EFFECTS OF EXERCISE THERAPY ON DIABETIC NEUROPATHY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Objective: To evaluate the effects of exercise therapy on neuropathic symptoms, signs, psychosocial aspects, and physical function in people with diabetic neuropathy (DN).

Methods: A search in PubMed, Web of Science, Physiotherapy Evidence (PEDro), and Cochrane databases was performed from inception to 24th February 2023. Randomized clinical trials (RCTs) were selected in patients with DN comparing exercise therapy with a control group. The studies' methodological quality was assessed with the PEDro scale. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the overall quality.

Results: Eleven RCTs (n=517 participants) were included. Nine studies showed high methodological quality. Mean (MD) and standardized mean differences (SMD) were observed in favor of exercise therapy for symptoms (MD= -1.05; confidence interval 95%= -1.90 to -0.20), signs (SMD= -0.66; confidence interval 95%= -1 to -0.32), and physical function (SMD= -0.45; confidence interval 95%= -0.66 to -0.24). No changes were found in psychosocial aspects (SMD= -0.37; confidence interval 95%= -0.92 to 0.18). The overall quality of evidence was very low.

Conclusion: The quality of evidence suggesting that exercise therapy provides short-term benefits in neuropathic symptoms, signs, and physical function in patients with DN is very low. Furthermore, there were no effects found on psychosocial aspects.

Keywords: diabetic neuropathy; therapeutic exercise; meta-analysis; systematic review

INTRODUCTION

Peripheral neuropathies could be caused by systemic or local affectation. In both cases, the clinical affectations are characterized by sensory, motor, autonomic, or mixed symptoms and signs (Rosenberger et al, 2020). One of the most prevalent peripheral neuropathies is diabetic neuropathy (DN) (Jensen et al, 2011; Singer, Vernino, and Wolfe, 2012). The global prevalence of diabetes mellitus has increased over the last years, with three million more adults affected since 2014. In 2019, 425 million patients (8.6%) were reported worldwide and 629 million are expected by 2045. Between 30 and 40% of patients with Diabetes Mellitus suffer from neuropathic pain (United Nations, 2022).

Diabetes Mellitus is characterized by disturbances in the glycemic control that results in high blood glucose levels. The high levels of glucose primarily affect different types of cells, such as vascular cells, Schwann cells, and neurons of the peripheral and central nervous system. This limits the capacity to regulate glucose levels, leading to an increase in endoneural capillary density and subsequent ischemia of the neural tissue. Additionally, vascular disturbances in the nervous system could cause hypoxia and less neural function (Tesfaye, Harris, Wilson, and Ward, 1992; Thrainsdottir et al, 2003).

Clinically, DN is characterized by sensory disturbance, hypo- or hypersensitivity, allodynia, or hyperalgesia. In most cases, DN affects the feet, calves and, in advanced cases, the upper extremities (Jensen and Finnerup, 2014). More than 50% of the patients with DN refer to high-intensity pain that influences negatively on work and social activities (Sadosky et al, 2015). Also, it has been related to psychosocial alterations decreasing the quality of life. Many patients with DN experience high levels of anxiety and depression, probably associated with pain interference in daily activities (Alleman et al, 2015; Finnerup et al, 2015, 2016).

To manage Diabetes Mellitus, the Spanish Society of Endocrinology and Nutrition recommends a comprehensive approach that includes individualized exercise therapy and therapeutic education (Spanish Society of Endocrinology and Nutrition, 2022). Exercise has shown to improve blood glucose level in patients with Diabetes Mellitus. Depending on the type of exercise, baseline physical condition and post-exercise recovery the level of insulin could change by the regulation of hormones (Gargallo-Fernández et al, 2022; Savikj and Zierath, 2020).

Therapeutic exercise refers to any patient-adapted physical activity prescribed to achieve therapeutic goals. Aerobic, strengthening, sensorimotor and mobility training have been suggested for patients with different neuropathies (Streckmann et al, 2022). Additionally, multimodal approaches have been proposed, including psychosocial therapy combined with therapeutic exercise (Van Laake-Geelen et al, 2019) or the integration of exercise with nutritional interventions (Zilliox and Russell, 2019). In the case of DN, therapeutic exercise has shown to improve posture, balance, and reduce the fear of falling (De Oliveira Lima, Piemonte, Nogueira, and Nunes-Nogueira, 2021; Thukral, Kaur, and Malik, 2020). However, the current evidence base has low level of certainty (Thukral, Kaur, and Malik, 2020), and the effects of exercise on symptoms and other clinical or psychosocial aspects of DN are still unclear.

Thus, the objective of this systematic review and meta-analysis was to evaluate the effects of therapeutic exercise in patients diagnosed with DN in terms of symptoms, signs, psychosocial aspects, and physical function.

MATERIALS AND METHODS

Study design

The protocol of this systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration code CRD42022308064. This study was carried out following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (Shamseer et al, 2015).

Search strategy

The bibliographical search was conducted in PubMed, Web of Science (WoS), Physiotherapy Evidence Database (PEDro) and Cochrane Library from inception to 24 February 2023. Medical Subject Headings (MeSH) and keywords "diabetic neuropathy", "diabetic neuropathies", "diabetic neuralgia", "exercise" and "physical activity" were combined linked with the Boolean operators (AND, OR) to the search strategy. The search strategy is shown in Appendix A.

Study selection

The included studies met the following criteria: (1) patients diagnosed with DN in the lower limbs; (2) exercise-based interventions, defined as any physical activity (e.g. aerobic, strengthening, sensorimotor, or its combination) targeted to achieve specific therapeutic goals; (3) comparison based on usual care, non-exercise conservative interventions, or no interventions; (4) outcomes consisted of neuropathic symptoms, signs, psychosocial aspects (anxiety, depression), and/or physical function as dependent variables; (5) randomized controlled trials (RCTs); (6) English or Spanish language. The exclusion criteria were: (1) no DN specific diagnostic; (2) inclusion of patients with ulcers in the lower limbs; (3) exercise interventions combined with other treatment modalities such as specific educational programs, whole-body vibration, electrotherapy, manual therapy, or invasive therapies; (4) pharmacological or surgical treatment as a primary intervention.

Data extraction

Two reviewers independently (IH and SJ) assessed title and abstract to select potentially relevant studies. The studies were considered potentially relevant if both reviewers selected them. Disagreements were resolved by a third reviewer (RM). Then, the same independent reviewers extracted the full manuscript of each abstract for detailed full-text review, quality evidence analysis, and data extraction.

The data extraction process was performed following the standardize process adapted from the Cochrane Collaboration including: 1) characteristics of the study population; 2) characteristics of the interventions; 3) outcome measures; 4) results; and 5) follow-up periods. Both reviewers compared the information and the third reviewer resolved any possible discrepancy.

Quality assessment

The PEDro scale was applied to assess the methodological quality of each study. The PEDro scale is an 11-item scale based on the Delphi list (Verhagen et al, 1998). The first item is related to external validity and was not taken into account for the total score (10 points). Each item is scored with yes or no, and a point is added for each affirmative answer. The PEDro scale has been validated to assess the methodological quality of clinical trials, with moderate inter-rater reliability (Maher et al, 2003; de Morton, 2009). A score <6 was considered low methodological quality (Hahne, Ford, and McMeeken, 2010; Umehara and Tanaka, 2018). Methodological quality of the studies was assessed by the same independent reviewers and discrepancies were resolved by a third reviewer.

