

INTRODUCTION

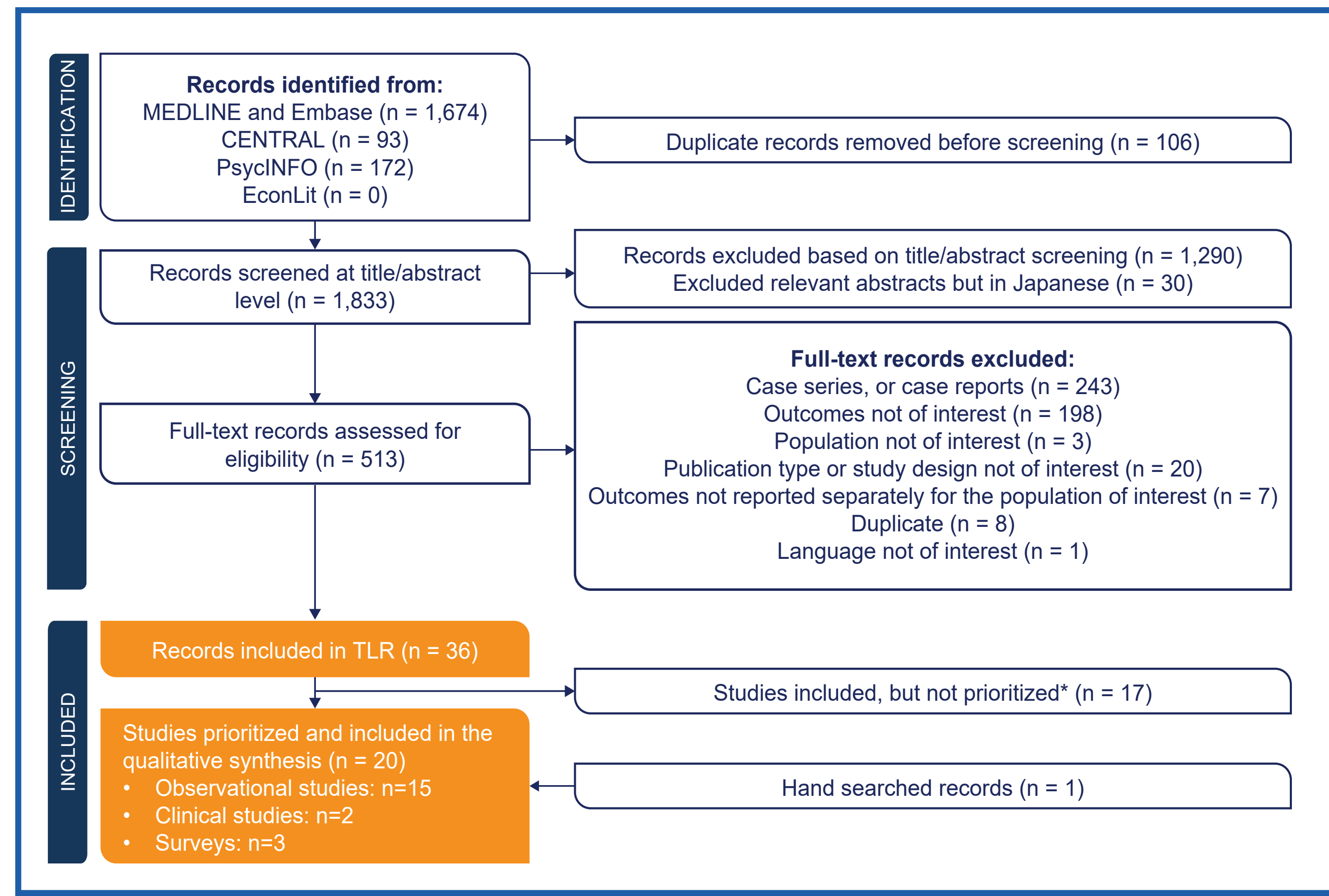
- Myotonic dystrophy type 1 (DM1) is a rare, genetic, progressive neuromuscular disorder with multisystemic involvement, including high morbidity and premature mortality.¹⁻⁵
- DM1 is driven by a spliceopathy caused by expansions of an unstable cytidine–thymidine–guanosine (CTG) trinucleotide region in the dystrophia myotonica protein kinase (DMPK) gene that can escalate during intergenerational transmission, leading to worsening of symptoms and earlier onset of disease as the mutation is passed from parent to offspring.⁶
- There are currently no approved therapies available; existing treatment focuses on managing symptoms and minimizing disability, but a substantial disease burden remains for this population.¹
- The objective of this literature review was to identify and summarize key evidence to enhance the understanding of the burden that DM1 has on the overall quality of life (QoL) of affected individuals and their caregivers.

