Journal of Neurology (2025) 272:483
https://doi.org/10.1007/s00415-025-13208-8

ORIGINAL COMMUNICATION

Equity in neuromuscular research: a 20-year analysis of race, ethnicity, sex, and age representation

Lorenzo Fontanelli[1,2] · **Gabriele Vadi**[1] · **Gabriele Bellini**[1] · **Andrea Cossu**[3] · **Gabriele Siciliano**[2]

Received: 7 April 2025 / Revised: 4 June 2025 / Accepted: 7 June 2025

Abstract

Objectives We conducted a systematic analysis of studies on neuromuscular diseases registered on ClinicalTrials.gov over the last 20 years to assess disparities in study populations.

Methods Data from interventional and observational neuromuscular disease studies initiated between January 1, 2004, and December 31, 2024, were retrieved from ClinicalTrials.gov and PubMed/MEDLINE. Collected variables included participant race, ethnicity, sex, eligible age range, mean and median ages, as well as study funding source, start year, and phase. These variables were analyzed to evaluate disparities in race, ethnicity, and age across studies and over time.

Results A total of 2166 studies were screened, with 462 meeting inclusion criteria, encompassing data from 37,131 participants. Most participants were male (61.4%), White (83.5%), and non-Hispanic/Latino (87.6%). While the proportion of studies reporting race and ethnicity increased over time ($p < 0.001$ and $p = 0.001$, respectively), the racial and ethnic composition of participants remained unchanged ($p = 1$). Studies on X-linked recessive disorders (i.e., Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, and spinal and bulbar muscular atrophy (SMA)) predominantly excluded female participants. Regarding age accessibility, 37.9% of studies allowed children. Similarly, trial accessibility for older adults was limited. Even in studies with broader age eligibility, mean and median participant ages clustered around midlife, with underrepresentation at both age extremes. Notably, about half of DMD and SMA studies excluded participants over 16 and 18 years, respectively.

Conclusion Significant disparities persist in race, ethnicity, and age representation in neuromuscular disease clinical research, highlighting the need for more inclusive study designs.

Keywords Health equity · Neuromuscular diseases · Clinical trials · Inclusivity · Minorities in medicine

Introduction

Equitable access to clinical research is a critical imperative [1], yet underrepresentation of non-white and non-male individuals remains a widespread issue, leading to a significant lack of diversity in clinical trials [2–4]. Similarly, individuals at both age extremes—children, adolescents and older adults—are frequently overlooked [5, 6] despite their unique physiologic responses to treatments. In fact, disparities in race, ethnicity, sex and age among participants of clinical studies may impair generalizability of findings [3, 7], reflect inequalities in accessing to therapeutic options, undermine trust in medical research, and perpetuate unfairness for marginalized groups [8]. Different strategies have been employed over time to evaluate minorities exclusion in clinical trials. In 1993, the guideline from the International Council for Harmonisation of Technical Requirements

Lorenzo Fontanelli and Gabriele Vadi contributed equally to this work.

✉ Lorenzo Fontanelli
Lorenzo.Fontanelli@santannapisa.it

[1] Health Science Interdisciplinary Center, Sant'Anna School of Advanced Studies, Piazza Martiri Della Libertà 33, 56127 Pisa, Italy

[2] Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma 55, 56126 Pisa, Italy

[3] Computer Science Department, University of Pisa, Largo Bruno Pontecorvo 3, 56127 Pisa, Italy

Published online: 30 June 2025

for Pharmaceuticals for Human Use [9], later adopted by the European Medicines Agency and the US Food and Drug Administration, stated that, as a general principle, drugs should be studied in all age groups for which they have significant utility. In 2001, the National Institute of Health (NIH) published the Policy and Guidelines on "The Inclusion of Women and Minorities as Subjects in Clinical Research" with the primary goal to ensure generalizability to the whole population [10]. In 2017, those guidelines were strengthened to require that investigators ensure valid analyses by sex/gender and race/ethnicity during the evaluation of clinical trial results [11]. Since 2020, all projects sponsored by the European Commission must account for sex and gender in both the design and analysis stages [12]. Regarding race and ethnicity, the Office of Management and Budget (OBM) Directive 15 has guided reporting standards for nearly half a century. Since its 1997 revision, the minimum categories for data on race were "American Indian or Alaska Native", "Asian", "Black or African American", "Native Hawaiian or Other Pacific Islander" and "White"; analogously, categories for ethnicity were "Hispanic or Latino" and "Not Hispanic or Latino". Indeed, race and ethnicity are inherently complex constructs [7] that evolve over time, making standardization a challenging task. In an effort to account for the demographic complexities, the recent revision of the directive in March 2024 combines previously separate questions on ethnicity and race into a single, consolidated question, allowing respondents to select one or multiple categories [13].

However, despite growing attention to diversity in clinical research, the awareness of inequalities extent in neuromuscular diseases studies lags behind other areas of neurology [14]. As such, enhancing the recognition and understanding of disparities in neuromuscular research appears to be an essential step to improve quality of care for vulnerable populations [14]. In this study, we conducted a systematic analysis of clinical studies on neuromuscular diseases registered on ClinicalTtrials.gov over the last 20 years to assess the representation of race, ethnicity, sex and age.

Methods

We searched the ClinicalTrials.gov database for studies started between January 1, 2004, and December 31, 2024, to retrieve clinical studies related to motor neuron, peripheral nerve, neuromuscular junction, and muscle disorders (detailed research methodology can be found in the Supplementary Materials). The authors independently assessed the relevance of the retrieved articles and, in cases of doubt, discussed individual instances to reach a consensus. Data concerning sex, race, ethnicity, ages eligible for study, mean and median age of participants included, year of study start, type of study (i.e., interventional or observational), phase and funding source were collected. All studies that had not reported results were searched by their NCT numbers in PubMed using a script in R. Data reflects all records available on ClinicalTrials.gov and PubMed/MEDLINE as of December 31 st, 2024. We considered race and/or ethnicity as "reported" for a specific study if the sum of all reported single race and/or ethnicity categories equalled the number of study participants. According to the recently updated OMB Directive 15 [13], we also considered race and ethnicity as "reported" if race or ethnicity labels were presented in a single mixed list, provided that the sum of individual items equalled or exceeded the number of participants. We labeled race and/or ethnicity as "reported as not standard" if the study provided race or ethnicity information 1) using terms not included in OMB Directive 15 and its amendments 2) only for a subset of participants (e.g., race or ethnicity was reported only for the majority group). Finally, we labeled race and/or ethnicity as "not reported" if they were not mentioned in the study. For the purposes of statistical analysis, we excluded studies reporting not standard race and/or ethnicities; when assessing the number of patients in each race/ethnicity category, we also excluded studies that, although compliant with the new OMB Directive 15, reported mixed race and ethnicity data given their low number in the whole set and the inconsistency with the majority of studies.

Standard protocol approvals, registrations, and patient consents

This study was conducted using publicly available data and did not involve human participants; as such, ethical approval, patient consent, and institutional review board IRB approval were not required.

