The efficacy and prescription of neuromuscular electrical stimulation (NMES) in adult cancer survivors: a systematic review and meta-analysis

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ABSTRACT:

Purpose

This study aims to; 1) summarise and critically evaluate the effects of neuromuscular electrical stimulation (NMES) on indices of health and quality of life (QoL) in adult cancer survivors, 2) assess the safety of NMES as a rehabilitation method in this population, and 3) identify commonly used NMES treatment parameters and describe treatment progression.

Methods

A systematic search of four electronic databases targeted studies evaluating the effects of NMES on physical function, aerobic fitness, muscle strength, body composition and health related quality of life (HR-QoL) in adult cancer survivors, published through March 2018. Two reviewers independently reviewed and appraised the risk of bias of each study

Results

Nine studies were included. Meta analyses found that the overall pooled effect favoured NMES for improving muscle strength, but the standardised mean difference was not significant (0.36, 95% CI -0.25, 0.96). Further meta-analyses indicated that NMES significantly improved HR-QoL (0.36, 95% CI 0.10, 0.62), with notable gains identified under the subcategories QoL Function (0.87, 95% CI 0.32, 1.42). Current NMES prescription is not-standardised and NMES is prescribed to target secondary complications of treatment. Risk of bias was high for most studies

Conclusions

NMES use in adult cancer survivors is an emerging field and current literature is limited by studies of poor quality, and a lack of adequately powered RCT's. Existing evidence suggests NMES is safe and may be more effective than usual care for improving HR-QoL. Prescription and progression should be tailored for the individual based on functional deficits.

KEYWORDS: neuromuscular electrical stimulation, adult cancer survivors, rehabilitation, oncology, physical function

Annual cancer diagnosis rates (>14 million per year) are set to increase by 50% before 2030 [1]. However, mortality from cancer is decreasing. Five-year survival rates in the US for all cancer combined have improved by almost 20%, from 49% in the 1970's to ~70% in 2016 [2]. Similar trends have been reported in Europe with mortality rates in men and women falling by 8% and 3% respectively since 2011 [3]. These favourable trends are linked to improved screening and more effective antineoplastic treatments [4].

Although cancer treatments (e.g. chemotherapy and hormone therapy) can be efficacious, they can lead to long-term side effects such as fatigue, muscle loss, and reductions in functional capacity [5]. Exercise which targets both the neuromuscular and cardiovascular systems is currently recommended to help offset some of the complications of treatment with guidelines recommending 150 mins of moderate or 75mins of vigorous aerobic exercise coupled with 2-3 resistance training (RT) sessions per week regardless of disease progression [6].

Nevertheless, exercise is not always possible due to treatment complications or contraindications to aerobic exercise and RT. Reports suggest that only ~35% of cancer survivors achieve current recommendations [7, 8] with breathlessness, fatigue, weakness and poor balance cited as common issues affecting basic exercise participation such as walking [9]. Thus, pragmatic alternatives to traditional exercise methods are required.

Neuromuscular electrical stimulation (NMES) involves controlled muscular contractions generated by electrical impulses delivered through surface electrodes, usually placed on major muscle groups such as the quadriceps and hamstrings [10]. The evoked contractions have proven efficacy in improving muscle strength and cardiorespiratory fitness across a variety of populations [11–18]. Thus, physician supervised NMES exercise to enhance the neuromuscular and cardiovascular systems has applicability within the cancer population to prevent the complications associated with treatment and improve health related quality of life (HR-QoL). However, NMES uptake clinically is low [19] and currently no published, high-level evidence supports its application in cancer survivorship.

Therefore, the objectives of this review are to evaluate published research investigating the use of NMES exercise in adult cancer survivors; synthesise the evidence evaluating its application in improving physical function and HR-QoL; assess the safety of NMES exercise in cancer populations and determine if specific prescription and progression patterns could be identified with NMES application in cancer survivorship.

METHODS

A systematic search and review of the literature was conducted using the PRISMA guidelines [20]. The following databases were searched up to March 2018: PubMed (1949 – 2018), EMBASE (1947 – 2018), CINAHL (1982 – 2018), and The Cochrane Library (1993 – 2018). A protocol detailing the planned search strategy and method for analysis for this review was registered online with PROSPERO, a register of systematic review (CRD42017073519).