METHODS

- A protocol-based targeted literature review of electronic databases (Embase, MEDLINE, the Cochrane Library, EconLit, and PsycINFO) and key conference proceedings (The World Muscle Society and Muscular Dystrophy Association) was conducted. Searches of electronic databases were limited to studies published in English from January 2010 to February 2022, and conference proceedings were limited to those published between 2020 and 2022.
- Studies were included if they assessed individuals living with DM1 in the US, Japan, or European countries, including the UK, and reported data regarding the QoL (including scales of physical or mental health) of affected individuals or caregivers.
- After screening, studies meeting the eligibility criteria underwent a final review; articles that met criteria but had too narrow a focus (e.g., reported the evaluation of a single treatment or focused on a single symptom) were excluded.
- Supplementary manual searches were also performed; these expanded the search to include studies that had mixed muscular dystrophy populations or were not strictly limited by geography.

- Nineteen studies from database searches met the inclusion criteria for the review (**Figure 1**), and a patient voice report not published in a peer-reviewed journal was included via manual searches (see online Appendix for full study listing).

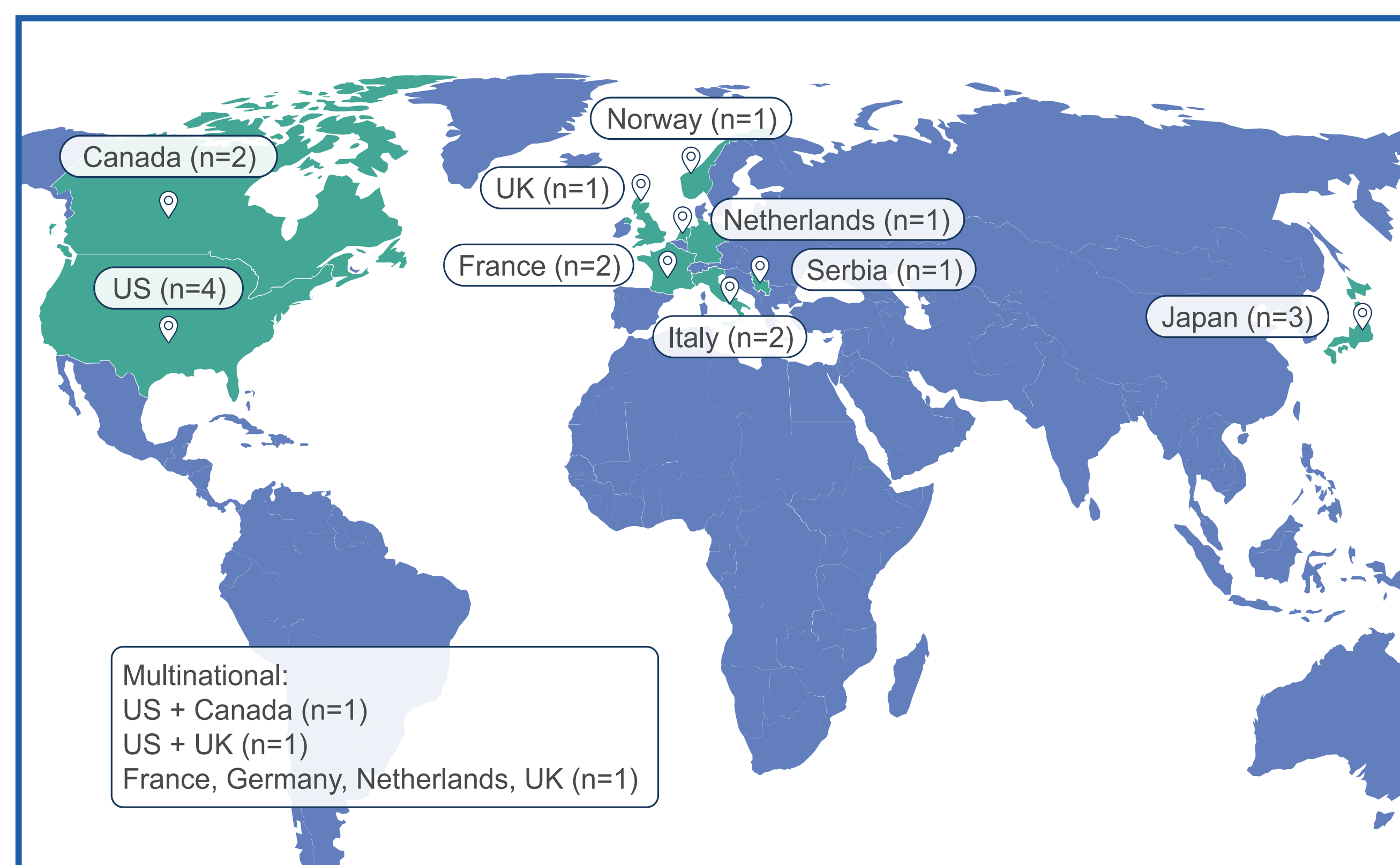
Figure 1. PRISMA Diagram



PICOS = population, intervention, comparison, outcomes, study design; TLR = targeted literature review

* These studies met the eligibility criteria per PICOS but were not selected for the final list of most relevant publications due to highly narrow focus.

