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Systematic review

# Effectiveness of conservative non-pharmacological interventions in people with muscular dystrophies: a systematic review and meta-analysis

Enza Leone <sup>1</sup>, Anand Pandyan,<sup>2</sup> Alison Rogers,<sup>1</sup> Richa Kulshrestha,<sup>3</sup> Jonathan Hill,<sup>4</sup> Fraser Philp<sup>5</sup>

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<sup>1</sup>School of Allied Health Professions, Keele University, Keele, Staffordshire, UK

<sup>2</sup>Faculty of Health and Social Sciences, Bournemouth University, Bournemouth, UK

<sup>3</sup>Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, Oswestry, UK

<sup>4</sup>School of Medicine, Keele University, Keele, UK

<sup>5</sup>School of Health Sciences, University of Liverpool, Liverpool, UK

## Correspondence to

Enza Leone, School of Allied Health Professions, Keele University, Keele, Staffordshire, ST5 5BG, UK; [e.leone@keele.ac.uk](mailto:e.leone@keele.ac.uk)

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## ABSTRACT

**Introduction** Management of muscular dystrophies (MD) relies on conservative non-pharmacological treatments, but evidence of their effectiveness is limited and inconclusive.

**Objective** To investigate the effectiveness of conservative non-pharmacological interventions for MD physical management.

**Methods** This systematic review and meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and searched Medline, CINHAL, Embase, AMED and Cochrane Central Register of Controlled Trial (inception to August 2022). Effect size (ES) and 95% Confidence Interval (CI) quantified treatment effect.

**Results** Of 31,285 identified articles, 39 studies (957 participants), mostly at high risk of bias, were included. For children with Duchenne muscular dystrophy (DMD), trunk-oriented strength exercises and usual care were more effective than usual care alone in improving distal upper-limb function, sitting and dynamic reaching balance (ES range: 0.87 to 2.29). For adults with Facioscapulohumeral dystrophy (FSHD), vibratory proprioceptive assistance and neuromuscular electrical stimulation respectively improved maximum voluntary isometric contraction and reduced pain intensity (ES range: 1.58 to 2.33). For adults with FSHD, Limb-girdle muscular dystrophy (LGMD) and Becker muscular dystrophy (BMD), strength-training improved dynamic balance (sit-to-stand ability) and self-perceived physical condition (ES range: 0.83 to 1.00). A multicomponent programme improved perceived exertion rate and gait in adults with Myotonic dystrophy type 1 (DM1) (ES range: 0.92 to 3.83).

**Conclusions** Low-quality evidence suggests that strength training, with or without other exercise interventions, may improve perceived exertion, distal upper limb function, static and dynamic balance, gait and well-being in MD. Although more robust and larger studies are needed, current evidence supports the inclusion of strength training in MD treatment, as it was found to be safe.

## INTRODUCTION

Muscular dystrophies (MD) have an estimated prevalence ranging between 19.8 and 25.1/100,000.<sup>1</sup> MD are a clinically and genetically heterogenous group of muscle disorders, sharing common dystrophic pathological features, such as variable muscle

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The management of muscular dystrophies (MD) primarily rely on conservative non-pharmacological interventions, including strength and aerobic training, orthotic devices, aids and assistive technologies, as there is currently no cure to halt MD progression. However, evidence supporting the effectiveness of these conservative non-pharmacological interventions is limited and inconclusive. This systematic review and meta-analysis was undertaken to better understand the effectiveness of these interventions on the physical manifestations of MD, including non-randomised and uncontrolled studies, which constitute the predominant body of literature in this field but have been omitted from prior evidence syntheses.

## WHAT THIS STUDY ADDS

⇒ This study revealed that strength training, alone or combined with other exercise interventions, may improve perceived exertion, distal upper limb function, static and dynamic balance, gait and well-being in individuals with MD despite no significant structural changes.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These positive findings, although based on low-quality evidence, have possible clinical implications as they contradict historical apprehensions about the potential harm associated with exercise interventions in MD. Therefore, our findings suggest that strength training, whether as a standalone intervention or within a multicomponent programme, should be considered a fundamental component in the treatment of MD.

fibre size and necrosis, resulting in fatty or fibrotic tissue replacement and progressive muscle wasting and weakness.<sup>2,3</sup> MD are commonly progressive and disabling over time, despite differences in their rate and pattern of progression with variation in how the limb, axial, facial, ocular and pharyngeal muscles are affected.<sup>4</sup> Specific MD forms can also affect respiratory and cardiac muscles.<sup>5</sup> These result

in people with MD experiencing reduced motor functioning, social participation and quality of life.<sup>6</sup>

There is no cure to halt MD progression despite therapeutic advances in the most common forms of MD in the last two decades.<sup>7</sup> Individuals with MD rely on surgical and non-pharmacological treatments, including strength and aerobic training, orthotic devices, aids and assistive technologies.<sup>8</sup> Although conservative non-pharmacological interventions are essential part of the MD management, evidence supporting their effectiveness is limited and inconclusive.<sup>9–10</sup> Despite some common impairments between MD, there may be pathobiological mechanisms unique to each MD subtype.<sup>2</sup> Therefore, the effectiveness of an intervention may not be transferrable between MD subtypes as the therapeutic mechanism may not be optimal. Conservative interventions require appropriately tailoring to the symptoms and abilities of individuals with MD in order to be beneficial and not harmful. Inappropriate intervention type and dose can lead to detrimental effects, such as overwork weakness, fatigue, discomfort and pain.<sup>11</sup>

A wider understanding of the effects of conservative non-pharmacological interventions in people with MD is needed. This systematic review and meta-analysis aimed to determine the effectiveness of existing interventions, focusing only on those targeting physical impairments, excluding respiratory management.

## METHODS

This systematic review with meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>12</sup> The review protocol was not registered.

### Literature search strategy

Medline, CINAHL, Embase, AMED and the Cochrane Central Register of Controlled Trial were systematically searched from inception to 22 August 2022. The search was supplemented by searching the reference lists of relevant articles and reviews. Search strategies available in online supplemental file 1.

### Study selection process

Records were exported into a reference management tool (Mendeley, Elsevier B.V.) and duplicates were removed. Any remaining duplicates were removed manually. One reviewer (EL) screened the records, with verification by two other researchers (FP, AP). Records were initially screened by title and abstract, followed by full-text analysis of relevant studies.

