The prevalence, characteristics and impact of chronic pain in people with muscular dystrophies: A systematic review

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Abstract

Background: Chronic pain is a frequent, yet under-recognised and under-assessed problem in people with muscular dystrophies (MDs). Knowledge of the prevalence and characteristics of chronic pain, and its impact on function and quality of life is limited and lacks systematic exploration.

Purpose: This study aims to systematically review and synthesise existing literature that addresses chronic pain prevalence, characteristics and impact in people with different types of MDs.

Methods: A systematic search of bibliographic electronic databases was performed for articles (up to March 2020) reporting chronic pain (pain persisting ≥ 3 months) in people with MDs. Quality assessment was conducted using the Risk of Bias Tool for Prevalence Studies. Pooled estimates of pain prevalence and average pain intensity were calculated for each diagnostic group and where the number of articles was sufficient, group comparison was performed.

Results: The estimated prevalence of chronic pain is similar across diagnostic groups of MDs: 68% in FSHD, 65% in DM, 62% in BMD/DMD, and 60% in LGMD. Generally, chronic pain is reported as mild to moderate by most people with FSHD and DM, with a mean value of moderate pain intensity (4.1/10 in FSHD and 4.7/10 in DM, respectively). Lower back, shoulder and legs are the most frequent sites of chronic pain among people with FSHD, DM, BMD/DMD, and LGMD, with minor variations. Diffuse pain across multiple body sites was reported by a notable proportion of these individuals. No clear pattern of pain descriptors relating to a specific diagnostic group of MDs could be identified from the included studies. Chronic pain has a negative impact on daily life activities in people with MDs, and may also contribute decreased quality of life. Occupational and domestic activities, recreational activities and mobility are the daily life domains most commonly affected by chronic pain. In children with DMD, mood may be significantly affected. Consistently, sleep is the least affected domain by chronic pain across different forms of MDs.

Implications: This is the first review that systematically explores the prevalence, characteristics and impact of chronic pain in people with MDs. It is also the first to attempt to quantitatively synthesise the prevalence and pain intensity data by diagnostic groups in this population. The present study demonstrates how common chronic pain is across

various MD populations and highlights the need for better recognition and understanding of the nature and impact of pain from health professionals. Future studies should focus on chronic pain in lesser explored MDs (including CMD, EDMD, OPMD and Distal MDs), geographic regions outside the USA and Europe and younger age groups. Further investigations on pain phenotypes (e.g. neuropathic vs nociceptive pain) and the associated response to treatments are also recommended.

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signed:_____

Meihuan Huang

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Abbreviations

AAC	Augmentative and alternative communication
BMD	Becker muscular dystrophy
BPI	Brief Pain inventory
CIS	Checklist Individual Strength
CMD	Congenital muscular dystrophy
CMT	Charcot-Marie-Tooth disorder
DMD	Duchenne muscular dystrophy
DOP	Daily Observed Pain score
DM	Myotonic dystrophy
Distal MDs	Distal Muscular Dystrophies
EDMD	Emery-Dreifuss Muscular Dystrophy
ESS	Epworth Sleepiness Scale
FSHD	Facioscapulohumeral muscular dystrophy
HADS	Hospital Anxiety and Depression Scale
INQoL	Individualised Neuromuscular Quality of Life Questionnaire
LLANS	Leeds Assessment of Neuropathic Signs and Symptoms
LGMD	Limb-girdle muscular dystrophy
LFK-index	Luis Furuya-Kanamori index
MDs	Muscular dystrophies
MPQ	McGill Pain Questionnaire
MPQ-PPI	Present pain intensity in the McGill Pain Questionnaire
MPQ-PRI	Pain rating index in the McGill Pain Questionnaire
MG	Myasthenia Gravis
NMDs	Neuromuscular diseases
NPRS	Numerical Pain Rating Scale
NPS	Neuropathic Pain Scale
OPMD	Occulopharyngeal Muscular Dystrophy
PSG	Polysomnographic
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of life
SCL	The Symptom Checklist-90
SF-36	36-Item Short-Form Health Survey
SMA	Spinal muscular atrophy
UPAT	Universal Pain Assessment Tool
VAS	Visual Analogue Scale
WHOQOL-BREF	World Health Organization Quality of Life Scale Brief Version

Chapter 1 Introduction

1.1 Definition of MDs

Muscular dystrophies (MDs) are a heterogeneous group of genetic diseases that are among the most common forms of neuromuscular diseases (NMDs). Clinically, MDs manifest as progressive muscle weakness related to loss of mobility, agility and physical movements as a consequence of defects in genes responsible for muscle protein synthesis (Emery, 2002; Huml, 2015). There is no cure for these MDs and they are frequently associated with severely reduced life expectancy. According to the National Institute of Neurological Disorders and Stroke (NINDS), there are nine major groups of MDs (NINDS, 2019): Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), Myotonic dystrophy (DM), Facioscapulohumeral muscular dystrophy (FSHD), Congenital muscular dystrophy (CMD), Limb-girdle muscular dystrophy (LGMD), Emery-Dreifuss Muscular Dystrophy (EDMD), Occulopharyngeal Muscular Dystrophy (OPMD), and Distal Muscular Dystrophies (Distal MDs or Distal myopathies).

1.2 Prevalence and clinical characteristics of MDs

The epidemiology and clinical presentations of the nine major groups of MDs are summarised in Table 1.

DMD and BMD are X-linked recessive diseases resulting from mutations of the dystrophin gene (Gardner-Medwin, 1980), which usually affects proximal muscles of the arms and legs and spares the face (Feldman et al., 2014; Gardner-Medwin, 1980). DMD is the most common hereditary muscle disorder of childhood, affecting 1in 3500 males, and is usually recognised between aged three and five years (Burghes et al., 1987; Mercuri & Muntoni, 2013). The disorder progresses quickly, with loss of ambulation typically occurring around aged 10 years and death typically occurring by late adolescence to early twenties as a result of respiratory or cardiac failure (Emery, 2002). Calf hypertrophy, muscle fibrosis, lower limb contractures, and scoliosis are commonly seen in this population (Feldman et al., 2014). The affected individuals often experience cognitive impairments, ranging from mild to severe (Emery, 2002; Feldman et al., 2014). BMD is a milder form of DMD, affecting nearly 1in 30,000 males (Nigro et al., 1983). It has a later age of onset (around 12 years) and a slower clinical progression, with loss of walking ability often varying from adolescence onwards, and death normally in the fourth or fifth decade of life (Emery, 2002). BMD results in weakness and disability similar to DMD

(Mercuri & Muntoni, 2013; Özsarlak et al., 2001), but some frequent early symptoms including calf pain, cramps, and myalgia are more often observed than in DMD and some other forms of MDs (Feldman et al., 2014).

DM is the most common type of MDs in adults, with an estimated prevalence of at least 1in 8,000 males/females (Mercuri & Muntoni, 2013; Udd & Krahe, 2012). The presence of myotonia (delayed relaxation of the skeletal muscles), mild muscular weakness, and other systems involvement characterise this condition (Udd & Krahe, 2012). To date, two types of myotonic dystrophy, DM1 and DM2, are known to exist (Ashizawa & Sarkar, 2011). DM1 and DM2 are similar but they present with some important variations in terms of disease severity, muscles affected, and associated multisystemic impairments. Adult-onset is the most prevalent form of DM1 and typically begins in the third decade. Action and percussion myotonia is the most common initial symptom of the disorder, with preferential involvement of the specific muscle groups of the jaw, tongue, forearm, and hand (Thornton, 2014). Weakness often follows a characteristic distribution, which typically affects the cranial, trunk, and distal limb muscles. Cardiac conduction defects and tachyarrhythmias, and gastrointestinal symptoms (ranging from constipation to diarrhoea and incontinence) are frequent complaints in individuals with DM1 (Ashizawa & Sarkar, 2011; Udd & Krahe, 2012). In later years, cataracts, cognitive impairment, behaviour changes, hypersomnolence, insulin resistance and diabetes may develop (Feldman et al., 2014; Udd & Krahe, 2012). Life span is usually reduced in this population. In DM2, only an adult-onset form has been described. Symptoms in DM2 are often milder, the clinical course is more favourable, and life expectancy is closer to normative values. Weakness typically occurs at the level of proximal limb muscles, with no evidence of respiratory and facial muscle weakness. Myotonia, cardiac autonomic nervous system impairments, and brain abnormalities (white matter hyperintensity on the brain Magnetic resonance imaging (MRI)) are less common in this type of disease (Feldman et al., 2014), but affected people can experience severe muscle pain, which is often described as the most disabling symptom by many patients (Ashizawa & Sarkar, 2011; George et al., 2004; Suokas et al., 2012).

FSHD is the second most common dystrophy in adults after DM, with an estimated prevalence of 1 in 20,000 males/females (Mercuri & Muntoni, 2013; Tawil & Van Der Maarel, 2006). The age of onset is typically in late childhood or adolescence (Feldman et al., 2014). The rate of progression is generally slow and life span is within normal limits. Muscle involvement develops in a consistent pattern. Initially the facial muscles and the

shoulder stabilizer are affected, then followed by muscles of the leg, thigh, and pelvic girdle (Padberg et al., 1991; Tawil & Van Der Maarel, 2006). Scapular winging and lumbar lordosis are prominent features as consequences of the shoulder and abdominal muscle weakness (Shahrizaila & Wills, 2005). Affected people develop varying degrees of disability, and about 20% lose the ability to walk and are confined to a wheelchair during their adulthood (Tawil & Van Der Maarel, 2006). Mild scoliosis may occur late in the course of the disorder, especially in wheelchair-dependent individuals (Özsarlak et al., 2001). Hearing loss and retinal telangiectasias are the most common extramuscular manifestations, but the heart is usually spared, and restrictive respiratory disease which requires intervention only occurs in a small minority of patients (Tawil & Van Der Maarel, 2006). Females appear to be less severely affected than males with FSHD (Zatz et al., 1998).

CMD consists of a group of heterogeneous muscle diseases that develop in the uterus or in the first year of life. These disorders are some of the most frequent and severe childhood muscular dystrophies (Tome et al., 1994; Voit, 1998). The exact incidence and prevalence of CMD in general is unknown. Fukuyama-CMD is the most common form in Japan, with an estimated incidence of 7-12 per 100,000 children (Fukuyama, 1960; Mercuri & Muntoni, 2013). The severe manifestations of CMD include early generalized hypotonia and muscle weakness, contractures (which are often associated with joint deformities), and markedly delayed motor milestones (Helbling-Leclerc et al., 1995). Brain malformation is typical in Fukuyama-CMD, often resulting in severe mental retardation (Voit, 1998).

LGMD is a very heterogeneous disorder, where the age of onset, pattern of inheritance, and clinical features depend on the gene or protein defect, but generally, muscle groups of the pelvic or shoulder girdle are primarily affected (Bushby, 1999; Feldman et al., 2014). The disorder can occur in childhood, especially autosomal recessive types, or in adulthood, especially autosomal dominant forms (Bushby, 1995). Autosomal recessive LGMDs are more prevalent, affecting 1:15,000 males/females cumulatively (Nigro, 2003). Affected patients usually progress rapidly, become unable to walk in late childhood and typically die in early adulthood. In contrast, autosomal dominant LGMDs, even of childhood onset, usually progress slowly. Depending on the types of LGMD, respiratory and cardiac involvement may occur in the late stages of the disease (Feldman et al., 2014), which may result in early death.

Distal myopathies (Distal MDs) represent a genetically heterogeneous group of muscle disorders with shared clinical features of predominant weakness in the feet and/or hands (Udd, 2012). The exact incidence of the Distal MDs is unknown. Symptoms may present in childhood in a few forms but are typically seen in early adulthood to middle age (Feldman et al., 2014). Cardiac involvement may develop in some forms of the disease (Finsterer & Stöllberger, 2016).

The remaining two diagnostic groups are the least common among all MDs. EDMD is a rare muscular disease with an incidence of 1 in 100,000 males/females (Randal et al., 2000), characterized by early contractures of the elbows, Achilles tendons and cervical extensors. Muscle wasting presents in proximal upper limbs and distal lower limbs early in the course of the disease. Systemic impairments include cardiomyopathy, which is often characterised by a cardiac autonomic nervous system defect (Bione et al., 1994; Emery, 1989). Symptoms of the disorder often become apparent by late childhood or adolescence and in absence of cardiomyopathy, most individuals are expected to survive into at middle age with varying degrees of disability (Emery, 1989). OPMD is a late adult-onset (usually in the fourth to sixth decade) rare neuromuscular degenerative disease, affecting 1 in 100,000 males/females (Brais et al., 1995). Affected individuals usually suffer from incomplete extraocular muscle paralysis and superior visual field defects. Other early symptoms are dysphagia and tongue weakness, which can lead to repeated aspiration attacks and possibly aspiration pneumonia (Brais et al., 1998). Weakness of the larynx may cause dysphonia. Weakness in limbs is usually mild and primarily affects proximal muscles.

Table 1 Prevalence and clinical characteristics of MDs by diagnoses

Diagnoses	Prevalence	Age of onset	Gender	Muscle affected	Other systems affected	Cognitive deficits	Life expectancy
DMD	1/3,500	Aged three to five years	Males	Proximal muscles of the arms and legs; calf hypertrophy, muscle fibrosis, contractures	Respiratory or cardiac failure in late stage	Mild to severe	Reduced; late teens to early twenties
BMD	1/30,000	Around 12 years	Males	Proximal muscles of the arms and legs; calf hypertrophy, calf pain, cramps	Dilated cardiomyopathy	Mild	Reduced; the fourth or fifth decade
DM	1/8,000	DM1:Variable from birth through to adulthood DM2: Adulthood	Males/ females	DM1: Cranial, trunk, and distal limb muscles; myotonia DM2: Proximal limb muscles; myalgia	Cardiac conduction defects, tachyarrhythmias, gastrointestinal symptoms, cataracts, hyperglycemia, brain abnormalities	Mild	DM1: reduced DM2: almost normal
FSHD	1/20,000	late childhood or adolescence	Males/ females	Facial, shoulder, leg, thigh, and pelvic girdle muscles; scapular winging	Hearing loss and retinal telangiectasias	Not common	Most normal
LGMD	Unknown	Childhood or adolescence or adulthood.	Males/ females	Pelvic or shoulder girdle muscles	Respiratory or cardiac involvement depends on forms	Not common	Most normal
CMD	Unknown	In the uterus or in the first year of life	Males/ females	Generalized hypotonia and muscle weakness	Brain malformation and visual loss depend on forms	Severe in FCMD	Reduced in some forms
EDMD	1/100,000	Late childhood or adolescence	Males/ females	Proximal in the upper limbs and distal in the lower limbs; contractures of the elbows, Achilles tendons and cervical extensors	Cardiomyopathy	Not common	Reduced; middle age
OPMD	1/100,000	The fourth to sixth decade	Males/ females	Extraocular muscle paralysis and mild proximal muscles weakness; dysphagia and dysphonia	Superior visual field defect	Not common	Normal
Distal MD	Unknown	Early adulthood to middle age	Males/ females	Predominant weakness in the feet and/or hands	Not common	Not common	Normal

DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; DM, Myotonic muscular dystrophy; FSHD, Facioscapulohumeral muscular dystrophy; LGMD, Limb-girdle muscular dystrophy; CMD, Congenital muscular dystrophy; FCMD, Fukuyama- Congenital muscular dystrophy; EDMD, Emery-Dreifuss Muscular Dystrophy, OPMD, Occulopharyngeal Muscular Dystrophy; Distal MD, Distal Muscular Dystrophies

1.3 Etiopathology of chronic pain in MDs

Chronic pain, defined as persistent or recurrent pain lasting 3 months or longer (Treede et al., 2015), has been recently identified as one of the primary causes of disability globally, according to the Global Burden of Disease reviews (Vos et al., 2015). Chronic pain is a common yet frequently under-recognised problem among people with MDs (Engel et al., 2009; Jensen et al., 2005; Tiffreau et al., 2006). The aetiology of MD-related chronic pain is largely unknown and may involve several different mechanisms. Chronic nociceptive pain seems to be the most common type of pain described, and is presumed to arise due to profound changes in the structure and function of tissues within the musculoskeletal system (George et al., 2004; Guy-Coichard et al., 2008; Jensen et al., 2008). The primary nociceptive source(s) in these populations may differ with disease duration.