Figure 2. Geographic Distribution of Studies



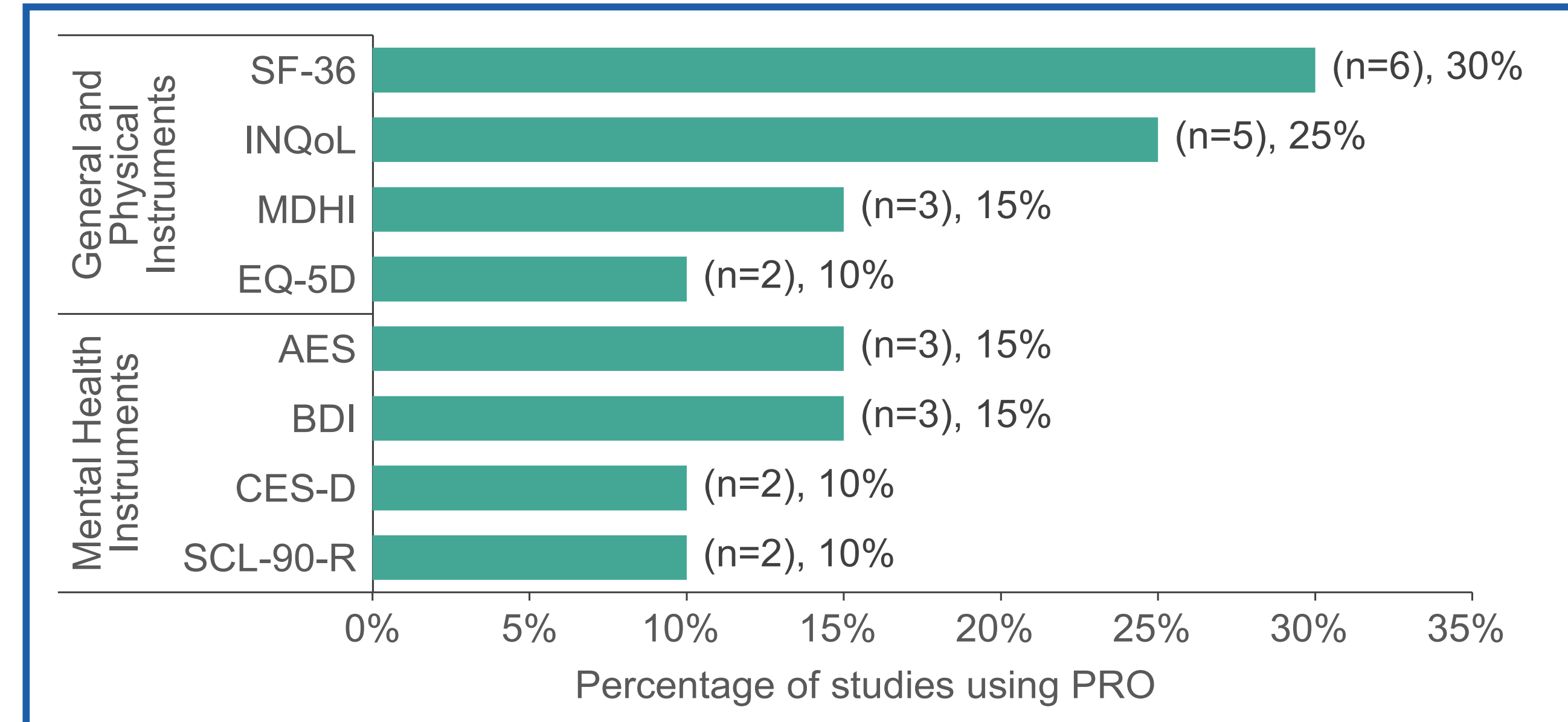
General and Physical QoL Findings

- Studies used a range of questionnaires to evaluate QoL, with the most common being the 36-item Short Form Health Survey (SF-36), which was used in six studies (including three studies that only measured SF-36 to validate other instruments; **Figure 3**; see online Appendix for descriptions of the most common instruments).⁷⁻¹³
- Overall, studies reported that QoL is negatively impacted in patients with DM1 despite the heterogeneity in study populations (**Table 1**).

RESULTS

- Although none of the identified studies provided comparative SF-36 scores against a reference population, the above studies qualitatively described the observed scores as being lower than those of healthy patients. The studies also noted that reported scores were similar to prior studies in mixed dystrophy populations, which found decreased SF-36 component scores vs. healthy controls.^{14,15}

Figure 3. Most Common QoL Instruments (Used in ≥2 Studies)



AES = Apathy Evaluation Scale; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; EQ-5D = EuroQol-5 Dimensions; INQoL = Individualized Neuromuscular Quality of Life; MDHI = Myotonic Dystrophy Health Index; PRO = patient-reported outcome; QoL = quality of life; SCL-90-R = Symptom Checklist-90-Revised; SF-36 = Short Form-36

Note: Most studies used >1 instrument, percentages are relative to the total number of included studies.

Table 1. SF-36 PCS and MCS Scores in DM1

Study	Age in years, mean (SD)	PCS, mean (SD)	MCS, mean (SD)
Peric et al, 2013 ^{††13} Serbia, N=120	46.4 (11.6)	41.8 (23.5)	47.0 (24.3)
Endo et al, 2019 [†] Japan, N=51	44.7 (10.3)	29.0 (15.0)	52.0 (9.3)
Laberge et al, 2013 ^{††11} Canada, N=200	47.0 (11.8)	42.0 (13.3)	52.5 (9.6)

DM1 = myotonic dystrophy type 1; MCS = mental component summary; PCS = physical component summary; QoL = quality of life; SD = standard deviation; SF-36 = 36-item Short Form Health Survey

Note: PCS and MCS scores range from 0 to 100, with higher values representing better QoL.¹¹

* Non-congenital DM1 only

† Included patients ≤18 years of age

- Decreases in specific cognitive functions, the presence of various psychological factors, participant unemployment status, cytosine, thymine, and guanine repeat length, and other clinical measures were negatively correlated with patients' QoL.^{8,9,16,17}
- Only one pharmacological treatment was examined in the included studies (mexiletine), but neither mexiletine nor its comparator (cognitive behavioral therapy) was found to improve QoL.^{12,18}
- Two studies reporting direct patient feedback noted several QoL-related issues reported by patients with DM1 and their caregivers, such as the negative effects of symptoms and

the impact of the disease on patients' abilities to perform activities of daily life.^{19,20}

- Using certain assistive equipment (e.g., continuous positive airway pressure machines, ankle/leg braces, cane/walking stick) or making lifestyle changes improved patients' lives somewhat (70.9%), but few reported a considerable improvement (3.6%).²⁰

Additional Mental Health Findings

- The most common tools used to evaluate mental health were the Beck Depression Inventory (BDI) and the Apathy Evaluation Scale (AES), reported in three studies each (**Figure 3**; see online Appendix for descriptions of the most common instruments).^{12,21-23}
- Overall, studies have reported that patients with DM1 experience a range of mental health-related symptoms such as depression, anxiety, and feelings of hostility, and have indicated that cognitive function correlated with mental health outcomes (**Table 2**).^{7,10-13,16,21-25}
 - General physical health also correlated with patients' mental health.^{7,10}

Table 2. Key Mental Health Findings

Measure	Key Findings
CES-D	Statistically significant correlations were found between CES-D score and the MCS and PCS of the SF-36 (p<0.01 for both), as well as between ESS score and the PCS (p<0.01) and MCS (p<0.05). ⁷ In a different study, CES-D was also significantly correlated with the SF-36 PCS (p<0.01), whereas caregiver CES-D was significantly correlated with caregiver SF-36 PCS and MCS (both p<0.05). ¹⁰
SCL-90-R	Using the SCL-90-R instrument, 19.4% of patients with DM1 in Italy reported a depressive state, 19.4% reported a high level of interpersonal sensitivity, 22.6% reported feelings of hostility, 16.1% reported paranoid ideation, and 16.1% reported the presence of psychotic symptoms. ²⁴ Thirteen percent of patients also scored a moderate-to-high burden on the Positive Symptom Total index, which measures the number of self-reported symptoms. ²⁴ Using the SCL-90-R instrument, psychological distress was reported in 18.5% of patients with DM1. ¹¹
BDI	Only 1% of healthy controls scored in the mild depression range of the BDI (the remaining 99% were normal), whereas 18% of those with DM1 showed symptoms of mild depression, and 10% showed symptoms of moderate depression. ²²
AES	Compared with healthy adults, patients with DM1 showed greater apathy based on the self-reported AES (t-value of comparison: 5.86, p<0.0001) as well as informant/caregiver-reported AES (t-value: 2.43, p=0.0221). ²² Patients with DM1 reported mixed mood conditions together with apathetic behavior on the AES assessment (mean score: 18.2) in a study conducted in Italy. ²¹
ZBI	Caregiver distress measured by the ZBI was observed even when patients were relatively high functioning. ¹⁰

AES = Apathy Evaluation Scale; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression Scale; DM1 = myotonic dystrophy type 1; ESS = Epworth Sleepiness Scale; MCS = mental component summary; PCS = physical component summary; SCL 90 R = Symptom Checklist-90-Revised; SF 36 = Short Form-36; ZBI = Zarit Caregiver Burden Interview

Limitations

- This review was restricted to the US, Europe, and Japan during the screening phase; reviewing the available QoL information in other regions (e.g., South America, Asia) will further contribute to understanding the humanistic burden of DM1.
- DM1 has a highly heterogeneous disease course,²⁶ which may increase the uncertainty of specific QoL impacts for different local DM1 populations.

CONCLUSIONS

- DM1 has been shown to have a considerable negative impact on the QoL of affected individuals, which can be exacerbated by a variety of clinical, cognitive, and psychosocial factors.
- The impact of DM1 is generally stronger on physical health vs. mental health, but a notable impact on mental health has nonetheless been observed across several studies.
- More meaningful assessments of QoL will be achieved through greater use and reporting of outcomes from disease-specific PROs such as the DM1 Activity and Participation Scale (DM1-Activ) and the DM1 Health Index (DM1-HI), as well as greater use of generic tools such as SF-36.

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DISCLOSURE INFORMATION

This study was sponsored by Dyne Therapeutics, Inc. AN, AG, and AD are employees of Dyne Therapeutics and may hold stock and/or stock options. CCC and RH are employees of Evidera, which has received consultancy fees from Dyne Therapeutics.

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Appendix available through ISPOR Conference App