Eligibility criteria

Selection criteria for inclusion in this review comprised: 1) article or abstract of original research, 2) population of adult cancer survivors, 3) interventions detailing NMES, and 4) measurement of outcomes pre-NMES and post-NMES to evaluate treatment effectiveness. No limitations were placed by study methodology to allow for a more comprehensive overview of this nascent area.

Exclusion criteria included studies involving transcutaneous electrical stimulation (TENS) for cancer pain or spinal cord stimulation.

Search

A search strategy (*Appendix 1*), guided by an institutional liaison Librarian, was based on the PICO method. The population was adult cancer survivors, the intervention was NMES, the comparator was no intervention or standard care and outcomes were physical function, aerobic fitness (cardiovascular capacity (VO_{2max}) or VO_{2peak} or submaximal exercise capacity), muscle strength, body composition, and HR-QoL.

Study selection

Figure 1 details the study selection process. Identified studies were screened by title by one reviewer (DO'C). Remaining studies were independently screened by abstract by two reviewers (DO'C., OL). Identified full text manuscripts were again independently reviewed by two reviewers (DO'C., OL). Reasons for exclusion were recorded.

Data collection process

Two reviewers (DO'C and OL) extracted data variables: type of study, study population (age, sex, disease type and disease stage), intervention, outcome measures, and results (*Table 1*). In addition, NMES intervention prescription and progression data were extracted using frequency, intensity, type and time (FITT) along with reported safety/adverse events (*Table 2).*

Quality assessment

Included studies were assessed independently by two reviewers (DO'C and OL) using the Effective Public Health Practice Project Quality Assessment Tool (EPHPP). In addition, the Cochrane Risk of Bias Tool was used for randomised controlled trials (RCTs). Disagreements were resolved by consensus.

Data synthesis

A narrative approach to analysis was first proposed, summarising all included studies by outcomes of interest. Secondary outcomes of NMES prescription and progression, and safety were also summarised narratively. Where two or more RCTs measured the same outcome, meta-analysis was proposed whereby differences between NMES based interventions and comparator groups from pre-to post intervention would be calculated using Review Manager (v5.2) software. Continuous outcome measures would be expressed as the mean difference from pre-to post treatment in each group and variances derived from standard deviations. Where studies reported median and ranges, these would be converted to mean and standard deviation using a previously published method [21]. A fixed effects inverse-variance meta-analysis for mean differences with 95% confidence intervals (CI) between NMES-based interventions and control groups was proposed. A small number of studies were anticipated in this area, making it difficult to estimate the between studies variance with any precision. Where treatment outcomes were measured using different outcome measures a standardised mean difference was calculated and where measured at more than one time point, the last measurement was used in the meta-analysis conducted. Sub-analysis for distinct follow-up periods would be conducted, where data permit.

RESULTS

Study selection

Figure 1 presents the flowchart of the study selection process. A total of 896 studies were identified from the databases. Eight full text articles and one abstract were included for final analysis; four RCTs [22–25], one case

