TITLE PAGE

Running head: Exercise prevents peripheral neuropathy

Title: **Can physical exercise prevent chemotherapy-induced peripheral neuropathy in patients with cancer? A systematic review and meta-analysis.**

Authors:

Maria Lopez-Garzon[a,b,c], MSc

Irene Cantarero-Villanueva[a,b,c,d,e], Ph.D

Paula Postigo-Martin[a,b,c,d], MSc

Ángela González-Santos[a,b,c], MSc

Mario Lozano-Lozano[a,b,c,d,e], Ph.D

Noelia Galiano-Castillo[a,b,c,d,e], Ph.D

Author affilations:

[a]'Cuídate' Support Unit for Oncology Patients (UAPO-Cuídate), University of Granada, Granada, Spain

[b]Department of Physical Therapy, Faculty of Health Sciences, University of Granada. Avenida de la Ilustración 60, 18016, Granada, Spain

[c]Instituto de Investigación Biosanitaria ibs.GRANADA, Av. de Madrid, 15, 18012 Granada, Spain

[d]Sport and Health Joint University Institute (iMUDS). University of Granada Av. del Conocimiento, s/n, 18007 Granada, Spain

[e]Unit of Excellence on Exercise and Health (UCEES), University of Granada, Granada, Spain.

Acknowledgment: This work is part of MLG's doctoral work at the Clinical Medicine and Public Health Doctoral Studies of the University of Granada, Spain.

Acknowledgment of financial support: The study is funded by 'Fondo de Investigación Sanitaria del Instituto de Salud Carlos III' (FI19/00230) and by 'Ministerio Español de Educación Cultura y Deporte' (FPU18/03575 and FPU17/00939).

Conflict of Interest: None

Corresponding author: Ángela González Santos. Address: Avda. de la Ilustración 60, 18016 Granada (Spain). Business telephone number: +34 958249590. E-mail: angelagonzalez@ugr.es

Registration number in PROSPERO: CRD42020214356

Can physical exercise prevent chemotherapy-induced peripheral neuropathy in patients with cancer? A systematic review and meta-analysis.

Abstract

Objective: This systematic review analyzed the effects of physical exercise programs in patients with cancer undergoing chemotherapy on Chemotherapy-induced Peripheral Neuropathy (CIPN) prevention.

Data Sources: PubMed, Web of Science, Scopus, and Cochrane Library were searched for relevant studies published before December 2020. Additional references were identified by manual screening of the reference lists.

Study Selection: Based on the PICOS strategy, randomized controlled trials in which physical exercise was applied before or during chemotherapy to prevent or ameliorate CIPN were included.

Data Extraction: Two reviewers blinded and independent screened the articles, scored methodologic quality, and extracted data for analysis. The review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA). Sensitivity and precision analysis databases was included. Risk of bias assessment and meta-analysis were conducted using the Cochrane tools.

Data Synthesis: Of 229 potentially relevant studies, eight randomized controlled trials were included and scored. They comprise a total of 618 patients with cancer. Medline and Scopus databases recorded the highest sensitivity. None of the studies achieved a “low” overall risk of bias. Four studies were included in meta-analysis for quality of life, and a significance standardized mean difference was found between groups from baseline of 14.62, 95% CI 6.03, 23.20, with a large effect size *g*= .83, 95% CI .48, 1.18) in favor to physical exercise program compared with usual care.

Conclusions: Physical exercise at the onset of chemotherapy has shown promising effects on the prevention of CIPN, specially improving quality of life.

Keywords: chemotherapy, exercise, peripheral nervous system diseases, quality of life, neoplasms

List of abbreviations:

CIPN: Chemotherapy-induced peripheral neuropathy

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of life Questionnaire core 30.

EORCT-CIPN20: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale

FACT/GOG-NTX: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity

FITT: Frequency, intensity, time and type

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines

PROSPERO: International Prospective Register of Ongoing Systematic Reviews

RCT: Randomized controlled trial

TOI: Trial Outcome Index

VAS: Visual Analog Scale

Introduction

The powerful effects of physical exercise are increasingly evident in worldwide populations[1]; its physical, mental and social benefits justify its success against systemic processes such as cancer[2]. In recent decades, physical exercise in patients with cancer has shifted from health to a therapeutic focus[3]. A recognized advance has been the initiation of physical exercise programs in patients who undergo active treatments[4–6]. Some researchers have shown that patients who are physically active following a diagnosis of cancer have a lower risk of cancer recurrence and mortality with less severe side effects[7,8]. Therefore, due to improvements in the immune system and chemotherapy delivery, physical exercise is considered an important adjunct therapy in the management of cancer itself[9]. For that reason, oncologists should encourage their patients (if there is no contraindication) to remain physically active[10]. Physical exercise must be tailored though prescriptions for frequency, intensity, time and type (FITT) following the guideline recommendations[11.]

One of the most commonly used therapeutic applications of physical exercise is to ameliorate chemotherapy-induced peripheral neuropathy (CIPN)[12,13], which is a dose-limiting toxicity exerted on the peripheral nervous system. CIPN symptoms are mainly sensory and usually include acral pain and paraesthesia, accompanied by allodynia and hyperalgesia[14] that appears in the hands and feet, including impaired perception of vibration sense and proprioception[15]. The loss of sensitivity plus possible muscle weakness lead to moderate to severe balance problems, which might result in falls[16,17]. Therefore, considering these symptoms and signs, it is logical to include CIPN among factors involved in the deterioration of a patient's quality of life[18]. This translates into an average $17,344 surcharge as a result of hospitalization and outpatient costs derived from CIPN[19]. CIPN is an alarming process because drugs or complementary therapies are not as effective as expected[20,21]. In contrast, physical exercise programs appear to be feasible and effective at reducing CIPN symptoms[12]. Thus, the impact of CIPN in addition to the associated health costs[19] has led researchers and clinicians to question which dose of physical exercise is more suitable in patients with cancer for prevention of CIPN.

To our knowledge, there are few reviews about the effects of physical exercise programs on CIPN prevention. One analyzed pharmacological and nonpharmacological therapies and revealed that

the level of evidence and grade of recommendation for exercise is IIC[21]; that is, insufficient evidence for efficacy does not outweigh the risk or disadvantages. This statement was justified by a single but well-designed randomized controlled trial (RCT) (although with low power and inconsistent findings). Another narrative review focused on different options for the prevention and treatment of CIPN suggested that exercise may be used in an attempt to avoid occurrences of CIPN[22]. However, this narrative review utilized a basic methodology whose results were inconclusive and called for additional supporting data. Recently, another review focused mainly on behavior and physical exercise[23]. Despite the identified evidence related to existing behavioral and exercise interventions for preventing or managing symptoms of CIPN, Tanay and colleagues[23] were interested in understanding the psychological mechanisms of action that may have influenced an individual to perform exercise to manage CIPN. Among potential records under review, there is one registration related to physical activity and exercise to prevent CIPN in a very early review phase, and it is not yet published[24]. Although it lacks a meta-analysis, its objective is largely focused on falls and impaired balance, although CIPN is a more complex syndrome, as described above. Furthermore, in 2019, A Hammond and colleagues[25] indicated that future research needs to identify the specifics of exercise prescriptions (intensity, frequency, duration, and type) to provide the most benefit for the prevention of CIPN. Thus, there are still some gaps to be addressed. More evidence is needed to justify the prevention or reduction of CIPN incidence as a primary endpoint[26] and to clarify the impact of physical exercise programs on CIPN and related outcomes[27].

In view of works already published, this could be the first systematic review with a meta-analysis that exclusively analyzes physical exercise programs in patients with cancer undergoing chemotherapy with special emphasis on clarifying the key points of physical exercise programs to prevent CIPN. For this reason, the aim of this review is a) to synthesize studies that perform physical exercise during chemotherapy; b) to identify the specific parameters of physical exercise programs that provide the most beneficial prevention of CIPN in patients with cancer; and c) to analyze the most relevant outcomes related to CIPN.

Method

Protocol and registration

To reduce duplication of effort and publication bias[28,29], this study was registered and accepted in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) on 20th November 2020 and can be accessed at https://www.crd.york.ac.uk/prospero/ with the following registration code: CRD42020214356. The registration in PROSPERO was done when preliminary searches and piloting of the study selection process were performed. This study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[30]. The specific question posed for this review was: *What kind of physical exercise program has the greatest effect on the prevention of CIPN in patients with cancer?*

Eligibility criteria

For this review, only published studies until 20th December 2020 were considered. No restrictions were placed on year, but publications were limited by English or Spanish language. Based on the PICOS strategy[31], RCTs in which physical exercise was applied before or during chemotherapy to prevent or ameliorate CIPN were included (Table 1). Prevention of CIPN has been stablished as any therapy administrated prior to the start of chemotherapy (primary prevention) or the appearance of moderate to severe CIPN during medical treatment in order to prevent worsening (secondary prevention)[32].

[INSERT TABLE 1]

Information sources

A detailed literature search was carried out in Medline [via PubMed searcher] (Table 2), Scopus, Web of Science, and Cochrane Library. The literature search was conducted from 20th October to 1st December 2020. Furthermore, an automatic alert notification for new publications was created in all databases. Apart from this, reference lists of retrieved reports were also manually searched for additional references.

Selection of sources of evidence

A literature search was conducted by a single reviewer (MLG) using relevant subject headings, keywords and modifications made according to the databases searched; modifications were made to fit each database. All articles were retrieved and exported to Rayyan where a single reviewer removed duplicates in Rayyan[33]. Then, two independent and blinded reviewers (MLG and AGS) identified and selected titles and abstracts according to the inclusion criteria. All articles identified in the first screening process were included in the following one, in which selected articles were thoroughly read and screened for the inclusion criteria by the same reviewers. Articles considered eligible after full-text view by mutual consent were included in the final analysis. Reasons for exclusion were recorded. In case of disagreement, a third external researcher (NGC) was consulted to make the final decision, and the last researcher calculated the percentage of agreement.

Synthesis of results

The following data will extract from each article by two independent and blinded reviewers review (MLG and AGS): (1) general study details: Title, authors, source, and year of publication; (2) study eligibility: type of study, participants characteristics including, number of participants, age, gender, diagnosis, type of cancer treatment, stage of cancer, methods including design/allocation, blinding, sampling, loss to follow-up, and adherence rates, intervention characteristics including type of physical exercise, types of outcome measures including self-reported outcomes, objective outcomes; (3) study details: details of intervention including, frequency, intensity, time and type, program length, and results of the study. The data extraction was documented in a Microsoft Excel spreadsheet. In addition, a narrative synthesis was carried out according to FITT prescription[11].

Risk of bias and quality of databases

Since one of the inclusion criteria was RCT design, each article was critically appraised using the Cochrane Risk of Bias tool RoB 2[34] by two blinded reviewers (NGC and PPM). The quality of the chosen databases was also determined by sensitivity/precision analysis.

Data analyses

Only those studies that measured quality of life, presented all available data, and used usual care as comparator, were included in our meta-analysis. In those studies, in which the data were not present in the manuscript, the authors were contacted. The data were extracted from the tables, the text of the article, or the images that were digitized using the online tool WebPlotDigitizer v. 4.4 (Pacifica, California, USA)[35]. All studies selected were combined using the random effects model of the DerSimonian and Laird method, which takes into account variations within and between studies. In addition, the Hartung-Knapp adjustment was used considering the uncertainty in the estimation of the variance among the studies of the random effect method[36]. Forest plots were used to visualize individual study summaries and pooled estimates. To assess heterogeneity among studies, the Cochran Q statistics were used along with the I^2 value. A mean difference was calculated for each of the original studies, and a two-sided p-value <.05 was considered statistically significant. Finally, a sensitivity analysis was carried out to study the consistency of the results. Additionally, Hegdes' *g* effect size of each study was calculated in the meta-analysis. Stata software was used to carry out quantitative combination of the studies.

Results

The initial searches returned 229 studies, 54 of which were removed during duplicate screening. The title and abstract screening of the remaining 175 studies resulted in 12 studies meeting the inclusion criteria. Five of these studies were subsequently excluded at the full text phase. One study was added from the reference list, and none were found with automatic alerts. A total of eight studies met the inclusion criteria and were assessed. Interrater agreement in the selection of studies was 48.1%[37]. After discussion, the reviewers reached consensus (100%). Details of the literature search and study selection are shown in Figure 1.

[Insert Figure 1]

Characteristics

A total of 618 patients were included in the narrative synthesis (Table 3). Considering all eight studies, 318 patients were allocated to the intervention group (IG), and 300 of them were allocated

to control group (CG). The sample size of the included studies ranged from 28 to 355 patients, of whom 78% were female, and the average age was 56.63 ± 23.17 years in IG and 57.53 ± 8.56 years in CG. The most predominant type of cancer was breast (17%)[38–41], followed by lymphoma (13%)[41,42], colorectal (8%)[41,43], lung (7%)[41,44], gastrointestinal cancer (4.5%)[45] and others not reported (4%). With respect to treatments, all of them were potentially neurotoxic[46]. The most common was the administration of docetaxel or paclitaxel in cycles distributed every one, two, three or four weeks[38–41]. Additionally, other regimens used were platinum derivatives[41,44] and FOLXOS therapy[43]. All patients were chemotherapy-naïve, except in one[43], where up to 60% of patients had received cycles of chemotherapy prior to the study. In another study the prior use of chemotherapy was not reported[44]. Most studies reported that the time of the physical exercise program coincided with chemotherapy treatment.

Comparator

Seven studies compared IG versus CG[38,40–45], and only one conducted superiority study with physical exercise interventions in all arms[39].

Physical exercise parameters according to FITT prescription[11].

Frequency

Among all eight studies, four studies were committed to exercising twice[38,42,43], three[39], five[44] sessions per week or daily[40,41]. Other authors not specified[45].

Intensity

The most commonly used intensity in endurance proposal was moderate in five studies[38,39,41,42,44]; follow by low-to moderate intensity[43,45] or not specified[40]. Intensity during resistance proposal was moderate[38,39,41–43] or not reported[38].

Time

The duration of physical exercise program was six[41], eight[39,43], 12[39,45], 18[38] or 36[42] weeks. Others not specified[40,44].

There is variability in the total number of sessions used 16[43], 36[38], 42[41], 60[39] and 72[42]. Another study reported 1800 minutes of walking throughout the program[45] or not specified[40,44].

The total session time lasted 15[40], 20-50[45], 60 minutes[41–43], or not specified[38,39,44]. In each session, the time of endurance exercise was ten minutes in two studies[43,44]. Other reported from 10 up to 50 minutes[39,42,45] or not specified[38,41].

Type

Four studies used the multimodal approach in their intervention[38,39,42,43], which included proposals of endurance, resistance and balance, two of them also hand and foot specific exercises[39] or coordination practice[43] were performed. Two studies used a concurrent physical exercise approach that only included endurance and resistance proposals[41,44]. Other physical exercises included nerve gliding exercises[40] and a walking program[45].

The sessions were as follows: supervised[38,42–44], home-based[40,41,45] or a mix between supervised and home-based[39].

Progression

Linear progression in each of the components was used in two studies[41,45]. While other two studies used non-linear- based on symptoms and the HR resting[39] or based on Borg dyspnea scale[44] was performed as endurance physical exercise progression.

Adherence

The intervention with lower average adherence was in patients with lymphoma (65%)[42]. The majority of studies obtained at least 80% adherence[39,43,45]. However, there was a decrease in adherence when resistance proposals were examined, 77%[41]. Three studies not specified[38,40,44].

Adverse effects

Some adverse effects were found, such as cancer recurrence[39], death[43,44], lymphopenia, neutropenia and multiorgan failure[41], hospitalization due to infection and severe fatigue[45]. None of them were directly related to the intervention. Two studies not specified any adverse effects[38,40].

Outcomes:

Neurotoxicity

Zimmer and colleagues[43] used the subscale of Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (FACT/GOG-NTX) and found an intergroup significant difference in favor of IG after intervention (p=.002) and at follow-up (p=.015). Additionally, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale (EORCT-CIPN20) was measured in two studies, but no intergroup significant difference was found[38,39].

Pain in CIPN

Two studies used the visual analog scale (VAS). Kleckner and colleagues[41] found an intergroup significant differences in favor of IG on hot and coldness symptoms (p=.045, *d*=.46, 95% CI .01, .91) after intervention. Hammond and colleagues[40] demonstrated a relevant clinical decrease in pain scores in favor of IG at the end of chemotherapy, although there was no intergroup significant difference.

Vibration sensitivity

Bland and colleagues[39] studied the percentages of participants who presented vibration impairments, and there was an intergroup significant difference in favor of the immediate exercise group (p< .01) at middle chemotherapy. In another study, a tuning fork with a graduating scale from 0 (no sensitivity) to 8 (highest sensitivity) was used, and the average incidence of CIPN was registered. There was an intergroup significant difference in favor of IG among symptoms dismissed (P < .001, 87.5% in IG vs 0% in CG) and the number of patients suffering impaired vibration (P =.002), both after intervention[42]. Other study used a vibration sensory analyzer that delivered random amplitudes while asking patients whether they felt vibration or not and did not find intergroup differences at any time point[40].

Balance

Vollmers and colleagues used the Fullerton Advances Balance Scale and found an intergroup significant difference in favor of IG after intervention (p= .004)[38]. Stuecher and colleagues[45] measured balance in three static standing positions, and their results did not show intergroup significant differences at any time point. Another study also measured dynamic balance, although no intergroup difference was found[43].

Sway area

Vollmers and colleagues[38] found an intergroup significant difference in favor of IG that showed a smaller sway area in monopedal stance after intervention (p< .001) and at follow-up (p< .01) in both feet. Sway area in bipedal stance also showed an intergroup significant difference in favor of IG after intervention (p= .039). Stuecher and colleagues[45] measured sway area on a static surface while patients stood bipodal and demonstrated an intergroup significant difference in favor of IG during middle chemotherapy (p= .001, *d*= .59, 95% CI -.10, 1.26) and after intervention (p =.003, *d*= .95, 95% CI .19, 1.67). Finally, Streckmann and colleagues[42] used static and dynamic surfaces to measure sway area on monopedal and bipedal stances and found an intergroup significant difference in favor of IG on static surfaces (p=.035) and on dynamic surfaces (p=.007), both after intervention, but no intergroup significant difference was found regarding bipedal stance.

Quality of life

Four studies used the European Organization for Research and Treatment of Cancer Quality of life Questionnaire Core 30 (EORTC QLQ-C30). First, Bland and colleagues[39] showed an intergroup significant difference in favor of the immediate exercise group after intervention (p=. 05). Second, Streckmann and colleagues[42] reported an intergroup significant difference in favor of IG during middle chemotherapy (p= .03), although there was no significance difference after intervention. Two studies did not report intergroup significant differences in quality of life at any time point[38,44]. Other study measured quality of life using the Trial Outcome Index (TOI) of the FACT/GOG-NTX and reported intergroup significant differences in favor of IG after intervention (p= .028) and at follow-up (p= .031)[43].

Risk of bias and quality of databases

The results of the assessment of risk of bias of the eight included RCTs are shown in Figure 2. Overall, most of the included studies had a high risk of bias in the overall bias assessment. The main methodological quality issue was outcome measurement, with "high risk" for a total of six of the eight studies (75%). Similarly, all of the included studies presented some concerns or a “high risk” of bias in the selection of the reported results. Therefore, none of the studies achieved a “low” overall risk of bias; one study demonstrated the least bias[43]. (Figure 3).

[Insert Figure 2 and Figure 3]

Sensitivity and precision of each database

The database that reported the majority of results was Scopus, although it had the lowest precision (Table 4). It was also the database that found the highest sensitivity together with Medline. None of the databases identified unique hits.

[Insert Table 4]

Meta-analysis

Of the six studies in the systematic review that measured quality of life, it was only possible to include four in the meta-analysis[39,42–44]. Three studies reported scores on the EORCT QLQ-C30[39,42,44] and the TOI[43]. Their scores all ranged from 0-100 before and after the physical exercise program, adding a total of 137 participants (66 in the intervention group and 71 in the control group). To homogenize the sample and include only control group studies, the "end of chemotherapy" evaluation was used in the study of Bland and colleagues[39] since one of the two groups can be considered a control up to that point. The overall pooled results showed a statistically significant improvement in quality of life after the intervention (mean difference: 14.62, 95% CI 6.03, 23.20; I^2: 0.00%, p-heterogeneity = .60) Pooled results are presented in Figure 4. To investigate whether the treatment estimate is robust when any of the studies are excluded and to explore the possible source of the heterogeneity, a sensitivity analysis was performed that excluded one study at a time. This analysis showed no substantial alteration of the main results. Given the number of articles included (below 10), publication bias was not possible[47]. Additionally, Hegdes’ *g* effect size was calculated in a secondary meta-analysis in which Bland and

colleagues[39] and Streckmann and colleagues[42] obtained the largest effect size (*g*= 1.57, 95% CI .71, 2.44 and *g*=.80, 95% CI .26, 1.34, respectively) (Figure 5).

[Insert Figure 4]

[Insert Figure 5]

Discussion

In this review, we synthesized physical exercise programs undertaken in patients with cancer undergoing chemotherapy and the relationship with CIPN prevention. The main finding was that physical exercise has shown promising effects on the prevention or amelioration of CIPN when prescribed during chemotherapy. The results of the meta-analysis present positive effects of physical exercise programs on improving cancer-related quality of life compared to usual care. After this review, we join the recommendation of other studies that suggest exercising regularly at the onset of neurotoxic treatment[48] and providing balance training[49] to avoid CIPN.

In summary, as suggested by our meta-analysis results according to FITT prescriptions, to improve quality of life in patients with cancer who start potentially neurotoxic chemotherapy, physical exercise programs should include at least two sessions per week[39,42,43], whose intensity of aerobic proposals should range between 60-80% HR max[43,50] or 50-75% HRR[39,44], while the resistance rate should be between 50-80% 1RM estimated[39,43,50]. With regard to type, multimodal (endurance, resistance and balance) physical exercise should be supervised. Finally, with respect to time, each session should last maximum one hour[39,43,50], between eight and 12 weeks[39,43,50]. If there are patients with inoperable lung cancer physical exercise program could coincide at least during chemotherapy cycles, increase number of sessions per week (up to six) and reduce the time during session (up to 8 minutes)[44]. Taking into account, that physical exercise intervention with hugest estimated effect size in quality of life was develop by Bland and colleagues[39] in patients with breast cancer (*g*= 1.57) and the second one was performed by Streckmann and colleagues[42] in patients with lymphoma (*g*= .80).

Analyzing the recommended FITT prescription, we found that the frequency was in accordance with the international guidelines for physical activity and cancer[51]. In this review, six studies that reported results in favor of physical exercise programs met the moderate intensity of aerobic exercise[38,39,41–43,45]. Although this makes it difficult to identify a definitive intensity recommendation, it is important to note that regardless of the intensity used, there were no adverse effects reported in any of the reviewed studies. With regard to resistance exercise, adding this proposal is related to a reduced risk of all-cause mortality in patients with cancer[52]. There was more coincidence around the intensity, the volume and the exercises used, which were highly analytically oriented to the lower or upper limbs[41,43]. Despite all of its benefits, we detected a decrease in adherence when resistance proposal was added, although in general adherence was high; according to the authors' criteria (> 75%)[53], in our review, the average adherence was 80%. Finally, our results suggest that multimodal physical exercise programs have more benefit; along this line, aerobic proposal has been recommended as a key component of physical exercise programs to treat CIPN by other authors[54]. Supervision of the modality by a healthcare professional could be more appropriate if balance task is included to avoid falls[55] because none of the home-based programs included balance proposals.

In view of the findings, we can only cautiously recommend that neurotoxicity assessment be measured with TOIs[43]. The neurotoxicity score of TOI is not structured to differentiate between changes in positive or negative neuropathic symptoms and instead proves its worth evaluating treatment-related neurotoxicity[56]. This could explain the good intergroup results, and TOI could be a useful tool for follow-up measurements.

For pain relief, concurrent home-based programs could be recommended accompanied by nerve gliding exercise. Nerve gliding exercises can reduce neural edema, decrease pressure and restore function by improving pain[57]. The acute effect of nerve gliding exercise, associated with the effects of physical exercise[2], is hypoalgesia; therefore, it may be a complement in programs whose objective will be to prevent CIPN, but there is also pain. However, a small effect size was obtained in this review in physical exercise intervention (d=.46)[41]. Looking at measurements, the VAS is a widely used tool to assess pain[58] and it is strongly recommended for either pain or heat/cold in patients undergoing chemotherapy.

Curiously, although vibration impairments are a characteristic symptom in patients suffering from CIPN[15], in the reviewed studies, this was a difficult symptom to evaluate. None of the three articles used the same measurement method, and only two studies found significant improvements, but not at the same measured time point. In view of these results, we encourage consensus in following the ACTTION recommendations[32] that emphasize the measurement of vibration within the Total Neuropathy Score scale.

Similarly, regarding balance, few studies measured it, or they reported global analysis of the balance test, which can make it difficult to find more explicit differences in more challenging balance tasks[43]. However, one study showed significant benefits in global balance after a physical exercise program compared to usual care[38]. All of the studies that measured sway area, especially monopodal sway (either on static or dynamic surfaces), found improvements in the group who performed physical exercise compared to the control group. Highlighted the Stuecher and colleagues study that showed an estimated medium and large effect size using a walking proposals during chemotherapy in the middle of chemotherapy (d= .59) and after intervention (d=.95)[45]. It is known that CIPN patients use less proprioceptive information, entailing less accurate sway area[17]. In our review, physical exercise, especially when the balance proposal is included, can partially correct sway area damage by chemotherapy, according to other studies[59,60].

We were unable to analyze every outcome in the meta-analysis due to the heterogeneity of both outcomes and programs; therefore, only quality of life was selected. Three of the four studies included in the meta-analysis were very similar in terms of FITT prescriptions[39,42,43]; therefore, the heterogeneity of the meta-analysis was absent (0.00%). In this sense, the results of the meta-analysis support, from a quantitative point of view, the evidence for the benefits of physical exercise in improving quality of life when performed at the start of chemotherapy. All included studies support this conclusion, in line with other authors[4,61,62]. These results should be viewed with caution because none of the four included studies were free of bias. The biggest problem was in reference to measurement of the outcome and selection of the reported results due to the lack of previously published or registered study protocols. Sensitivity analysis performed by

excluding one study at a time showed that the exclusion of studies with more or less risk of bias did not affect the results[63].

To the best of our knowledge, sensitivity/precision analyses to identify relevant databases have never been documented within this area. Despite efforts, the sensitivity and precision of most of the databases were very low; we believe that the lack of the concept of 'CIPN' in the thesauri of notable databases such as Medline and Cochrane influenced our results. We recommend studying its inclusion given the relevance of the topic.

Strengths and limitations

The strengths of this review were as follows: the reporting was made according to the PRISMA guidelines; risk of bias assessment was included; a meta-analysis and sensitivity/precision analyses was conducted. The limitations include the following: none of the studies achieved low overall risk of bias assessments and heterogeneity in outcomes; the majority of the patients were women with breast cancer receiving taxane-based chemotherapy, which limits the generalizability of the data. Besides, one of the main objectives, to identify the specific parameters of physical exercise programs that provide prevention of CIPN in patients with cancer was not answered completely because heterogenicity of outcomes. However, it seems that multimodal physical exercise (balance training included) is more valuable that other interventions.

Future studies should report that the total dose of chemotherapy received during the intervention due to dose-dependent toxicity[46]. Additionally, we believe that the main problem of these studies has been delimiting the onset of CIPN with a unique outcome. A single dose may damage the peripheral nervous system[64], but patient-reported onset does not occur until 60 days after chemotherapy[65]. An assessment not made after 60 days could be responsible for missing true cases of CIPN.

Conclusion

In summary, this review presents all physical exercise programs to date to prevent CIPN and establishes the essential dose for clinicians and patients for success. Supervised multimodal

physical exercise is feasible and has the potential to improve quality of life and prevent CIPN symptoms in patients with cancer undergoing chemotherapy. The role of the rehabilitation staff is to address side effects mostly after the completion of treatments, and they could take care of prehabilitation interventions to control the impact of treatments against cancer.

Acknowledgements

This work is part of MLG's doctoral work at the Clinical Medicine and Public Health Doctoral Studies of the University of Granada, Spain.

Conflict of interest statement

None

Funding

The study is funded by ‘Fondo de Investigación Sanitaria del Instituto de Salud Carlos III’ (FI19/00230) and by ‘Ministerio Español de Educación Cultura y Deporte’ (FPU18/03575 and FPU17/00939).

References

1. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br. J. Sports Med. 2020;54:1451–62.

2. Ferioli M, Zauli G, Martelli AM, Vitale M, McCubrey JA, Ultimo S, et al. Impact of physical exercise in cancer survivors during and after antineoplastic treatments. Oncotarget [Internet]. 2018 [cited 2021 Mar 12];9:14005–34. Available from: www.impactjournals.com/oncotarget

3. Idorn M, thor Straten P. Exercise and cancer: from “healthy” to “therapeutic”? Cancer Immunol. Immunother. [Internet]. 2017 [cited 2020 May 21];66:667–71. Available from: http://link.springer.com/10.1007/s00262-017-1985-z

4. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. Cochrane Database Syst. Rev. [Internet]. 2012 [cited 2020 Dec 16];2012. Available from: /pmc/articles/PMC7389071/?report=abstract

5. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: A meta-analysis of randomised controlled trials. Clin. Oncol. [Internet]. 2010 [cited 2020 Dec 16];22:208–21. Available from: https://pubmed.ncbi.nlm.nih.gov/20110159/

6. Lopez P, Galvão DA, Taaffe DR, Newton RU, Souza G, Trajano GS, et al. Resistance training in breast cancer patients undergoing primary treatment: a systematic review and meta-regression of exercise dosage. Breast Cancer [Internet]. 2021 [cited 2020 Dec 9];28:16–24. Available from: https://doi.org/10.1007/s12282-020-01147-3

7. Cormie P, Zopf EM, Zhang X, Schmitz KH. The impact of exercise on cancer mortality, recurrence, and treatment-related adverse effects. Epidemiol. Rev. [Internet]. 2017 [cited 2020 Dec 16];39:71–92. Available from: https://academic.oup.com/epirev/article/39/1/71/3760392

8. Johnsson A, Broberg P, Krüger U, Johnsson A, Tornberg ÅB, Olsson H. Physical activity and survival following breast cancer. Eur. J. Cancer Care (Engl). [Internet]. 2019 [cited 2021 Apr 20];28. Available from: https://pubmed.ncbi.nlm.nih.gov/30895677/

9. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as Adjunct Therapy in Cancer. Semin. Radiat. Oncol. [Internet]. 2019 [cited 2020 Jul 1];29:16–24. Available from: /pmc/articles/PMC6656408/?report=abstract

10. Cantwell M, Walsh D, Furlong B, Loughney L, McCaffrey N, Moyna N, et al. Physical Activity Across the Cancer Journey: Experiences and Recommendations From People Living With and Beyond Cancer. Phys. Ther. [Internet]. 2020 [cited 2020 Dec 9];100:575–85. Available from: https://academic.oup.com/ptj/article/100/3/575/5581639

11. CAMPBELL KL, WINTERS-STONE KM, WISKEMANN J, MAY AM, SCHWARTZ AL, COURNEYA KS, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. Med. Sci. Sport. Exerc. [Internet]. 2019 [cited 2021 Mar 21];51:2375–90. Available from: https://journals.lww.com/10.1249/MSS.0000000000002116

12. Duregon F, Vendramin B, Bullo V, Gobbo S, Cugusi L, Di Blasio A, et al. Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review. Crit. Rev. Oncol. Hematol. [Internet]. 2018 [cited 2020 Dec 15];121:90–100. Available from: https://pubmed.ncbi.nlm.nih.gov/29198853/

13. Brayall P, Donlon E, Doyle L, Leiby R, Violette K. Physical Therapy-Based Interventions Improve Balance, Function, Symptoms, and Quality of Life in Patients with Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review. Rehabil. Oncol. 2018;36:161–6.

14. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. Ann. Neurol. [Internet]. 2017 [cited 2020 Apr 12];81:772–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28486769

15. Jordan B, Jahn F, Sauer S, Jordan K. Prevention and management of chemotherapy-induced polyneuropathy. Breast Care. 2019;14:79–84.

16. Bao T, Basal C, Seluzicki C, Li SQ, Seidman AD, Mao JJ. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. Breast Cancer Res. Treat. 2016;159:327–33.

17. Müller J, Ringhof S, Vollmer M, Jäger LB, Stein T, Weiler M, et al. Out of balance – Postural control in cancer patients before and after neurotoxic chemotherapy. Gait Posture [Internet]. 2020;77:156–63. Available from: https://doi.org/10.1016/j.gaitpost.2020.01.012

18. Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. Support. Care Cancer [Internet]. 2014 [cited 2020 Aug 11];22:2261–9. Available from: https://doi.org/10.1007/s00520-014-2255-7

19. Pike CT, Birnbaum HG, Muehlenbein CE, Pohl GM, Natale RB. Healthcare Costs and Workloss Burden of Patients with Chemotherapy-Associated Peripheral Neuropathy in Breast, Ovarian, Head and Neck, and Nonsmall Cell Lung Cancer. Chemother. Res. Pract. [Internet]. 2012 [cited 2020 Dec 10];2012:1–10. Available from: /pmc/articles/PMC3312207/?report=abstract

20. Gordon-Williams R, Farquhar-Smith P. Recent advances in understanding chemotherapy-induced peripheral neuropathy. F1000Research [Internet]. 2020 [cited 2020 Apr 12];9:177. Available from: https://doi.org/10.12688/f1000research.21625.1

21. Jordan B, Margulies A, Cardoso F, Cavaletti G, Haugnes HS, Jahn P, et al. Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO–EONS–EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. Ann. Oncol. 2020;31:1306–19.

22. Kachrani R, Santana A, Rogala B, Pawasauskas J. Chemotherapy-Induced Peripheral Neuropathy: Causative Agents, Preventative Strategies, and Treatment Approaches. J.

Pain Palliat. Care Pharmacother. [Internet]. 2020 [cited 2020 Mar 4];1–12. Available from: https://www.tandfonline.com/doi/full/10.1080/15360288.2020.1734144

23. Tanay MAL, Armes J, Moss-Morris R, Rafferty AM, Robert G. A systematic review of behavioural and exercise interventions for the prevention and management of chemotherapy-induced peripheral neuropathy symptoms. J. Cancer Surviv. [Internet]. 2021 [cited 2021 Mar 16];1–24. Available from: http://link.springer.com/10.1007/s11764-021-00997-w

24. Rebekah Friday AB. Effects of physical activity and exercise for patients with chemotherapy-induced peripheral neuropathy (CIPN) on improving or reducing CIPN during and post-chemotherapy: a systematic review. [Internet]. [cited 2021 Jan 26];Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=162490

25. Andersen Hammond E, Pitz M, Shay B. Neuropathic Pain in Taxane-Induced Peripheral Neuropathy: Evidence for Exercise in Treatment. Neurorehabil. Neural Repair. 2019;33:792–9.

26. Brami C, Bao T, Deng G. Natural products and complementary therapies for chemotherapy-induced peripheral neuropathy: A systematic review. Crit. Rev. Oncol. Hematol. [Internet]. 2016 [cited 2020 Dec 15];98:325–34. Available from: https://doi.org/10.1016/j.critrevonc.2015.11.014

27. Coughlin SS, Caplan LS, Williams V. Home-based physical activity interventions for breast cancer patients receiving primary therapy: a systematic review. Breast Cancer Res. Treat. [Internet]. 2019 [cited 2020 Dec 15];178:513–22. Available from: https://pubmed.ncbi.nlm.nih.gov/31493034/

28. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, et al. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. Syst. Rev. [Internet]. 2012;1:2. Available from: https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/2046-4053-1-2

29. Heinemann A, Brodsky M, Hoenig H, Chan L. Archives of Physical Medicine and Rehabilitation Recommends Prospective Registration of Systematic Reviews [Internet]. Arch. Phys. Med. Rehabil. 2021 [cited 2021 Jul 5];102:167–8. Available from: https://pubmed.ncbi.nlm.nih.gov/32980340/

30. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. [Internet]. 2009 [cited 2020 Nov 24];6:e1000097. Available from: https://dx.plos.org/10.1371/journal.pmed.1000097

31. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care. University of York: by Centre for Reviews and Dissemination (CRD); 2009.

32. Gewandter JS, Brell J, Cavaletti G, Dougherty PM, Evans S, Howie L, et al. Trial designs for chemotherapy-induced peripheral neuropathy prevention. Neurology. 2018;91:403–13.

33. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan---a web and mobile app for systematic reviews. Syst. Rev. [Internet]. 2016;5:210. Available from: http://dx.doi.org/10.1186/s13643-016-0384-4

34. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

35. Drevon D, Fursa SR, Malcolm AL. Intercoder Reliability and Validity of WebPlotDigitizer in Extracting Graphed Data. Behav. Modif. [Internet]. 2017 [cited 2021 Jan 12];41:323–39. Available from: http://journals.sagepub.com/doi/10.1177/0145445516673998

36. Röver C, Knapp G, Friede T. Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. BMC Med. Res. Methodol. [Internet]. 2015 [cited 2021 Jan 12];15:99. Available from: http://www.biomedcentral.com/1471-2288/15/99

37. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data.

Biometrics. 1977;33:159.

38. Vollmers PL, Mundhenke C, Maass N, Bauerschlag D, Kratzenstein S, Röcken C, et al. Evaluation of the effects of sensorimotor exercise on physical and psychological parameters in breast cancer patients undergoing neurotoxic chemotherapy. J. Cancer Res. Clin. Oncol. 2018;144:1785–92.

39. Bland KA, Kirkham AA, Bovard J, Shenkier T, Zucker D, Mckenzie DC, et al. Effect of Exercise on Taxane Chemotherapy e Induced Peripheral Neuropathy in Women With Breast Cancer : A Randomized Controlled Trial. Clin. Breast Cancer [Internet]. 2019;19:411–22. Available from: https://doi.org/10.1016/j.clbc.2019.05.013

40. Hammond EA, Pitz M, Steinfeld K, Lambert P, Shay B. An Exploratory Randomized Trial of Physical Therapy for the Treatment of Chemotherapy-Induced Peripheral Neuropathy. Neurorehabil. Neural Repair. 2020;

41. Kleckner IR, Kamen C, Gewandter JS, Mohile NA, Heckler CE, Culakova E, et al. Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. Support. Care Cancer. 2018;26:1019–28.

42. Streckmann F, Kneis S, Leifert JA, Baumann FT, Kleber M, Ihorst G, et al. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. Ann. Oncol. [Internet]. 2014;25:493–9. Available from: https://doi.org/10.1093/annonc/mdt568

43. Zimmer P, Trebing S, Timmers-trebing U, Schenk A, Baumann FT. Eight-week , multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients : a randomized controlled trial. Support. Care Cancer. 2018;615–24.

44. Henke CC, Cabri J, Fricke L, Pankow W, Kandilakis G, Feyer PC, et al. Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV. Support. Care Cancer [Internet]. 2014 [cited 2020 Nov 25];22:95–101. Available from: https://link.springer.com/article/10.1007/s00520-013-1925-1

45. Stuecher K, Bolling C, Vogt L, Niederer D, Schmidt K, Dignaß A. Exercise improves functional capacity and lean body mass in patients with gastrointestinal cancer during chemotherapy : a single-blind RCT. Support. Care Cancer [Internet]. 2019;2159–69. Available from: https://doi.org/10.1007/s00520-018-4478-5

46. Velasco R, Bruna J. Neuropatía inducida por quimioterapia: Un problema no resuelto. Neurologia. 2010;25:116–31.

47. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2019.

48. Banach M, Juranek JK, Zygulska AL. Chemotherapy-induced neuropathies—a growing problem for patients and health care providers. Brain Behav. 2017;7:1–8.

49. van der Leeden M, Huijsmans RJ, Geleijn E, de Rooij M, Konings IR, Buffart LM, et al. Tailoring exercise interventions to comorbidities and treatment-induced adverse effects in patients with early stage breast cancer undergoing chemotherapy: a framework to support clinical decisions. Disabil. Rehabil. [Internet]. 2018;40:486–96. Available from: http://dx.doi.org/10.1080/09638288.2016.1260647

50. Streckmann F, Kneis S, Leifert JA, Baumann FT, Kleber M, Ihorst G, et al. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. Ann. Oncol. 2014;25:493–9.

51. Pollán M, Casla-Barrio S, Alfaro J, Esteban C, Segui-Palmer MA, Lucia A, et al. Exercise and cancer: a position statement from the Spanish Society of Medical Oncology. Clin. Transl. Oncol. [Internet]. 2020 [cited 2021 Apr 6];22:1710–29. Available from: https://pubmed.ncbi.nlm.nih.gov/32052383/

52. Hardee JP, Porter RR, Sui X, Archer E, Lee IM, Lavie CJ, et al. The effect of resistance exercise on all-cause mortality in cancer survivors. Mayo Clin. Proc. [Internet]. 2014 [cited 2021 Mar 12];89:1108–15. Available from: /pmc/articles/PMC4126241/

53. Castro CM, King AC. Telephone-Assisted Counseling for Physical Activity. Exerc. Sport

Sci. Rev. [Internet]. 2002;30:64–8. Available from: http://journals.lww.com/00003677-200204000-00004

54. Kanzawa-Lee GA, Larson JL, Resnicow K, Smith EML. Exercise Effects on Chemotherapy-Induced Peripheral Neuropathy: A Comprehensive Integrative Review. Cancer Nurs. 2020;43:172–85.

55. Shier V, Trieu E, Ganz DA. Implementing exercise programs to prevent falls: systematic descriptive review. Inj. Epidemiol. [Internet]. 2016 [cited 2021 Mar 5];3:16. Available from: https://injepijournal.biomedcentral.com/articles/10.1186/s40621-016-0081-8

56. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: Properties, applications, and interpretation [Internet]. Health Qual. Life Outcomes. 2003 [cited 2021 May 27];1:1–7. