinical institutions.

Existing Registries not published	
Name	Pathology
1) Coalition to Cure Calpain Registry https://www.curecalpain3.org/registry/ **Operated by Coalition to cure Calpain**	**Calpainopathy**
2) LGMD-1D DNAJB6 Foundation and International Registry https://lgmd1d.org **Operated by LGMD-1D DNAJB6 Foundation**	**LGMD-1D**
3) International Dysferlin Registry https://dysferlinregistry.jain-foundation.org/ **Operated by Jain Foundation**	**Dysferlinopathy**
4) International LGMD2C Patient Registry https://www.kurtpeterfoundation.org/patient-registry/ **Operated by kurt + peter Foundation**	**Gamma-Sarcoglycanopathy**
5) International LGMD2D Patient Registry https://www.lgmd2l-foundation.org/registry **Operated by LGMD2D Foundation**	**Alpha-Sarcoglycanopathy**
6) Congenital Muscle Disease International Registry ▲ https://www.cmdir.org/user/register Operated by Cure CMD	Telethonin
7) International Myotubular and Centronucelar Myopathy Patient Registry https://mtmcnmregistry.org Operated by TREAT-NMD en partenariat avec le Myotubular Trust et Muscular Dystrophy UK	Titinopathie
8) Congenital Muscle Disease International Registry ▲ https://www.cmdir.org/user/register Operated by Cure CMD	POMT1
9) LGMD2L Patient Registration https://www.lgmd2l-foundation.org/patient-registration **Operated by LGMD2L Foundation**	**Anoctamine 5**
10) Congenital Muscle Disease International Registry ▲ https://www.cmdir.org/user/register Operated by Cure CMD	FKTN (Fukutin)
11) Congenital Muscle Disease International Registry ▲ https://www.cmdir.org/user/register Operated by Cure CMD	POMT2
12) Congenital Muscle Disease International Registry ▲ https://www.cmdir.org/user/register Operated by Cure CMD	POMGnT1
13) LGMD R23 related to the laminin alpha-2 protein Congenital Muscle Disease International Registry ▲ https://www.cmdir.org/user/register Operated by Cure CMD	LGMD R23 related to the laminin alpha-2 protein

papers. Finally, quality of life and pain, while newer parameters, were the least represented data types, with wearable devices proposed in only one natural history study. A distinguishing feature of more recent registries was the tracking of patient participation in clinical trials. However, challenges such as maintaining patient participation and ensuring data standardization persist. Furthermore, a key tension emerged between patient selection based on clinical versus genetic criteria; thus, while clinical selection sacrifices diagnostic precision, genetic selection risks compromising ethnic diversity within the cohorts. These challenges underscore the importance of standardized protocols and resource allocation, necessitating a global effort, to ensure equitable data collection and representation in registries.

Unpublished and ongoing studies

The first limitation of this review is that not all registries and natural history studies available for LGMD patients are published (Tables 4 and 5). These LGMD registries (Table 4) are

Table 5. Natural history studies including LGMDR1 not yet published (according to clinicalTrials.gov). Summarizes natural history studies that include LGMDR1 and are registered on ClinicalTrials.gov but have not yet published their findings. These studies are being conducted across a range of countries and settings, reflecting growing international efforts to better characterize the progression of LGMD subtypes.

Natural history studies including LGMDR1 not yet published				
NCT Number	Study Title	Study status	Condition	Settings
NCT05956132[57]	*Clinical and Biochemical Features for the Identification of Dominant Calpainopathies*	Ongoing	LGMDR1	Italy
NCT03488784[58]	*Natural History of Limb Girdle Muscular Dystrophy Type 2A and Type 2E*	Ongoing	LGMDR1, LGMDR4	USA
NCT04349566[59]	*Fast Troponin as a Biomarker to Assess Exercise-induced Muscle Damage in Muscle Diseases*	Completed	BMD, McArdle Disease, LGMDs	Denmark
NCT05618080[60]	*LGMD R1 Natural History Study*	Ongoing	LGMDR1	USA, UK, Netherlands
NCT04475926[54]	*A Study of the Natural History of Participants With LGMD2E/R4, LGMD2D/R3, LGMD2C/R5, and LGMD2A/R1 ≥ 4 Years of Age, Who Are Managed in Routine Clinical Practice*	Ongoing	LGMDs	USA, Canada, Brazil, Turkey, Spain, UK, Sweden, Italy, Germany, Belgium
NCT06390566[55]	*Evolution of the Functional and Muscular State of Patients With Muscular Dystrophy 2A (CALNATHIS)*	Ongoing	LGMDs	France
NCT05989620[56]	*Long-Term Development of Muscular Dystrophy Outcome Assessments*	Ongoing	LGMDs	USA
NCT00893334[61]	*Evaluation of Limb-Girdle Muscular Dystrophy*	Completed	BMD, LGMDR1, LGMDR2, LGMDR9	USA
NCT04989751[62]	*A Multicenter Phenotype-Genotype Analysis of LGMD Patients in China*	Ongoing	LGMDs	China

focusing on specific subtypes and are still in the recruitment phase. These more recent registries tend to be global rather than national, forming international cohorts. However, global data on patient distribution remains limited, with many natural history studies still ongoing. For example, ClinicalTrials.gov lists nine natural history studies for LGMDR1 (Table 5), of which only two have been completed. The geographical distribution of these studies is primarily concentrated in Europe and North America, with one study in China, which is the only one linked to a registry, and one international study involving Brazil and Turkey. Notably, most focus broadly on NMDs, while only two specifically target calpainopathy—both European initiatives: one in Italy, and the prospective multicenter French study CALNATHIS (CALpainopathy NATural HIStory Study) (NCT06390566).[56] It is designed to better understand the natural history of LGMDR1, or calpainopathy. Coordinated by our group at Assistance Publique Hôpitaux de Paris Henri Mondor Hospital, the study follows 25 adult patients with a confirmed genetic diagnosis over a two-year period. Its primary objective is to quantify the progression of muscle weakness using functional, imaging, and laboratory assessments. CALNATHIS plays a crucial role in preparing for future therapeutic trials, particularly those involving gene therapy approaches. By identifying robust clinical endpoints, CALNATHIS is contributing to the advancement of care and research in LGMDR1.