149 control study [26], three interventional cohort studies [27–29], and one case report [30]. Authors were contacted
150 for further information for four additional studies identified [31–34]. Following three contact attempts with the
151 corresponding authors, studies were excluded where no response was received.
152
153 **Risk of bias within studies**
154 The overall risk of bias was deemed high in 3 RCTs [22–24], with 1 study marked as unclear [25]. When all
155 studies were evaluated using the EPHPP tool, 2 of the 9 studies received a strong global rating for quality [23,
156 29], 5 a moderate quality rating [22, 24, 25, 28, 30] and 1 was rated as weak [26]. With limited data available to
157 the reviewers, the abstract included in the review [27] was also rated as weak.
158
159 **Participant demographics**
160 A total of 229 adult cancer survivors from the 9 studies were included in this review. Of these, 111 were males
161 (48.5%) and 118 were women (51.5%). Two studies included only women [23, 30]. The pooled mean age of
162 participants (n=229) in this review was 57.9 ± 9.3 years (min/max: 47/68 years). Participant body mass index
163 (BMI-kg/m^2) was reported in 5 studies (n = 120) and ranged from 23.1 to 30.47 kg/m^2.
164
165 *Cancer types*: breast cancer [23], non-small cell lung cancer (NSCLC) [22, 24], metastatic lung cancer [30],
166 cerebral glioma [27], nasopharyngeal carcinoma [26], low rectal cancer [29], and foregut cancers including
167 liver, pancreas and stomach [25]. One study comprised a heterogeneous group including lung (n=5),
168 gastrointestinal (n=1), breast (n=1), ovarian (n=1), endometrial (n=1) and haematological cancers (n=1) [28]
169
170 **Intervention**
171 *Location*: Three interventions were home based [22, 24, 28]. Other locations included hospital outpatient
172 departments [23, 26, 29, 30], and in-patient hospital rehabilitation units [25, 27]. Five studies used an
173 experimental control group. Two studies reported using a "no NMES" treatment control group [22, 24], two
174 reported usual care controls [23, 26]. One study reported the contralateral limb as the control [25]. Three studies
175 reported no control group [27–29].
176
177 **Evidence supporting NMES application in Cancer survivorship**
178 **Meta-analyses**

Sufficient data were extracted from RCTs to enable meta-analysis of two outcomes of interest, muscle strength as measured by fixed [22] and manual muscle test dynamometry [24], and HR-QoL as measured by the EORTC QLQ C-30 [24] and the FACT-B+4 [23]. In each measure, the higher the score the better the outcome.

Strength: Data were pooled from two RCT studies with a total of 44 participants with lung cancer (Figure 2) [22, 24]. Compared to usual care controls, the standardised mean effect of the NMES intervention on muscle strength was not statistically significant (SMD 0.36, 95% CI -0.25, 0.96, Z=1.15, p=0.25).

Health related Quality of life: Data were pooled from two RCT studies with a total of 60 participants with breast cancer or lung cancer (Figure 3) [23, 24]. Compared to usual care controls, meta-analysis demonstrates that the standardised mean effect of an NMES intervention for HR-QoL was significantly greater (SMD 0.36, 95% CI 0.10, 0.62, Z=2.69, p=0.007). When considered under sub-categories of HR-QoL, the gains identified were notable in the QoL Functional domain (SMD 0.87, 95% CI 0.32, 1.42, Z=3.09, p=0.002).

Narrative summary of individual studies

Effects of NMES on body function and structure

Submaximal exercise capacity

Exercise capacity was measured using the 6-minute walk test (6MWT) in 2 studies [28, 30] and the endurance shuttle walk test (ESWT) [22] in another.. Maddocks et al., [22] in a RCT involving NSCLC patient, recording 0 or 1 on the Eastern Cooperative Oncology Group performance status and at least 4 weeks post treatment, reported no significant difference between the NMES and "no NMES" groups in the ESWT (-20m vs -158m, p=0.27). Windholz et al., [28] in their prospective pilot study reported no significant change in 6MWT performance after the intervention period from baseline (-21.1m, p=0.7). Crevenna et al., [30] in a case study reported improvements of 44% in 6MWT performance (420m to 603m).

Functional strength

One study analysed functional strength using the timed up and go test (TUG) [30]. One study used the sit to stand test (STS) [28]. Windholz et al., [28] reported no significant change in STS time from pre-to post NMES intervention (-1.2s, p=0.3). Crevenna et al [30] in their case report reported a 20% reduction in TUG performance with this equating to a 1s reduction in time taken to complete the test (pre-6s vs post-5s).

Body composition

Dual Energy X-ray absorptiometry (DXA) was used to assess thigh and whole body lean tissue mass in one study [24]. No significant difference between the NMES and control groups was noted in thigh lean mass ($p=0.44$) or whole body lean mass ($p=0.31$).