Data availability

Data from ClinicalTrials.gov and PubMed are publicly available. The database used for the analyses obtained from the retrieved studies has been deposited to https://doi.org/10.5281/zenodo.15110063.

Statistical analysis

Categorical data are presented as absolute counts and relative frequencies, while quantitative data as median and range. Categorical variables were compared using the Chi-square test, with post hoc analysis based on residuals performed when significant. Fisher's exact test was used to assess whether the distribution of race and ethnicity proportions across years differed significantly. Due to the large contingency table, p values were estimated using a Monte Carlo simulation with 1,000,000 iterations to ensure accurate

approximation of the exact p value. Qualitative and quantitative data were compared using Mann–Whitney test, with Cliff's delta calculated to measure effect size. Kendall's Tau correlation was used to assess the strength and direction of the association between the proportion of study reporting race/ethnicity and the study start year. To assess the similarity of racial composition across included studies, we performed a multivariate dispersion analysis using the PERMDISP method implemented in the R package vegan [15]. Racial proportion data for each study were first normalized so that each row summed to one. Using Bray–Curtis dissimilarity, pairwise distances between studies were computed based on their racial distribution profiles. We then quantified the average distance of each study to the group centroid, providing a measure of variability in racial composition across studies. Change point analysis was performed using the changepoint package in R [16] to detect structural breaks in the time series data. The Pruned Exact Linear Time method was applied to identify significant change points, optimizing the penalty using a modified Bayesian information criterion (MBIC). Statistical analyses were performed using R version 4.4.1 (R Core Team, 2024). A significance level of 0.05 was used to determine statistical significance.

Results

Two thousand one hundred sixty-six studies were screened for eligibility. After assessing their relevance, 462 studies were included in the analysis (Fig. 1), encompassing data from 37,131 patients. Table 1 shows detailed characteristics of the retrieved studies.

Race was reported in 246 (53.2%) studies covering a total of 20,852 (51.1%) patients. In particular, race was reported using non-standard terminology and in a mixed list with ethnicity in 18 (3.9%) and 6 (1.3%) studies, respectively. Since their data were not comparable, these studies were excluded from the analyses of race composition. Of the remaining 222 studies, encompassing 17,841 patients, 39 (0.2%) patients were American Indian or Alaska Native, 1507 (8.4%) were Asian, 385 (2.2%) were Black, 29 (0.2%) were Native Hawaiian or other pacific islander (0.2%), 14,905 (83.5%) were White; 116 (0.7%) patients were listed as more than one race and 862 (4.8%) as unknown/not reported. Regarding ethnicity, 153 (33.0%) studies reported data for a total of 12,144 (32.7%) patients. In detail, ethnicity was reported using non-standard terminology and in a mixed list with race in 11 (2.4%) and 5 (1.1%) studies respectively, which were excluded from the analyses regarding ethnicity composition

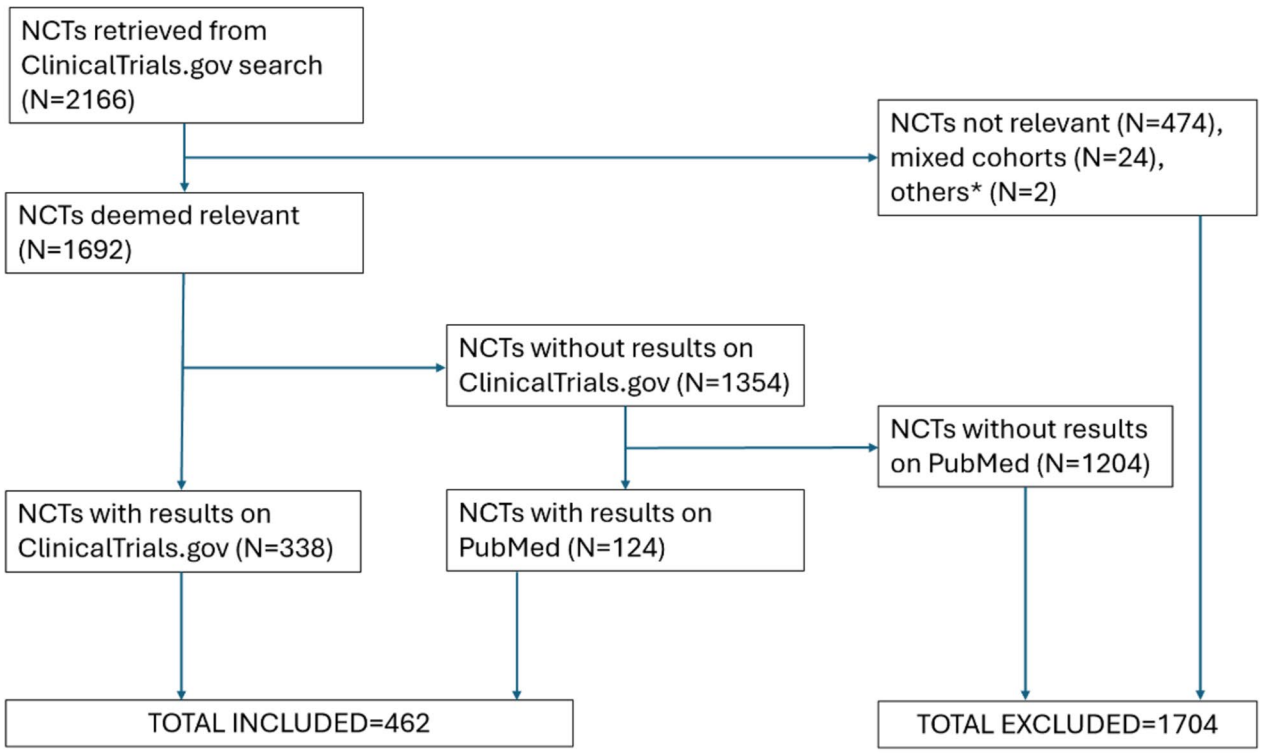

Fig. 1 Studies selection chart. *Studies enrolling patients already included in previously analyzed studies. Further details on the research methodology are available in the Supplementary Materials