### Inclusion and exclusion criteria

Studies were included if (1) involved humans with MD or neuromuscular diseases (NMD), data were separate for MD, (2) investigated conservative non-pharmacological interventions, alone or combined with other conservative non-pharmacological therapies, (3) had  $\geq 5$  participants per group, (4) had full texts available and (5) published in peer-reviewed journals.

Studies were excluded if (1) included pharmacological or surgical treatments, (2) unavailable data, (3) assessed conservative non-pharmacological interventions for respiratory and cognitive manifestations and (4) solely focused on non-pertinent outcomes (e.g. respiratory and cognitive outcomes).

Authors were contacted for missing data. If no response or unextractable data, studies were excluded.

### Data extraction

One reviewer (EL) extracted data (online supplemental file 2). Non-English articles were translated by the research team where appropriate.

### Quality assessment

Two reviewers (EL, FP) independently assessed the methodological quality of the included Randomised Controlled Trials (RCTs) using the Cochrane 'Risk of Bias' Tool.<sup>13</sup> Studies with research designs other than RCT are by nature at high risk of bias, and so no formal quality appraisal was undertaken. Uncertainties and disagreements between reviewers were resolved in team discussions.

### Statistical analysis

ES was calculated using Cohen's *d* formula.<sup>14</sup> As most available evidence comes from non-randomised, uncontrolled studies, ES calculation was performed in all studies, including quasi-controlled studies, although they were a priori considered at high risk of bias. Further information about ES calculation is provided in online supplemental file 3. The absolute magnitude of ES was classified as small (0.20–0.49), medium (0.50–0.79), large (0.80–1.29) and very large ( $\geq 1.3$ ).<sup>14</sup> If the 95% Confidence Interval (CI) range of the ES did not include zero, the result was considered statistically significant. Included studies were primarily clustered based on the type of intervention tested (orthotic devices, manual therapy, assistive technologies and exercise interventions), secondly by intervention subtype.

ESs were reported for the intervention types and subtypes, and outcomes were mapped to the International Classification of Functioning, Disability and Health (ICF).<sup>15</sup> Formal heterogeneity assessment was not conducted as statistical heterogeneity was expected due to variability in sample sizes, MD type, conservative non-pharmacological treatment types and outcome measures. Following data extraction, ES data were normalised. Regardless of the direction of change in the outcome, positive signs were used to represent positive changes from baseline, while negative signs were used to indicate negative changes with scores worsening compared with baseline.

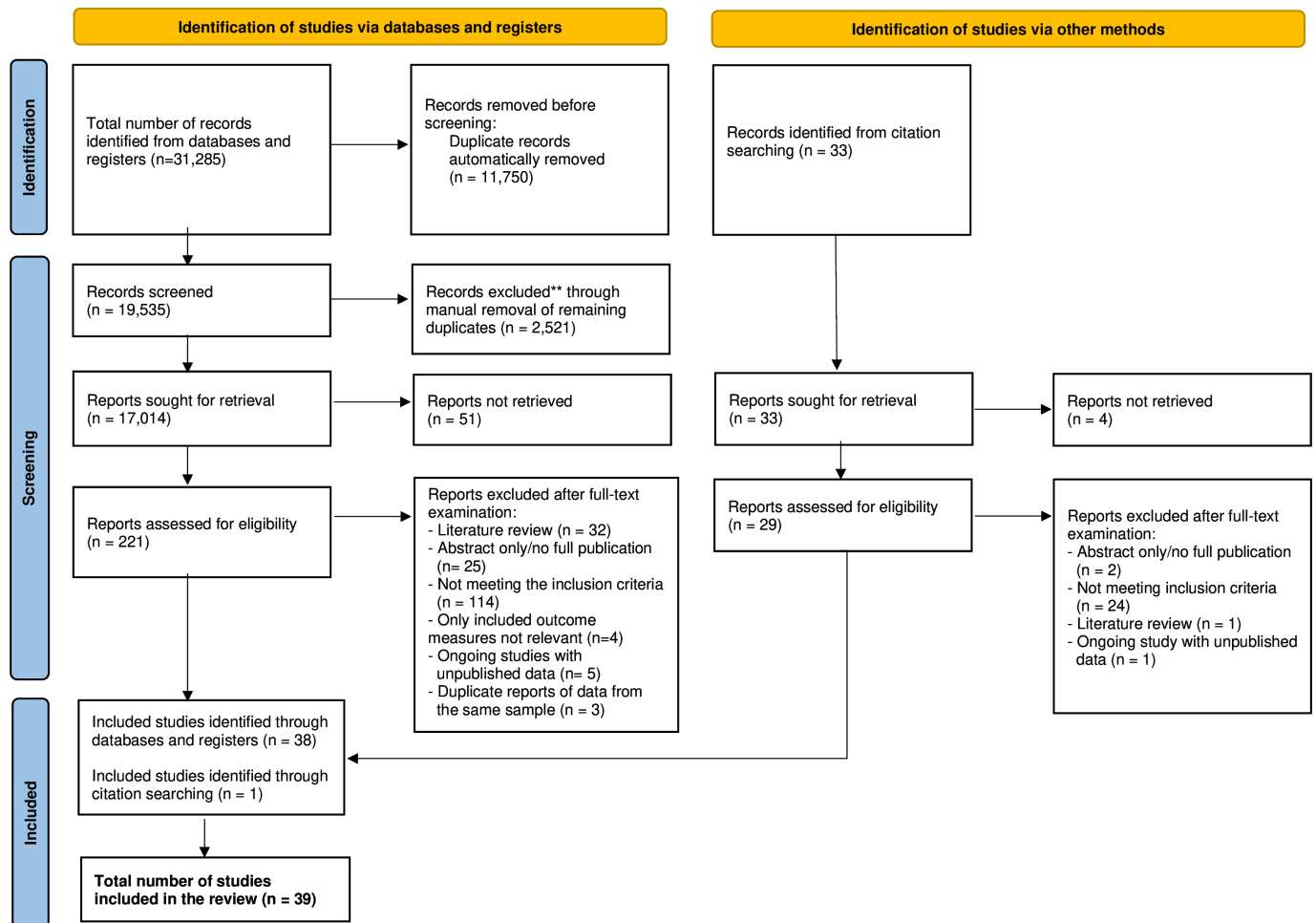
## RESULTS

### Study identification

The search identified 31,285 articles, reduced to 17,014 after removing duplicates. After screening the titles and abstracts, 221 were deemed suitable for full-text review; 38 of them fulfilled the eligibility criteria and were included. A further manual search identified 33 additional articles; of them, 29 progressed to full-text review and once reviewed, one was considered eligible for this study. Finally, a total of 39 articles were included. [Figure 1](#) describes the study selection process.

### Study characteristics

Included studies comprised 15 RCTs and 21 quasi-controlled studies, predominantly before–after designs without a control group (18/21). Most studies were published in the last decade (74%, 29/39), mainly from Europe (69%, 27/39). Included studies involved a total of 957 participants (range: 6–255). DMD ( $n=13$  studies), DM1 ( $n=11$  studies) and FSHD ( $n=8$  studies) were the most explored MD forms (online supplemental file 4). Most cohorts consisted of adults only (67%, 26/39). All except one<sup>16</sup> of the paediatric studies involved children with DMD. Most studies had a male predominance (male:female ratio=2:1). Most studies included ambulatory participants, but mobility



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study selection process. CBT, Cognitive Behavioural Therapy.

levels were variable, ranging from independently mobile,<sup>17–22</sup> mobile with or without assistive aids<sup>23–28</sup> to wheelchair dependent.<sup>29 30</sup> Similarly, upper-limb abilities varied from grade one, where individuals could lift their arms above their head, to grade four on the Brooke Upper-Extremity Scale,<sup>31</sup> where they could raise hands to mouth, but they could not bring a glass of water to their mouth. Further study characteristics supplied in online supplemental file 5.

**Risk of bias**

Figure 2 shows the risk of bias for the included RCTs. Twelve of the 15 RCTs<sup>17 23 28–30 32–38</sup> were considered at high risk of bias and ‘some concerns’ arose for three RCTs.<sup>20 24 39</sup> All studies confirmed randomisation, but four studies<sup>29 36–38</sup> did not report concealed allocation information. Baseline differences between study groups were observed in three studies.<sup>17 24 35</sup> Patient participants were not blinded in any of the RCTs, but six studies<sup>20 24 30 35 38 39</sup> reported blinding of the assessors. Nevertheless, almost 50% of studies (7/15)<sup>17 28 29 32–34 36</sup> were considered at high risk of bias in outcome measurement as they adopted assessor dependent outcome measures. Eight studies<sup>3 17 23 28–30 35 38</sup> had attrition bias due to missing outcome data or study participants’ drop out<sup>17 23 28–30 35 38 39</sup>; however, most studies adopted an appropriate analysis to explore the effect of assignment to intervention. Only one study documented protocol deviations.<sup>23</sup> Thirteen studies did not provide a statistical analysis plan, causing selection bias risk.

**Conservative non-pharmacological interventions**

Conservative non-pharmacological interventions were classified into four types: orthotic devices, manual therapy, assistive technologies and exercise interventions. An overview of the intervention types, subtypes and MD subgroups studied is presented in figure 3. Further details are available in online supplemental files 6 and 7.

Of the 39 included studies, seven<sup>19–21 25 34 36 40</sup> (three RCTs<sup>20 34 36</sup> and four non-RCTs<sup>19 21 25 40</sup>) observed a statistically significant treatment effect in one or more of their outcomes, with a total of nine outcome measures being improved. Significant improvements were mainly seen in functional outcomes (5/9),<sup>21 25 32 34</sup> mostly pertaining balance abilities (3/9).<sup>25 34</sup> Most outcomes (7/9) improved following supervised exercise interventions.<sup>21 25 34 36 40</sup> Seven of the nine outcomes, which included perceived exertion, distal upper-limb function, gait, static and dynamic balance and self-perceived physical condition, improved following training programmes including strength exercises alone<sup>25 40</sup> or combined with other exercise modalities (e.g. aerobic and balance training).<sup>20 21 34</sup> Non-exercise interventions significantly improved only a small number of outcome measures (2/9).<sup>19 41</sup> The largest significant ES was observed in Borg Rating of Perceived Exertion (RPE) (ES: 3.83 (95% CI: 2.86 to 4.79)),<sup>20</sup> and the smallest significant ES was observed in dynamic balance (sit-to-stand ability) following strength training (ES: 0.83 (95% CI: 0.08 to 1.58)).<sup>25</sup> There were a large number

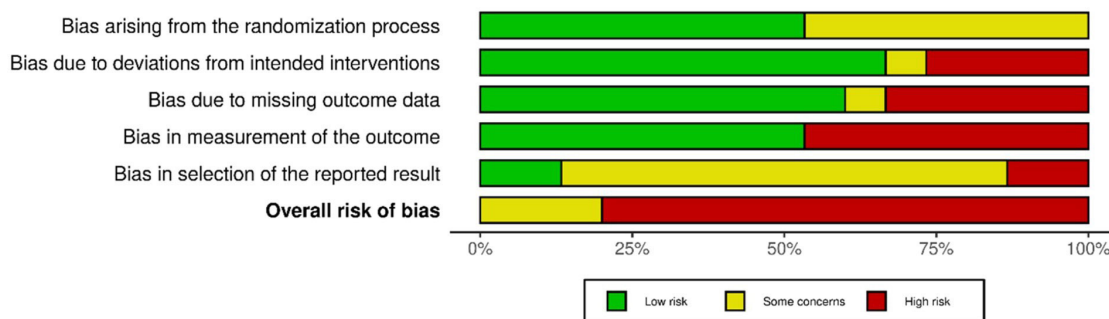
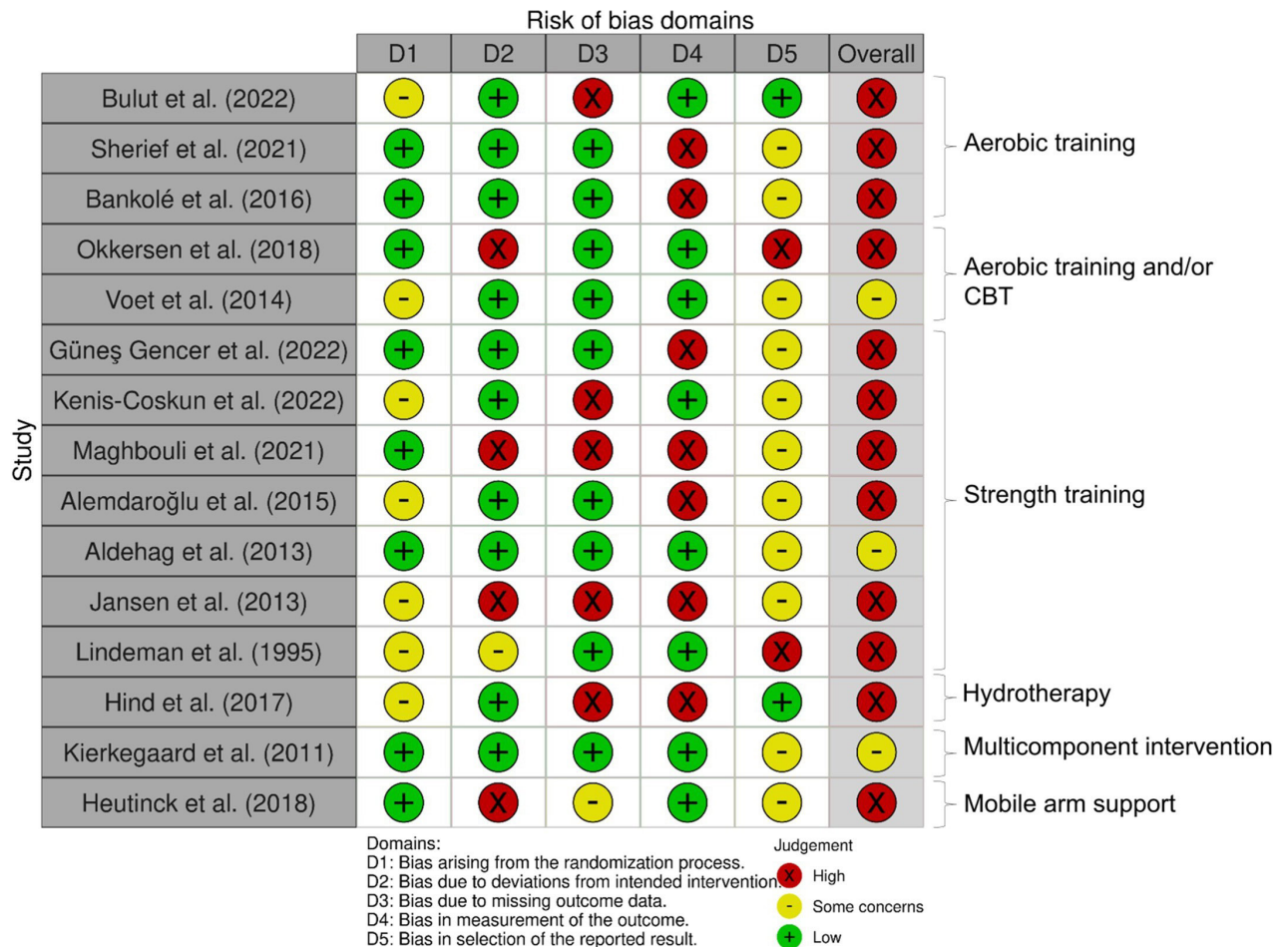


Figure 2 Risk of bias summary for randomised controlled trials only.

of outcomes, and many studies reported non-significant treatment effects. Therefore, the following paragraphs will provide a narrative overview only of those intervention subtypes with fewer studies. For intervention subtypes with a large number of studies, only the largest and significant ESs will be reported. Results for all interventions are displayed in figure 4 with further details presented in online supplemental file 8. A graphical representation of statistically significant ESs across all included studies is presented in figure 5.

**Orthotic devices**

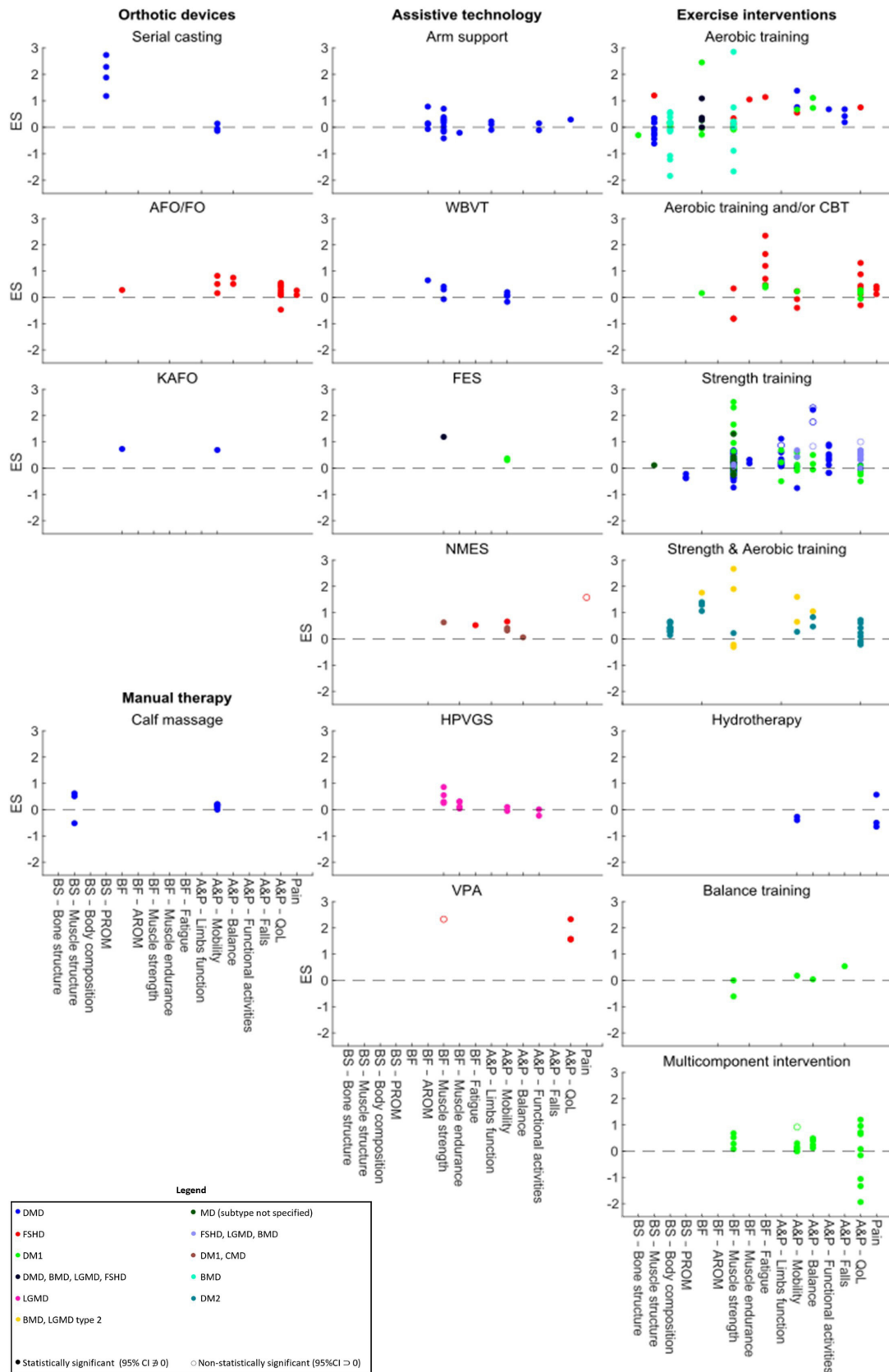
Three studies<sup>42-44</sup> (two<sup>43 44</sup> before-after studies without control group and one<sup>42</sup> case series study) involving a total of 33