Biomarkers of muscle hypertrophy and atrophy

One study assessed biomarkers of muscle hypertrophy and muscle atrophy [25]; After 4 days of 30mins/day NMES application, no significant effect of NMES treatment on IGF-1Ea mRNA was noted in the treated limb in comparison to the contralateral control limb ($p=0.516$). Of note, total RNA content was 26% greater in the NMES treated leg than in the contralateral control limb (9.6μg/mg vs 7.6μg/mg; $p=0.033$). In addition, sarcoplasmic protein content increased by 20%, and this change was significant when compared to the control limb ($p=0.029$). NMES treatment had no effect on myofibrillar proteins ($p=0.393$). In the NMES limb, the expression of ubiquitin-conjugated proteins of sarcoplasmic fraction were significantly less (-23%) than that of the control limb ($p=0.0005$). Proteasome activity was significant reduced in the NMES limb also (-34%) in comparison to the control ($p=0.048$).

Effects of NMES on HR-QoL

Six studies measured HR-QoL using diverse outcome measures, often reflecting the cancer type or aim of treatment. One study [24] used the multidimensional European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Crevenna et al., [30] assessed quality of life using the SF-36 Health survey. Lin et al., [26] assessed the swallowing aspect of HR-QoL using the M.D. Anderson Dysphagia Inventory (MDADI). Belmonte et al., [23] measured HR-QoL using the Functional Assessment of Cancer Therapy Questionnaire for Breast Cancer Therapy version 4 (FACT-B+4). Rozumenko & Khoroshun [27] measured HR-QoL using a Karnofsky Performance Status (KPS) scale of functional impairment. Kuo et al [29] measured faecal incontinence HR-QOL using the Wexner Cleveland Clinic Florida Grading scale.

Maddocks et al., [24] reported no significant changes following NMES in the EORTC QLQ-C30's 6 sub-scales (General Health score, Physical, Role, Emotional, Cognitive, Social) when compared to "no NMES" controls.

Belmonte et al., [23] reported significant within group pre-vs post HR-QoL mean change scores in the NMES group across FACT-B+4 summary scores: FACT-General (p=0.006), FACT-Breast (p=0.013) and FACT-Trial Outcome Index (TOI) (p=0.015). However, when mean change scores were compared, no significant difference was reported across the three HR-QoL summary-scales (FACT-General, p=0.197; FACT-Breast, p=0.130; FACT-TOI, p=0.074). Lin et al., [26] in their case control study reported that FES significantly improved swallowing HR-QoL from 45.1 to 53.1 (p=0.003). Kuo et al., [29] in their interventional cohort study reported significant improvements in the Wexner's score post NMES treatment (17.74 vs 12.93; p<0.001). Rozumenko & Khoroshun [27] reported the proportion of patients with a KPS>70 score before treatment and post rehabilitation as the outcome of interest, noting an increase from 43.7% to 83.5%, no p value was reported. The case report by Crevenna et al., [30] showed improvements in all HR-QoL scales of the SF-36 with the exception of the social functioning sub-scale.

Safety of NMES

Three studies reported no adverse events [22, 24, 30] in lung cancer populations when NMES was applied to the lower limbs. One study employing NMES for lymphedema treatment following breast cancer reported dermatological adverse events [23]., including erysipelas on the upper limb (n=1), skin irritation (n=1) and erythema on the back of the hand (n=1). Four studies did not report adverse events as an outcome [25, 26, 28, 29]. In one study, available in abstract form, NMES safety was indeterminate, despite attempts to contact the authors [27].

Stimulation parameters: Three studies employed a biphasic symmetrical current [22, 24, 30]. Kuo et al [29] reported a square waveform. Rozumenko & Khoroshun [27] reported an asymmetrical waveform. Four studies did not report waveform [23, 25, 26, 28]. Pulse frequency was reported in all studies (range: 0.31Hz - 63.3Hz). Pulse duration was reported in 8 studies (range: 250μs – 700μs). Duty cycles varied from 2s – 12s in the on phase and 4s – 30s in the off phase. Three studies commented on the rationale for protocol selection [22, 24, 30]; justifying for pragmatic reasons, protocols previously used successfully in chronic obstructive pulmonary disease (COPD) and in heart failure patients.

Electrode placement: Two studies reported stimulation of the anterior thigh over the quadriceps [22, 24, 25]. One study reported the motor point of the vastus medialis oblique distally, and over the midpoint of the

quadriceps muscle belly more proximally [28]. Crevenna et al., [30] reported quadriceps and gluteal stimulation. Belmonte et al., [23] stimulated areas corresponding to lymphnodal stations. Kuo et al., [29] stimulated the anal canal and Lin et al., [26] placed electrodes between the hyoid bone and thyroid cartilage. One study reported that electrodes were placed in areas according to the clinical indications of motional defects, although no further information was provided by the authors upon request [27].