Table 1 Characteristics of the included studies

	ALS	SBMA	SMA	GBS	CIDP	CMT	LEMS	MG	BMD	DMD	FSHD	DM1	DM + PM	IBM	GSDII
Total*	150	2	48	7	17	9	4	42	4	89	16	9	30	8	29
Interventional	142	2	43	5	15	7	4	37	2	85	13	9	28	8	25
Phase I	15	0	7	0	0	0	2	1	0	7	1	1	2	0	1
Phase II	53	2	12	4	5	5	2	15	2	34	4	2	14	2	4
Phase III	18	0	9	1	9	1	0	20	0	16	0	0	5	2	4
Phase IV	2	0	1	0	0	0	0	0	0	1	0	0	2	0	11
More than one phase	21	0	7	0	0	1	0	0	1	15	4	4	2	4	5
NA	*33*	0	7	0	1	0	0	1	0	12	4	2	3	0	0
Observational	8	0	5	2	2	2	0	5	2	4	3	0	2	0	4
Funding															
Private	55	1	32	1	7	4	3	32	0	59	8	3	12	5	22
Public	95	1	16	6	10	5	1	10	4	30	8	6	18	3	7
Reporting race															
Yes	66	0	24	1	8	2	3	26	1	46	6	4	15	2	19
No	75	2	24	6	8	7	1	10	3	38	9	5	14	6	8
Non standard	8	0	0	0	1	0	0	4	0	4	1	0	1	0	0
Mixed	1	0	0	0	0	0	0	2	0	1	0	0	0	0	2
Reporting ethnicity															
Yes	50	0	20	3	5	3	3	15	1	25	3	2	4	0	6
No	94	2	28	6	11	6	1	21	3	62	13	7	26	8	22
Non standard	5	0	0	0	1	0	0	4	0	1	0	0	0	0	0
Mixed	1	0	0	0	0	0	0	2	0	1	0	0	0	0	1

*Two studies included mixed cohorts, which were separately analyzed and reported in the table

ALS Amyotrophic Lateral Sclerosis, *BMD* Becker Muscular Dystrophy, *CMT* Charcot-Marie-Tooth Disease, *CIDP* Chronic Inflammatory Demyelinating Polyneuropathy, *DM and PM* Dermatomyositis and Polymyositis, *DMD* Duchenne Muscular Dystrophy (DMD), *FSHD* Facioscapulohumeral Muscular Dystrophy (FSHD), *GSDII* Glycogen Storage Disease Type II, *GBS* Guillain–Barré Syndrome, *IBM* Inclusion Body Myositis, *LEMS* Lambert–Eaton Myasthenic Syndrome, *MG* Myasthenia Gravis, *DM1* Myotonic Dystrophy Type 1, *SBMA* Spinal and Bulbar Muscular Atrophy, *SMA* Spinal Muscular Atrophy

thereafter. Of the remaining 137 studies, encompassing 10,380 patients, 815 (7.9%) were Hispanic or Latino, 9088 (87.6%) were not Hispanic or Latino, and 477 (4.6%) were listed as unknown/not reported. Race and ethnicity distributions per disease are shown in Fig. 2. Extended data can be consulted in Table S1. White race was the most represented across all diseases, except in Guillain–Barré syndrome (GBS), where only two studies on Asian patients reported race. Multivariate dispersion analysis revealed a median Bray–Curtis distance to the centroid of 0.08 (range: 0.02–0.96), indicating that most studies exhibited relatively similar racial compositions, while a small subset showed substantially greater distances, reflecting more distinct profiles. The most dissimilar studies corresponded to ten trials that enrolled only Asian participants. Regarding ethnicity, the median Bray–Curtis distance to the centroid was also 0.08, with a narrower range (0–0.51), indicating even less variability in ethnicity composition across the included studies. Although interventional studies reported race and ethnicity more frequently than observational studies, the differences were not statistically significant (race: 52.7% vs. 35.1%, $p = 0.06$; ethnicity: 34.2% vs. 21.1%, $p = 0.144$). We did not find any difference in race or ethnicity reporting rates across interventional studies of different phases ($p = 0.139$ and $p = 0.492$, respectively). Industry-sponsored studies reported race and ethnicity more often than publicly funded ones (race: 67.1% vs. 33.2%, $p < 0.001$; ethnicity: 39.1% vs. 23.1%, $p < 0.001$). We observed a significant increase in the proportion of studies reporting race and ethnicity over time ($p < 0.001$, and $p = 0.001$, respectively) (Figure S1 and Figure S2). Regarding race, change point analysis identified two significant breaks in 2014 and 2016 (median proportion of studies reporting race between 2004 and 2014: 0.27 (0.1–0.53); mean proportion between 2015 and 2016: 0.61 (0.55–0.67); mean proportion after 2016: 0.69 (0.67–0.78)). To further verify the significance of this change, we confirm a significant and large increase of reported race in studies after 2014 compared to the 10 years before ($p < 0.001$, Cliff's delta = 1). Regarding ethnicity, change point analysis identified three significant breaks in 2014, 2019 and 2021 [median proportion of studies reporting ethnicity between 2004 and 2014: 0.2 (0–0.34), median proportion of studies