Evidence quality of each meta-analysis was assessed by two investigators using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADE evidence profiles and tables were made using the GRADE pro software, based on the data obtained in the meta-analyses and the PEDro scale scores. The overall classification categorizes the evidence into 4 levels: high, moderate, low, or very low. The evidence quality was downgraded based on the presence of risk of bias, inconsistency of results, indirectness of evidence, and imprecision (Cohen, 1988; The Cochrane Colaboration, 2019; Xie and Machado, 2021). The criteria established for the downgrading of evidence in each domain are detailed in Table 1.

Data analysis and synthesis

A qualitative synthesis of results was carried out according to the proposed objectives. Four different meta-analyses were performed for the outcomes of signs, symptoms, physical function, and psychosocial aspects (anxiety and depression). Short-term assessment mean, standard deviation (SD), and sample size from each group were extracted. The between-groups mean differences (MD) and SDs were used.

Data were pooled for meta-analysis using a minimum of two trials assessed as clinically homogeneous. A statistical significance value of $p<0.05$ was determined. The 95% confidence interval (95% CI) of standardized mean difference (SMD) were presented in the forest plots. Trials were considered homogeneous if there was a common intervention and outcome measures. Moderate to high heterogeneity were considered if the I^2 value exceeded 50%. The scores were transformed according to Cochrane recommendations when the studies used two or more different measurement tools for the same outcome (The Cochrane Colaboration, 2019). All meta-analyses were conducted using RevMan 5.4 software.

To test each study's influence, we visually examined the forest plot and performed an exclusion sensitivity analysis. Funnel plots asymmetry to assess publication bias in the meta-analyses was not conducted in this study because the meta-analysis did not meet the rule of at least 10 trials included.

RESULTS

Characteristics of the eligible studies

The search yielded 2621 records. Eleven RTCs (n= 517 participants) were eligible for inclusion in the qualitative and quantitative synthesis. The description of the selection process is shown in the PRISMA flowchart diagram (Figure 1).

[Insert Figure 1]

The included studies were published from 2014 to 2022. The mean ages of the participants ranged from 52 to 72 years, 50.1% were women and 49.9% men. The sample size was different in the included studies, only 1 RCT recruited more than 100 participants (Venkataraman et al, 2019), 3 RCTs selected more than 50 participants (Monteiro et al, 2022; Sartor et al, 2014; Toth, Brady, Gagnon, and Wigglesworth, 2014), and 4 RCTs recruited less than 30 participants (Abdelbasset et al, 2020; Cruvinel-Júnior et al, 2022; Gholami, Khaki, Mirzaei, and Howatson, 2021; Parsa, Attarzadeh Hosseini, Bije, and Hamedi Nia, 2018; Perrin et al, 2021).

Exercise therapy interventions lasted from 8 to 24 weeks. The average training frequency was 2.5 weekly sessions, with a minimum of 1 (Venkataraman et al, 2019) and a maximum of 5 sessions (Parsa, Attarzadeh Hosseini, Bije, and Hamedi Nia, 2018). The duration of each session ranged from 15 to 90 minutes. Most of the studies used combined exercise types (Monteiro et al, 2022; Parsa, Attarzadeh Hosseini, Bije, and Hamedi Nia, 2018; Perrin et al, 2021; Sartor et al, 2014; Toth, Brady, Gagnon, and Wigglesworth, 2014; Venkataraman et al, 2019; Vrátná et al, 2022); aerobic exercise and strengthening were combined in 3 studies (Parsa, Attarzadeh Hosseini, Bije, and Hamedi Nia, 2018; Perrin et al, 2021; Venkataraman et al, 2019), balance training was also used in mixed exercise interventions (Monteiro et al, 2022; Sartor et al, 2014; Venkataraman et al, 2019; Vrátná et al, 2022). Other studies applied proprioceptive (Abdelbasset et al, 2020), resistance (Gholami, Khaki, Mirzaei, and Howatson, 2021), or aerobic training (Gholami, Nazari, and Alimi, 2020) in isolation. Eight studies compared exercise therapy with no intervention (Abdelbasset et al, 2020; Gholami, Khaki, Mirzaei, and Howatson, 2021; Gholami, Nazari, and Alimi, 2020; Monteiro et al, 2022; Parsa, Attarzadeh Hosseini, Bije, and Hamedi Nia, 2018; Sartor et al, 2014; Venkataraman et al, 2019; Vrátná et al, 2022), and 2 studies compared exercise with an educational intervention (Perrin et al, 2021; Toth, Brady, Gagnon, and Wigglesworth, 2014). Sociodemographic, clinical, and intervention characteristics of each study are shown in Table 2.

[Insert Table 2]

DN symptoms were assessed in 5 studies using the self-reported section of the Michigan Neuropathy Screening Instrument (MNSI) (Gholami, Khaki, Mirzaei, and Howatson, 2021; Monteiro et al, 2022; Parsa, Attarzadeh Hosseini, Bije, and Hamedi Nia, 2018; Perrin et al, 2021; Sartor et al, 2014). Signs of DN were assessed in 5 studies; 3 studies used the physical examination section of the MNSI (Parsa, Attarzadeh Hosseini, Bije, and Hamedi Nia, 2018; Perrin et al, 2021; Sartor et al, 2014) and 2 studies used the Michigan Diabetic Neuropathy Score (MDNS) (Gholami, Khaki, Mirzaei, and Howatson, 2021; Gholami, Nazari, and Alimi, 2020). Psychosocial aspects were assessed in two studies; anxiety was assessed using the Beck Anxiety Inventory

(Abdelbasset et al, 2020) and the anxiety subscale of the Hospital Anxiety and Depression Scale (Toth, Brady, Gagnon, and Wigglesworth, 2014), and depression was assessed using the Hamilton Depression Rating Scale (Abdelbasset et al, 2020) and the depression subscale of the Hospital Anxiety and Depression Scale (Toth, Brady, Gagnon, and Wigglesworth, 2014). The 6-Minute Walk (Abdelbasset et al, 2020), 30-Second Chair Stand (Perrin et al, 2021; Vrátná et al, 2022), 5 Times Sit-to-Stand and Timed Up and Go tests (Venkataraman et al, 2019) were used to assess physical function. Outcome measures were recorded at baseline and post-intervention (short-term effect) in all studies. Only Monteiro et al. (2022), Cruvinel-Júnior et al. (2022), and Venkataraman et al. (2019) performed follow-up at 4, 9 and 12 months, respectively. Heterogeneity in the outcome measures prevented a quantitative analysis in the medium to long term.

Quality of evidence

According to PEDro scale, 9 studies presented high methodological quality (Abdelbasset et al, 2020; Cruvinel-Júnior et al, 2022; Gholami, Khaki, Mirzaei, and Howatson, 2021; Gholami, Nazari, and Alimi, 2020; Perrin et al, 2021; Sartor et al, 2014; Toth, Brady, Gagnon, and Wigglesworth, 2014; Venkataraman et al, 2019) and 2 studies showed low methodological quality (Parsa, Attarzadeh Hosseini, Bije, and Hamedi Nia, 2018; Vrátná et al, 2022). All studies provided central and dispersion values, and between-group comparisons for the main outcomes. Conversely, no study performed blinding of therapists or participants. The PEDro scores of each study are shown in Table 3.