Session duration: NMES session duration varied from 5 mins [27] to 60 mins [26].

Duration of treatment: Four studies reported treatment durations as the number of sessions delivered (4 sessions: [25]; 12 sessions: [29]; 15 sessions: [26]; 7-12 sessions: [27]. The duration of NMES treatment reported in remaining studies in weeks varied from 2 weeks [23] to 11 weeks [24].

FITT Prescription and progression patterns (Table 2): Only 4 studies reported progression patterns [22, 24, 27, 28]. One study reported progression from 30 min/day to 60 min/day after week 1 [22]. One reported progression from 5 to 15 mins [27]. Two studies reported a progression in the proportion of the treatment which was active stimulation. This progressed weekly from 2s on: 10s off (11%) to 5s on: 25s off (18%) to 10s on: 30s off (25%) and constant there after [22, 24].

Discussion

The overall findings of this study suggest that NMES may be more effective than standard care for improving HR-QoL (Figure 2.). The current evidence does not support the use of NMES over and above usual care for improving submaximal exercise capacity, functional capacity or body composition. Meta-analysis of strength drawn from a total of 44 participants (Figure 3.), showed the overall pooled effect favouring application of NMES for improving muscle strength but results were non-significant. No major adverse events following NMES application in cancer survivors were reported in the studies reviewed. This paper provides a comprehensive overview of the current evidence base in NMES research and oncology, not limited by year, language or study type. However, high risk of bias noted in 3 of the 4 RCTs limits the current conclusions relating to higher level evidence that can be drawn. This is clearly an emerging field with a lack of large, adequately powered RCTs.

Cancer survivors experience poorer HR-QoL in response to disease/treatment [35]. Therefore, this review evaluated the efficacy of NMES for improving domains of HR-QoL. Overall meta-analysis demonstrated effectiveness of NMES over standard care for improving HR-QoL, and in particular function QoL. Conflicting findings were reported in overall studies and mediating factors such as fatigue and exercise intensity must be considered in the interpretation of the findings. Maddocks et al., [24] reported no significant differences between NMES and "no NMES" control across 6 HR-QoL subscales in patients receiving chemotherapy. However, ongoing treatments are linked to increased fatigue levels [36]. Moderate to vigorous intensity voluntary exercise delivered during active treatment has been shown to improve HR-QoL and function QoL [35]. Crevenna et al., [30] reported both improvement in aerobic exercise capacity and better HR-QoL following NMES in a case study, with the exception of the "social functioning" subscale. Therefore, moderate to vigorous intensity NMES prescription which can improve aerobic exercise capacity and dissipate fatigue may be required to see sufficient improvements in HR-QoL subscales such as function QoL.

Specific HR-QoL outcomes were reported in studies for faecal incontinence in low rectal cancer [29] and dysphagia in nasopharyngeal carcinoma patients [26], highlighting the diverse nature of HR-QoL assessment in cancer survivors. In breast cancer patients with lymphedema, Belmonte et al., [23] reported improvements in HR- QoL following NMES which met the minimal clinically important change score as reported by Eton et al., [37], a finding not replicated in the control group receiving manual drainage. While the magnitude of change was larger in the NMES group statistical power was noted as a limitation limiting conclusions that can be drawn.

Interestingly, muscle strength was not a commonly reported outcome and overall, meta-analysis of pooled effect from 2 RCTs did not demonstrate effectiveness of NMES over standard care in this outcome. However, two factors must be considered. First, Maddocks et al [22] reported similar improvements in lower limb muscle strength (+22%) to those reported in a healthy elderly population (+15%) after 8 weeks of HF-NMES [13]. A small sample size conferring a lack of statistical power may have contributed to this finding. Secondly, poor adherence to un-supervised home-based interventions may lead to an inadequate exercise dosage for a training effect. Exercise intensity, mostly reported as visible muscle contractions or maximum tolerable intensities may also be a contributing factor. Strength improvements from NMES are linearly related to NMES training intensity and therapeutic exercise intensities of 15-25% of maximal voluntary contraction (MVC) have been

noted [38]. No studies included in this review reported training intensity as a percentage of MVC. In addition, a habituation period of 1-2 may be required to achieve these strengthening thresholds and to identify non-responders [19]. Indeed, 10% of patient groups and elderly cohorts do not tolerate NMES [19, 39] and an extended intervention period may be required to realise the true magnitude of adaptation to NMES stimulus in the elderly [40]. Therefore, habituation to NMES should be considered in future studies. This will allow practitioners to identify non-responders, and for them consider alternative therapeutic strategies.

The optimal parameters for the safe use of NMES across all cancer populations cannot be determined from the studies included in this review. Only 3 studies [22, 24, 30] explicitly reported no adverse events and these were all related to individuals with lung cancer (NSCLC and metastatic lung cancer). NMES, in the main appeared to be well tolerated with only one study reporting minor adverse events [23]. Skin irritations are not uncommon in NMES application [41], however it is interesting to note the population (post breast cancer lymphedema patients) and the treatment parameters employed in this case (Carrier frequency -0.31-6.16Hz, modulation between 400-1200Hz, low offset voltage between +12 and -12 V). The author did report that after stimulation intensity was reduced, skin irritations did not reoccur. The high intensity in this study was likely required due to the higher levels of fluid present within the tissue.

Prescription and progression patterns relating to NMES treatment provided to adult cancer survivors appears to be underdeveloped and a lack of standardisation was evident across studies. Despite a call for standardisation over 30 years ago [42], this remains a common find in NMES research [43]. The diverse cancer populations in the included studies is acknowledged and may in part contribute to this finding with respect to the site of application, and variables such as frequency and intensity, and electrode size and placement. NMES was predominantly prescribed in those unable to partake in voluntary exercise due to their underlying disease or who were determined to be at risk of harm [30] and to combat secondary complications of cancer treatment relating to muscle weakness with 7 studies involving participants who were post treatment. Studies included in this review where indices of physical function were the primary outcomes [22, 24, 30, 44] adopted a homogenous prescription approach (3-5x/week, 50-63.3Hz, 300-400us). Although this prescription has been successful and safe in other patient groups (i.e. COPD, CHF), including those with implantable cardioverter defibrillators (when delivered to lower imbs) [45, 46], such a general approach in cancer survivors may mask NMES's potential, given that cancer survivors can experience day to day variability in their readiness to train. The

prescription of voluntary exercise in cancer survivorship is mostly individualised and adapted to optimise the therapeutic effect and minimise injury [47]. However, whilst voluntary exercise prescription adheres to the principles of training, NMES prescription in cancer survivors currently does not.

Specificity, the prescription of exercise designed to improve the primary outcome of interest, is another recognised principle of exercise training in cancer survivorship [47] that warrants further consideration in NMES prescription to improve physical function. Three of the included studies which considered the effects of NMES on submaximal exercise capacity employed high frequency protocols (50-63.3Hz), and demonstrated negative results. The application of high frequency NMES favours adaptations in muscle strength [12]. Current exercise oncology guidelines recommend the inclusion of aerobic exercise [6] and where the outcomes of interest include both strength and exercise capacity, employing both low and high frequency NMES modalities may be more efficacious in future studies with acknowledgement that adaptations to low and high frequency NMES are uniquely different [48].

In this review, NMES sessions were mostly delivered in the hospital or rehabilitation and outpatient clinics with only 3 being home-based interventions. Supervised sessions allow for regular oversight and are pragmatic as dose and compliance can be easily monitored. However, patient preferences may lean towards home-based interventions [9]. Self-report diaries are commonly used to monitor adherence to unsupervised home-based interventions; however, over-reporting is common [49]. Therefore, it is possible home-based NMES may suffer from these same limitations, potentially masking benefits to primary outcomes. Future studies should consider cancer type and use adequate methods to monitor adherence for home-based interventions such as regular home visits or technologies such as app based systems which can be used to monitor adherence, collect data and provide remote support [50].

Conclusion

The use of NMES in cancer rehabilitation is an emerging field. The current literature is limited by studies of poor quality and a lack of adequately powered RCTs. Existing studies suggest that NMES is safe and may be more effective than usual care for improving HR-QoL. However, its effects on objective measures of strength, body composition and functional measures is less clear. A periodised approach including greater progression and defined prescriptive guidelines to maximise adherence to NMES prescription in the future may help

improve its efficacy. High quality RCTs in cancer survivorship to definitively evaluate the effectiveness of NMES are required where the parameters chosen and progression patterns are tailored to the individual and outcomes of interest.

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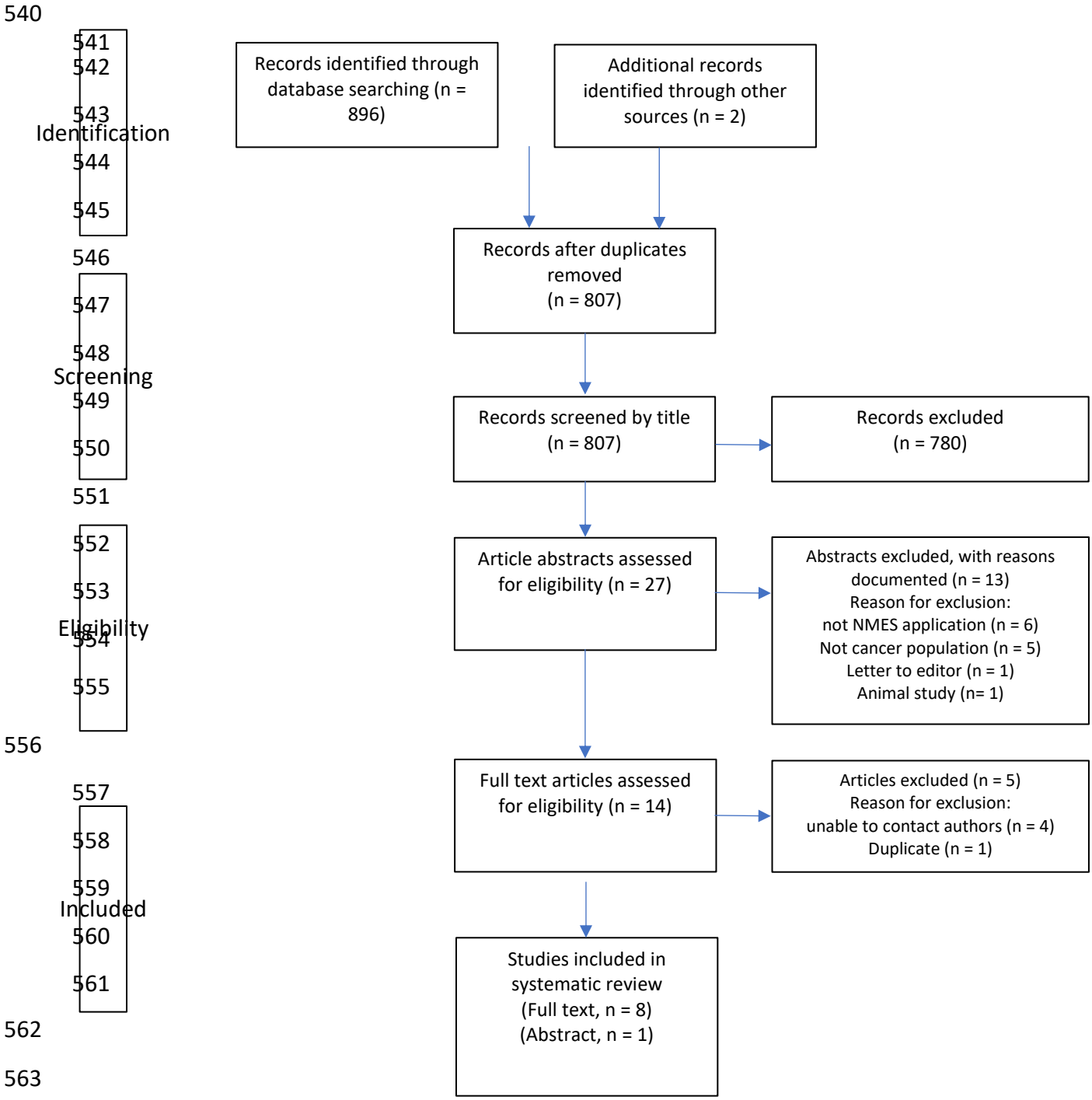

Figure 1. PRISMA flow diagram of the study selection process

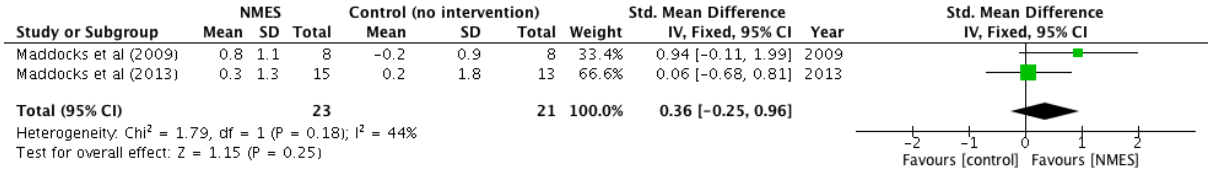

Figure 2. Pooled analysis of strength for NMES versus usual care.

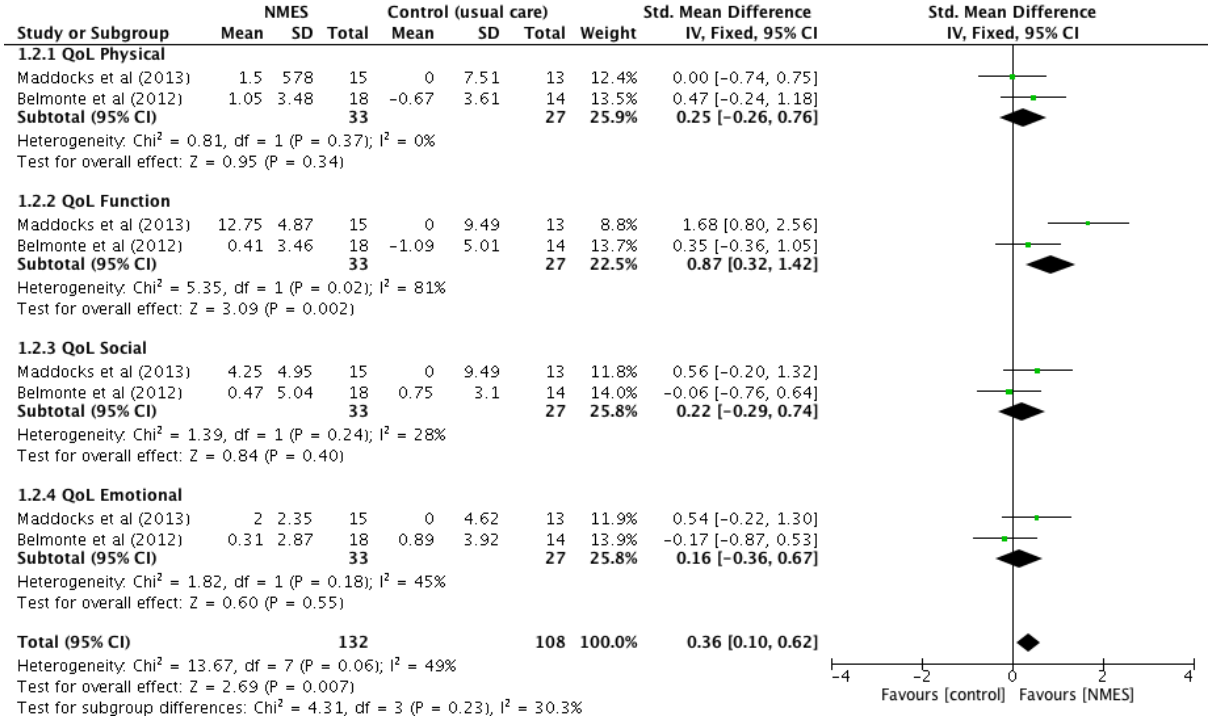

Figure 3. Pooled analysis of NMES versus usual care in HR-QoL domains