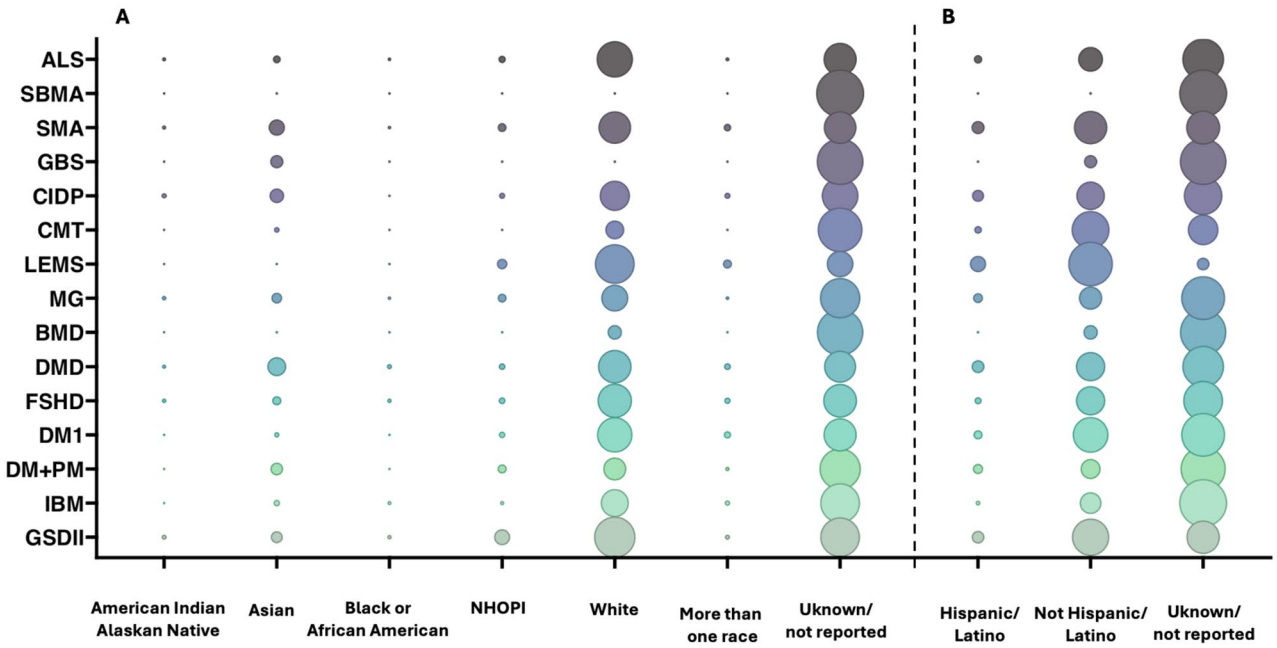

Fig. 2 Race and ethnicity distribution across studies in neuromuscular diseases. Dots size reflects the number of patients of a given race and ethnicity for each neuromuscular disease. **a** Race was unknown for a considerable portion of patients (41.2% of enrolled participants). White patients represented the majority of those with reported race. Asian was the second most frequent race. Among GBS studies, only one study out of seven reported participants' race, with all individuals being Asian. We could not be able to retrieve race information for the participant of the other studies, so this percentage is likely not representative and should be interpreted with caution. American Indian or Alaska Native, Black, and Native Hawaiian or other pacific islander represented only a small fraction of total participants. **b** Ethnicity was available for even fewer patients, with not Hispanic or Latino being the most common across all neuromuscular diseases. *ALS* Amyotrophic Lateral Sclerosis, *BMD* Becker Muscular Dystrophy, *CMT* Charcot-Marie-Tooth Disease, *CIDP* Chronic Inflammatory Demyelinating Polyneuropathy, *DM + PM* Dermatomyositis and Polymyositis, *DMD* Duchenne Muscular Dystrophy, *DM1* Myotonic Dystrophy Type 1, *FSHD* Facioscapulohumeral Muscular Dystrophy, *GSDII* Glycogen Storage Disease Type II, *GBS* Guillain–Barré Syndrome, *IBM* Inclusion Body Myositis, *LEMS* Lambert–Eaton Myasthenic Syndrome, *MG* Myasthenia Gravis, *NHOPI* Native Hawaiian or Other Pacific Islander, *SBMA* Spinal and Bulbar Muscular Atrophy, *SMA* Spinal Muscular Atrophy

between 2015 and 2019: 0.41 (0.37–0.52), median proportion of studies between 2020 and 2022: 0.39% (0.33–0.52)]. Post-hoc analysis confirmed a significant large increase in studies reporting ethnicity during the 5-year period from 2015 to 2019 compared to the period 2004–2014 ($p = 0.002$, Cliff's delta = 1). No difference was found between the proportion of studies reporting ethnicity between the period 2015–2019 and 2020–2022 ($p = 0.571$). However, year did not significantly influence the racial and ethnicity proportions over time ($p = 1$ and $p = 1$) (Table S2). We found a significant difference in race composition among industry-funded and publicly funded study ($p < 0.001$). In detail, industry-funded study had fewer participants with unknown/not reported race, with an increase in participants from other racial groups, especially White and Asian (Table S3). Interventional studies exhibited a similar pattern when compared to observational studies (Table S4). Regarding ethnicity, no significant differences were found in Hispanic proportions among industry and publicly funded studies, and interventional and observational studies ($p = 0.092$ and $p = 0.912$, respectively). We observed a significant difference in racial and ethnicity composition across interventional studies of different phases ($p < 0.001$ and $p < 0.001$). In detail, phase II studies had an overrepresentation of participant with unknown/not reported race, and a reduction in the number of people of Asian race compared to expected values. Phase III studies had more participants with reported race and an increase of White and Asian people. Phase IV studies show an overrepresentation in patients with unknown/not reported race and an almost symmetrical underrepresentation of White participants (Table S5). Considering ethnicity, a greater-than-expected proportion of non-Hispanic/Latino participants was observed in Phase I and II studies. In contrast, Phase III and Phase IV studies had a higher number of participants with unreported ethnicity and a specular reduction of non-Hispanic/Latino participants (Table S6).

All studies reported data on sex, except for one observational study which reported gender only without specifying sex. Most patients (61.4%) were male, with a predominance in interventional studies compared to observational ones

(median of males enrolled in interventional and observational studies: 60.5% (0–100%) and 51.5% (0–100%), respectively; $p=0.127$), and the remaining being females. No intersex patients were included in the retrieved studies. No differences over time, nor among industry and publicly funded, interventional and observational studies, phases of interventional studies were found in the proportion of sex enrolled ($p=0.414$, $p=0.883$, $p=0.128$ and $p=0.527$, respectively). Regarding recessive X-linked diseases, such as Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), and Spinal and Bulbar Muscular Atrophy (SBMA), all studies excluded female patients apart from one clinical trial enrolling DMD female carriers and six DMD trials that allowed enrollment of both sexes; although these latter trials permitted the enrollment of both sexes, no females were ultimately recruited. In clinical trials on facioscapulohumeral muscular dystrophy (FSHD) and myasthenia gravis, we found a higher proportion of men enrolled compared to the to the male-to-female prevalence ratio reported in the literature. Regarding amyotrophic lateral sclerosis (ALS), chronic inflammatory demyelinating polyneuropathy (CIDP), glycogen storage disease type II (GSDII), inflammatory body myositis, dermatomyositis and polymyositis, the male-to-female ratio aligned with the values reported in the literature [17–30]. In GBS trials, while men were more frequently enrolled, their representation did not reflect the predominance of males reported in the literature. We observed a higher number of enrolled females, both in absolute terms and relative to the expected sex distribution, for Lambert–Eaton myasthenic syndrome

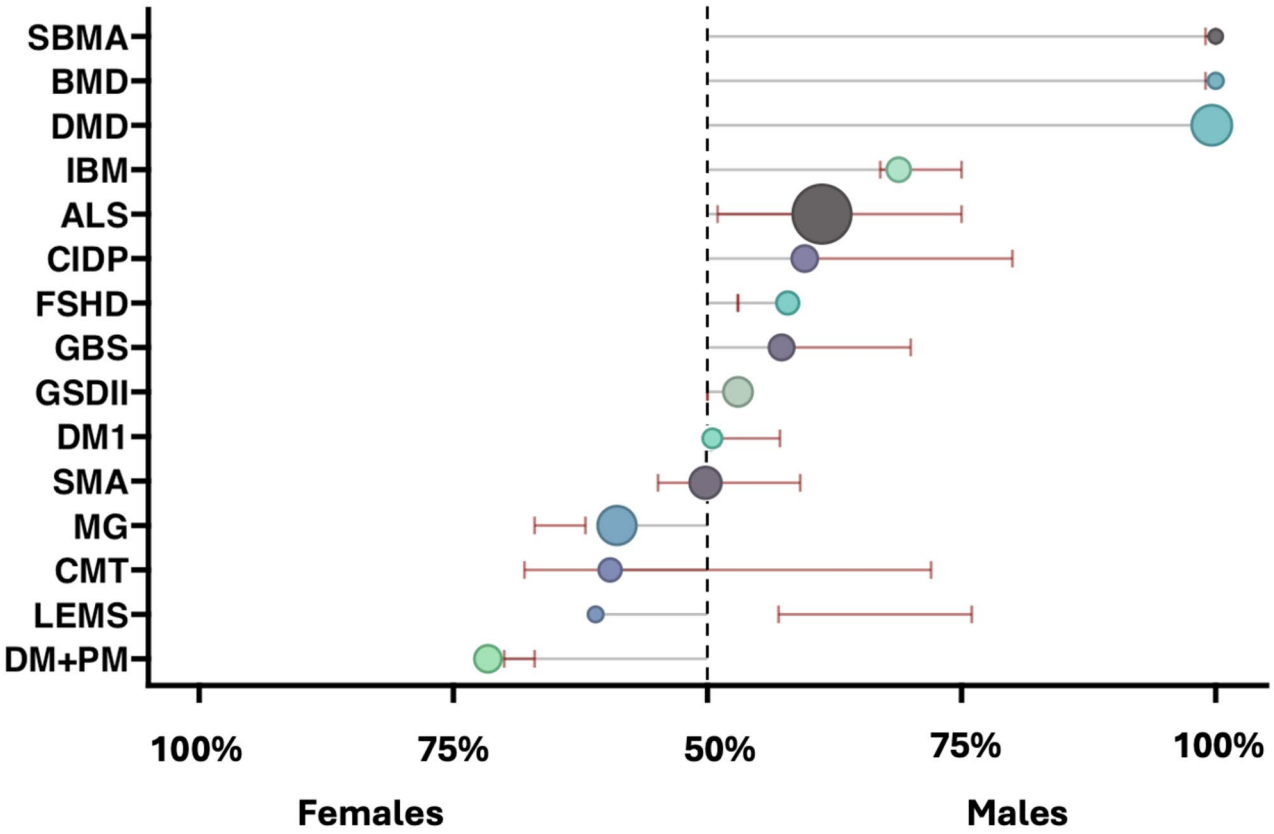

Fig. 3 Sex proportion across trials in neuromuscular diseases. For each disease, the predominance of male and female participants across all studies is reported. Equity between males and females is represented by midline, shift to right indicates more males than females, while the opposite reflects an abundance of females. Size of the dots reflects the total number of patients. Red intervals represent male-to-female prevalence ratios reported in literature for each disease. Overall, most patients were males. Dystrophinopathies enrolled almost exclusively males, as well as studies on SBMA. In studies on FSHD, GSDII and MG, the proportion of men enrolled was higher than the male-to-female prevalence ratio reported in the literature. In LEMS females were overrepresented to their reported prevalence. *ALS* Amyotrophic Lateral Sclerosis, *BMD* Becker Muscular Dystrophy, *CMT* Charcot-Marie-Tooth Disease, *CIDP* Chronic Inflammatory Demyelinating Polyneuropathy, *DM and PM* Dermatomyositis and Polymyositis, *DMD* Duchenne Muscular Dystrophy (DMD), *FSHD* Facioscapulohumeral Muscular Dystrophy, *GSDII* Glycogen Storage Disease Type II, *GBS* Guillain–Barré Syndrome, *IBM* Inclusion Body Myositis, *LEMS* Lambert–Eaton Myasthenic Syndrome, *MG* Myasthenia Gravis, *DM1* Myotonic Dystrophy Type 1, *SBMA* Spinal and Bulbar Muscular Atrophy, *SMA* Spinal Muscular Atrophy

and Charcot-Marie-Tooth disease. Studies on myotonic dystrophy type 1 (DM1) and Spinal Muscular Atrophy (SMA) enrolled roughly the same number of females and males (Fig. 3).

Regarding the accessibility of clinical trials by age, 175 (37.9%) studies allowed children, though most of these studies involve DMD and SMA (88 and 44 studies, respectively). Notably, no studies on DM1 allowed minors to participate and only one study on CIDP focused on the juvenile form. Furthermore, only a small proportion of studies on ALS, FSHD, and BMD allowed participants under 18 years of age (3.3%, 12.5% and 25%, respectively). Similarly, accessibility for older adults was limited. Of note, about half of the studies on DMD and SMA excluded people over 16 and 18, respectively. Table 2 shows median lower and upper age limits across all diseases included in our analysis and Fig. 4 summarizes the age representation across neuromuscular diseases. In detail.

Table 2 Age eligibility criteria

Disease	Lower eligibility age years, median (range)	Upper eligibility age years, median (range)
ALS	18 (0–40)	90 (60–all ages)
SBMA	18 (18–18)	All ages
SMA	0.08 (0–18)	18 (0.12–100)
GBS	18 (0–18)	All ages
CIDP	18 (5–20)	All ages (21—all ages)
CMT	18 (0–18)	All ages (25—all ages)
LEMS	18 (18–45)	All ages (65—all ages)
MG	18 (0–21)	All ages (17–100)
BMD	18 (7–18)	65 (16–70)
DMD	5 (0–18)	16 (2—all ages)
FSHD	18 (9–18)	72.5 (25—all ages)
DM1	18 (18–21)	65 (55–80)
DM + PM	18 (0–18)	80 (18–80)
IBM	42.50 (25–50)	92.5 (75—all ages)
GSDII	8 (0–18)	All ages (1—all ages)

ALS Amyotrophic Lateral Sclerosis, *BMD* Becker Muscular Dystrophy, *CMT* Charcot-Marie-Tooth Disease, *CIDP* Chronic Inflammatory Demyelinating Polyneuropathy, *DM and PM* Dermatomyositis and Polymyositis, *DMD* Duchenne Muscular Dystrophy (DMD), *FSHD* Facioscapulohumeral Muscular Dystrophy (FSHD), *GSDII* Glycogen Storage Disease Type II, *GBS* Guillain–Barré Syndrome, *IBM* Inclusion Body Myositis, *LEMS* Lambert–Eaton Myasthenic Syndrome, *MG* Myasthenia Gravis, *DM1* Myotonic Dystrophy Type 1, *SBMA* Spinal and Bulbar Muscular Atrophy, *SMA* Spinal Muscular Atrophy

Discussion

The principal aim of scientific research is to establish reliable evidence. Yet, when trial samples do not adequately represent the diversity of the general population there is a considerable risk that the findings may not be broadly generalizable. Race and ethnicity, while complex social constructs, can affect drug pharmacokinetics and pharmacodynamics [31]. Similarly, biologic differences between sexes and across ages shape both pharmacologic responses and adverse effect profiles. These challenges are particularly relevant in the context of neuromuscular diseases, which often exhibit distinct characteristics based on sex and race [32–42]. In this work, we analyzed race, ethnicity, sex and age distribution across 20 years of clinical studies on neuromuscular diseases conducting stratified analyses by disease and study characteristics to avoid limitations associated with aggregated data.

Our results show that the vast majority of patients across all retrieved studies on the various diseases were of white race and non-Hispanic ethnicity, with Asian being the second most represented race. Studies were quite similar regarding race and ethnicity composition. Of note, race and ethnicity data of a high proportion of participants remain not available. While the percentage of studies reporting race and ethnicity has substantially increased over time, likely due to the adoption of NIH guidelines, there have been no meaningful shifts in the demographic composition of clinical trials, and minorities remain highly underrepresented. Our data show that racial and ethnic disparities are especially relevant in this group of diseases; this may be partly explained by the fact that trials are more frequently conducted in geographic areas where White and Asian populations are overrepresented. However, even within these regions, individuals from other racial and ethnic groups may encounter additional systemic barriers—such as limited proficiency in the dominant language and related communication challenges, along with logistical obstacles—that impede their access to clinical trials [43, 44]. Indeed, among trial design shortcomings, those related to racial and ethnic inequities are particularly unacceptable. It is worth noting that interventional, phase III, and industry-sponsored studies showed significant higher rate of Asian subjects, compared to observational and public sponsored studies, likely due to the enrollment of Asian patients in clinical trials in the East region of the word. In addition to the fact that other racial groups remain particularly underrepresented, the limited diversity of patients enrolled in Phases I and II may compromise the evidence available for the authorization of larger Phase III studies. Therefore, greater inclusivity in the early stages of drug development is highly desirable.

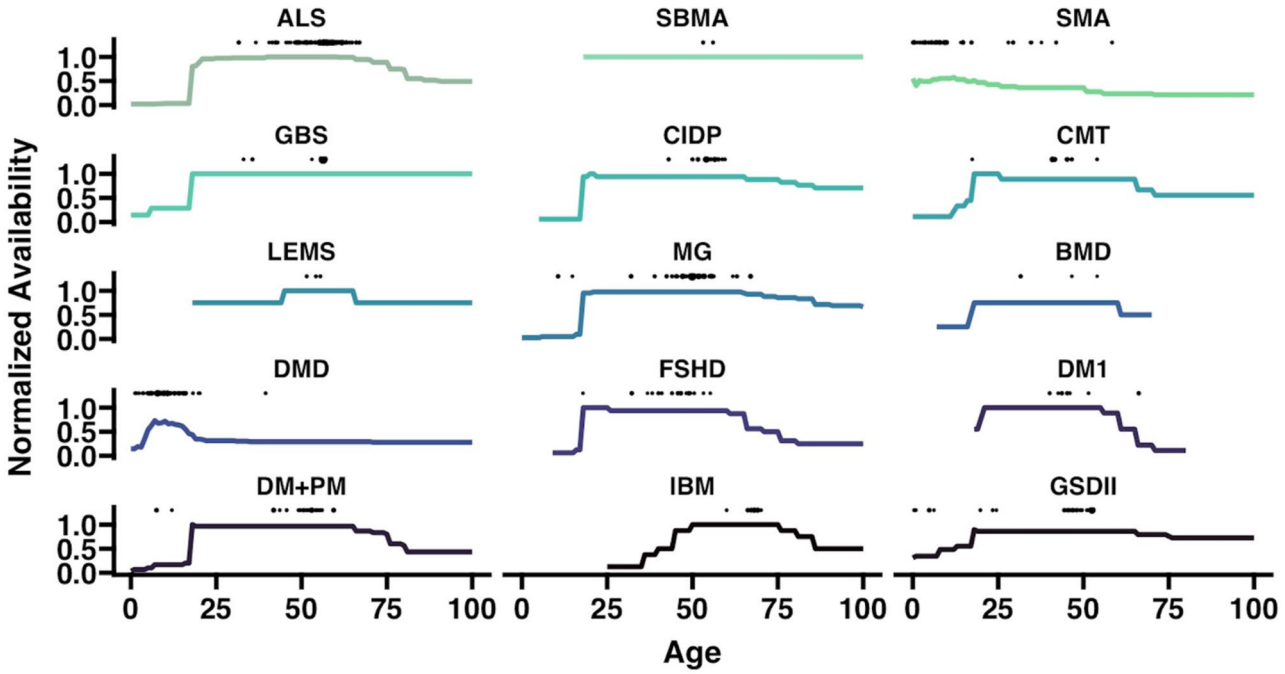

Fig. 4 Age representation across trials in neuromuscular diseases. The proportion of studies that allow patients of each age is represented across various neuromuscular diseases (colored lines). Mean and median ages of enrolled patients in each analyzed study is represented in black dots (size of the dots reflects the number of patients). Most studies neglect patients at age extremes, even for diseases that affect childhood (e.g., DM1 and GSDII), and measures of central tendency predominantly reflect adult populations. Of note, in SMA and DMD, measures of central tendency are shifted toward childhood despite their growing burden in older ages. *ALS* Amyotrophic Lateral Sclerosis, *BMD* Becker Muscular Dystrophy, *CMT* Charcot-Marie-Tooth Disease, *CIDP* Chronic Inflammatory Demyelinating Polyneuropathy, *DM and PM* Dermatomyositis and Polymyositis, *DMD* Duchenne Muscular Dystrophy (DMD), *FSHD* Facioscapulohumeral Muscular Dystrophy (FSHD), *GSDII* Glycogen Storage Disease Type II, *GBS* Guillain–Barré Syndrome, *IBM* Inclusion Body Myositis, *LEMS* Lambert–Eaton Myasthenic Syndrome, *MG* Myasthenia Gravis, *DM1* Myotonic Dystrophy Type 1, *SBMA* Spinal and Bulbar Muscular Atrophy, *SMA* Spinal Muscular Atrophy

Regarding sex, when considering the whole studies, the preponderance of male participants over females is mainly driven by the higher enrollment of patients in those diseases that more commonly affect men [17–30] (Fig. 3). The relative overrepresentation of males compared to the sex ratios reported in the literature for conditions such as FSHD and MG might be explained by the potential impact of clinical trial participation on pregnancy and breastfeeding, two conditions that can limit access to novel treatments [45]. It is worth noting that the majority of studies on recessive X-linked diseases, such as DMD, BMD, and SBMA, excluded female participants. While it is reasonable that female patients are not included in the same trials of males due to the specific pathogenic mechanism of the disease (viz. including patients harboring a non-mutated allele could confound the interpretation of treatment effects), is it advisable that parallel studies are conducted on female patients. Although the incidence of female DMD is about 1:50,000,000 of newborns—being in fact a rarity among rare disease—preclusion of female participants in these trials have broad implications: female DMD and SBMA carriers often exhibit symptoms ranging from mild to severe, including muscle weakness, cardiomyopathy, and other systemic manifestations [46, 47]; excluding these individuals not only limits our understanding of disease progression and therapeutic responses in female sex but also overlooks their unique healthcare needs.

Concerning age, with the exception of studies on DMD and SMA, most research excludes children and adolescents from participation. This is especially critical for neuromuscular diseases that affect childhood, such as DM1, juvenile ALS and CMT. On the other hand, exclusion of older people is also a significant issue, as many studies fail to include the elderly, limiting treatment options and insights into the disease's progression in this age group. Over the last decades, advances in care have significantly increased life expectancy in DMD, and many patients now reach adult age. However, patients of these ages are excluded from nearly half of the relevant trials [48, 49]. Moreover, even though a part of the studies have a broader range of age inclusivity, the majority of mean and median ages of the enrolled patients fall within central ages with exclusion of the extremities. Such

Table 3 Determinants of participant underrepresentation in neuromuscular studies, approaches to address them and desirable outcomes

	Challenges	Contributing factors	Possible solutions	Desirable outcomes
Race/ethnicity	The majority of enrolled patients are White and there is little variability in race proportion between studies and over time	Trials are frequently concentrated in Western regions where certain racial groups may be less prevalent Systemic barriers may further limit participation	Increase geographic diversity of research sites Engage with local stakeholders in underrepresented regions Promote equitable inclusion of participants from all racial backgrounds	Broaden the evidence on the efficacy of therapeutic interventions across racial and ethnic groups also by enabling appropriately powered meta-analyses to assess differential treatment effects Promoting social justice ensuring that individuals of all racial and ethnic groups can access and benefit from experimental research
Sex	The majority of patients are males	Exclusion of women of childbearing potential or those who are pregnant/lactating For X-linked diseases, including females with a functional allele may confound the results	Ensure sex-balanced recruitment, where feasible Stratify analyses by sex where biologically relevant design specific trials for female patients and carriers in X-linked diseases	Expand the evidence for female participants in clinical trials Enhance the characterization and understanding of carrier phenotypes in X-linked disorders
Age	Individuals at age extremes are often underrepresented; in certain conditions (e.g.: SMA) evidence on adult populations remains limited	Recruitment across age groups is challenging due to differing clinical presentations, comorbidities, and outcome relevance	Design age-stratified trials with tailored endpoints	Broaden the evidence on therapeutic interventions in underrepresented age groups to enable more accurate estimation of the expected treatment benefit across age ranges

SMA Spinal Muscular Atrophy

inequities may result in a significant lack of evidence concerning therapeutic opportunities: for example, as most studies in patients with SMA are conducted in infants and children—often using improvements in ambulation parameters or the attainment of specific motor milestones as primary outcomes—caution is warranted when generalizing these findings to individuals across all age groups [50]. Indeed, many adult patients may have lost the ability to ambulate and there is a clear need for clinical trials tailored to this population, using outcome measures and functional scales appropriate for their age group.

When designing a clinical trial, multiple factors must be considered, and the careful identification of the study population is of paramount importance. The importance of improving diversity in clinical trials not only arises because pharmacologic responses, side effect profiles, and therapeutic efficacy can differ across populations [2, 31]—but also from the need to promote fairness for marginalized groups and to build trust in the medical system [8]. Designing trials that allow for subgroup analyses requires increasing the sample size, which in turn raises costs and logistical complexity [8]. While increasing participant diversity within individual trials poses logistical challenges, both NIH and European Commission guidelines mandate the performance of subgroup analyses [11, 12]. Even when such analyses may be underpowered due to small subgroup sizes, systematically recording race and ethnicity and maximizing participant representativeness enables the possibility of conducting tailored meta-analyses across studies for different racial and ethnic groups. Such analyses are essential to assess the consistency of treatment effects across populations, identify potential disparities in efficacy or safety, and guide more equitable and evidence-based clinical decision-making. There is therefore a need to adopt approaches that generate broadly applicable evidence while minimizing the risk of underrepresentation. Table 3 summarizes possible strategies to overcome disparities in neuromuscular clinical trials and desirable results.

This study has several limitations. First, data from a considerable number of NCTs lacking results on ClinicalTrials.gov could not be retrieved even from the search on PubMed, which limited the total number of patients we could analyze. However, although only about 20% of studies reported data suitable for inclusion in this work, the relatively low medians of multivariate dispersion for both race and ethnicity in the available studies support the assumption that participant composition was generally consistent across the included studies, and that those lacking data are unlikely to differ substantially. Second, while comparing race and ethnicity distributions of clinical trials with real-world patient data would have provided an additional measure of equity, such values were not available. Finally, categorical data on age distribution within each trial (e.g., the number of patients per decade of age) were not consistently reported and, therefore, could not be included in the analyses.

Conclusion

In conclusion, this study highlights a relevant burden of disparities concerning race, ethnicity, sex and age inclusion among clinical trials in neuromuscular research. Although males constituted the majority of patients, their representation in studies reflected the proportions reported in the literature for most of the diseases. However, female patients and carriers of X-linked recessive diseases tended to be overlooked. While there is an increasing awareness within the scientific community regarding the need for equitable and inclusive research, substantial progress is still required. This includes both the measurement of disparities in neurologic subspecialties where such assessments are still lacking and the implementation of efforts to enhance real-world representativeness in those areas where disparities have already been identified.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-025-13208-8.

Author contributions Lorenzo Fontanelli: Drafting/revision of the manuscript for content, including medical writing for content. Major role in the acquisition of data; study concept or design; analysis or interpretation of data. Gabriele Vadi: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. Gabriele Bellini: Drafting/revision of the manuscript for content, including medical writing for content. Andrea Cossu: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. Gabriele Siciliano: Drafting/revision of the manuscript for content, including medical writing for content.

Declarations

Conflict of interests On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This study was conducted using publicly available data and did not involve human participants; as such, ethical approval, patient consent, and institutional review board IRB approval were not required.

References

1. Bibbins-Domingo K, Helman A, Dzau VJ (2022) The imperative for diversity and inclusion in clinical trials and health research participation. JAMA 327:2283–2284
2. Knepper TC, McLeod HL (2018) When will clinical trials finally reflect diversity? Nature 557:157–159
3. Tur C, Carvajal R, Otero-Romero S, Tintore M (2024) Generalizing the results of clinical trials if participants are not from

diverse racial and ethnic groups. Neurology. https://doi.org/10.1212/WNL.0000000000209730
4. Rosendale N, Wong JO, Flatt JD, Whitaker E (2021) Sexual and gender minority health in neurology: a scoping review. JAMA Neurol 78:747–754
5. Pasquali SK, Lam WK, Chiswell K, Kemper AR, Li JS (2012) Status of the pediatric clinical trials enterprise: an analysis of the US ClinicalTrials.gov registry. Pediatrics 130:e1269–e1277
6. van Marum RJ (2020) Underrepresentation of the elderly in clinical trials, time for action. Br J Clin Pharmacol 86:2014–2016
7. Cardenas-Iniguez C, Gonzalez MR (2024) Recommendations for the responsible use and communication of race and ethnicity in neuroimaging research. Nat Neurosci 27:615–628
8. Schwartz AL, Alsan M, Morris AA, Halpern SD (2023) Why diverse clinical trial participation matters. N Engl J Med 388:1252–1254
9. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use ICH harmonised tripartite guideline studies in support of special populations: geriatrics E7 Current Step 4 version; 1993.
10. Inclusion of women and minorities as participants in research involving human subjects|Grants & Funding. https://grants.nih.gov/policy-and-compliance/policy-topics/inclusion/women-and-minorities.
11. NOT-OD-18–014: Revision: NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-014.html.
12. White J, Tannenbaum C, Klinge I, Schiebinger L, Clayton J (2021) The integration of sex and gender considerations into biomedical research: lessons from international funding agencies. J Clin Endocrinol Metab 106:3034–3048
13. Federal Register: Revisions to OMB's statistical policy directive No. 15: standards for maintaining, collecting, and presenting federal data on race and ethnicity. https://www.federalregister.gov/documents/2024/03/29/2024-06469/revisions-to-ombs-statistical-policy-directive-no-15-standards-for-maintaining-collecting-and.
14. Porter NC, Morgenstern LB (2022) Racial and ethnic equity in neuromuscular care-time for our action to live up to potential. JAMA Neurol 79:1221–1222
15. Oksanen, J. *et al.* Community ecology package [R package vegan version 2.6–10]. CRAN: Contributed Packages; 2025. https://doi.org/10.32614/CRAN.PACKAGE.VEGAN.
16. Killick R, Eckley IA (2014) changepoint: an R package for changepoint analysis. J Stat Softw 58:1–19
17. McCombe PA, Henderson RD (2010) Effects of gender in amyotrophic lateral sclerosis. Gend Med 7:557–570
18. Broers MC, Bunschoten C, Nieboer D, Lingsma HF, Jacobs BC (2019) Incidence and prevalence of chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review and meta-analysis. Neuroepidemiology 52:161–172
19. Theadom A et al (2019) Prevalence of Charcot-Marie-Tooth disease across the lifespan: a population-based epidemiological study. BMJ Open 9:e029240
20. Wang Z et al (2021) Prevalence and disease progression of genetically-confirmed facioscapulohumeral muscular dystrophy type 1 (FSHD1) in China between 2001 and 2020: a nationwide population-based study. Lancet Reg Health West Pac 18:100323
21. Yuki N, Hartung H-P (2012) Guillain-Barré syndrome. N Engl J Med 366:2294–2304
22. Paltiel AD et al (2015) Demographic and clinical features of inclusion body myositis in North America. Muscle Nerve 52:527–533
23. Dimachkie MM, Barohn RJ (2014) Inclusion body myositis. Neurol Clin 32:629–646
24. Motomura M, Nakata R, Shiraishi H (2016) Lambert-Eaton myasthenic syndrome: clinical review. Clin Exp Neuroimmunol 7:238–245
25. Sciancalepore F et al (2024) Prevalence, incidence, and mortality of myasthenia gravis and myasthenic syndromes: a systematic review. Neuroepidemiology. https://doi.org/10.1159/000539577/914586/PREVALENCE-INCIDENCE-AND-MORTALITY-OF-MYASTHENIA
26. Poulas K, Tzartos SJ (2001) The gender gap in autoimmune disease. Lancet 357:234
27. Hernáez L et al (2024) Prevalence of Steinert's myotonic dystrophy and utilization of healthcare services: a population-based cross-sectional study. Healthcare (Basel) 12:838
28. Vanacore N et al (2016) An age-standardized prevalence estimate and a sex and age distribution of myotonic dystrophy types 1 and 2 in the Rome province. Italy Neuroepidemiology 46:191–197
29. Souza FH, Levy-Neto M, Shinjo SK (2011) Prevalence of clinical and laboratory manifestations and comorbidities in polymyositis according to gender. Rev Bras Reumatol 51:428–483
30. Cox S, Limaye V, Hill C, Blumbergs P, Roberts-Thomson P (2010) Idiopathic inflammatory myopathies: diagnostic criteria, classification and epidemiological features. Int J Rheum Dis 13:117–124
31. Ramamoorthy A, Pacanowski MA, Bull J, Zhang L (2015) Racial/ethnic differences in drug disposition and response: review of recently approved drugs. Clin Pharmacol Ther 97:263–273
32. Beland B, Jewett G, Lee A, Perera T, Korngut L (2023) Sex differences in therapy for myasthenia gravis (P7–8.002). Neurology 100:3421
33. Vinciguerra C et al (2023) Sex differences in neuromuscular disorders. Mech Ageing Dev 211:111793
34. Sun J, Harrington MA, Porter B (2023) Sex difference in spinal muscular atrophy patients—are males more vulnerable? J Neuromuscul Dis 10:847–867
35. Vorster E, Essop FB, Rodda JL, Krause A (2020) Spinal muscular atrophy in the black South African population: a matter of rearrangement? Front Genet 11:54
36. Zamani A, Thomas E, Wright DK (2024) Sex biology in amyotrophic lateral sclerosis. Ageing Res Rev 95:102228
37. Roberts AL, Johnson NJ, Chen JT, Cudkowicz ME, Weisskopf MG (2016) Race/ethnicity, socioeconomic status, and ALS mortality in the United States. Neurology 87:2300–2308
38. Abukhalil F, Mehta B, Saito E, Mehta S, McMurtray A (2015) Gender and ethnicity based differences in clinical and laboratory features of myasthenia gravis. Autoimmune Dis 2015:197893
39. Thomsen JLS, Vinge L, Harbo T, Andersen H (2021) Gender differences in clinical outcomes in myasthenia gravis: a prospective cohort study. Muscle Nerve 64:538–544
40. Oh SJ et al (2009) Racial differences in myasthenia gravis in Alabama. Muscle Nerve 39:328–332
41. Crossnohere NL et al (2024) Barriers to diverse clinical trial participation in Duchenne muscular dystrophy: engaging Hispanic/Latina caregivers and health professionals. Orphanet J Rare Dis 19:207
42. Dogan C et al (2016) Gender as a modifying factor influencing myotonic dystrophy type 1 phenotype severity and mortality: a nationwide multiple databases cross-sectional observational study. PLoS ONE 11:e0148264
43. Rubin E (2021) Striving for diversity in research studies. N Engl J Med 385:1429–1430
44. Velez MA et al (2023) Consent document translation expense hinders inclusive clinical trial enrolment. Nature 620:855–862
45. Vadi G et al (2025) Pregnancy in the era of disease-modifying therapies for spinal muscular atrophy: considerations from a case report. Muscle Nerve 71:685–687
46. Bushby K, Muntoni F, Bourke JP (2003) 107th ENMC international workshop: the management of cardiac involvement in

muscular dystrophy and myotonic dystrophy. 7th–9th June 2002, Naarden, the Netherlands. Neuromusc Disord 13:166–172
47. Giliberto F et al (2014) Symptomatic female carriers of Duchenne muscular dystrophy (DMD): genetic and clinical characterization. J Neurol Sci 336:36–41
48. De Die-Smulders CEM et al (1998) Age and causes of death in adult-onset myotonic dystrophy. Brain 121(Pt 8):1557–1563
49. Broomfield J, Hill M, Guglieri M, Crowther M, Abrams K (2021) Life expectancy in duchenne muscular dystrophy: reproduced individual patient data meta-analysis. Neurology 97:E2304–E2314
50. Fontanelli L, Di Rauso G, Bellini G (2023) Spinal muscular atrophy: Should we prescribe approved drugs to cohorts of patients in which they are unproven? Eur J Neurol. https://doi.org/10.1111/ENE.16103