[Insert Table 3]

Synthesis of results

Effects on neuropathic symptoms

Six RCTs (n= 231) assessed the effects of exercise therapy compared to control on neuropathic symptoms (Cruvinel-Júnior et al, 2022; Gholami, Khaki, Mirzaei, and Howatson, 2021; Monteiro et al, 2022; Parsa, Attarzadeh Hosseini, Bije, and Hamedi Nia, 2018; Perrin et al, 2021; Sartor et al, 2014). Statistically significant differences were observed in favor of exercise therapy (MD= -1.05; 95%CI= -1.90 to -0.2; I^2: 72%) (Figure 2A).

Effects on neuropathic signs

Five RCTs (n= 154) examined the effects on DN signs and were included in the analysis (Gholami, Khaki, Mirzaei, and Howatson, 2021; Gholami, Nazari, and Alimi, 2020; Parsa, Attarzadeh Hosseini, Bije, and Hamedi Nia, 2018; Perrin et al, 2021; Sartor et al, 2014). Statistically significant differences were observed in favor of exercise therapy in the short term (SMD= -0.66; 95%CI= -1 to -0.32; I^2: 43%) (Figure 2B).

Effects on psychosocial aspects

Two RCTs (n= 82) examined the effects of exercise therapy compared to control on psychosocial aspects (Abdelbasset et al, 2020; Toth, Brady, Gagnon, and Wigglesworth, 2014). No statistically significant differences were found in the anxiety level (SMD= -0.26; 95%CI= -1.31 to 0.8; I^2: 80%), the depression level (SMD= -0.52; 95%IC= -1.29 to 0.25; I^2: 62%), or the pooled analysis (SMD= -0.37; 95%CI= -0.92 to 0.18; I^2: 66%) in the short term (Figure 2C).

Effects on physical function

Four RCTs (n= 225) assessed the effects of exercise therapy compared to control on physical function (Abdelbasset et al, 2020; Perrin et al, 2021; Venkataraman et al, 2019;

Vrátná et al, 2022). There were statistically significant differences in favor of exercise therapy in the short term (SMD= -0.45; 95%CI= -0.66 to -0.24; I^2: 37%) (Figure 2D).

The overall quality of evidence according to GRADE was rated as very low for all the outcomes (Table 4).

[Insert Figure 2]

[Insert Table 4]

DISCUSSION

The present systematic review and meta-analysis found that the application of exercise therapy is superior to usual care or non-exercise educational interventions on neuropathic symptoms, signs, and physical function in patients with DN in the short-term, but the overall quality of evidence was very low.

The main reasons for the downgrade of evidence quality according to the GRADE approach were the absence of therapists or participants blinding, heterogeneity in measurement methods and interventions, and small sample sizes. Regarding PEDro scale scores, common methodological flaws were lack of allocation concealment and blinding. Thus, the absence of blinding among therapists and participants resulted in a decrease of the internal study quality and the overall quality of evidence. It should be noted that blinding of therapists may not be practicable in non-pharmacological interventions, but the incorporation of a sham exercise group or blinded assessors could be used to reduce the risk of bias.

The meta-analyses of neuropathic symptoms and signs showed moderate statistically significant improvements in favor of exercise therapy. Parsa et al. (2018) and Perrin et al. (2021) proposed a combined intervention of aerobic exercise and strengthening.

Only Parsa et al. (2018) achieved statistically significant benefits, probably due to a longer intervention (16 weeks vs. 8 weeks). The primary exercise intervention lasted for 12 weeks, with a frequency of 3 sessions per week. From a clinical perspective, these parameters appear to be the most consistent for improving neuropathic signs and symptoms in DN patients, and longer interventions may also be effective. However, further high quality studies are needed to confirm these hypotheses. The type of exercise were different in the studies: aerobic (Gholami, Nazari, and Alimi, 2020) or resistance exercises (Gholami, Khaki, Mirzaei, and Howatson, 2021); global (Gholami, Khaki, Mirzaei, and Howatson, 2021; Gholami, Nazari, and Alimi, 2020) or foot and ankle-targeted exercises (Cruvinel-Júnior et al, 2022; Monteiro et al, 2022; Sartor et al, 2014); and isolated (Gholami, Khaki, Mirzaei, and Howatson, 2021; Gholami, Nazari, and Alimi, 2020) or combined exercises (Monteiro et al, 2022; Sartor et al, 2014). Thus, the heterogeneous interventions in the studies could condition the results. The RTCs included in the meta-analyses used the MNSI self-report questionnaire was used to assess pain, sensitivity, and perceived weakness as neuropathic symptoms, while physical examination tools (MNSI and MDNS) were used to assess the main signs of DN. Other meta-analyses showed improvements on total MNSI scores (Tatikola et al, 2022) and nerve conduction velocity (Streckmann et al, 2022) in patients with different neuropathies. However, we found no meta-analysis independently assessing symptoms and signs of DN after the exercise therapy intervention.

The meta-analysis of physical function showed differences in favor of exercise therapy. Although the intervention length varied slightly (8 to 12 weeks) in the studies included, the frequency of sessions ranged from 1 to 4 sessions per week and there was greater variability in the forms of exercise application. Regarding the type of exercise, the studies applied proprioceptive training in isolation (Abdelbasset et al, 2020) or combined exercise programs with different components such as strengthening, aerobic, ankle mobility, stretching, proprioceptive, and/or balance (Perrin et al, 2021; Venkataraman et al, 2019; Vrátná et al, 2022). Different tools were used to assess physical function among studies, but all of them measured the ability to walk and/or sit-to-stand. The quality of evidence probably has been reduced by the heterogeneity of the intervention and measurement methods.

Therapeutic exercise appears to have a positive impact on patients with DN by reducing pro-inflammatory levels and promoting cardiovascular and neuromuscular adaptations leading to potential improvements in physical function, signs, and symptoms (Chapman et al, 2017; Cobianchi, Arbat-Plana, López-Álvarez, and Navarro, 2017; Thakur et al, 2022), consequently resulting in a positive impact on activities of daily living. Additionally, as previous studies have reported, patients with DN often lead an inactive lifestyle due to pain and impaired physical function (Correia et al, 2021; McCarthy, Davey, Wackers, and Chyun, 2014). The improvements shown after the intervention based on exercise therapy could be a relevant factor to avoid sedentary behavior.

Only two studies were included in the meta-analysis of psychosocial aspects (Abdelbasset et al, 2020; Toth, Brady, Gagnon, and Wigglesworth, 2014). Abdelbasset et al. (2020) found statistically significant improvements after the application of an intervention based on proprioceptive on the lower limbs. Toth et al. (2014) found no difference after the intervention consisted of aerobic exercise and stretching. Thus, exercise therapy applied in isolation could not be enough to achieve an impact in psychosocial status, but there was limited evidence that generates low certainty. Since Diabetes Mellitus is a chronic condition that usually courses with anxiety and depression (Abuhegazy et al, 2022; Mersha, Tollosa, Bagade, and Eftekhari, 2022), the implementation of educational interventions could be beneficial for psychosocial status of patients with DN.

From a clinical perspective, these results suggested with very low certainty that exercise therapy may be useful for improving neuropathic symptoms, signs, and physical function in patients with DN in the short term. The addition of other treatment modalities may be required to achieve improvements in psychosocial well-being. Mixed exercise interventions are the most commonly proposed, but the most beneficial components are unknown. No medium or long-term effects were reported due to the lack of follow-up in the eligible studies. Therefore, the exhaustive literature search, the methodological consistency, and rigorous data extraction and analysis were considered the main strengths. Some important limitations were the inadequate or unspecific description of the interventions, the heterogeneity in measurement methods and interventions, the small sample sizes, and the small number of studies included in the meta-analyses. Finally, medium- (Venkataraman et al, 2019) or long-term (Monteiro et al, 2022) outcomes were provided by two studies but different outcome measures were assessed, which prevented us from conducting a quantitative analysis.

Future studies should provide a more specific and standardized description of exercise interventions for better applicability. In addition, medium- and long-term effects of exercise therapy should be investigated using homogeneous, valid and reliable measurement tools, such as the MNSI.

CONCLUSION

The results of this systematic review and meta-analysis found very low quality of evidence suggesting that exercise therapy provide short-term benefits in neuropathic symptoms, signs, and physical function in patients with DN, but no effects were found in psychosocial aspects. Exercise interventions lasting for around 12 weeks, with 3 sessions per week, based on mixed exercise programs, have been commonly proposed for these patients. However, additional research is necessary to determine the optimal training protocol, as well as to determine the medium- and long term effects of exercise therapy in patients with DN.

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REFERENCES

Abdelbasset WK, Alrawaili SM, Nambi G, Yassen E, Moawd SA, Ahmed AS 2020 Therapeutic effects of proprioceptive exercise on functional capacity, anxiety, and depression in patients with diabetic neuropathy: a 2-month prospective study. Clinical Rheumatology 39: 3091–3097.

Abuhegazy H, Mujairi A, Banah F, Agdi Y, Elkeshishi H, Kamel A, Abdullah A, Elsheikh M 2022 Depression and Associated Risk Factors Among Type 2 Diabetic Patients: A Cross Sectional Study on a Convenience Sample from the Diabetic Center, Khamis Mushait; Saudi Arabia. Neuropsychiatric Disease and Treatment 18: 1975–1984.

Alleman CJM, Westerhout KY, Hensen M, Chambers C, Stoker M, Long S, Nooten FE van 2015 Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: A review of the literature. Diabetes Research and Clinical Practice 109: 215–225.

Chapman A, Meyer C, Renehan E, Hill KD, Browning CJ 2017 Exercise interventions for the improvement of falls-related outcomes among older adults with diabetes mellitus: A systematic review and meta-analyses. Journal of Diabetes and Its Complications 31: 631–645.

Cobianchi S, Arbat-Plana A, López-Álvarez VM, Navarro X 2017 Neuroprotective Effects of Exercise Treatments After Injury: The Dual Role of Neurotrophic Factors. Current Neuropharmacology 15: 495.

Cohen J 1988 Statistical Power Analysis for the Behavioral Sciences. Statistical Power Analysis for the Behavioral Sciences. New York: Routledge.

Correia MA, Silva GO, Longano P, Trombetta IC, Consolim-Colombo F, Puech-Leão P, Wolosker N, Cucato GG, Ritti-Dias RM 2021 In peripheral artery disease, diabetes is associated with reduced physical activity level and physical function and impaired cardiac autonomic control: A cross-sectional study. Annals of Physical and Rehabilitation Medicine 64: 101365.

Cruvinel-Júnior RH, Ferreira JSSP, Veríssimo JL, Monteiro RL, Suda EY, Silva ÉQ, Sacco ICN 2022 Could an Internet-Based Foot–Ankle Therapeutic Exercise Program Modify Clinical Outcomes and Gait Biomechanics in People with Diabetic Neuropathy? A Clinical Proof-of-Concept Study. Sensors 22: 9582.

Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, et al 2015 Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet Neurology 14: 162–173.

Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DLH, Bouhassira D, Cruccu G, Freeman R, Hansson P, Nurmikko T, et al 2016 Neuropathic pain: an updated grading system for research and clinical practice. Pain 157: 1599–1606.

Gargallo-Fernández M, Escalada-San Martín J, Chico-Ballesteros A, Lecumberri-Pascual E, Tejera-Pérez C, Fernández-García JC, Rozas-Moreno P, Marco-Martínez A, Gómez-Peralta F, López- Fernández J 2022 Executive summary of the consensus statement of: Clinical recommendations for sport practice in people with diabetes (RECORD Guide). Update 2021. Diabetes Mellitus Area of the Spanish Society of Endocrinology and Nutrition (SEEN).

Endocrinologia, Diabetes y Nutricion 69: 732–743.

Gholami F, Khaki R, Mirzaei B, Howatson G 2021 Resistance training improves nerve conduction and arterial stiffness in older adults with diabetic distal symmetrical polyneuropathy: A randomized controlled trial. Experimental Gerontology 153: 111481.

Gholami F, Nazari H, Alimi M 2020 Cycle Training improves vascular function and neuropathic symptoms in patients with type 2 diabetes and peripheral neuropathy: A randomized controlled trial. Experimental Gerontology 131: 110799.

Hahne AJ, Ford JJ, McMeeken JM 2010 Conservative management of lumbar disc herniation with associated radiculopathy: A systematic review. Spine 35: E488-504.

Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, Treede RD 2011 A new definition of neuropathic pain. Pain 152: 2204–2205.

Jensen TS, Finnerup NB 2014 Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. The Lancet Neurology 13: 924–935.

Laake-Geelen CCM Van, Smeets RJEM, Quadflieg SPAB, Kleijnen J, Verbunt JA 2019 The effect of exercise therapy combined with psychological therapy on physical activity and quality of life in patients with painful diabetic neuropathy: a systematic review. Scandinavian Journal of Pain 19: 433–439.

Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M 2003 Reliability of the PEDro Scale for Rating Quality of Randomized Controlled Trials. Physical Therapy 83: 713–721.

McCarthy MM, Davey J, Wackers FJT, Chyun DA 2014 Predictors of physical inactivity in men and women with type 2 diabetes from the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. The Diabetes Educator 40: 678–687.

Mersha AG, Tollosa DN, Bagade T, Eftekhari P 2022 A bidirectional relationship between diabetes mellitus and anxiety: A systematic review and meta-analysis. Journal of Psychosomatic

Research 162: 110991.

Monteiro RL, Ferreira JSSP, Silva ÉQ, Cruvinel-Júnior RH, Veríssimo JL, Bus SA, Sacco ICN 2022 Foot–ankle therapeutic exercise program can improve gait speed in people with diabetic neuropathy: a randomized controlled trial. Scientific Reports 12: 7561.

Morton NA de 2009 The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Australian Journal of Physiotherapy 55: 129–133.

Oliveira Lima RA De, Piemonte GA, Nogueira CR, Nunes-Nogueira VDS 2021 Efficacy of exercise on balance, fear of falling, and risk of falls in patients with diabetic peripheral neuropathy: a systematic review and meta-analysis. Archives of Endocrinology and Metabolism 65: 198–211.

Parsa TA, Attarzadeh Hosseini SR, Bije N, Hamedi Nia MR 2018 The Study of the Effect of a 16-Week Program of Resistance-Aerobic Training on BDNF, Hba1c, Pain, and Michigan Neuropathy Score Among Type 2 Diabetic Patients with Peripheral Neuropathy. Journal of Diabetes & Metabolism 9: 811.

Perrin BM, Southon J, McCaig J, Skinner I, Skinner TC, Kingsley MIC 2021 The Effect of Structured Exercise Compared with Education on Neuropathic Signs and Symptoms in People at Risk of Neuropathic Diabetic Foot Ulcers: A Randomized Clinical Trial. Medicina (Lithuania) 58: 59.

Rosenberger DC, Blechschmidt V, Timmerman H, Wolff A, Treede RD 2020 Challenges of neuropathic pain: focus on diabetic neuropathy. Journal of Neural Transmission (Vienna) 127: 589–624.

Sadosky A, Mardekian J, Parsons B, Hopps M, Bienen EJ, Markman J 2015 Healthcare utilization and costs in diabetes relative to the clinical spectrum of painful diabetic peripheral neuropathy. Journal of Diabetes and Its Complications 29: 212–217.

Sartor CD, Hasue RH, Cacciari LP, Butugan MK, Watari R, Pássaro AC, Giacomozzi C, Sacco

IC 2014 Effects of strengthening, stretching and functional training on foot function in patients with diabetic neuropathy: Results of a randomized controlled trial. BMC Musculoskeletal Disorders 15: 137.

Savikj M, Zierath JR 2020 Train like an athlete: applying exercise interventions to manage type 2 diabetes. Diabetologia 63: 1491–1499.

Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Altman DG, Booth A, et al 2015 Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ 350: g7647.

Singer MA, Vernino SA, Wolfe GI 2012 Idiopathic neuropathy: new paradigms, new promise. Journal of the Peripheral Nervous System : JPNS 17: 43–49.

Spanish Society of Endocrinology and Nutrition 2022 Abordaje integral de la diabetes mellitus tipo 2. https://www.seen.es/portal/areas-conocimiento/diabetes/documentos.

Streckmann F, Balke M, Cavaletti G, Toscanelli A, Bloch W, Décard BF, Lehmann HC, Faude O 2022 Exercise and Neuropathy: Systematic Review with Meta-Analysis. Sports Medicine (Auckland, NZ) 52: 1043–1065.

Tatikola SP, Natarajan V, Desai VK, Asirvatham AR, Rajsekhar H 2022 Effect of various exercise protocols on neuropathic pain in individuals with type 2 diabetes with peripheral neuropathy: A systematic review and meta-analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 16: 102603.

Tesfaye S, Harris ND, Wilson RM, Ward JD 1992 Exercise-induced conduction velocity increment: a marker of impaired peripheral nerve blood flow in diabetic neuropathy. Diabetologia 35: 155–159.

Thakur A, Sharma R, Sharma SK, Thakur K, Jelly P 2022 Effect of buerger allen exercise on foot perfusion among patient with diabetes mellitus: A systematic review & meta-analysis. Diabetes & Metabolic Syndrome 16: 102393.

The Cochrane Colaboration 2019 Cochrane handbook for systematic reviews of interventions. Chichester: Wiley & Sons.

Thrainsdottir S, Malik RA, Dahlin LB, Wiksell P, Eriksson KF, Rosén I, Petersson J, Greene DA, Sundkvist G 2003 Endoneurial Capillary Abnormalities Presage Deterioration of Glucose Tolerance and Accompany Peripheral Neuropathy in Man. Diabetes 52: 2615–2622.

Thukral N, Kaur J, Malik M 2020 A Systematic Review and Meta-analysis on Efficacy of Exercise on Posture and Balance in Patients Suffering from Diabetic Neuropathy. Current Diabetes Reviews 17: 332–344.

Toth C, Brady S, Gagnon F, Wigglesworth K 2014 A randomized, single-blind, controlled, parallel assignment study of exercise versus education as adjuvant in the treatment of peripheral neuropathic pain. Clinical Journal of Pain 30: 111–118.

Umehara T, Tanaka R 2018 Effective exercise intervention period for improving body function or activity in patients with knee osteoarthritis undergoing total knee arthroplasty: a systematic review and meta-analysis. Brazilian Journal of Physical Therapy 22: 265.

United Nations 2022 World Population Prospects - Population Division. https://population.un.org/wpp/.

Venkataraman K, Tai BC, Khoo EYH, Tavintharan S, Chandran K, Hwang SW, Phua MSLA, Wee HL, Koh GCH, Tai ES 2019 Short-term strength and balance training does not improve quality of life but improves functional status in individuals with diabetic peripheral neuropathy: a randomised controlled trial. Diabetologia 62: 2200–2210.

Verhagen AP, De-Vet HCW, De-Bie RA, Kessels AGH, Boers M, Bouter LM, Knipschild PG 1998 The Delphi list: A criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology 51: 1235–1241.

Vrátná E, Husáková J, Jarošíková R, Dubský M, Wosková V, Bém R, Jirkovská A, Králová K, Pyšková B, Lánská V, et al 2022 Effects of a 12-Week Interventional Exercise Programme on Muscle Strength, Mobility and Fitness in Patients With Diabetic Foot in Remission: Results From BIONEDIAN Randomised Controlled Trial. Frontiers in Endocrinology 13: 869128.

Xie CX, Machado GC 2021 Clinimetrics: Grading of Recommendations, Assessment, Development and Evaluation (GRADE). Journal of Physiotherapy 67: 66.

Zilliox LA, Russell JW 2019 Physical activity and dietary interventions in diabetic neuropathy: a systematic review. Clinical Autonomic Research : Official Journal of the Clinical Autonomic Research Society 29: 443–455.

Table 1. Criteria for downgrading the quality of evidence in each domain according to the GRADE approach (The Cochrane Colaboration, 2019).

Domains of evidence quality	Downgrading of evidence quality	
	One level	Two levels
Risk of bias	>25% of participants from studies with low methodological quality, lack of randomization or allocation concealment, no sample size estimation, or no participants or assessors blinding.	>50% of participants from studies with low methodological quality, lack of randomization or allocation concealment, no sample size estimation, or no participants or assessors blinding.
Inconsistency of results	Significant heterogeneity in outcome measurement or intervention	
	I^2 value ≥50%	I^2 value ≥75%
Indirectness of evidence	Strict selection criteria established to circumvent indirectness evidence domain reassessment.	
Imprecision	95%CI of an SMD >0.2 points	95%CI of an SMD >0.5 points
	Sample sizes <50 individuals	Sample sizes <30 individuals
	95%CI of the risk ratio crossing the null value	

95% IC: 95% confidence interval; SMD: standardized mean difference.

Table 2. Characteristics of included studies.

Author, year, country	Group characteristics: *N* participants; age ± SD	Type of diabetes	Exercise group (dose, type)	Control group	Outcome (tool)	PEDro score
Cruvinel-Júnior et al, 2022 Brazil	EG: n= 15; 56.5±9.9 CG: n= 15; 51.1±10.2	90% DM type II	12 weeks, 3/week, 20-30 min/session Functional, stretching, and strengthening exercises of the extrinsic and intrinsic foot muscles	Usual care	Symptoms (MNSI)	8/10
Vrátná et al, 2022 Czech Republic	EG: n= 16; 63.7±7.3 CG: n= 16; 66.1±6.5	DM type II	12 weeks, 3-4/week, 150 min/week Ankle mobility and strengthening, stretching, proprioception	Usual care	Physical function (30s-CST)	5/10
Monteiro et al, 2022 Brazil	EG: n= 39; 61.5±11.7 CG: n= 39; 60.1±8.9	-	12 weeks, 4/week Foot and ankle strengthening, gait and balance	Usual care	Symptoms (MNSI)	7/10
Perrin et al, 2021 Australia	EG: n= 10; 70.1±12.9 CG: n= 12; 72.2±7.1	95,8% DM type II	8 weeks, 3/week, 60 min/session Aerobic (50% - 70% HR reserve), strengthening (RPE 7-8/10)	Educational intervention	Signs and symptoms (MNSI) Physical function (30s-CST)	6/10
Gholami et al, 2021 Iran	EG: n= 15; 63±3 CG: n= 14; 64±3	DM type II	12 weeks, 3/week, 90 min/session Resistance (50-60% RM)	Usual care	Symptoms (MNSI) Signs (MDNS)	7/10
Abdelbasset et al, 2020 Saudi Arabia	EG: n= 14; 53.4±5.3 CG: n= 14; 52.8±5.7	DM type II	8 weeks, 3/week, 45 min/session Proprioceptive training focused on the lower limbs	Usual care	Anxiety (BAI) Depression (HDRS) Physical function (6MWT)	7/10
Gholami et al, 2020 Iran	EG: n= 16; 53.4±9.1 CG: n= 15; 52.2±8.5	DM type II	12 weeks, 3/week, 30-45 min/session Aerobic (50%-70% HR reserve)	Usual care	Signs (MDNS)	6/10
Venkataraman et al, 2019 Singapore	EG: n= 70; 62 CG: n= 73; 62	DM type II	8 weeks, 1/week Strengthening, ankle mobility, aerobic, balance	Usual care	Function (TUG, 5STS)	6/10

Parsa et al, 2018 Iran	EG: n= 10; 56.4±4.1 CG: n= 7; 58.7±3.9	DM type II	16 weeks, 3/week Strengthening, aerobic (50-75% HR reserve)	Usual care	Signs and symptoms (MNSI)	3/10
Sartor et al, 2014 Brazil	EG: n= 26; 59±4 CG: n= 29; 60±12	94.5% DM type II	12 weeks, 2/week, 40-60 min/session Ankle mobility and strengthening, balance and gait	Usual care	Signs and symptoms (MNSI)	8/10
Toth, 2014 Canada	EG: n= 28; 54.8±6.7 CG: n= 26; 55.4±7	-	24 weeks, 3-5/week. 15-60 min/session Stretching, aerobic (40-60% HR reserve)	Educational intervention	Anxiety (HADS-A) Depression (HADS-D)	8/10

SD: standard deviation; EG: exercise group; GC: control group; DM: diabetes mellitus; HR: heart rate; RPE: Rating of Perceived Exertion; MNSI: Michigan Neuropathy Screening Instrument, 30s-CST: 30-second Chair Stand Test; MDNS: Michigan Diabetic Neuropathy Score; 6MWT: 6-Minute Walk Test; BAI: Beck Anxiety Inventory; HDRS: Hamilton Depression Rating Scale; TUG: Timed Up and Go test; 5STS: 5 Times Sit-to-Stand test; HADS-A: Hospital Anxiety and Depression Scale – Anxiety Subscale; HADS-D: Hospital Anxiety and Depression Scale – Depression Subscale.

Table 3. PEDro scale scores.

Reference	Items											Total score
	1	2	3	4	5	6	7	8	9	10	11	
Cruvinel-Júnior et al, 2022	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
Vrátná et al, 2022	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5/10
Monteiro et al, 2022	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	7/10
Perrin et al, 2021	Y	Y	Y	N	N	N	Y	Y	N	Y	Y	6/10
Gholami et al, 2021	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7/10
Abdelbasset et al, 2020	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7/10
Gholami et al, 2020	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6/10
Venkataraman et al, 2019	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6/10
Parsa et al, 2018	Y	Y	N	Y	N	N	N	N	N	Y	Y	4/10
Sartor et al, 2014	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
Toth et al, 2014	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10

Out of ten; Y = criterion satisfied and N = criterion not satisfied. 1. Specified eligibility criteria. Not calculated in overall score. 2. Subjects randomly allocated to groups. 3. Concealed allocation. 4. Similar groups at baseline. 5. Blinding of subjects. 6. Blinding of therapists. 7. Blinding of assessors. 8. Measures of key outcomes obtained from more than 85% of those initially allocated to groups. 9. All subjects received the treatment or control condition as allocated or intent-to-treat analysis was performed. 10. Statistical comparisons reported for at least one key outcome. 11. Central and variability measures reported.

Table 4. GRADE assessment of exercise therapy vs. control.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Exercise therapy]	[Control]	Relative (95% CI)	Absolute (95% CI)		
Neuropathic symptoms (assessed with: Michigan Neuropathy Screening Instrument)												
6	randomised trials	serious[a]	serious[d]	not serious	very serious[f,h]	none	115	116	-	MD **1.05 SD lower** (1.90 lower to 0.20 lower)	⨁◯◯◯ Very low	CRITICAL
Signs (assessed with: Michigan Neuropathy Screening Instrument, Michigan Diabetic Neuropathy Score)												
5	randomised trials	serious[a]	serious[e]	not serious	very serious[g,h]	none	77	77	-	SMD **0.66 SD lower** (1 lower to 0.32 lower)	⨁◯◯◯ Very low	CRITICAL
Anxiety (assessed with: Beck Anxiety Inventory, Hospital Anxiety and Depression Scale-Anxiety)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Exercise therapy]	[Control]	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious[a]	very serious[c,e]	not serious	very serious[f,h]	none	42	40	-	SMD **0.26 SD lower** (1.31 lower to 0.8 higher)	⊕◯◯◯ Very low	IMPORTANT
Depression (assessed with: Hamilton Depression Rating Scale, Hospital Anxiety Depression Scale-Depression)												
2	randomised trials	very serious[a,b]	very serious[d,e]	not serious	very serious[f,h]	none	42	40	-	SMD **0.52 SD lower** (1.29 lower to 0.25 higher)	⊕◯◯◯ Very low	IMPORTANT
Physical function (assessed with: 6-Minute Walk, 30-Second Chair Stand, 5 Times Sit-to-Stand, Timed Up and Go)												
4	randomised trials	very serious[a]	serious[e]	not serious	serious[g]	none	110	115	-	SMD **0.45 SD lower** (0.66 lower to 0.24 lower)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; MD: mean difference; SMD: standardized mean difference; SD: standard deviation; a: more than 50% of participants were from studies without blinding of participants or assessors; b: more than 50% of participants were from studies with lack of allocation concealment; c: heterogeneity among results of studies (I^2 ≥75%); d: heterogeneity among results of studies (I^2 ≥50%); e: heterogeneity among measurement methods and interventions; f: 95% CI of SMD >0.5; g: 95% CI of SMD >0.2; h: sample sizes <50 individuals.

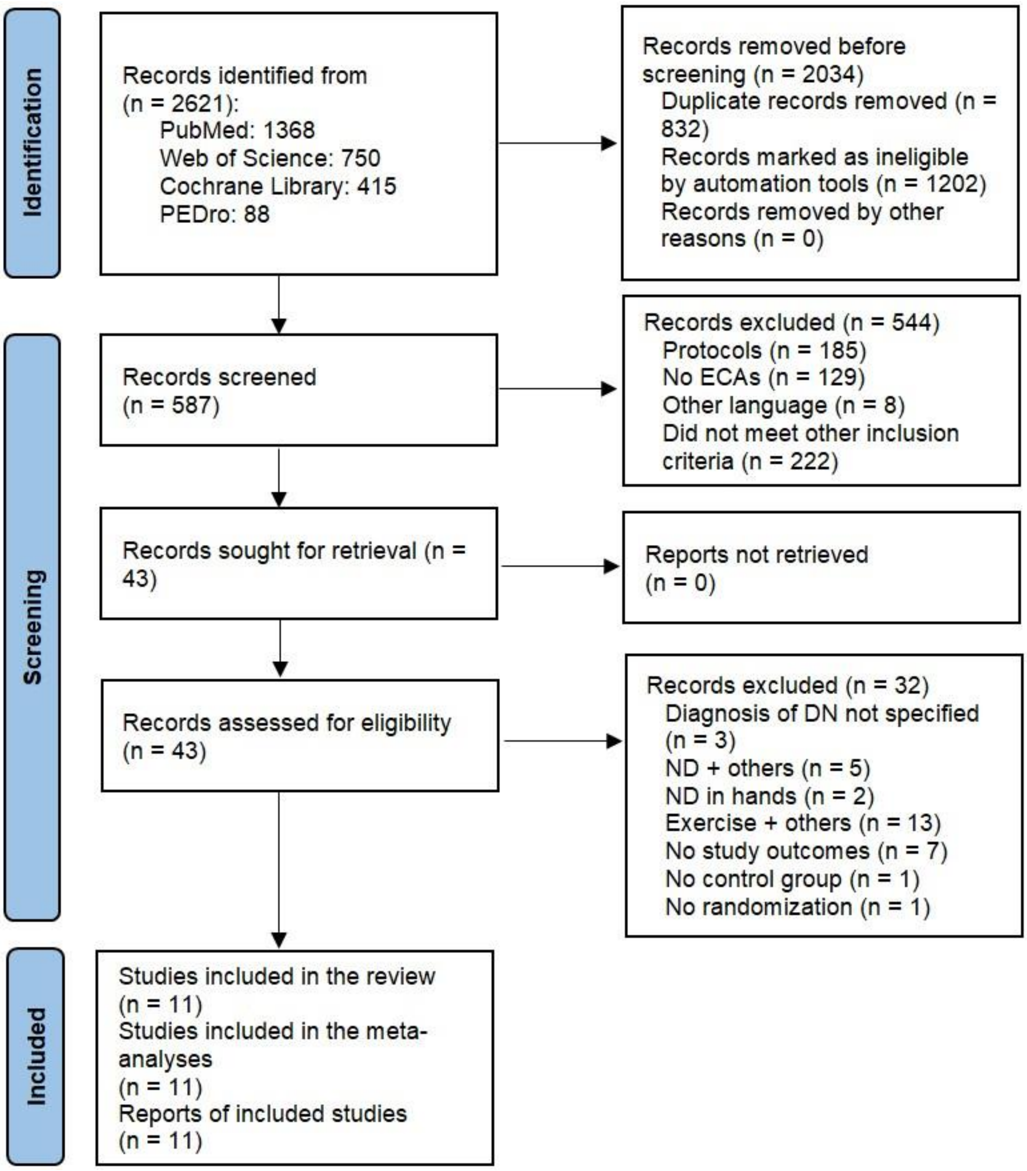
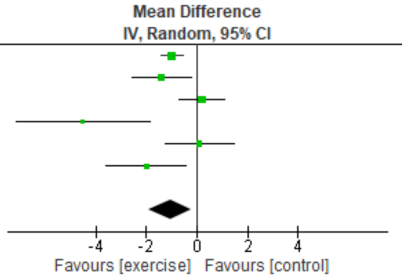


Figure 1. Flow diagram.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cruvinel-Júnior et al. 2022	5.1	0.6	15	6.1	0.6	15	24.9%	-1.00 [-1.43, -0.57]
Gholami et al. 2021	6.6	1.4	15	8	1.79	14	17.6%	-1.40 [-2.58, -0.22]
Monteiro et al. 2022	5.9	1.9	39	5.7	2.2	39	20.4%	0.20 [-0.71, 1.11]
Parsa et al. 2018	1.81	1.32	10	6.33	3.39	7	7.5%	-4.52 [-7.16, -1.88]
Perrin et al. 2021	3.7	1.9	10	3.6	1.2	12	15.8%	0.10 [-1.26, 1.46]
Sartor et al. 2014	4	3	26	6	3	29	13.8%	-2.00 [-3.59, -0.41]
Total (95% CI)			**115**			**116**	**100.0%**	**-1.05 [-1.90, -0.20]**

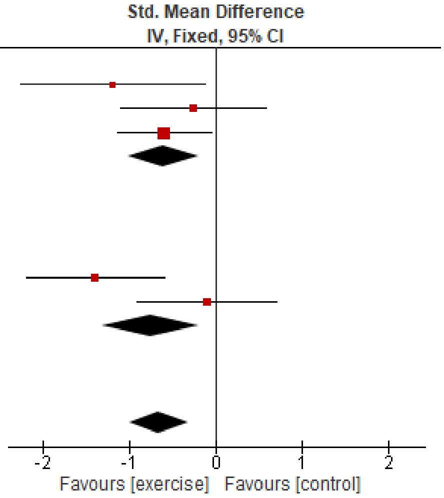
Heterogeneity: Tau² = 0.71; Chi² = 17.63, df = 5 (P = 0.003); I² = 72%
Test for overall effect: Z = 2.43 (P = 0.02)



(A)

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.1.1 Michigan Neuropathy Screening				
Parsa et al. 2018	-1.1978	0.5457	9.9%	-1.20 [-2.27, -0.13]
Perrin et al. 2021	-0.2608	0.4304	16.0%	-0.26 [-1.10, 0.58]
Sartor et al. 2014	-0.6021	0.2766	38.6%	-0.60 [-1.14, -0.06]
Subtotal (95% CI)			**64.5%**	**-0.61 [-1.03, -0.19]**
Heterogeneity: Chi² = 1.82, df = 2 (P = 0.40); I² = 0%				
Test for overall effect: Z = 2.85 (P = 0.004)				
1.1.2 Michigan Diabetic Neuropathy Score				
Gholami et al. 2020	-1.3974	0.4065	17.9%	-1.40 [-2.19, -0.60]
Gholami et al. 2021	-0.1052	0.41	17.6%	-0.11 [-0.91, 0.70]
Subtotal (95% CI)			**35.5%**	**-0.76 [-1.32, -0.19]**
Heterogeneity: Chi² = 5.01, df = 1 (P = 0.03); I² = 80%				
Test for overall effect: Z = 2.62 (P = 0.009)				
Total (95% CI)			**100.0%**	**-0.66 [-1.00, -0.32]**

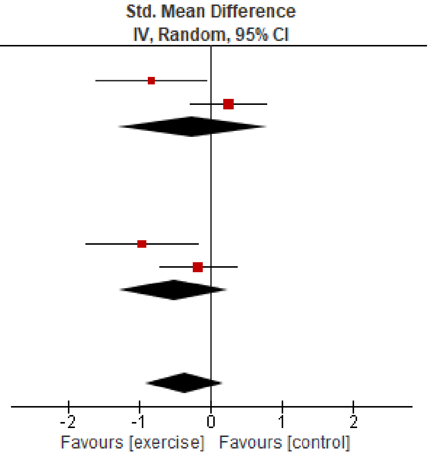
Heterogeneity: Chi² = 7.00, df = 4 (P = 0.14); I² = 43%
Test for overall effect: Z = 3.85 (P = 0.0001)
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%



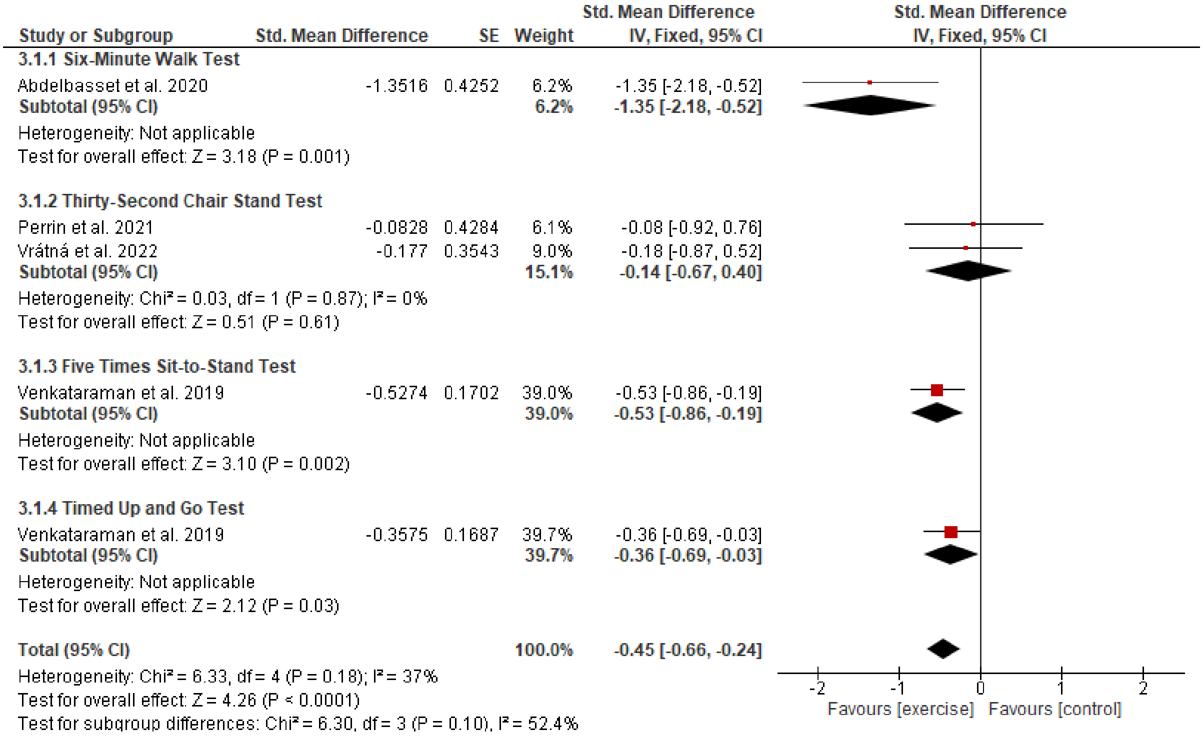
(B)

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
2.4.1 Anxiety				
Abdelbasset et al. 2020	-0.8343	0.3966	21.8%	-0.83 [-1.61, -0.06]
Toth et al. 2014	0.2463	0.2735	28.3%	0.25 [-0.29, 0.78]
Subtotal (95% CI)			**50.1%**	**-0.26 [-1.31, 0.80]**
Heterogeneity: Tau² = 0.47; Chi² = 5.03, df = 1 (P = 0.02); I² = 80%				
Test for overall effect: Z = 0.47 (P = 0.64)				
2.4.2 Depression				
Abdelbasset et al. 2020	-0.968	0.4029	21.5%	-0.97 [-1.76, -0.18]
Toth et al. 2014	-0.1746	0.2729	28.3%	-0.17 [-0.71, 0.36]
Subtotal (95% CI)			**49.9%**	**-0.52 [-1.29, 0.25]**
Heterogeneity: Tau² = 0.20; Chi² = 2.66, df = 1 (P = 0.10); I² = 62%				
Test for overall effect: Z = 1.31 (P = 0.19)				
Total (95% CI)			**100.0%**	**-0.37 [-0.92, 0.18]**

Heterogeneity: Tau² = 0.20; Chi² = 8.71, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%



(C)



(D)

Figure 2. (A) Forest plot of neuropathic symptoms for exercise therapy versus control in the short term. (B) Forest plot of neuropathic signs for exercise therapy versus control in the short term. (C) Forest plot of anxiety, depression and pooled analysis (psychosocial aspects) for exercise therapy versus control in the short term. (D) Forest plot of physical function for exercise therapy versus control in the short term.

Appendix A. Search strategy.

PubMed	#1	("diabetic neuropathies"[MeSH Terms] OR ("diabetic"[All Fields] AND "neuropathies"[All Fields]) OR "diabetic neuropathies"[All Fields] OR ("diabetic"[All Fields] AND "neuropathy"[All Fields]) OR "diabetic neuropathy"[All Fields] OR ("diabetic neuropathies"[MeSH Terms] OR ("diabetic"[All Fields] AND "neuropathies"[All Fields]) OR "diabetic neuropathies"[All Fields]) OR ("diabetic neuropathies"[MeSH Terms] OR ("diabetic"[All Fields] AND "neuropathies"[All Fields]) OR "diabetic neuropathies"[All Fields] OR ("diabetic"[All Fields] AND "neuralgia"[All Fields]) OR "diabetic neuralgia"[All Fields])) AND ("exercise"[MeSH Terms] OR "exercise"[All Fields] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields] OR "exercise s"[All Fields] OR "exercised"[All Fields] OR "exerciser"[All Fields] OR "exercisers"[All Fields] OR "exercising"[All Fields] OR ("exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields]))
		Filter: Clinical trial
Cochrane	#1	(diabetic neuropathies AND exercise) in Title, Abstract, Keywords in Trials
	#2	(diabetic neuropathy AND exercise) in Title, Abstract, Keywords in Trials
	#3	(diabetic neuralgia AND exercise) in Title, Abstract, Keywords in Trials
	#4	#1 OR #2 OR #3
PEDro	#1	“diabetic neuropathy” AND “exercise”
	#2	“diabetic neuropathy” AND “physical activity”

Web of Science	#1	(diabetic neuropathy OR diabetic neuropathies OR diabetic neuralgia) AND (exercise) (Topic)