Myalgia can be found early in several forms of MDs, for example, FSHD, BMD, DM (especially type 2), and the adult-onset autosomal recessive form LGMD (Ashizawa & Sarkar, 2011; Feldman et al., 2014; Wokke et al., 2013). However, investigation of the underlying mechanisms of myalgia is difficult as pain appears to present in individuals with very diverse histories. In subjects with DM2, myalgia may be triggered and maintained by molecular changes in the muscle. Compared with a non-myalgia group, unique transcriptome profiles were found in patients with myalgia (Moshourab et al., 2016). In the early stage of the disorder, inflammatory mechanisms may be important. Inflammatory changes in muscle are a common histological feature, for instance, in FSHD, and may contribute to ongoing muscle pain (Arahata et al., 1995).

For pain later in the natural disease history, mechanical problems caused by prolonged muscle weakness and immobility could become more important. Severely abnormal postures such as protracted shoulders and exaggerated lumbar lordosis are commonly seen in the diseases that affect the trunk and proximal limb muscles, which may lead to pain in the shoulder and lower back (Morís et al., 2018). Altered gait pattern in individuals with DMD have also been suggested as potential reasons of the high frequency of pain in the back and legs, with excessive anterior pelvic tilt, knee hyperextension in the loading response phase and an over plantarflexed foot common features (D'Angelo et al., 2009), have also been suggested as potential reasons of the high frequency of pain in the back and legs (Lager & Kroksmark, 2015). Joint contractures could also be a possible cause of pain, for example when the joint is close to its end range, during transfers or activities of

daily living. Scoliosis is common in wheelchair-dependent children, especially during the pubertal growth spurt (Mercuri & Muntoni, 2013), often leading to skin breakdown and general discomfort in a wheelchair, and painful costo-iliac impingement with progression (Archer et al., 2016). Vertebral compression fracture may be another cause of pain in the neck/back in people with DMD, due to immobility-induced osteoporosis and long term use of corticosteroid (Bushby et al., 2010). Finally, people who have undergone corrective surgeries for scoliosis or contracture may experience postsurgical pain at the operated site (Emery, 2002).

Given the widespread and prolonged nociceptive input associated with many MDs, it seems likely that central sensitisation and a mixed nociceptive/nociplastic pain phenotype may develop, at least in a subgroup of people. However, to the best of our knowledge, this has not yet been explored in people with MDs. Similarly, clinical evidence seems to be limited for neuropathic pain in individuals with MDs. So far, very few studies have investigated the frequency of this type of pain. In an observational cross-sectional cohort study, eight of 23 individuals (35%) with DM2 reported their pain had burning and radiating qualities, according to the McGill Pain Questionnaire (MPQ) (Moshourab et al., 2016). Although neuropathic pain seems to be under-recognised among people with MDs, possible causes should not be overlooked. For example, small fibre dysfunction has been observed in people with DM1, without evidence of large fibre neuropathy (Boland-Freitas & Ng, 2019). Secondary nerve damage has also been identified in various forms of MDs (Siegel, 1996). Ankle-foot-orthosis (AFO) use prevents muscle contracture and prolongs ambulation in individuals with DMD. However, long-term use of an ill-fitting AFO may cause a neuropathy of the peroneal nerve by pressure from the proximal edge of the orthosis (Siegel, 1993). Compression neuropathy has been reported in wheelchair-bound individuals with DMD. The most commonly seen is ulnar neuropathy as a consequence of pressure on the elbow and forearm from the wheelchair armrest (Chamberlain & Rando, 2006). Focal entrapment neuropathy such as carpal tunnel syndrome has also been identified. It is often caused by median nerve pinching with forced wrist flexion that accompanies the “praying mantis” deformity of wrists in FSHD and DMD (usually in the late stage) (Siegel, 1996). Finally, individuals with DM may develop diabetes associated with muscle induced changes in insulin resistance (Perseghin et al., 2003). These individuals may be predisposed to diabetic peripheral neuropathy, leading to neuropathic pain affecting the distal limbs.

1.4 Prevalence and characteristics of chronic pain in MDs

Although in recent years there has been an increasing number of studies highlighting the presence of pain in different types of MDs (Hunt et al., 2016; Miró et al., 2014; Morís et al., 2018; Peric et al., 2015; Richard T et al., 2002; Suokas et al., 2012; Zebracki et al., 2008), limited research has specifically focussed on assessing chronic pain in these populations, and there is little consensus concerning the nature and impact of pain in these people.

The prevalence of chronic pain among MDs differs across studies, which were performed in different settings, across different types of MDs and with varied methods of data retrieval. One estimate from a national survey in the US suggested that up to 82% of adults with FSHD experienced chronic pain over the past three months (Jensen et al., 2008). Another estimate from a national retrospective study in the UK (Morís et al., 2018), however, revealed a much lower prevalence of chronic pain (55.6%) in people with FSHD. In individuals with BMD/DMD and DM, the reported prevalence of chronic pain varies considerably, from 41% (Lager & Kroksmark, 2015) to 67% (Tiffreau et al., 2006), and from 65.7% (Moshourab et al., 2016) to as high as 95.8% (George et al., 2004), respectively.

Similarly, there are reported variations in pain intensity and severity. For instance, while most estimates of average pain intensity in DM were considered mild (Guy-Coichard et al., 2008; Jensen et al., 2008; Moshourab et al., 2016), some studies suggest that a notable proportion of the population live with severe pain (Jensen et al., 2005). Regarding pain location, findings tend to be consistent across studies and generally similar across diagnoses, with the most frequently reported pain sites in the lower back, shoulder and legs, and to a lesser degree in the neck, hips and knees (George et al., 2004; Jensen et al., 2005; Jensen et al., 2008; van der Kooi et al., 2007).

1.5 Symptomatic burden and functional impact in MDs

Over the past two decades, both the natural history and long-term prognosis of MDs have been greatly improved through a better understanding of the mechanisms underlying these disorders, improvements in health care standards, and the development of new treatment approaches, including evidence based clinical guidelines. Although these changes have led to better survival and improved prevention and management of secondary complications (Bach & Martinez, 2011; Eagle et al., 2002; Eagle et al., 2007),

a person's motor function, daily activities, participation and quality of life may remain chronically and massively affected (Carter et al., 2010; Grootenhuis et al., 2007; Molton et al., 2008), due to the progressive nature of these diseases.

While different MDs differ in terms of the age of onset, rate of progression, distribution and extent of muscle weakness, and other body system involvement, most of them will lead to various degrees of disability. This can range from difficulties in transferring and long-distance walking to a total inability of performing basic activities of daily living including walking, eating, dressing, and bathing. Respiratory impairment and cardiac involvement are frequent in many MDs (Feldman et al., 2014; Mercuri & Muntoni, 2013), compounding the physical disabilities and associated limitations in activities of daily living, significantly impacting the individual's quality of life (Giovanni Antonini et al., 2006; Grootenhuis et al., 2007; Padua et al., 2009; Uzark et al., 2012).

Chronic pain is a common problem in these populations. Pain may negatively influence motor function by reducing the muscle activation of the (painful) agonist as well as non-painful synergists and antagonists, and interfering with cortical sensorimotor processes related to movement planning and execution, which often result in protective motor behaviour and compensation of other muscles (Bank et al., 2013). This is likely to exacerbate the physical disabilities observed in individuals with MDs, and may accelerate the deterioration of motor function. As indicated by many studies, pain experience interferes with various aspects of people's lives and negatively affects their daily activities, physical and mental health, family and social relationships, and their interaction in the workplace (Breivik et al., 2006; Dueñas et al., 2016; Langley et al., 2011). Furthermore, sleep disturbance is found to be reciprocally associated with chronic pain (Finan et al., 2013). While sleep impairment is a common complaint in several forms of MDs (Bloetzer et al., 2012; Bushby et al., 1998), the presence of chronic pain probably aggravates the development of sleep disturbance, which in turn, contributes to the maintenance of chronic pain. Depression and pain commonly occur together, and the presence of pain has been found to negatively affect the recognition and treatment of depression (Bair et al., 2003). Individuals with DM are susceptible to personality changes in a later stage of the disease, and a definite tendency toward depression is evident among these people (Duveneck et al., 1986). Therefore, the high frequency of chronic pain in this population may have a detrimental impact to the individual's mental health.

Evidence and knowledge of the impact of MD-related chronic pain on function, psychological distress and quality of life is very limited and lacks systematic exploration.

1.6 Challenges to pain assessment in people with MDs

Considering the nature of pain (a subjective and individual experience) and the context of the disorder (physically disabling and multisystem involvement), assessing pain in people with MDs can be challenging. Firstly, in children or teenagers affected by MDs, assessment of pain is particularly problematic. Parents often rely on proxy reporting of their children's complaints, despite pain being a subjective and individualised event. This often leads to an underestimation of the child's symptoms (Chambers et al., 1998). A survey of pain in children with BMD and DMD shows that the actual agreement between parent and child report on pain symptoms appears to be poor to fair (Zebracki et al., 2008). This indicates that parent-reported pain of the child may not represent the pain the child actually experiences. Thus, self-report measures appropriate to the child's age, language, and cognitive maturity are required (Lee et al., 2017).

Secondly, comorbid cognitive deficits occur in several diagnostic groups such as DMD, DM, and Fukuyama-CMD. The assessment of pain in people with cognitive impairments presents unique challenges (Buffum et al., 2007). People with memory, language, and speech deficits may be unable or have difficulty communicating their pain. Furthermore, in addition to mild cognitive impairments, individuals with DM1 often experience characteristic behavioural changes (avoidant personality traits) including avoidance and reduced perception of disease symptoms and signs, and later apathy (Udd & Krahe, 2012). This may further complicate both the pain experience and its ability to be communicated to carers or health care professionals.

Thirdly, as the disease progresses, weakness of tongue and laryngeal muscles (e.g in OPMD) and deteriorating respiratory support, (e.g. in DMD and BMD), may result in dysphonia or decreased speech intelligibility. This can greatly hinder these individuals' ability to express pain complaints, especially among those who are not able to access assistive technology, for example, augmentative and alternative communication (AAC) systems, which are now considered standard practice in individuals with progressive neuromuscular disease (Ball et al., 2012).

1.7 Statement of the problem

Chronic pain appears to be a frequent, yet under-recognised and under-assessed problem in people with MDs. Knowledge of the prevalence of chronic pain, its characteristics and its impact on function and quality of life is limited and lacks systematic exploration. Reported estimates of prevalence and characteristics of chronic pain in different forms of MD are often variable across studies conducted in different contexts and geographical locations. Moreover, many studies to date have reported findings from a mixed population of patients with MDs with limited sample sizes that prevent meaningful comparison of pain related measures across different diagnoses.

To date, only one systematic review has assessed the prevalence, characteristics and functional impact of pain in people with MDs (Silva et al., 2016). This review, however, focused only on DMD and did not clearly focus on 'chronic' pain based on a definition that aligns with that of the International Association for the Study of Pain (as described above) (Treede et al., 2015), instead, exploring pain in general, including acute pain that may have been transient in nature. Moreover, the authors did not formally appraise the literature and were therefore unable to report on the strengths and limitations of the evidence included in the review. To the best of our knowledge, no other systematic reviews or meta-analyses have assessed chronic pain in any other type of MD or in MDs more broadly.

Therefore, the aim of this study is to systematically review and synthesise existing literature that addresses chronic pain prevalence, intensity, severity, location, quality, frequency, duration, and its impact in people with different types of MDs. By using a meta-analysis approach, and statistically combining data from individual studies we may be able to provide a more precise estimate of chronic pain prevalence and allow meaningful comparison of pain related outcome measures between different diagnostic groups.

1.8 Significance of the research

The findings from this systematic review have significance for health professionals and caregivers involved in the management of people affected by different forms of MDs. The study findings will allow better recognition of chronic pain among health professionals and caregivers, and a better understanding of the features and impact of chronic pain in people with MDs, which are important for subsequent care planning. The

findings may strengthen the evidence for making pain assessment and management part of the standards of care in these conditions and guide health professionals to develop more appropriate assessment and treatment of chronic pain in these populations. Finally, this research may help to identify gaps in the existing literature and highlight the need for future research related to the prevalence, characteristics and the impact of chronic pain in people with different types of MDs.

Chapter 2 Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A protocol for this review was developed and registered on PROSPERO (CRD: 42020168096).

2.1 Search strategy

A systematic search of bibliographic electronic databases, including PubMed, MEDLINE (via EBSCO), CINAHL (via EBSCO), CENTRAL, Scopus, Web of Science, and Allied and Complementary Medicine Database (AMED), was performed for articles (up to March 2020) reporting chronic pain in people with MDs. Medical subject headings and most common key terms searched to identify literature relating to the research question included “muscular dystrophy”, “myotonic dystrophy”, “Facioscapulohumeral dystrophy ”, “chronic pain”, “persistent pain”, and “long-term pain”. Key terms differed slightly according to the databases being searched. The complete search strategy for all databases involved in this review is reported in Appendix A.

2.2 Inclusion and exclusion criteria

The identified articles were included if they: (1) involved a population with a diagnosis of any type of MDs, (2) assessed pain in this population, and (3) were published in English. Articles were excluded if they were: (1) not peer-reviewed, (2) performed in a mixed population where independent data on pain in each diagnostic subgroup of MD could not be extracted, or less than ten MD participants were included, (3) not clearly focused on chronic pain (defined as pain persisting or recurring for a period of 3 months or longer) (Treede et al., 2015).

2.3 Study selection

The search strategy was applied to all databases by a reviewer (MH). All the identified studies were downloaded to a reference manager software (EndNote X9) where duplicates were removed. Title and abstract screening were performed by two reviewers (MH and NM) according to the inclusion and exclusion criteria. For the eligible studies, full-text screening was performed. Disagreements on articles inclusion/exclusion were discussed between the two reviewers, and if agreement could not be reached, a third person (DR) was involved. Reference and forward citation searches (via reference lists

and Scopus, respectively) were performed for all the articles deemed suitable for inclusion. Full text of the potentially eligible studies identified from the above searches was reviewed to validate the inclusion.