participants investigated orthotic devices (serial casting<sup>42</sup> and AFO/FO<sup>43</sup> in children with DMD, and KAFO in adults with FSHD<sup>44</sup>). None of the improvements recorded were statistically significant; positive ESs ranged from 0.09 (VAS pain after AFO/FO<sup>43</sup>) to 2.73 (ankle dorsiflexion passive range of motion after serial casting<sup>42</sup>).

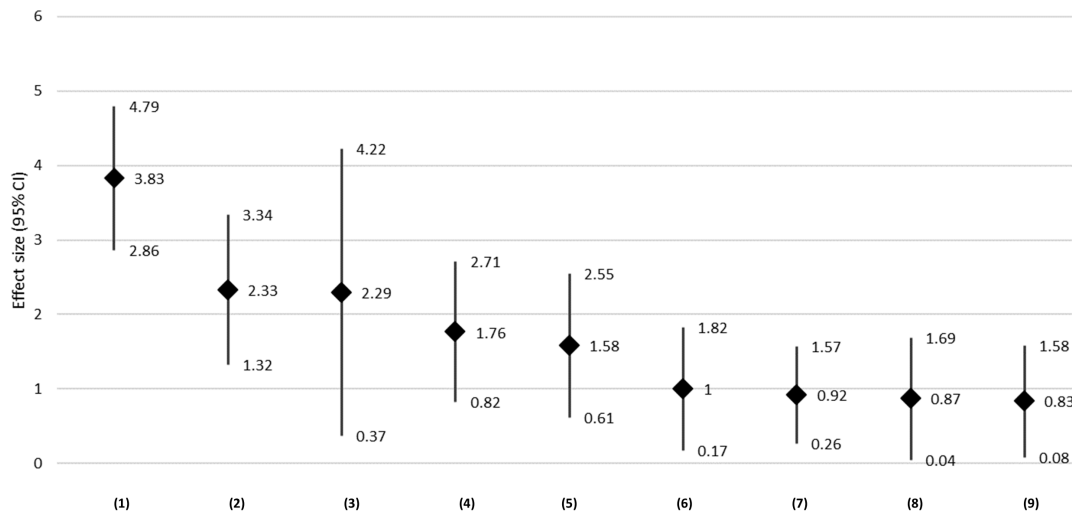
**Manual therapy**

One crossover study<sup>18</sup> investigated calf massage in children with DMD. Small to moderate ESs observed in lower-limb muscles length and gait were not statistically significant. ESs ranged from -0.52 in knee extension range of motion after calf massage to 0.62 in ankle dorsiflexion range of motion with knee extended.





**Figure 4** Scatter plots of the effect sizes of the included conservative non-pharmacological interventions. A&P, Activity and Participation; AFO/FO, Ankle Foot Orthosis/Foot Orthosis; AROM, Active Range of Motion; BF, Body Function; BMD, Becker Muscular Dystrophy; BS, Body Structure; CBT, Cognitive Behavioural Therapy; CMD, Congenital Muscular Dystrophy; DM1, Myotonic Dystrophy type 1; DM2, Myotonic Dystrophy type 2; DMD, Duchenne Muscular Dystrophy; ES, Effect Size; FES, Functional Electrical Stimulation; FSHD, Facioscapulohumeral Muscular Dystrophy; HPVGS, High Volt Pulsed Galvanic Stimulator; KAFO, Knee Ankle Foot Orthosis; LGMD, Limb-Girdle Muscular Dystrophy; MD, Muscular Dystrophy; NMES, Neuromuscular Electrical Stimulation; PROM, Passive Range Of Motion; QoL, Quality of Life; VPA, Vibratory Proprioceptive Assistance; WBVT, Whole-Body Vibration Training.



ID	Study authors	Intervention	Outcome	ES	95% CI
1	Kierkegaard et al. (2011)	Multicomponent program*	Perceived Exertion (Borg RPE)	3.83	(2.86; 4.79)
2	Ribot-Ciscar et al. (2015)	VPA	Shoulder abduction MVIC	2.33	(1.32; 3.34)
3	Güneş Gencer et al. (2022)	Trunk-oriented strength training plus usual care vs usual care alone	Dynamic reaching balance (TCMS)	2.29	(0.37; 4.22)
4	Güneş Gencer et al. (2022)	Trunk-oriented strength training plus usual care vs usual care alone	Sitting balance (TCMS)	1.76	(0.82; 2.71)
5	Colson et al. (2010)	NMES program	Pain (VAS)	1.58	(0.61; 2.55)
6	O'Dowd et al. (2022)	Strength training	Self-perceived physical condition (PSPP-R)	1	(0.17; 1.82)
7	Missaoui et al. (2010)	Multicomponent program*	Gait speed	0.92	(0.26; 1.57)
8	Güneş Gencer et al. (2022)	Trunk-oriented strength training plus usual care vs usual care alone	PUL distal score	0.87	(0.04; 1.69)
9	Bostock et al. (2019)	Strength training	Dynamic balance (STS)	0.83	(0.08; 1.58)

**Figure 5** Forest plot of the significant effect sizes in the included studies. ES, Effect Size; MVIC, Maximum Voluntary Isometric Contraction; NMES, Neuromuscular Electrical Stimulation; PSPP-R, Physical Self-Perception Profile Revised; PUL, Performance of Upper Limb; RPE, Rating of Perceived Exertion; STS, Sit To Stand; TCMS, Trunk Control Measurement Scale; VAS, Visual Analogue Scale; VPA, Vibratory Proprioceptive Assistance.

to 3.34).<sup>41</sup> ESs across studies ranged from -0.42 in shoulder abduction strength after arm support<sup>30</sup> to 2.33 in both shoulder abduction muscle strength and self-rated health state after VPA.<sup>41</sup>

**Exercise interventions**

A total of 27 studies,<sup>17 20 21 23-29 32-40 48-55</sup> including 14 RCTs,<sup>17 20 23 24 28 29 32-39</sup> 12 before-after studies<sup>25-27 29 40 48-50 52-55</sup> (three with a control group<sup>49 54 55</sup>) and one retrospective study,<sup>21</sup> explored exercise interventions lasting from four weeks to 10 months (807 total participants, range: 6-255). Interventions included strength training or aerobic training, alone or in combination with each other or other conservative treatments like cognitive-behavioural therapy (CBT), balance training and hydrotherapy. Overall evidence quality was low, with 13 studies at high risk of bias due to study design. Fourteen RCTs were at either moderate or high risk of bias, predominantly due to assessor-dependent outcome measures, attrition and inappropriate analysis of intervention assignment.

ESs ranged from -1.94 in the social functioning item of the 36-Item Short Form Survey (SF-36) after a multicomponent intervention<sup>20</sup> to 4.00, observed in lunges performance after an intervention combining aerobic and strength training.<sup>51</sup>

**Aerobic training**

Six studies<sup>32 33 38 53-55</sup> used aerobic training as an intervention, with five studies<sup>32 38 53-55</sup> using a cycle ergometer, either solely for lower-limb training<sup>32 38 53 54</sup> or compared with a treadmill.<sup>32</sup> One study<sup>37</sup> used a stationary ergo-cycle for lower-limb training only. Half of the studies were RCTs<sup>32 33 38</sup> and half were before-after studies<sup>53-55</sup> (two had a control group<sup>54 55</sup>). A total of 115 participants underwent

aerobic training (range: 11-30 participants), with follow-up periods ranging from 12 weeks to 12 months. Quality of evidence was low due to a high risk of bias resulting from missing outcomes and outcome measurement.

None of the aerobic exercise interventions yielded statistically significant effects in the measured outcomes.

**Aerobic training and/or CBT**

Two RCTs<sup>23 24</sup> explored aerobic training and CBT, given alone, in combination with each other or in addition to usual care, in 312 adults with FSHD<sup>24</sup> and DM1.<sup>23</sup> Okkersen *et al*<sup>23</sup> found no superiority of CBT and aerobic training combined with usual care over usual care alone (ES range: -0.05 to 0.45). Despite improvements in fatigue (ES range: 0.41 to 2.35) and quality of life (ES range: 0.12 to 1.31), Voet *et al.*<sup>24</sup> showed no statistically significant changes in any outcomes.

**Strength training**

Twelve studies,<sup>25-29 34-37 39 40 49</sup> predominantly using RCT design (7/12),<sup>28 29 34-37 39</sup> explored strength interventions in 276 participants (range: 9-40 participants). Four<sup>29 34-36</sup> studies involved children with DMD, while the remaining studies<sup>25-28 37 39 40 49</sup> examined adults with DM1, DM2, FSHD, LGMD, BMD and unspecified MD subtypes. The quality of evidence for RCTs ranged from 'some concerns' to 'high' due to moderate risk of selection bias and high risk of bias from missing data and outcome measurement.

Strength training interventions did not yield statistically significant changes in terms of muscle structure,<sup>49</sup> passive range of motion,<sup>29</sup> muscle strength<sup>25-29 35-37 39</sup> and mobility.<sup>25-27 29 35 36</sup> Nevertheless, Güneş-Gencer *et al*<sup>34</sup> found that eight weeks of

trunk-oriented training combined with conventional care was significantly more effective than conventional care alone for improving distal wrist and hand function (PUL distal subscore) (ES: 0.87 (95% CI: 0.04 to 1.69)) in children with DMD.

Balance abilities significantly improved following strength training in two studies.<sup>25,34</sup> Güneş Gencer and Yılmaz<sup>34</sup> observed that eight-week trunk-oriented exercises combined with usual care were more effective than usual care alone in improving static sitting (ES: 1.76 (95% CI: 0.82 to 2.71)) and dynamic reaching balance (ES: 2.29 (95% CI: 0.37 to 4.22)) in children with DMD. Additionally, Bostock *et al*<sup>25</sup> observed that the timed sit to stand test of adults with FSHD, LGMD and BMD significantly improved after a 12-week strength training (ES: 0.83 (95% CI: 0.08 to 1.58)).

In adults with FSHD, LGMD and BMD, the same research group<sup>25</sup> observed a significant improvement in self-perception of physical condition (ES: 1.00 (95% CI: 0.17 to 1.82)).<sup>40</sup> Strength training did not improve any other quality-of-life domains (ES range: -0.50 to 0.67).<sup>29,35,39,40</sup>

### Strength and aerobic training

Three before–after studies without control group<sup>50–52</sup> adopted intervention programmes involving strength and aerobic training in a total of 26 adults (range: 8–10 participants) with DM2, BMD and LGMD2I. One study<sup>52</sup> used a four-week programme (two times/week) on a stationary bicycle, while the other two studies,<sup>50,51</sup> from the same research group, used a 10-week programme (three times/week, 40 min/session) on an antigravity treadmill. No statistically significant differences were noted in the outcome measures assessed.

### Hydrotherapy

One RCT<sup>17</sup> involving 12 children with DMD found that six-month hydrotherapy combined with land-based exercises had non-significant effects on all outcome measures (ES range: -0.65 to -0.27).

### Balance training

One uncontrolled before–after study<sup>48</sup> with 11 adults with DM1 explored a group balance programme (one to three times/week, 60 min/session, for 10 weeks), reporting non-significant treatment effects.

### Multicomponent interventions

Two studies,<sup>20,21</sup> one RCT<sup>20</sup> and one retrospective study,<sup>21</sup> used multicomponent rehabilitation programmes, comprising flexibility, aerobic, strength and balance training, for a total of 55 adults with DM1. One study<sup>21</sup> showed significantly greater fast walking speed (ES: 0.92 (95% CI: 0.26 to 1.57)), while the other<sup>31</sup> observed statistically significant changes in the Borg RPE score after training (ES: 3.83 (95% CI: 2.86 to 4.79)).

### Adverse events

Over 35% (14/39) of studies reported adverse events, with low frequency among participants. The most reported adverse event was pain (n=33 participants)<sup>24,27,29,30,37,42,45,49</sup> which mostly affected the lower back<sup>24,27,37</sup> and lower limbs.<sup>29,49</sup> Other adverse events were muscle soreness,<sup>17</sup> cramp,<sup>45</sup> fatigue,<sup>53</sup> falls,<sup>17,23</sup> foot fracture,<sup>45</sup> physical discomfort,<sup>49</sup> skin redness<sup>19,42</sup> and skin irritation.<sup>45</sup> Most participants successfully completed programmes with only transient symptoms consistent with the interventions. Okkersen *et al*<sup>23</sup> reported that that 50% of the participants (n=255) experienced adverse events, which were

serious in 13% of the cases. However, not all reported adverse events were directly attributed to the exercise interventions (e.g. upper respiratory tract infection and neoplasm). Another three studies<sup>17,29,30</sup> reported adverse events unrelated to the intervention tested. Only one study<sup>27</sup> reported significant long-term adverse events (low back pain) from exercise protocol. Only two patients dropped out due to adverse events (back pain) related to the intervention.<sup>37,49</sup>

## DISCUSSION

This systematic review and meta-analysis explored the effectiveness of conservative non-pharmacological interventions for the MD physical management. Although various improvements were observed, most intervention effects were non-significant. Low-quality evidence suggests that exercise interventions incorporating strength training may enhance functional abilities. Specifically, a multicomponent rehabilitation programme, consisting of strength, flexibility and balance training, improved gait speed in adults with DM1.<sup>20</sup> Additionally, adults with FSHD, LGMD and BMD<sup>25</sup> showed enhanced dynamic balance (sit-to-stand ability) after strength exercises. For children with DMD, trunk-oriented strength exercises combined with usual care were more effective than usual care alone to improve distal upper-limb function, static sitting and dynamic reaching balance.<sup>34</sup> Interestingly, these functional improvements occurred without substantial muscle strength changes. Only one study implementing VPA in FSHD<sup>41</sup> found statistically significant muscle strength changes. This may suggest that conservative non-pharmacological interventions, including strength training, may help maintain, rather than improve, muscle strength in MD. However, the strength interventions durations did not exceed six months, making it unclear whether continuous interventions can maintain muscle strength in the long term despite the MD progressive nature. Furthermore, it is important to acknowledge the divergence in muscle strength findings; while some studies reported non-significant improvements, others observed non-significant declines after training. This decline could be attributable to the MD degenerative nature, but the exact cause remains uncertain, as the variability in intervention characteristics (e.g. intensity, duration) and study populations (e.g., disease type and severity) where this was observed makes it difficult to determine the responsible factors.

The positive findings from strength training interventions have possible clinical implications given historical concerns about exercise interventions potentially causing harm in MD.<sup>56</sup> They support the use of strength training, either independently or with complementary exercise interventions, as this approach not only has proven to be safe when carried out using existing parameters and could be cost-effective, but also seem to ensure an efficient training stimulus.<sup>9</sup> Using strength training in multimodal interventions may address multiple impairments simultaneously. While intervention characteristics were variable, the strength training component within interventions that yielded statistically significant differences typically included supervised active or active-assisted strength exercises, using free weights or exercise machines. Exercise sessions generally took place twice a week (ranging from twice a week to daily) for eight weeks, and each session lasted approximately 40–45 min (range: 40 min to two hours); exercises typically consisted of five to 10 repetitions for one to three sets. While available studies suggest the beneficial effects of this dosage, there is not yet sufficient evidence to make recommendations. Notably, supervision may have influenced health behaviour change and the effectiveness



of these interventions, resulting from education, opportunities and capability which facilitate adherence levels.<sup>57</sup> It is important to note that strength interventions improved balance abilities, while balance-specific programmes failed to yield any significant balance changes.<sup>47</sup> This may indicate that (1) strength training, alone or combined with other exercise forms, may be more beneficial than balance-specific exercises alone; (2) strength loss significantly impacts other body structures and activities and (3) some balance assessments (e.g. timed up and go test) may show improvements reflective of muscle strength changes. These observations also suggest that intervention effectiveness assessment through functional outcomes may be more appropriate than relying solely on strength measures, considering that muscle strength improvements may not always occur due to progressive muscle weakness in these conditions.

Most non-exercise interventions (manual therapy, orthotic devices and assistive technologies interventions) did not produce statistically significant treatment effects. This was likely due to study limitations, including small sample sizes, lack of blinding, missing data and dropouts. These limitations were more pronounced in non-exercise interventions due to their smaller scale, potentially explaining their lower frequency of significant results compared with exercise interventions. Non-exercise intervention studies typically involved the smallest sample sizes (range: 9–24 participants), further exacerbated by dropouts observed in a third of the non-exercise intervention studies. Furthermore, most non-exercise interventions were tested within single MD clinical groups, leaving treatment effects variations across MD conditions unexplored. Unlike exercise interventions that often used more structured and supervised regimens, non-exercise interventions were primarily unsupervised, leaving adherence rates uncertain and potentially influencing their effectiveness. Additionally, the assessment of non-exercise interventions focused on a limited number of outcome measures, which may have not captured the full spectrum of potential effects, possibly leading to an underestimation of their impact. Despite most non-exercise interventions lacking statistical significance, it is important to acknowledge that many of them are commonly integrated into the MD clinical management or recommended on an individual basis. In the absence of a robust evidence base, healthcare professionals and clinical services use these interventions as they are deemed to be acceptable, feasible, and beneficial by healthcare providers and people with MD. With no cure available, offering these conservative non-pharmacological interventions addresses symptoms, meets patient expectations, and empowers healthcare professionals to make a positive impact on their patients' lives. For individuals living with MD, receiving these interventions goes beyond merely alleviating physical symptoms; it potentially cultivates hope and fosters resilience, improving their overall experiences of living with MD. In clinical practice, these interventions target impairments affecting fatigue levels, psychological well-being, independence, engagement in social activities and quality of life. However, the perceived benefits of these interventions have not been substantiated by this systematic review and meta-analysis due to inherent study limitations, rather than the ineffectiveness of the interventions themselves, which may have confounded their true effects, making them appear less impactful than they are in routine clinical practice.

Existing guidelines for conservative non-pharmacological management of MD, as well as other NMD, are limited<sup>56</sup> or neglect conservative non-pharmacological approaches<sup>58</sup> due to the absence of robust evidence supporting their clinical benefits, negatively affecting clinical decision-making.<sup>59</sup> While existing

guidelines often overlook these interventions, their role within an evidence-based practice framework, their potential efficacy, their safety and the absence of alternative treatments may justify their clinical use, especially strength training alone or combined with other exercise forms. However, to employ conservative non-pharmacological interventions of which evidence is yet to fully become available, these interventions should align with first principles, be acceptable to patients and healthcare professionals, pose no harm or financial burden, and be continually reviewed for adherence to evidence-based practice. Where the evidence suggests treatment is beneficial (e.g. strength training), we should continue to work towards monitoring risk of harm while also exploring how to optimise the prescriptions to maximise benefits. Furthermore, while this review and meta-analysis did not include studies combining conservative non-pharmacological treatments with pharmacological interventions, preventing a direct comparison of their effectiveness, previous research in MD and NMD suggests that conservative non-pharmacological interventions have comparable, if not superior, effectiveness than pharmacological treatments.<sup>60 61</sup> For instance, very large, although non-significant, ESs (range: 1.46–8.93) strongly favoured conservative interventions over pharmacological treatments in specific outcomes (e.g. Berg balance, grip strength, 2-min walk test, physical functioning, role limitations due to physical health and emotional problems) in the study by Connor *et al.*<sup>60</sup>

Numerous questions regarding the effectiveness of these interventions remain unanswered, specifically about certain outcomes, populations and intervention types. Pain, a common and distressing symptom in MD,<sup>62 63</sup> offers anecdotal indications of potential relief through non-pharmacological interventions such as hydrotherapy. However, the impact of conservative interventions on pain is underexplored, with most studies failing to demonstrate statistically significant improvements. Only a small-scale NMES study in adults with FSHD reported a significant reduction in pain.<sup>19</sup> Furthermore, most studies involved adults only, and all except one<sup>16</sup> of the studies involving children were conducted in DMD. No studies have explored the effectiveness of conservative non-pharmacological interventions in infantile and juvenile cases of MD forms other than DMD. Additionally, there is limited exploration of interventions in the early stages of these conditions. Most studies focused on exercise interventions, leaving the effectiveness of non-exercise interventions unknown. Studies on conservative non-pharmacological interventions in adults with DMD are scarce, and the effectiveness of upper-limb orthoses remain unclear.

Future studies are required to advance current understanding of the effectiveness of conservative non-pharmacological interventions for MD. To overcome existing challenges and conduct studies that genuinely capture the effectiveness of these interventions, several actions are imperative.

Alternative study designs and methods for determining effectiveness of therapy interventions in MD are needed. While RCTs remain the gold standard for assessing intervention effectiveness, the diseases rarity, MD phenotypic heterogeneity, logistical complexities and patients' geographical dispersion often make RCTs challenging. Where existing treatment options are limited or non-existent, people with MD usually prefer access to an active intervention rather than a placebo. Within a research landscape increasingly focused on developing disease-modifying treatments, individuals may find participation in drug trials more attractive than enrolling in conservative non-pharmacological intervention studies. This preference can hinder the recruitment of participants for future non-pharmacological clinical research,

as this may also make them ineligible. Additionally, RCTs can be cost-prohibitive, and the substantial costs may not align with the priorities of funding bodies, which may prefer to allocate resources to research in more common diseases. While government research councils have offered funding schemes, these opportunities are relatively limited, and industry or charitable organisations often serve as primary research funding sources in this field. Relying on non-governmental sources can complicate building sustainable research infrastructure, requiring innovative funding and collaborative efforts to advance MD research effectively.

A universally agreed core outcome set for evaluating therapy interventions in MD is still lacking. Validated outcome measures specific to MD are often scarce, necessitating the use of measures validated for other conditions. However, differences in disease mechanisms, progression, manifestations and the heterogeneity of MD diseases can compromise the validity of these extrapolated measures. Additionally, outcome measures designed for different clinical populations may lack face validity for some MD subgroups, potentially leading to underestimation of the interventions' significance and inaccurate conclusions regarding effectiveness. The absence of standardised core outcome sets also complicates the intervention effectiveness assessment and hinders meaningful comparisons between studies. Future efforts should focus on developing patient-centred core outcome sets, which should reflect what is important to individuals living with different MD, account for the unique MD progressions, establish clinically meaningful differences and ensure measures are valid and reliable.

Registries and clinical databases serve as valuable tools for gathering data on individuals with NMD.<sup>64</sup> In cases where evidence is scarce, they offer a potentially sustainable approach to determining effectiveness.<sup>65 66</sup> However, their effectiveness depends on the engagement of patient and centres, integration of relevant electronic health records, consideration of measurement burden, appropriate outcome measures inclusion, high data completion rates and regular updates in response to emerging evidence. While existing registries have been used for exploratory research, their utility in informing clinical decision-making has not been fully developed, possibly owing to a failure to address the requirements above.

The scarcity of comprehensive natural history data in MD poses a significant challenge for assessing intervention effectiveness. Without this baseline knowledge, distinguishing intervention effects from natural disease progression is difficult, as exemplified by the challenging interpretation of strength decline following strength training. Additionally, the lack of natural history data affects decisions on intervention timing and duration. Robust natural history studies are necessary to provide insights into disease progression, guide treatment strategies and establish a benchmark for intervention impact evaluation.

Taken together, these actions will enhance research quality, inform guidelines, support healthcare professionals, standardise care across clinical sites and ultimately improve care for individuals with MD.

### Strengths

The analysis of the effectiveness of conservative non-pharmacological interventions in MD was comprehensive. This was achieved by search strategies without restrictions on date, language, study designs and outcomes.

### Limitations

Most data came from non-RCT studies, which may have limitations such as overestimated treatment effects, uncontrolled designs and small sample sizes. This study focused on the conservative non-pharmacological interventions for the MD physical manifestations, excluding respiratory interventions that however are integral to the non-pharmacological management of these conditions. Included articles predominantly involved adults, and paediatric studies consisted largely of children with DMD, which could limit the applicability of the findings to children with MD forms other than DMD. Limitations also included heterogeneity in the study populations and outcome measures, use of non-validated outcome measures and, in some studies, inclusion of multiple patient populations whose data could not be separated by individual conditions. Future studies should present separate MD group data to identify specific group intervention interactions.

### CONCLUSION

This systematic review and meta-analysis indicated that most conservative non-pharmacological interventions produced non-statistically significant treatment effects. Nevertheless, identified interventions did not appear to be harmful. Furthermore, low-quality evidence suggested that supervised strength training, alone or combined with other exercise interventions, may improve perceived exertion, distal arm function, balance, gait and well-being despite no significant structural changes. Therefore, strength training, alone or as part of a multicomponent programme, should be considered as the mainstay in the treatment of MD. Evidence on the effectiveness of assistive technologies, orthotic devices and manual therapy interventions remains limited and inconclusive. Future large-scale, well-designed and well-reported studies are needed to clarify the role of non-pharmacological interventions in MD and to support their clinical use.

X Enza Leone @leone\_enza

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## ORCID ID

Enza Leone <http://orcid.org/0000-0003-3493-0073>

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