Limited visibility of LGMDs in Major international registries

One significant limitation of our review is that some large registries or networks, while published, do not explicitly mention their involvement in studies on specific conditions like LGMDs. For instance, the EURO-NMD registry, part of the European Reference Network (ERN) for rare NMDs, integrates data from 82 European healthcare providers to address fragmentation in research and care. This registry uses a federated FAIR (Findable, Accessible, Interoperable, and Reusablenable) infrastructure, ensuring data standardization through common and disease-specific data elements. Designed as a patient-centered initiative, it supports clinical trials, epidemiological studies, and care optimization by linking over 120 existing registries. Despite this, EURO-NMD's publications do not mention LGMDs, limiting their visibility within the research community. This lack of inclusion reduces awareness and hinders research on LGMDs, underscoring the need for more focused attention on these conditions within

large-scale registries. Furthermore, it is important to note that natural history study protocols can be particularly demanding in terms of time and energy for patients, often requiring frequent visits, extensive assessments, and long-term commitment. These burdens, especially in conditions characterized by progressive disability and fatigue, may significantly limit both patient participation . This patient-side limitation further complicates the implementation of natural history studies and may contribute to the underrepresentation of LGMDs within broader registry networks.

The importance of registry-based natural history studies

On a global scale, approximately 7000 rare diseases affect around 30 million people, yet only 30% of patients are included in registries. In recent years, however, the critical role of registries mapping the natural history in rare diseases has become increasingly recognized.[63] Registries, and by extension networks, provide a vital foundation for collecting longitudinal data to track disease progression, phenotypic variability, and treatment responses. Among all the existing natural history studies, only 12 selected publications in this review were linked to registries or networks.

Natural history studies, by definition, are strictly observational, meaning they exclude interventional patients from the cohort, representing a missed opportunity to leverage well-characterized populations. Registry-based cohorts could optimize research by not only yielding natural history outcomes but also facilitating biomarker discovery. These cohorts would attract industry interest for conducting more clinical trials of new disease-modifying drugs and enable the subsequent collection of real-world drug effect data after approval.[64] Such an approach could enhance both the sustainability and effectiveness of registry-based research, which is especially critical when dealing with the limited patient population available for rare diseases like LGMDs. Future research should focus on demonstrating the direct impact of registry data on clinical trial design and the development of outcome measures.

Despite the limitations and challenges faced by current LGMD registries and networks, there is a growing potential for innovative technologies to address these issues and improve research outcomes. Artificial Intelligence (AI) plays a crucial role in enhancing LGMDs registry-based research.[65] It enhances patient stratification by categorizing individuals based on genetic and clinical profiles, optimizing recruitment for clinical trials. AI-driven predictive models analyze longitudinal data to forecast disease progression and prognosis, while pattern recognition capabilities help identify subtle progression patterns that may be missed by clinicians. Additionally, AI enables automated image analysis, refining MRI-based biomarkers and increasing diagnostic precision. By integrating registry data with real-world data, AI accelerates the development of targeted therapies and supports global collaboration by helping standardize data across multiple registries.[65]

Conclusion

The findings highlight the pivotal role that registries and networks play in facilitating comprehensive data collection, which benefits the entire medical environment, ranging from patients and clinicians to researchers and industries focused on therapeutic development. However, there remains a notable gap in the number of registry-based natural history studies which hinders the establishment of centralized, comprehensive datasets. Unlike traditional natural history studies, registries offer greater flexibility, enabling the creation of diverse study designs that can enhance our understanding of complex diseases like LGMDs and expedite the development of effective treatments. Despite this potential, several challenges persist, including variability in registry design, issues with data interoperability. Moreover, there is a critical need for increased diversity in patient representation across global regions, as current datasets do not fully capture all demographic groups. The establishment of a global registry network that incorporates data interoperability and standardized datasets could help resolve these issues and promote more inclusive research. Additionally, the integration of advanced tools such as artificial intelligence and big data technologies holds immense promise. These technologies can significantly enhance the accuracy, efficiency, and scope of LGMD research, accelerating the identification of biomarkers, optimizing patient stratification, and ultimately driving the development of targeted, effective therapies.

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Author contributions

Author 1: Writing – Original Draft Preparation, Investigation, Formal Analysis, Visualization, Supervision. Author 2: Writing – Original Draft Preparation, Investigation, Formal Analysis, Supervision. Author 3: Investigation, Supervision. Author 4: Investigation, Resources, Supervision. Author 5: Supervision. Author 6: Supervision. Author 7: Investigation, Supervision. Corresponding Author: Conceptualization, Supervision, Writing – Review & Editing.

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Data availability statement

The data analyzed in this review are all from publicly available sources. Specific citations for the included studies can be found in the references section of this article.

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