2.4 Study quality and risk of bias appraisal

The full text of all included articles was critically appraised by two reviewers (MH and NM) independently. Disagreement between reviewers was resolved by discussion and with the involvement of a third reviewer (DR) if necessary.

Quality assessment was conducted using the Risk of Bias Tool for Prevalence Studies (Hoy et al., 2012). The tool is specifically designed to examine the risk of bias in population-based prevalence studies. It includes 10 items to evaluate the external (items 1 to 4) and internal (items 5 to 10) validity and a summary risk of bias assessment. Response options for individual items are either low or high risk of bias, and marked as 'Yes' for low risk or 'No' for high risk in the scoring sheet. Where not enough information was available on a specific item, high risk of bias was selected.

A summary assessment of the overall risk of study bias at three levels (low, moderate, or high risk of bias) was chosen, based on the reviewer's subjective judgement given responses to the preceding 10 items in the Risk of Bias Tool for Prevalence Studies. This approach is in accordance with the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) and Cochrane approaches (Hoy et al., 2012). While giving the subjective judgement on the overall risk of study bias, the two reviewers agreed that the first four items which explore selection bias and non-response bias should be assigned more weight. This was because the present systematic review aimed to explore the prevalence of a health issue (chronic pain) in a specific population (people with MDs), where estimates from a biased sample may bring substantial uncertainties to the synthesised findings.

2.5 Data extraction

For each included study, the research design, participant characteristics, and outcome measures were recorded. Data extraction was performed by one reviewer (MH), and then checked by the second reviewer (NM) to confirm all extracted data were consistent with the original papers. For studies where outcomes where measured at multiple time points, only baseline data of participants were extracted. Where further information was required, the corresponding authors were contacted by email.

2.6 Data analysis

Estimates for the pain prevalence were incorporated into a meta-analysis. Data synthesis was performed by using the MetaXL version 5.3 (EpiGear International, Noosa, Queensland, Australia) (an add-in for Microsoft Excel). A double arcsine transformation was used while pooling the prevalence data in order to address the problem of confidence limits outside the 0..1 range and that of variance instability, which arises when the prevalence proportions get close to the limits of the 0..1 range (Barendregt et al., 2013). A quality effects model was used to weight the pooled prevalence data, which was displayed on forest plots with 95% confidence intervals (CIs). Under this model, weights were redistributed due to Qi, a synthetic value computed by dividing each quality score of the studies included in data synthesis by the maximum score in the list of studies (Doi et al., 2015). Quality scores in this review were referred to the summary assessment of overall risk of bias: low=3, moderate=2, and high=1. A one-way analysis of variance (ANOVA) was used to determine whether there were significant differences on pooled prevalence across different diagnostic groups. The standard deviation (SD) for each group was obtained by the following formula: SD= $\sqrt{}$ N x (Upper limit of CI – Lower limit of CI)/3.92, N = group sample size, CI = 95% confidence interval (Higgins et al., 2019).

Pooled average pain intensity estimates were calculated using random effects model meta-analysis. Means and standard deviations were used to summarise the data with mean and 95% CIs. Where number of articles was sufficient, group comparison was performed for studies that reported data for multiple diagnostic groups. While it is recognised that alignment between different pain scales is not always perfect (Williamson & Hoggart, 2005), to allow comparison between different MD groups, the scores of Visual Analogue Scale (VAS) were transformed into the Numerical Pain Rating Scale (NPRS). Since the MetaXL does not support meta-analysis of single means, the 'meta' package in R was applied to calculate the overall mean of pain intensity estimates (Schwarzer, 2007).

Heterogeneity between studies was examined using Higgins's I^2, with values of 25%, 50%, and 75% considered as low, moderate, and high, respectively (Higgins et al., 2003). Stratified analysis was performed to explore the source of heterogeneity, where sufficient studies allowed this approach. Sensitivity analysis was conducted according to the results of the risk of bias assessment to examine how the quantitative findings of this review were affected by the individual studies with high risks of bias. A narrative synthesis was provided for other outcomes where meta-analysis was not feasible.

2.7 Risk of bias across studies

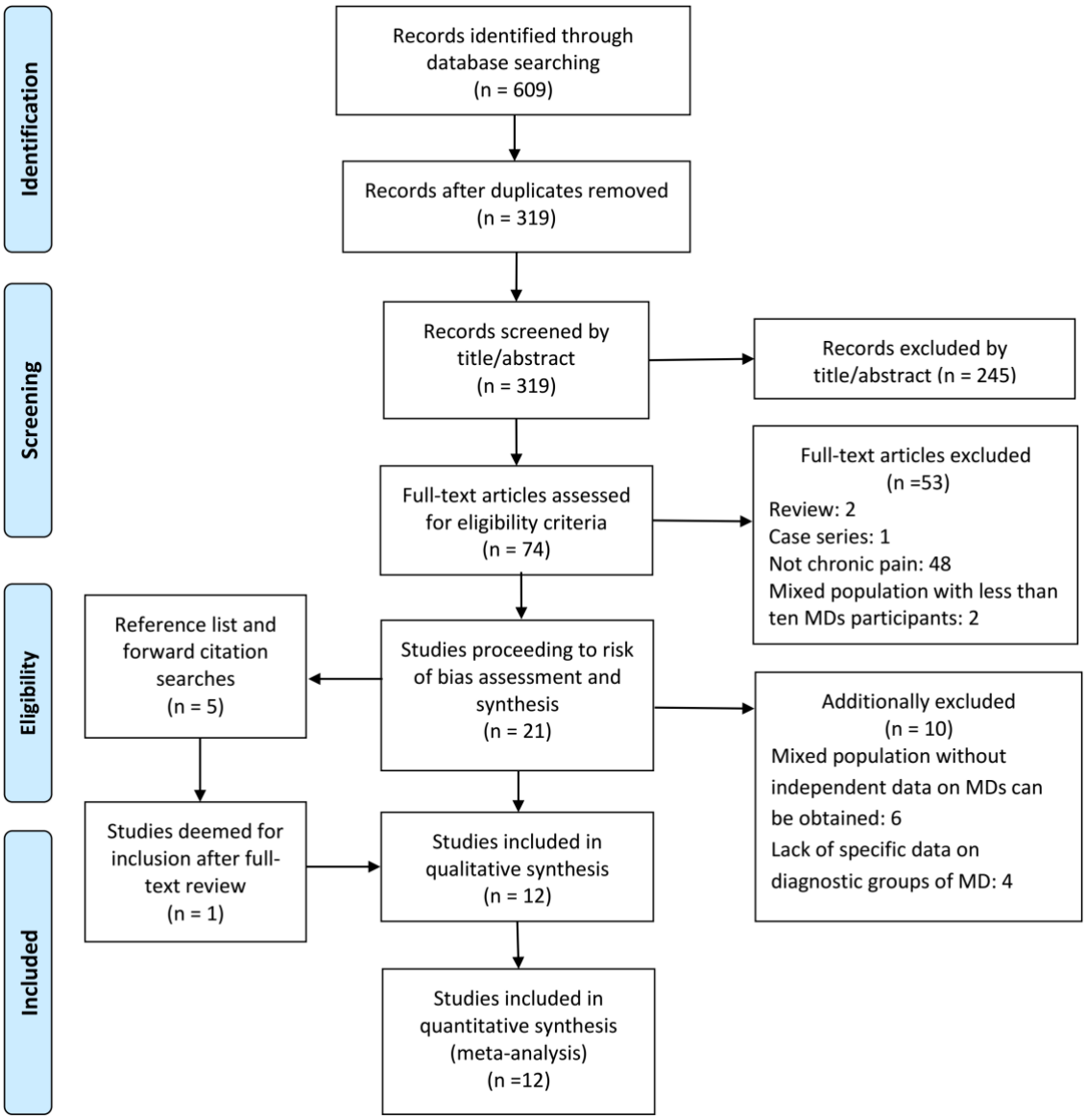
We evaluated the possibility of publication bias by visually assessing Doi plots for asymmetry. Doi plots are more sensitive than funnel plots which are hard to interpret when there are less than ten studies (Furuya-Kanamori et al., 2018). A quantitative measure of the Doi plot asymmetry was performed using the Luis Furuya-Kanamori (LFK) index, where the detected asymmetry can be interpreted into three levels: no asymmetry (LFK index within ±1), minor asymmetry (LFK index exceeds ±1 but within ±2), or major asymmetry (LFK index exceeds ±2) (Furuya-Kanamori et al., 2018). It was hypothesised that, if publication bias was an issue, papers indicating greater prevalence of chronic pain in muscular dystrophies would be more likely to be published. A positive direction of bias for the LFK index was therefore selected a-priori (LFK index > 1).

Chapter 3 Findings

3.1 Study selection

A total of 609 records were identified through the search. After duplicate removal, 319 studies were deemed suitable for further screening. After title and abstract screening, 74 studies met the inclusion and exclusion criteria. Full-text review identified 11 studies suitable for inclusion. Reference list and forward citation searches of the included studies identified 5 potentially suitable studies of which only one was eligible for inclusion. This led to a total of 12 studies being included in this review. The main reasons for exclusion of articles were the lack of independent data on MDs. We contacted ten authors in an attempt to obtain independent data for individual subgroups which were published as a whole (involving more than one diagnostic subgroup of MDs) or in combination with other populations (e.g. other NMDs or physical disabilities). Two responded, but they were not able to provide the necessary data as they did not keep track of specific MD diagnoses in the dataset. The other eight did not respond within one month of the emails

being sent and were therefore marked as "no response".



shows the study screening and selection processes.

3.2 Characteristics of included studies

Characteristics of included studies are presented in Table 2.

3.2.1 Study design

The final 12 articles consisted of nine cross-sectional studies (Della Marca et al., 2013; George et al., 2004; Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Lager & Kroksmark, 2015; Moshourab et al., 2016; Pangalila et al., 2015; Tiffreau et al., 2006), two retrospective studies (Morís et al., 2018; Steel et al., 2019), and one randomized controlled trial (RCT) (van der Kooi et al., 2007). Of the 9 studies with a cross-sectional design, six were surveys (Guy-Coichard et al., 2008; Jensen et al., 2005;

Jensen et al., 2008; Lager & Kroksmark, 2015; Pangalila et al., 2015; Tiffreau et al., 2006), with a response rate ranging from 45% to 78%.

Sample sizes varied dramatically across the included articles, ranging from 18 to 398 participants with MDs, with a median participant number of 65. Five studies included a mixed population (one or more diagnostic groups), which consisted of MDs, Spinal muscular atrophy (SMA), Charcot-Marie-Tooth disorder (CMT) and Myasthenia Gravis (MG) (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Lager & Kroksmark, 2015; Tiffreau et al., 2006).

Figure 1 Flow chart of study selection

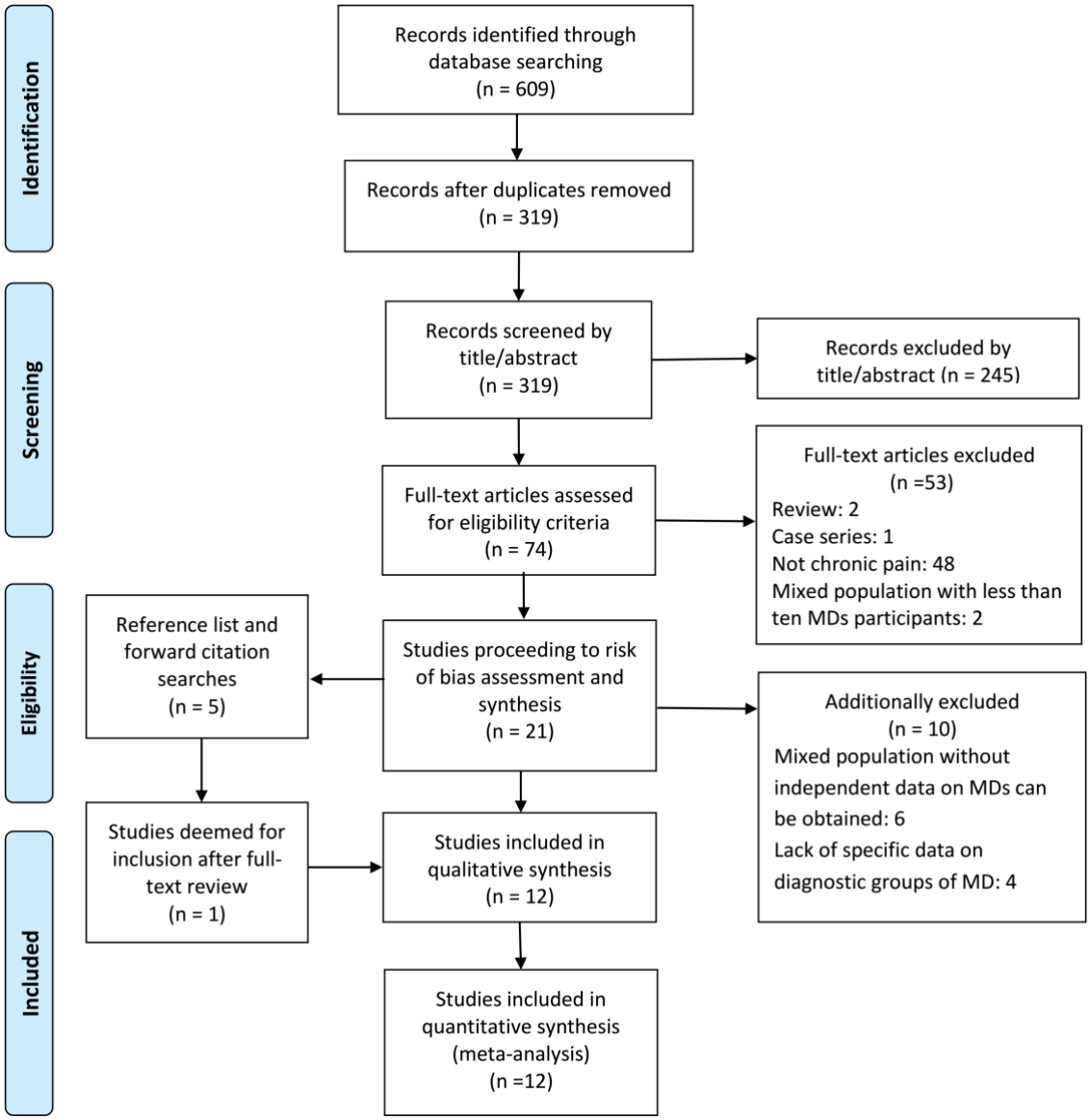


Table 2 Characteristics of studies

Study	Study design	Region	Sample source	Diagnostic group	Sample size	Response rate	Age (years) Mean (SD)	Gender (Female %)	Primary aims
Della Marca 2013	Cross-sectional	Italy	An NMD rehabilitation centre	FSHD	55	-	49.6(15.1)	42%	To explore the relationship between sleep disruption and chronic musculoskeletal pain
George 2004	Cross-sectional	The UK	NMD training institution	DM2	24	-	57 (35-69)*	-	To characterize DM2 -associated musculoskeletal pain
Guy-Coichard 2008	Cross-sectional	France	30 centres for NMD consultation	DMD/BMD DM1 FSHD	132 134 121	65%	32.8 (12.5) 46.0 (13.4) 45.7 (14.8)	2% 54% 48%	To assess the characteristics of chronic pain in people with NMDs.
Jensen 2005	Cross-sectional	The USA	NMD rehabilitation clinic and training and research centre	DM FSHD LGMD	26 18 44	47%	51.7 (15.6)	52%	To evaluate the characteristics of chronic pain in people with NMDs.
Jensen 2008	Cross-sectional	The USA	National registry and clinic list	DM FSHD	130 127	78%	46.9 (11.6) 51.8 (13.8)	59% 52%	To evaluate the characteristics of chronic pain in working-aged individuals with DM and FSHD.
Lager 2015	Cross-sectional	Sweden	Swedish national network for NMD	DMD BMD	33 5	71%	15.6 (2.1) 14.2 (2.3)	0 0	To explore the characteristics of chronic pain in adolescents with DMD/BMD and SMA and does the pain differ between diagnoses
Morís 2018	Retrospective	The UK	FSHD Patient Registry	FSHD	398	-	47.0 (60.6)	50%	To examine the characteristics and impact of pain on QoL in people with FSHD.
Moshourab 2016	Cross-sectional	Germany	A Muscle Disorders Outpatient Clinic	DM2	35	-	54.3 (12.7)	54.3%	To analyse the clinical and molecular profile of myalgia in DM2.
Steel 2019	Retrospective	The UK	Tertiary paediatric neuromuscular centre	FSHD	18	-	13.8(3.8)	61%	To explore the clinical course of patients presenting with FSHD in childhood

Study	Study design	Region	Sample source	Diagnostic group	Sample size	Response rate	Age (years) Mean (SD)	Gender (Female %)	Primary aims
Tiffreau 2006	Cross-sectional	France	Lille University Medical Centre's PMR clinic	FSHD DM LGMD DMD/BMD CMD	19 15 15 15 4	45%	41 (14.5)	43%	To evaluate the characteristics of chronic pain in people with NMDs.
van der Kooi 2007	RCT	Netherlands	Dutch NMD Association and an NMD training Centre	FSHD	65	-	38(10)	40%	To explore the features of pain and experienced fatigue in people with FSHD, and to study the effects of albuterol and strength training on self-reported pain, experienced fatigue, functional status and psychological distress in these individuals.
Pangalila 2015	Cross-sectional	Netherlands	Multiple home ventilation centres, rehabilitation centres and patient organization for NMDs in Netherlands	DMD	79	53%	28.2 (6.3)	0	To evaluate the frequency of pain, fatigue, anxiety, and depression in adults with DMD and to analyse their relationship with QoL

NMD, neuromuscular diseases/disorders; FSHD, Facioscapulohumeral muscular dystrophy; DM, Myotonic muscular dystrophy; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; LGMD, Limb-girdle muscular dystrophy; CMD, Congenital muscular dystrophy; SMA, Spinal muscular atrophy; QoL, quality of life; RCT, randomized controlled trial.
*Age was reported as Median and range in this study.

3.2.2 Participants

A total of 1512 participants were included across all the studies, with six diagnostic groups of MDs: DM (n=364), FSHD (n=821), DMD/BMD (n=264), LGMD (n=59) and CMD (n=4). These participants were largely recruited from Europe (including Italy, the UK, France, Sweden, the Netherlands, and Germany) and North America (the USA). Sources of participants generally included NMD clinics or rehabilitation centres, and national patient registry of NMDs/MDs. The involved participants may be divided into two age groups: adults (18 years of older) and adolescents (less than 18 years). Of the 12 articles included, ten studies investigated chronic pain in adults (mean age ranging from 28 to 57 years), with the remaining two only including teenagers (mean age ranging from 13 to 14 years). The gender distribution across articles tended to be similar, except for the DMD/BMD group, which is an inherited disorder typically affecting males.

3.3 Outcomes and measurements

Table 3 reports the pain-related outcomes and associated assessment tools utilised by the included studies.

Pain prevalence, pain location, pain intensity and severity, and pain interference were the most common pain outcome measures reported. Other pain domains such as pain quality, frequency, and duration (of episodes) were reported by a few papers only. Most studies utilised validated questionnaires assessing various dimensions of chronic pain.

The VAS and NPRS were the most common outcome measures for pain intensity. Present pain intensity index (MPQ-PPI) in the McGill Pain questionnaire (MPQ) (Della Marca et al., 2013), Daily Observed Pain score (DOP) (van der Kooi et al., 2007), and the Universal Pain Assessment Tool (UPAT) (Morís et al., 2018) were also utilised in some studies for pain intensity evaluation. Pain severity categories were typically determined according to the level of pain intensity assessed by the 0-10 NPRS scale: mild - rated 4 or lower, moderate - rated 5 or 6, severe - rated 7 or higher (Jensen et al., 2005; Jensen et al., 2008; Tiffreau et al., 2006). One study specifically asked participants to rate pain severity on a 0 (no pain) to 4 (severe pain) scale (van der Kooi et al., 2007).

Body map (Guy-Coichard et al., 2008; Tiffreau et al., 2006), MPQ (Morís et al., 2018; Moshourab et al., 2016; van der Kooi et al., 2007), and Brief Pain inventory (BPI) (Jensen et al., 2005; Jensen et al., 2008; Lager & Kroksmark, 2015) were tools most frequently utilised to record pain location among the included studies. For pain frequency and

duration, relevant questions were added to the questionnaire or interview (George et al., 2004; Guy-Coichard et al., 2008). Pain quality was assessed through the MPQ (George et al., 2004; Moshourab et al., 2016), and the Neuropathic Pain Scale (NPS) (Jensen et al., 2005).

Concerning the evaluation of pain interference, most included studies used BPI (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Lager & Kroksmark, 2015) to explore the impact of chronic pain on interference in ten different domains (e.g. sleep, walking ability, relationships with others). Other outcomes where pain may have an important influence included: fatigue, evaluated by the Fatigue severity subscale of the Checklist Individual Strength (CIS) (van der Kooi et al., 2007); sleep quality, examined by polysomnographic (PSG) recording, Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS) (Della Marca et al., 2013); depressive symptoms, assessed by the Hospital Anxiety and Depression Scale (HADS) (Tiffreau et al., 2006), and the Symptom Checklist-90 (SCL) (van der Kooi et al., 2007); and quality of life, measured by 36-Item Short-Form Health Survey (SF-36) (Jensen et al., 2005), Individualized Neuromuscular Quality of Life Questionnaire (INQoL) (Morís et al., 2018), and World Health Organization Quality of Life Scale Brief Version (WHOQOL-BREF) (Pangalila et al., 2015).

Table 3 Outcomes and measurements

Study	Pain-related outcomes								Outcome measures	Methods of data collection
	Prevalence	Intensity (scale)	Severity (categorical)	Location	Frequency	Duration	Quality	Interference		
Della Marca 2013	√	√		√					VAS, MPQ,	Questionnaire and face-to-face interview
George 2004	√			√	√	√	√		VAS, MPQ	Questionnaire and clinical examination
Guy-Coichard 2008	√	√	√	√	√	√		√	NPRS, BPI, MPQ, Body map	Postal questionnaire
Jensen 2005	√	√	√	√			√	√	NPRS, NPS, BPI	Postal questionnaire
Jensen 2008	√	√	√	√				√	NPRS, BPI	Postal questionnaire
Lager 2015	√	√		√				√	VAS, BPI	Questionnaire
Morís 2018	√		√	√					SF-MPQ, UPAT	Patient registry database
Moshourab 2016	√	√		√			√		VAS, MPQ, QST	Questionnaire and clinical examination
Steel 2019	√			√					Clinical-records	Face-to-face interview
Tiffreau 2006	√	√		√					NPRS, Body map, VAS	Postal questionnaire
van der Kooi 2007	√	√	√	√					VAS, MPQ, DOP, Pain severity scale*	Questionnaire and clinical examination
Pangalila 2015	√			√					SF-36	Questionnaire

VAS, Visual analogue scale; NPRS, Numerical Pain Rating Scale; BPI, Brief Pain inventory; MPQ, McGill Pain questionnaire; SF-MPQ, Short Form of the McGill Pain Questionnaire; NPS, Neuropathic Pain Scale; QST, Quantitative sensory testing; UPAT, The universal pain assessment tool; DOP, Daily Observed Pain score; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey. * Pain severity was rated on a scale of 0 (no pain) to 4 (severe pain)

3.4 Study quality and risk of bias

Agreement between reviewers on study bias assessment was 94%. As depicted in Table 4, the risk of bias of the included articles in this systematic review was generally moderate to low. Items 5-10 for internal validity (measurement bias and analysis bias) were most frequently met. However, with respect to the external validity (selection bias and nonresponse bias) assessed by items 1 to 4, nearly half of the included articles failed to meet the criteria for item 1, 3 and 4 owing to a biased sample (not a true or close representation of the national population, using inappropriate sampling methods such as a convenience sample) or omitting a comparative analysis of non-responders.

Table 4 Quality and risk of bias of included studies

Study	External Validity				Internal Validity						Summary of overall risk of bias
	1	2	3	4	5	6	7	8	9	10	11
Della Marca 2013	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
George 2004	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	High
Guy-Coichard 2008	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Jensen 2005	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Jensen 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Lager 2015	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Morís 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Low
Moshourab 2016	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Steel 2019	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	High
Tiffreau 2006	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
van der Kooi 2007	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Pangalila 2015	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate

1, was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation; 2, was the sampling frame a true or close representation of the target population; 3, was some form of random selection used to select the sample, OR, was a census undertaken; 4, was the likelihood of non-response bias minimal; 5, were data collected directly from the subjects (as opposed to a proxy); 6, was an acceptable case definition used in the study; 7, was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary); 8, was the same mode of data collection used for all subjects; 9, was the length of the shortest prevalence period for the parameter of interest appropriate; 10, were the numerator(s) and denominator(s) for the parameter of interest appropriate; 11, summary item on the overall risk of study bias (Hoy et al., 2012).

Yes, low risk; No, high risk.

Low risk of bias: Further research is very unlikely to change our confidence in the estimate.

Moderate risk of bias: Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.

High risk of bias: Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

3.5 Key findings

3.5.1 Pain prevalence

While all included studies focused on chronic pain, the reporting period for pain related measures varied across studies. As showed in Table 5, five studies investigated pain prevalence over the previous three months (Della Marca et al., 2013; Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Lager & Kroksmark, 2015). The reporting time period of the remaining studies varied from pain right now (Moshourab et al., 2016), in the past two to four weeks (Pangalila et al., 2015; Tiffreau et al., 2006; van der Kooi et al., 2007) or in the past five years (Morís et al., 2018). Two studies did not provide relevant information regarding pain reporting period (George et al., 2004; Steel et al., 2019).

Eight studies (n=821) presented prevalence data for chronic pain in people with FSHD (Della Marca et al., 2013; Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Morís et al., 2018; Steel et al., 2019; Tiffreau et al., 2006; van der Kooi et al., 2007). Reported prevalence of chronic pain in FSHD ranged from 55.6% to 89% (pooled estimate 67.6%, 95% CI 51.7% to 81.9%). A forest plot of the studies included in meta-analysis was presented in **Error! Reference source not found.**, demonstrating high heterogeneity among the estimates (I^2 87%, P=0.00). Potential sources of heterogeneity were explored using stratified and sensitivity analyses of the included studies. There was little difference in gender and age distributions between the studies, and thus it was impossible to justify different categories. Five different countries were involved in the eight included studies. Pooling of estimates according to geography suggested that prevalence of FSHD was higher in the USA (pooled prevalence 82%, 95% CI 76% to 88%), compared to that of France (pooled prevalence 75%, 95% CI 63% to 85%) and in particular, the UK (pooled prevalence 56%, 95% CI 51% to 60%) (Figure 3). Differences were also apparent across publication date for studies published within 2000s (pooled prevalence 79%, 95% CI 74% to 83%) and studies published within 2010s (pooled prevalence 57%, 95% CI 35% to 78%) (Figure 4), suggesting a decrease in pain prevalence over time.

Sensitivity analysis suggested that the exclusion of studies with high risk of bias (Della Marca et al., 2013; Steel et al., 2019) did not significantly impact the pooled estimate or heterogeneity. Across all studies, only one provided gender-specific data, with 50.3%

males and 61.0% females reporting chronic paint among individuals with FSHD, indicating possible gender differences with respect to chronic pain prevalence (Morís et al., 2018).

Table 5 Studies reporting estimates for chronic pain prevalence

Study	Reporting period	FSHD		DM		DMD/BMD		LGMD		Quality score	Qi
		Participants (n)	Prevalence	Participants (n)	Prevalence	Participants (n)	Prevalence	Participants (n)	Prevalence		
Della Marca 2013	Previous three months	55	76.4%							1	0.33
George 2004	Not mentioned			24	95.8%					1	0.33
Guy-Coichard 2008	Previous three months	121	75.8%	134	66.7%	132	66.4%			3	1
Jensen 2005	Previous three months	18	89%	26	69%			44	64%	2	0.67
Jensen 2008	Previous three months	127	82%	130	60%					3	1
Lager 2015	Previous three months					38	41%			3	1
Morís 2018	Past 5 years	398	55.6%							3	1
Moshourab 2016	Current-point prevalence			35	65.7%					2	0.67
Steel 2019	Not mentioned	18	61.1%							1	0.33
Tiffreau 2006	Previous 3 weeks	19	63%	15	46%	15	67%	15	50%	2	0.67
van der Kooi 2007	Previous 2 weeks	65	80%							2	0.67
Pangalila 2015	Previous 4 weeks					79 (DMD only)	65%			2	0.67

FSHD, Facioscapulohumeral muscular dystrophy; DM, Myotonic muscular dystrophy; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; LGMD, Limb-girdle muscular dystrophy.
Qi, a synthetic value computed by dividing each quality score of the studies included in data synthesis by the maximum score in the list of studies.

Figure 2 Pooled chronic pain prevalence for FSHD

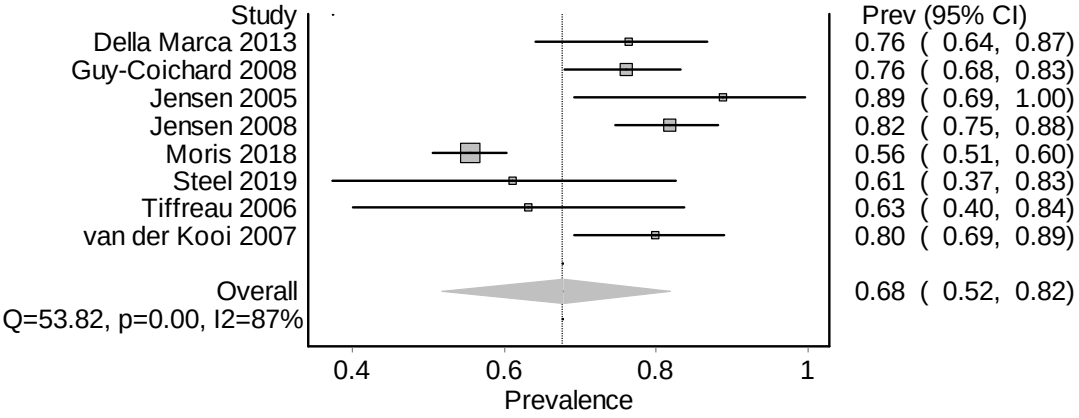


Figure 3 Pooled chronic pain prevalence for FSHD by geography

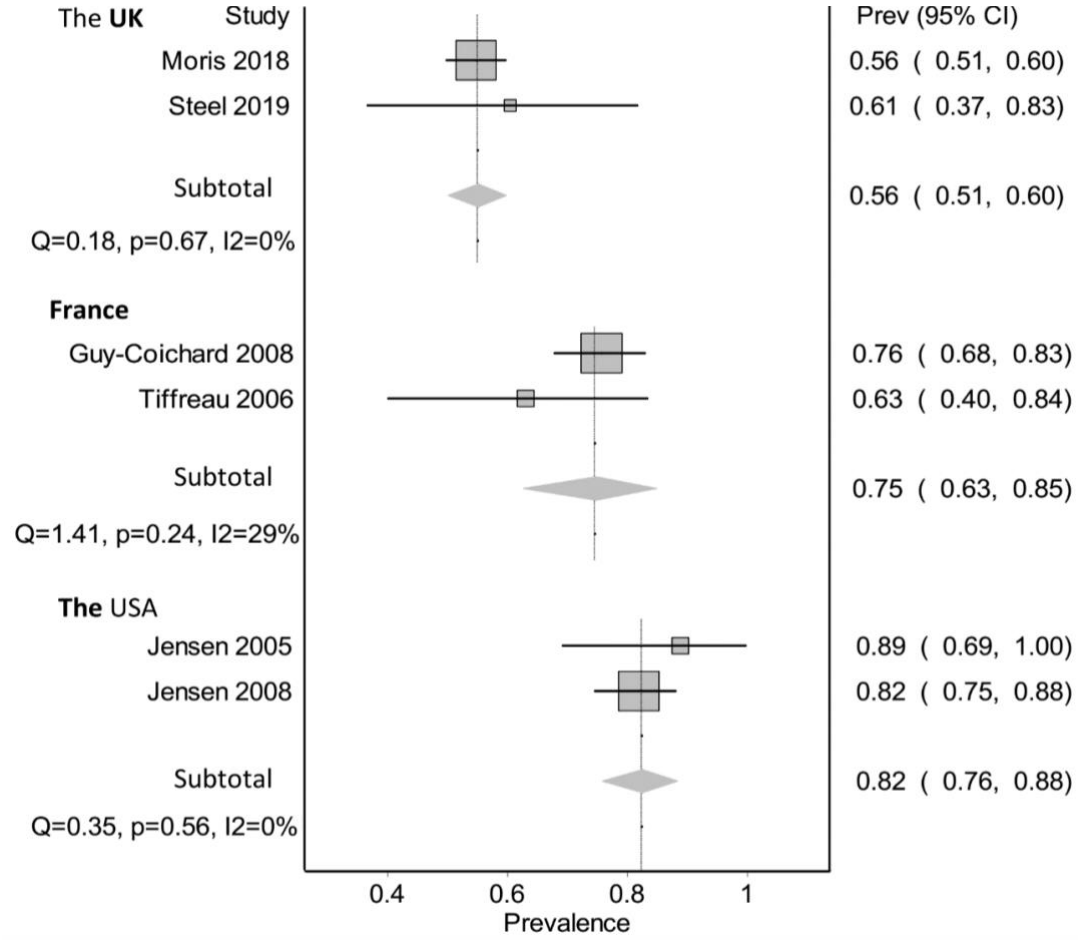
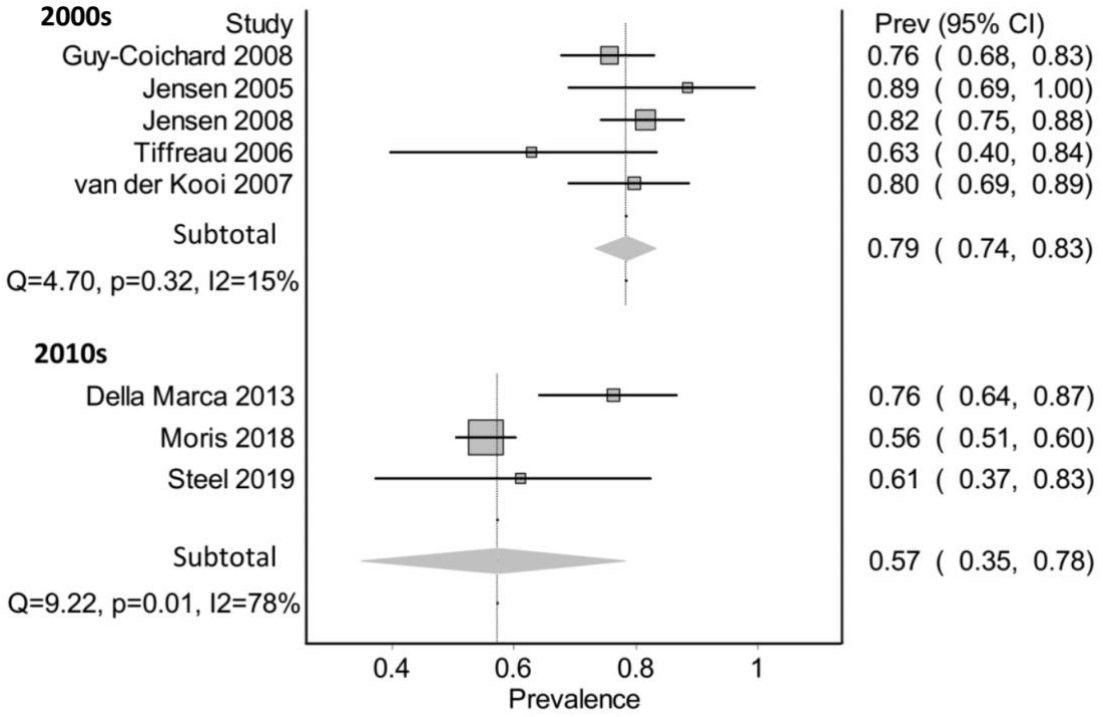
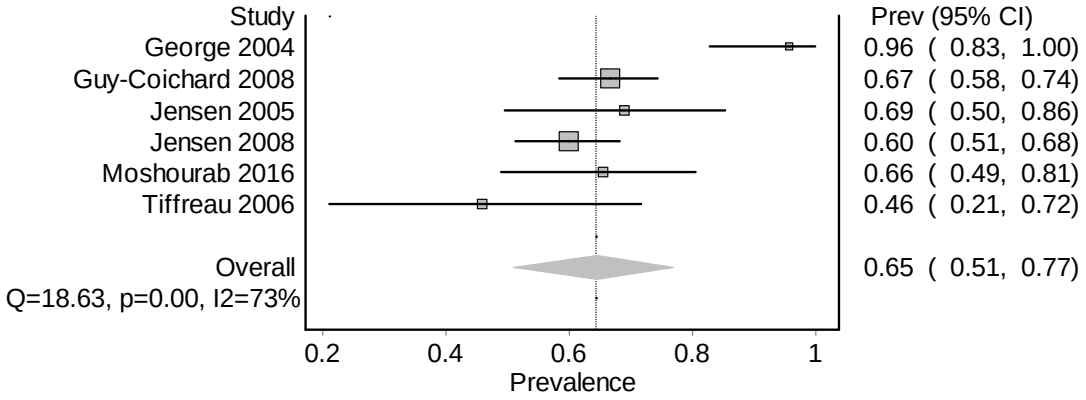


Figure 4 Pooled chronic pain prevalence for FSHD by publication date



Six articles (n=364) specifically examined the prevalence of chronic pain in people with DM (George et al., 2004; Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Moshourab et al., 2016; Tiffreau et al., 2006). Prevalence rates ranged widely in this diagnostic group (46%-95.8%). The pooled prevalence estimate is reported in Figure 5 (65%, 95% CI 51% to 77%), with high heterogeneity (I^2 73%, P<0.001) being detected. Sensitivity analysis showed that the exclusion of one article with high risk of bias (George et al., 2004) dramatically reduced heterogeneity (I2 = 0%, P=0.485), but did not impact the pooled prevalence (63%, 95%CI 58% to 68%). Stratified analysis concerning age, gender, publication date, and geography distribution among studies was not considered due to an insufficient number of studies for comparison or a lack of variability across the included studies.

Figure 5 Pooled chronic pain prevalence for DM



As presented in Table 5, four studies (n=264) reported chronic pain prevalence in people with DMD and BMD, three of them were reported in a combined group (BMD/DMD) (Guy-Coichard et al., 2008; Lager & Kroksmark, 2015; Tiffreau et al., 2006), and the other one only included DMD participants (Pangalila et al., 2015). Prevalence rates ranged from 41% to 67% (pooled prevalence 62%, 95% CI 50% to 73%; Figure 6), and moderate heterogeneity was observed (I^2 63%, P=0.04).

Only two studies (n=59) investigated the prevalence of chronic pain in LGMD (Jensen et al., 2005; Tiffreau et al., 2006). The pooled prevalence was similar to the other diagnostic categories (pooled prevalence 60%, 95% CI 48% to 73%). As shown in Figure 7, heterogeneity in this meta-analysis was very low (I^2 0%, P=0.35).

Figure 6 Pooled chronic pain prevalence for BMD/DMD

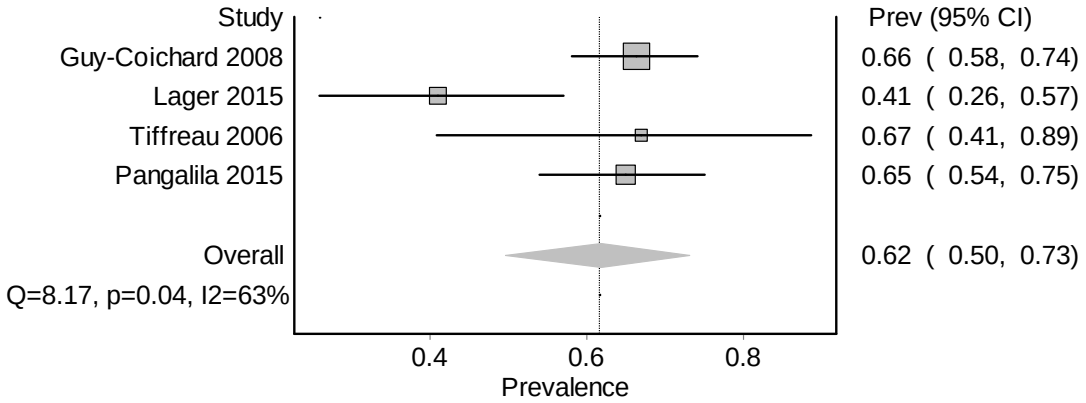
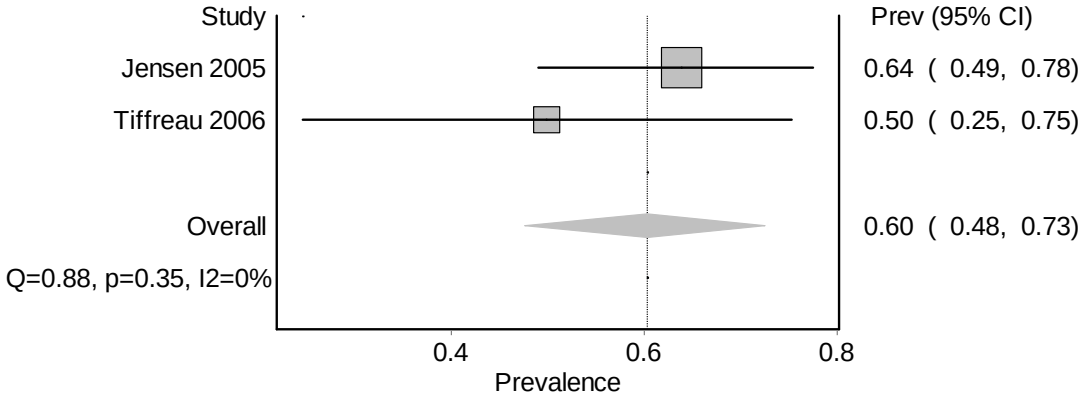


Figure 7 Pooled chronic pain prevalence for LGMD



One study involved CMD participants (n=4), but no independent data on chronic pain prevalence were provided (Tiffreau et al., 2006).

There were no statistically significant differences between the pooled prevalence of FSHD, DM, BMD/DMD and LGMD groups as determined by one-way ANOVA ($F(3,1504) = 0.10$, $p = 0.96$).

3.5.2 Pain intensity

Studies that reported estimates for pain intensity were presented in Table 6. The reporting periods varied across studies, including average pain intensity of right now (van der Kooi et al., 2007), in the past week (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008) and in the past three months (Della Marca et al., 2013). One study did not mentioned the associated recall period (Moshourab et al., 2016).

Five studies assessed pain intensity in people with FSHD (Della Marca et al., 2013; Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; van der Kooi et al., 2007), with average pain intensity estimates ranging widely from 1.6 to 5.1 (pooled mean intensity 4.1, 95% CI 2.6 to 5.5). Four studies provided average pain intensity data in DM, ranging from 4.2 to 6.3 (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Moshourab et al., 2016), with a pooled mean intensity of 4.7 (95% CI 4.2 to 5.2). Forest plots for the above estimates are shown in Figure 8 and Figure 9, respectively. For the three studies that reported average pain intensity data both for individuals with FSHD and DM, a between group comparison was performed. As presented in Table 6, these studies used the same assessment tool (NPRS) and similar reporting periods (7 or 8 days). The meta-analysis results suggested that no significant difference on average pain intensity between the two diagnostic groups (Figure 10).

Table 6 Studies reporting estimates for average pain intensity

Study	Measurement	Reporting period	FSHD		DM		DMD/BMD		LGMD	
			Participants (n)	Estimates Mean(SD)	Participants (n)	Estimates	Participants (n)	Estimates	Participants (n)	Estimates
Della Marca 2013	VAS	Previous three months	55	50.9 (27.3)						
Guy-Coichard 2008	NPRS	Previous eight days	121	5.0(2.5)	134	4.6 (2.4)	132	4.1(2.3)		
Jensen 2005	NPRS	Over the past week	18	4.3(2.2)	26	6.3 (3.2)			44	5.3 (2.5)
Jensen 2008	NPRS	Over the past week	127	4.4 (2.4)	130	4.5 (2.8)				
Moshourab 2016	VAS	Not mentioned			35	42.0(22.0)				
van der Kooi 2007	VAS	Pain at the moment	65	16.1 (17.7)						

VAS, Visual analogue scale; NPRS, Numerical Pain Rating Scale; FSHD, Facioscapulohumeral muscular dystrophy; DM, Myotonic muscular dystrophy; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; LGMD, Limb-girdle muscular dystrophy.

Figure 8 Pooled mean of average pain intensity for FSHD

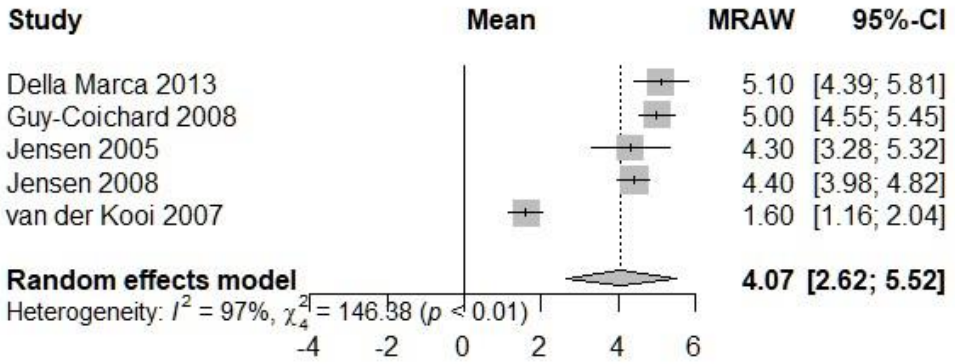


Figure 9 Pooled mean of average pain intensity for DM

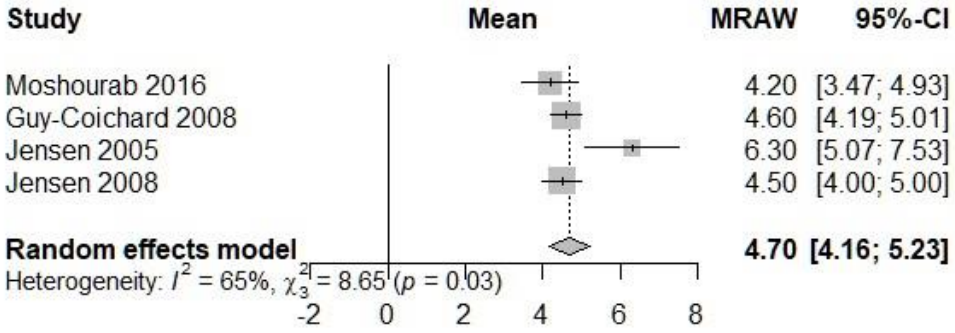
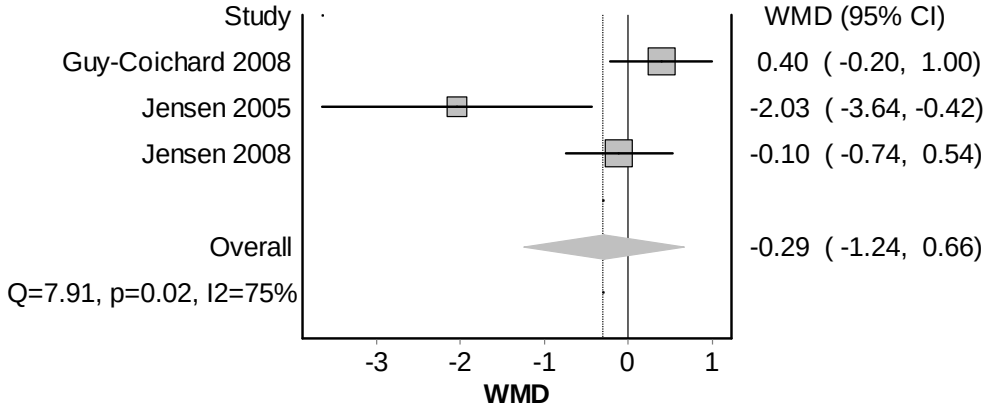


Figure 10 Group comparison of average pain intensity between FSHD and DM



Only one study reported data on the average intensity of chronic pain (evaluated by NPRS) in people with BMD/DMD (Guy-Coichard et al., 2008) and LGMD (Jensen et al., 2005), with mean (SD) values of 4.1 (2.3) and 5.25 (2.52), respectively.

Two articles reported pain intensity for the whole sample of people with pain (including acute and chronic pain) and data for the chronic pain subgroup only could not be extracted (Lager & Kroksmark, 2015; Tiffreau et al., 2006).

3.5.3 Pain severity

Five studies reported pain severity categories among participants (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Morís et al., 2018; van der Kooi et al., 2007), with four of them providing specific data on the percentages (Table 7). The RCT performed by van der Kooi et al. (2007) did not provided percentage data, instead only reporting that most participants with FSHD described their pain as mild to moderate when scores on a pain severity scale ranging from 0 (no pain) to 4 (severe pain). As presented in Table 7, three studies (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008) categorised pain severity based on the pain intensity assessed by a 0 (no pain) to 10 (pain as bad as it can be) NPRS while the remaining article considered the pain severe when reported as horrible or excruciating by the participants (Morís et al., 2018).

Within the FSHD diagnostic group, 19%-21% participants with chronic pain reported their pain as moderate, and 19% to 30% rated their pain as severe (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Morís et al., 2018). There was greater variability among participants with DM, with 11% to 28% reporting their pain as moderate, and 22% to 50% reporting severe pain (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008). The distribution of pain severity for the other two diagnostic groups was broadly comparable: BMD/DMD (24% moderate, 19% severe) (Guy-Coichard et al., 2008), and LGMD (39% moderate, 25% severe) (Jensen et al., 2005).

3.5.4 Pain location

Eight studies presented the percentages of participants with chronic pain (all FSHD and DM) who reported pain at different locations (as listed in Table 8; only studies with diagnosis specific data were presented) (Della Marca et al., 2013; George et al., 2004; Jensen et al., 2005; Jensen et al., 2008; Morís et al., 2018; Moshourab et al., 2016; Steel et al., 2019; van der Kooi et al., 2007). While some variation was apparent between the two diagnostic groups, the most frequently reported pain sites were similar, and often widespread, including lower back, shoulders, legs, hip, and knees. According to Guy-Coichard et al. (2008)'s findings, diffuse pain sites were seen in 45% of FSHD, 38% of DM, and 36% of BMD/DMD cases. Tiffreau et al. (2006) revealed an even higher proportion of widespread pain for the whole sample (including DM, FSHD, BMD/DMD, LGMD, and other NMDs; no independent data for each group), with 79% reporting at least two pain sites and 63% reporting at least three pain sites.

Results from the survey conducted by Jensen et al. (2008) demonstrated that there were significant differences in terms of the frequency of chronic pain at specific locations in shoulders, hips, and feet. Individuals with FSHD reported pain more frequent in their shoulders and hips and individuals with DM reported pain more frequent in their feet. However, findings from Tiffreau et al. (2006) suggested that pain locations did not differ between diagnostic groups (including DM, FSHD, BMD/DMD, LGMD, and other NMDs), with the most frequent pain site at the spinal column (81%), followed by shoulder (54%), hip (47%) and knee (47%), similar to the overall data presented in Table 7

Pain severity distribution reported by the included studies

es	FSHD			DM			BMD/DMD				
	Mild	moderate	Severe	Mild	moderate	Severe	Mild	moderate	Severe	Mild	m
chard *	49%	21%	30%	50%	28%	22%	57%	24%	19%		
005*	62%	19%	19%	39%	11%	50%				36%	
008*			23%			24%					
018§			30.4%								

FSHD, Facioscapulohumeral muscular dystrophy; DM, Myotonic muscular dystrophy; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; LGMD, Limb-girdle muscular dystrophy.
*Assessed by using NPRS (a 0 to 10 pain intensity scale) for participants with chronic pain. Moderate pain is pain rated as 5 or 6. Severe pain is pain rated as 7 or greater.
§The pain was considered to be severe when reported as horrible or excruciating.

Table 8.

3.5.5 Pain quality

Only three studies reported pain quality (George et al., 2004; Jensen et al., 2005; Moshourab et al., 2016). Two of them assessed the pain quality in people with DM by using MPQ pain descriptors (George et al., 2004; Moshourab et al., 2016). As reported by both articles, “tugging”, “cramping”, “dull” and “tiring” were the descriptors most frequently chosen by the participants with chronic pain. Of interest, a subgroup of individuals described their pain as “radiating” (35%) and “burning” (35%) (Moshourab et al., 2016).

Jensen et al. (2005) used the NPS (a list of 10 descriptors of pain quality) among participants with FSHD, DM, LGMD and other NMDs. Additionally, four descriptors (tiring, sickening, fearful, and punishing) extracted from the SF-MPQ were added to the list to assess the affective component of pain. Their findings suggested that “deep,” “tiring,” “sharp,” and “dull” descriptors were frequently used and were rated (on a 0 to 10 scale) as significantly higher than all the other pain descriptors, which were similar to

the results reported by George et al. (2004) and Moshourab et al. (2016). In contrast, pain descriptors that may indicate neuropathic pain such as were rated as significantly lower than others. Importantly, according to Jensen et al. (2005), it appeared that no clear pattern of pain description differentiating pain related to any 1 NMD diagnostic group from the others.

Table 7 Pain severity distribution reported by the included studies

Studies	FSHD			DM			BMD/DMD			LGMD		
	Mild	moderate	Severe	Mild	moderate	Severe	Mild	moderate	Severe	Mild	moderate	Severe
Guy-Coichard 2008*	49%	21%	30%	50%	28%	22%	57%	24%	19%			
Jensen 2005*	62%	19%	19%	39%	11%	50%				36%	39%	25%
Jensen 2008*			23%			24%						
Morís 2018§			30.4%									

FSHD, Facioscapulohumeral muscular dystrophy; DM, Myotonic muscular dystrophy; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; LGMD, Limb-girdle muscular dystrophy.
*Assessed by using NPRS (a 0 to 10 pain intensity scale) for participants with chronic pain. Moderate pain is pain rated as 5 or 6. Severe pain is pain rated as 7 or greater.
§The pain was considered to be severe when reported as horrible or excruciating.

Table 8 Pain location reported by the included studies

Location	FSHD						DM		
	Della Marca 2013	Jensen 2005	Jensen 2008	Morís 2018	Steel 2019	van der Kooi 2007	George 2004	Jensen 2008	Moshourab 2016
Head			14%					17%	
Face						5%			
Jaw							13%		
Neck	18%		57%			37%		44%	
Chest			10%					13%	
Abdomen			19%			8%		21%	
Back		78%			36%			23%	
Upper back			41%					31%	

Location	FSHD						DM		
	Della Marca 2013	Jensen 2005	Jensen 2008	Morís 2018	Steel 2019	van der Kooi 2007	George 2004	Jensen 2008	Moshourab 2016
Lower back	47%		74%			32%	74%	66%	
Shoulders		67%	69%	45%	27%	51%		49%	40%
Limbs	40%								
Limb girdles							65%		
Arms			40%			20%	74%	35%	
Elbows			19%					12%	
Forearms							52%		26%
Wrist			25%			14%		26%	
Hands			32%				17%	47%	
Buttocks		61%	20%					17%	
Hip			55%			14%		36%	
Thighs						22%	83%		46%
Knee			52%			9%	35%	43%	
Legs			72%				74%	64%	23%
Ankles			33%			35%		32%	
Feet			29%				22%	48%	

FSHD, Facioscapulohumeral muscular dystrophy; DM, Myotonic muscular dystrophy; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy.

3.5.6 Pain frequency and duration

Pain frequency and duration were reported by only two of the included studies (George et al., 2004; Guy-Coichard et al., 2008). Findings from George et al. (2004) in people with DM 2 (n=24) suggested that the majority of the participants with chronic pain experienced pain once or several times per week (78%), with nearly half of them experiencing the condition in a frequency of once or several times per day (48%). The duration of episodes varied from seconds to days, with most lasting for hours (87%), followed by seconds to minutes (83%), and days (65%) (George et al., 2004). However, different findings were presented by Guy-Coichard et al. (2008) who investigated the characteristics of chronic pain among several MD diagnostic groups: FSHD (n=121), DM(n=134), and BMD/DMD (132). No group differences relating to pain frequency and duration were found by diagnoses. For the whole sample, pain occurred daily or almost daily only in 3% of the participants with chronic pain, which was much lower than that reported by George et al. (2004). For the duration of pain episodes, 53% episodes were identified as lasting for less than one day, and 47% were lasting for more than one day (Guy-Coichard et al., 2008).

3.5.7 Pain interference

3.5.7.1 Daily life activities

Four studies investigated pain interference on daily life activities by using BPI (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Lager & Kroksmark, 2015).. Among adults with FSHD, DM and BMD/DMD, Guy-Coichard et al. (2008) found that overall pain interference was greatest in FSHD, followed by DM and DMD, while Jensen et al. (2008) reported no difference between FSHD and DM in overall pain interference. According to Guy-Coichard et al. (2008), among people with FSHD, DM and BMD/DMD, the domains most affected by pain were recreational activities and general activities (including occupational and domestic activities), followed by mobility and mood, while sleep and relationships with others were the least affected. Similarly, recreational activities were found most affected for participants with FSHD, DM, and LGMD (Jensen et al., 2005) and for participants with DM only (Jensen et al., 2008). However, in the latter study pain was found to interfere most on mobility in participants with FSHD, followed by recreational activities (Jensen et al., 2008).

Among boys with BMD/DMD general activity and mood were the domains most affected by pain, followed by mobility and (school)work, with sleep and relationships the least affected (Lager & Kroksmark, 2015).

3.5.7.2 Quality of life

Three studies explored the relationships between chronic pain and quality of life (QoL) (Jensen et al., 2005; Morís et al., 2018; Pangalila et al., 2015). Participants with FSHD, DM and LGMD who experienced pain tended to report significantly greater dysfunction in physical functioning, role-physical, bodily pain, general health, vitality, and social functioning than the normative sample of SF-36 in the US (Jensen et al., 2005). However, it was unclear whether the dysfunction was primarily caused by chronic pain or the disabling nature of the disorder itself, owing to the lack of comparison between participants with and without pain. Morís et al. (2018) examined the association of QoL with demographic factors and pain presence in people with FSHD by using multiple regression analysis. Their findings demonstrated that disease duration (Beta=0.17, P=0.003), presence of chronic pain (Beta=0.12, P=0.029) and the total score of MPQ (Beta=0.4, P=0.001) was directly related to an increase in the total INQoL scores (greater score indicating the greater impact on QoL) (adjusted R^2=0.284), suggesting that chronic pain had an important negative impact on the QoL in FSHD. In participants with DMD, those with chronic pain had higher odds of poor physical functioning (OR=2.75, 95%CI 1.35 to 5.62, P=0.005), but not overall poor QoL, according to the results of univariate logistic regression analysis (Pangalila et al., 2015).

3.5.7.3 Sleep quality

Only one study examined the impact of chronic pain on sleep quality, and only in FSHD (Della Marca et al., 2013). In the group of participants with pain, an increase in the amount of alpha electroencephalogram (EEG) activity during slow-wave sleep (SWS) (defined as Alpha-Sleep Anomaly) was detected, as compared with the no-pain group, suggesting that pain might interfere with the process of cortical synchronization during sleep. Additionally, the alpha-sleep anomaly showed a positive linear correlation with pain indexes: the VAS score, the Pain Rating Index (MPQ-PRI) and the MPQ-PPI. A trend of decreased sleep quality and increased daytime sleepiness was shown by the higher PSQI and ESS score in the pain group, but the difference was not statistically significant, compared to the no pain group.

3.5.7.4 Fatigue

The relationship between chronic pain and fatigue was explored in one study (van der Kooi et al., 2007). The mean CIS-fatigue score of the pain subgroup (30.1 ± 12.4) was higher compared to pain-free group (23.6 ± 9.7), but this difference was not statistically significant.

3.5.7.5 Depression and anxiety

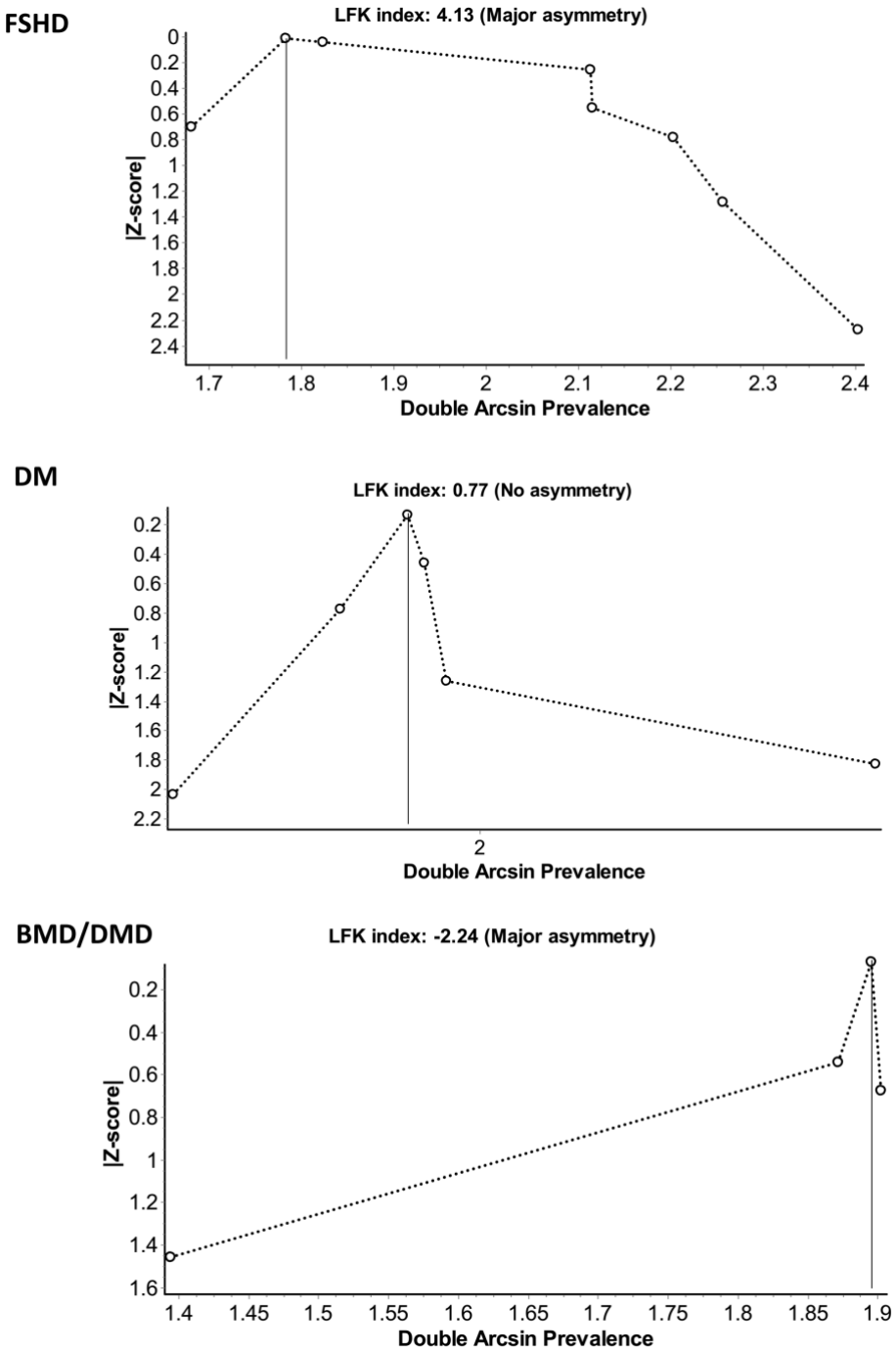
In FSHD, depressive symptoms of participants with chronic pain did not differ significantly when compared to the participants without pain (van der Kooi et al., 2007). Looking at the whole sample that involved a mixed population of MDs, there was a very low correlation between pain intensity and anxiety or depression scores (Tiffreau et al., 2006).

3.6 Publication bias

It was hypothesised that papers indicating greater prevalence of chronic pain in muscular dystrophies would be more likely to be published. A positive direction of bias for the LFK index was therefore selected a-priori (LFK index > 1).

Through visual checking and quantitative measure of Doi plots, major asymmetry were identified for the meta-analysis outcome of pain prevalence in the diagnostic groups of FSHD (LFK index: 4.13) (Figure 11), suggesting possible publication bias. No asymmetry was detected for the estimates of DM (LFK index: 0.77) or BMD/DMD (LFK index: -2.24) (Figure 11). Doi plot analysis for prevalence in LGMD was impossible owing to the limited number of studies, and the same applied for the pain intensity outcome in FSHD and DM.

Figure 11 Doi plots and LFX index using the double arcsin transformation of chronic pain prevalence by diagnostic groups



Chapter 4 Discussion

To our knowledge, this is the first review that systematically explores the prevalence, characteristics and impact of chronic pain in people with MDs. It is also the first to attempt to quantitatively synthesise the prevalence data by diagnostic groups in this population.

4.1 Prevalence of chronic pain in MDs

Based on the findings of the present study, chronic pain is a very common and frequent issue in population with MDs. The estimated prevalence of chronic pain seems to be similar across diagnostic groups: 68% in FSHD, 65% in DM, 62% in BMD/DMD, and 60% in LGMD, since no statically significant differences were detected. These figures are considerably higher than the estimates of the prevalence of chronic pain in the general population established by the study of World Health Organization in 1998 (with a prevalence estimated to be 22%) (Gureje et al., 1998), and in some regional or national studies, such as 37.3% of the population across developed countries (Tsang et al., 2008) and 43% people in the UK (Fayaz et al., 2016) who are estimated to experience chronic pain. Participants of the included studies are mostly adults and are mainly from Europe and the USA. While FSHD and DM are the most frequently investigated disorders, information of BMD/DMD and LGMD is relatively limited, with the remaining diagnostic groups including CMD, EDMD, OPMD and Distal MDs barely explored.

In people with FSHD, a high number of studies (n=8) allowed us to explore possible sources of heterogeneity in prevalence estimates. Of interest, the prevalence rate of chronic pain in FSHD appeared to decrease from a pooled estimate of 79% in the 2000s to 57% in the 2010s. Due to the lower number of studies published in recent years and the significant heterogeneity among these studies (Figure 4), we cannot be confident that a true reduction of chronic pain prevalence has occurred over time. However, over the past ten years, the field of neuromuscular disorders has gained increased attention from health professionals and researchers, and evidence based guidelines have been developed to advise standards of care and management of patients with FSHD (Attarian et al., 2012; Tawil et al., 2015; Tawil et al., 2010). Adoption of evidence-based guidelines and improvement in long-term care and management of the disorder, may have resulted in a reduced prevalence of chronic pain. Furthermore, the recognition of chronic pain in FSHD in the 2000s (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Tiffreau et al., 2006) may have led to better recognition of pain as an important problem

in people with FSHD among health professionals, and, subsequently, improved pain management that may also have contributed to a decreasing prevalence in the following decade.

There is some evidence of geographical variation regarding chronic pain prevalence in FSHD, with the highest pooled prevalence estimate in America (82%), followed by France (75%) and the UK (56%). This geographical difference may be ascribed to genetic differences, the methods of data retrieval and/or possible publication bias. Firstly, it is possible that variations in prevalence could reflect genetic differences between populations. However, other factors may also have an important influence. Notably, studies of the American (n=2) and French (n=2) FSHD population were undertaken using cross-sectional surveys. The two studies conducted in the UK were both retrospective analyses. One analysed patient-reported data obtained from the UK FSHD Patient Registry (Morís et al., 2018), while the other reviewed clinical records of children with FSHD in a single paediatric neuromuscular disorder centre (Steel et al., 2019). As mentioned by both articles, information on pain was not always available for each participant. Thus, it is possible that people with chronic pain were not documented in the registry or clinical records and the UK studies provide an underestimate of the true population prevalence. Alternatively, the possibility of publication bias was identified for prevalence estimates in FSHD, with the LFK index suggesting that studies with a higher prevalence of chronic pain were more likely to be published. Thus, it is possible that publication bias is at least partly responsible for the greater prevalence of chronic pain observed in people with FSHD in the USA and France.

We are unable to quantitatively analyse other potential moderating factors that could also probably impact the prevalence such as recall period, age and gender due to the limited number of studies or missing data. It is important to note that several MDs including BMD, DMD, FSHD and DM (juvenile form) have an age of onset in childhood and adolescence. However, only 2 of the included studies (Lager & Kroksmark, 2015; Steel et al., 2019) attempted to capture pain outcomes in children or adolescents, with most including only adult populations. In the general population, the prevalence of chronic pain increases with age (Fayaz et al., 2016), which has also been detected in populations with a specific phenotype such as chronic low back pain (LBP) (Meucci et al., 2015) and chronic widespread pain (CWP) (Mansfield et al., 2016). It is unknown whether this pattern is applicable to MDs as well. Jensen et al. (2008) attempted to analyse the relationship between age and the incidence of chronic pain in people with FSHD and DM.

According to their findings, age seems not to impact pain in a significant way in these populations. Since MD is a group of inheritable muscular conditions with a progressive clinical course, an association may be more likely to be seen between chronic pain and disease duration (or the age of onset) instead of the current age. However, findings from Morís et al. (2018)'s investigation suggest that there is no correlation between chronic pain and current age, age of onset or disease duration in individuals with FSHD. This study is also the only investigation that explored differences by gender. As reported by Morís et al. (2018), chronic pain tends to be more prevalent in women with FSHD, in line with the findings of other systematic reviews examining pain prevalence in the general population (Heidari et al., 2017; Mansfield et al., 2016; Meucci et al., 2015). This is an interesting finding because gender influences the clinical expression of FSHD in an opposite way, with males normally presenting with an earlier onset of motor impairment and more severe disability (Ricci et al., 2013).

4.2 Characteristics of chronic pain in MDs

To our knowledge, this is the first attempt to synthesise estimates of pain intensity in MDs and perform a group comparison across diagnoses using meta-analysis.

Chronic pain intensity appears to range from mild to severe across people with FSHD and DM. The average pain intensity was typically moderate, with a mean value of 4.1 in FSHD and 4.7 in DM, and no differences observed between groups. Among studies of FSHD, the RCT conducted by van der Kooi et al. (2007) reported relatively lower average pain intensity of 1.6 compared to estimates from other studies, which ranged from 4.3 to 5.1. This is likely due to the inclusion criteria adopted, with participants required to walk independently, suggesting a population with less advanced disease and relatively mild disability that may also explain their lower pain ratings.

The proportion of people reporting severe chronic pain ranged from 19%-30% in FSHD, and 22% to 50% in DM. As suggested by Jensen et al. (2005), who attempted to evaluate chronic pain in a number of diagnostic groups of MDs, it appears that people with DM more frequently experience severe pain than other MDs such as FSHD and LGMD. The underlying reasons for this remain unknown. The distinct nature of DM with predominant myotonia, myalgia and multisystemic involvement (e.g. diabetes in the latter stage of DM1 (Ashizawa & Sarkar, 2011), which could lead to diabetic peripheral neuropathy) may contribute to the high frequency of severe chronic pain. Studies that assess pain intensity and severity in BMD/DMD and LGMD are very limited. BMD/DMD seems to

be the diagnostic group with the least proportion (19%) of participants who report severe pain, as supported by the only study that provides relevant data (Guy-Coichard et al., 2008).

Findings of pain frequency and duration of episode suggest chronic pain is a significant burden of people with MDs. It is particularly intense in people with DM2, as nearly half of them may experience the condition once or several times per day, with more than half of the episodes lasting for days (George et al., 2004). The near ubiquitous presence of myalgia in DM2 (Ashizawa & Sarkar, 2011; Suokas et al., 2012) may be responsible for this phenomenon.

Lower back, shoulder and legs are the most frequent sites of chronic pain among people with FSHD, DM, BMD/DMD, and LGMD. These localities reflect the body areas that are most commonly affected by these MDs. In FSHD, sustained abnormal postures are thought to contribute to pain in the shoulder and lower back, with protracted shoulders, winging scapula and exaggerated lumbar lordosis commonly observed as a consequence of muscle weakness and imbalance (Morís et al., 2018). Pain located in hands and feet is more frequently seen in people with DM1 than other diagnostic groups (Jensen et al., 2008). DM1 is a distal myopathy, along with the skeletal muscles, muscles of hands and feet can also be affected early in the disease course (Udd & Krahe, 2012). Unlike DM1, proximal limb muscles are primarily affected in DM2. Thus, in this form of the disorder, pain in limb girdles, arms and thighs are more common than in distal limbs (George et al., 2004). Moreover, a notable proportion of the individuals with FSHD (45%), DM (38%), and BMD/DMD (36%) have reported more than two pain sites (Guy-Coichard et al., 2008).

No clear pattern of pain descriptors relating to a specific diagnostic group of MDs could be identified from the included studies. “Tugging”, “sharp”, “dull” and “tiring” were the most common descriptors used. A subgroup of individuals described their pain as “radiating” (35%) and “burning” (35%), indicating the possibility of neuropathic pain in some forms of MDs (Moshourab et al., 2016). However, it is not possible to define the phenotypes of chronic pain (nociceptive or neuropathic) in these diseases only based on descriptors from the MPQ or NPS scales. To diagnose neuropathic pain and distinguish it from nociceptive pain, a more standardised diagnostic assessment is needed (Baron et al., 2010). As the underlying pathophysiological mechanisms (Woolf & Mannion, 1999) and first line treatments (Gilron et al., 2015) are distinct, the differentiation between

neuropathic pain and nociceptive pain should be further explored in future studies as it may be critical for planning effective pain mechanism-based treatment(s) in people with MDs.

4.3 Impact of chronic pain in MDs

Chronic pain has a negative impact on activities of daily living in people with MDs, and may also contribute to decreased quality of life. According to the findings from the BPI, occupational and domestic activities, recreational activities and mobility are daily life domains with the highest levels of pain interference in people with MDs, similar to the findings from the survey of the general population in Europe that chronic pain seriously affects the various domains of daily and working lives (Breivik et al., 2006).

Emotional aspects such as mood generally seem to be less affected by pain (Guy-Coichard et al., 2008; Jensen et al., 2005; Jensen et al., 2008; Lager & Kroksmark, 2015; Tiffreau et al., 2006) and poorly correlated to pain intensity across a range of MDs (Tiffreau et al., 2006). However, the evidence supporting this conclusion is limited and it is notable that only two studies included specific measures of depression and/or anxiety and attempted to relate these to pain outcomes (Tiffreau et al., 2006; van der Kooi et al., 2007). Interestingly, in contrast to other studies, among youngsters with BMD (mean age 14.2 (2.3) years) and DMD (mean age 15.6 (2.1) years), mood appears to be one of the BPI domains most affected by pain and have a moderate correlation with the average pain intensity (Lager & Kroksmark, 2015). This may indicate that children and adolescents are more likely to experience emotional distress as a consequence of chronic pain compared to adults with MDs. This could relate to several factors, including their environment and/or ability to regulate emotion. For example, following general activities, mood and mobility, schoolwork was another aspect frequently impacted by chronic pain (Lager & Kroksmark, 2015). It has been highlighted that school impairment (e.g. poor school attendance, decreased academic performance and competence) could be a significant source of anxiety and depressive mood among adolescents with chronic pain (Jastrowski Mano, 2017). Another possibility could be the developing nature of children and adolescents, who may be less able to regulate their mood, and thus more easily emotionally influenced by their present condition (Connelly et al., 2011; Tottenham et al., 2011).

It is a consistent finding from studies using the BPI that sleep is the least affected domain by chronic pain in different forms of MDs. This is supported by the one study that

specifically explored the relationship between sleep quality and chronic pain in FSHD (Della Marca et al., 2013). While objective differences in sleep quality were observed, self-reported differences were not greatly affected by the presence of pain.

According to the limited findings from this review, it appears the presence and severity of chronic pain may have an important negative impact on quality of life in people with FSHD, which, along with disease duration, may contribute to a significant proportion of decreased QoL (Morís et al., 2018). However, among adults with DMD, chronic pain does not appear to impact overall QoL, as physical functioning seems to be the only domain associated with the presence of chronic pain (Pangalila et al., 2015). Taken together, these findings suggest that there may be an association between the presence of chronic pain and decreased quality of life in people with MDs, but further research is required to support these findings. Notably, features of chronic pain (e.g. intensity, location, quality) with the greatest impact on quality of life have been barely explored, and would be important to include in future studies.

4.4 Strengths and limitations of the research

This is the first systematic review that has explored the prevalence, characteristics and impact of chronic pain in different forms of MD and is the first review to explore differences in pain prevalence and intensity across diagnoses using meta-analysis. Our findings highlight the prevalence and severity of chronic pain across MD populations and emphasise the need for better recognition and understanding of the nature and impact of pain in the effective management of these conditions.

There are several limitations of the present research. Firstly, the studies included in this review were most targeted at the adult population with FSHD and DM and were largely conducted in Europe and the USA. As such, information on the nature and scope of chronic pain among other diagnostic groups, in other regions of the world, and among children and teenagers is limited. Secondly, the tests for statistical heterogeneity among estimates of pain prevalence in FSHD and DM demonstrated high variability between studies. There were limited opportunities to explore sources of this variability because of the insufficient number of studies for comparison and a lack of variability in the characteristics of the included studies. Overall, the risk of bias of the included studies in this review was moderate to low. However, nearly half of the included studies had high risk of selection bias and nonresponse bias. Five of the 12 included studies recruited their participants from either an NMD clinic or training centre, and researchers were often

deemed to use an inappropriate sampling method (a convenience sample) while selecting participants. Moreover, one study (van der Kooi et al., 2007) only included FSHD participants with the ability to walk independently and defined levels of strength in specific muscle groups, which is not representative of the target population. Response rates of the survey studies (ranging from 45-78%) were generally low, with only one survey (Jensen et al., 2008) matching the criteria of low-risk response rate (>/=75 %) based on the appraisal tool utilised to assess study quality (Hoy et al., 2012). Nevertheless, none of these surveys performed an analysis to compare relevant demographic characteristics between responders and non-responders, and thus, were exposed to high risk of non-response bias. These biases may generate a sample that is not representative of the national population or the general population of the target disorder, which, therefore, hinders the generalisability of our findings. Furthermore, the possibility of publication bias was detected concerning estimates of pain prevalence in FSHD, with studies reporting high pain prevalence more likely to be published. This may explain part of the high heterogeneity presented across estimates of FSHD. Finally, due to limitations in the number of studies and outcome measures utilised, this review was not able to provide a clear appreciation on the most common causes of pain problems or whether different phenotypes of chronic pain (e.g. neuropathic vs nociceptive pain) exist in people with MDs.

4.5 Strengths and limitations of the methodology

This systematic review was performed by strictly following the guideline of PRISMA. We utilised a meta-analysis approach to provide a more precise estimate of pain prevalence and average pain intensity and allow a meaningful comparison of these outcomes between diagnostic groups. A risk of bias tool specifically developed for prevalence studies was used to evaluate the quality of included studies, where studies with high risk of bias were directed to sensitivity analysis to assess their impact on relevant findings. Double arscin transformation was applied while pooling prevalence estimates to address the problems derived from prevalence rates close to the extreme limits of 0…1 range. We utilised a quality effect model which favours studies with larger sample size and lower risk of bias to generate the pooled prevalence, in order to minimise the impact of estimates from studies with high risk of bias. Where possible, subgroup analyses were performed to explore potential sources of heterogeneity.

There are several limitations concerning the methods of the present study. First of all, missing data could be a substantial issue. Ten studies did not report independent data on individual diagnostic groups involved or did not fully report the outcomes of interest. We contacted the authors of these studies, but unfortunately, we were unable to obtain the data as requested owing to either no response or a response with data not available, so we had to exclude them. Secondly, we did not blind the reviewers from the author information of each article while scoring the risk of bias of the included studies. Finally, while definitions of chronic pain employed by most included studies were in line with that published by the International Association for the Study of Pain (IASP) in 2015 (Treede et al., 2015), one study used an old definition of chronic pain from IASP (Merskey, 1986) that apart from a duration of persisting for three months, a frequency of at least once per week was added to as an extra requirement of defining chronic pain. However, the estimate of chronic pain prevalence in this article was comparable with estimates from most of the other studies.

Chapter 5 Implications for practice

Findings from this review indicate that chronic pain is a common and significant problem in people with MDs interferes with daily life activities across various domains and may negatively impact quality of life. Despite this, pain in these people seems to be under-recognised and undertreated in clinical practice (Jensen et al., 2005; Zebracki et al., 2008). Several factors may contribute to this problem. These include a lack of knowledge of the nature and impact of pain in people with MDs among health professionals and the primacy of the progressive loss of motor function, where pain may not be viewed as the most disabling aspect in most conditions. Furthermore, assessing pain in these populations may pose unique challenges when dealing with children or people with cognitive and communication impairments, which are not uncommon in many types of MDs (Ashizawa & Sarkar, 2011; Mercuri & Muntoni, 2013).

This review highlights the importance of systematically assessing and recognising pain among all individuals with MDs. Clinical assessment should differentiate between acute and chronic pain, and between different phenotypes of chronic pain as the optimal treatment may differ according to the underlying causes and mechanisms of pain. For example, chronic musculoskeletal pain caused by abnormal postures or contractures would require different interventions than acute pain resulting from wearing an unfitted thoracic orthosis and would also be different from neuropathic pain that may result from nerve impingement or peripheral diabetic neuropathy. While a quick distinction can be drawn between chronic and acute pain by referring to the duration of pain, to differentiate neuropathic from nociceptive (and nociplastic) pain can be a challenging task. To do this, a standardised diagnostic assessment is required (Baron et al., 2010; Dworkin et al., 2003). Screening tools such as the Douleur Neuropathique en 4 questions (DN4) and Leeds Assessment of Neuropathic Signs and Symptoms (LLANS) can help identify potential patients with neuropathic pain (Bennett et al., 2007). Thereafter, a thorough physical and neurological examination assists to localise the lesion and evaluate the nature of the person's pain, which should include a standardised bedside examination for sensory symptoms with components of touch, pin prick, pressure, cold, heat, vibration, and temporal summation (Baron et al., 2010). Diagnosis of neuropathic pain is usually confirmed by a neuroanatomically plausible pain location, laboratory tests suggesting a specific cause and the presence of negative and positive sensory signs in the same area of innervation (Dworkin et al., 2003; Treede et al., 2008).

Clinical assessment should address multidimensional aspects of pain, considering the specific context of the person with the disorder. Evaluation of the nature of pain should include pain intensity, severity, location, frequency, duration of episode, quality (sensory and affective descriptors), relieving and aggravating factors, and response to pain treatment, and measurements of pain impact should cover various physical and psychosocial domains of the person's life. The most disabling features of pain and the most significantly interfered life domains may differ between individuals, and thus it is critical to obtain a comprehensive insight of these pain aspects to develop an individualised pain management plan and identify important outcome measures of effectiveness. Specific considerations should be given to pain assessment among children and people with cognitive and communication impairments (Buffum et al., 2007; Herr et al., 2011). While assessing pain among the child population with MDs, health professionals should select self-report measures of pain and related measures that reflect the child's age, as well as language and cognitive development (Engel et al., 2005; Stinson et al., 2006). For instance, while the Faces Pain Scale-Revised a better option for evaluating pain intensity in children between aged 4 and 12 years, a 100mm VAS is often recommended for children over 8 years of age and adolescents (Stinson et al., 2006). Proxy reporting from parents or caregivers is normally recommended in the case that the child is unable to self-report (Herr et al., 2011). Individuals with cognitive deficits may have difficulties in completing and comprehending verbal pain measurements such as self-report pain rating scales and associated questionnaires. In this case, behavioural observation-based pain assessment is recommended as best practice (Buffum et al., 2007). Health professionals rate the presence or absence, intensity, duration, or frequency of pain behaviours in a behavioural observation scale through observing the patient (Persons, 2002). For people with impairments in speech, clinicians should consider the employment of assistive technology such as an augmentative and alternative communication (AAC) system (Ball et al., 2012) to help the person to more clearly communicate their pain and associated problems.

The nature of chronic pain across different diagnostic groups of MDs tends appears to be fairly similar. However, some important variations exist, especially in pain location which is associated with the body areas frequently affected by these conditions. Since there is a clear pattern of pain localisation, preventive interventions such as the use of a well-fitting orthoses (Bushby et al., 2010; de Souza et al., 2016; Hyde et al., 2000), stretching and supervised physical training (Jansen et al., 2013) can be targeted at the commonly

involved areas including lower back, shoulders and legs for the general population of MDs. This may help reduce pain caused by abnormal postures and muscle contracture. Regarding people with DM, attention should also be paid to their hands and feet, which often suffer from painful muscle cramping because of myotonia.

Considering the progressive and disabling nature of MDs, the multifactorial mechanisms of chronic pain and its significant impact on various life domains of the person affected, a plan of care for pain management and prevention needs to be developed in collaboration with the multidisciplinary team. Pain in these populations should be routinely assessed through disease progression, with pain management being part of the standard of care for all affected individuals. Apart from pain control, interventions should also address the disabilities related to pain which include limitations in physical activities, impairments in school functioning (of youths) and social participation, , and the potential for emotional distress and depressive symptoms. Such an approach may both reduce pain and help to improve the various domains of life experience that can be impacted by pain.

Chapter 6 Recommendations for future research

This review highlighted several gaps for future research. To address the frequent sample bias and improve the quality and reporting of epidemiological data, futures studies of chronic pain in different forms of MD should be undertaken based on a national population and following standardised methods for data collection and reporting, such as the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2007). Efforts should be made to maximise response rates and, where possible, statistical comparison should be made between responders and non-responders to evaluate possible responder bias. Additional studies of chronic pain in lesser explored MDs (including CMD, EDMD, OPMD and Distal MDs), geographic regions outside the USA and Europe and younger age groups will also be needed. The latter point be especially relevant for DMD and BMD, which mainly affect children and adolescents. Importantly, pain and related outcomes measures should be presented separately for different diagnoses, rather than pooled across all MDs. These efforts may strengthen the generalisability of the present findings to the wider population of people suffering from MDs and allow important comparisons across different diagnostic groups.

In the interests of developing a full picture of the nature of chronic pain among people with MDs, future studies with an additional focus on pain phenotypes (e.g. neuropathic vs nociceptive pain) and the associated response to treatments are recommended. We would encourage future clinical trials of pain management to adhere to the recommendations on core outcome measures of chronic pain developed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group (Dworkin et al., 2005), thus addressing the presence and intensity of pain as well as its multidimensional impact on physical and emotional functioning, and the person's global impression of change in response to the intervention.

Age and gender are possible moderators of the presence and impact of chronic pain among people with MDs. Future population studies that explore pain related outcome measures across age groups and gender, are therefore suggested. Finally, while it is clear that most individuals with MDs experience significant limitations in physical function, participation and decreased quality of life, it is not yet clear to what extent chronic pain contributes to these limitations compared to other impairments such as loss of muscle strength, reduced range of motion and psychological factors. Since existing evidence is limited, future work is required to address this important issue.

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Appendices

Appendix A Search strategy

PubMed

#1 "Muscular dystrophies" [mh]

#2 "Muscular dystroph*".tw

#3 "Myotonic dystroph*".tw

#4 "Distal Myopath*".tw

#5 "Facioscapulohumeral Dystrophy".tw

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 "Chronic pain" [mh]

#8 Pain.tw

#9 (Chronic OR persistent OR "long term" OR long-term).tw

#10 #7 OR (#8 AND #9)

#11 #6 AND #10

#12 Sort by best match

MEDLINE – via EBSCO

S1 MH "Muscular Dystrophies +"

S2 "Muscular dystroph*" OR "Myotonic dystroph*" OR "Distal Myopath*" OR "Facioscapulohumeral Dystrophy"

S3 S1 OR S2

S4 MH "Chronic Pain"

S5 Pain

S6 Chronic OR persistent OR "long term" OR long-term

S7 S4 OR (S5 AND S6)

S8 S3 AND S7

CINAHL – via EBSCO

S1 MH "Muscular Dystrophy +"

S2 "Muscular dystroph*" OR "Myotonic dystroph*" OR "Distal Myopath*" OR "Facioscapulohumeral Dystrophy"

S3 S1 OR S2

S4 MH "Chronic Pain"

S5 Pain

S6 Chronic OR persistent OR "long term" OR long-term

S7 S4 OR (S5 AND S6)

S8 S3 AND S7

CENTRAL

#1 MeSH descriptor: [Muscular dystrophies] explode all trees

#2 "Muscular dystroph*":ti,ab,kw (Word variations have been searched)

#3 "Myotonic dystroph*":ti,ab,kw (Word variations have been searched)

#4 "Distal Myopath*":ti,ab,kw (Word variations have been searched)

#5 "Facioscapulohumeral Dystrophy":ti,ab,kw (Word variations have been searched)

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 MeSH descriptor: [Chronic pain] explode all trees

#8 Pain:ti,ab,kw (Word variations have been searched)

#9 (Chronic OR persistent OR "long term" OR long-term):ti,ab,kw (Word variations have been searched)

#10 #7 OR (#8 AND #9)

#11 #6 AND #10

#12 Trials

Scopus

#1 TITLE-ABS-KEY ("Muscular dystroph*" OR "Myotonic dystroph*" OR "Distal Myopath*" OR "Facioscapulohumeral Dystrophy")

#2 TITLE-ABS-KEY (chronic OR persistent OR "long term" OR long-term)

#3 TITLE-ABS-KEY (pain)

#4 #1 AND #2 AND #3

Web of Science

1. TS=("Muscular dystroph*" OR "Myotonic dystroph*" OR "Distal Myopath*" OR "Facioscapulohumeral Dystrophy")
2. TS=Pain
3. TS=(chronic OR persistent OR "long term" OR long-term)
4. 1 AND 2 AND 3
5. Articles

Allied and Complementary Medicine Database (AMED)

1. Muscular dystroph*.mp
2. Myotonic dystroph*.mp
3. Distal Myopath*.mp
4. Facioscapulohumeral Dystrophy.mp
5. 1 OR 2 OR 3 OR 4
6. Pain.mp
7. Chronic OR persistent OR long term OR long-term.mp

5 AND 6 AND 7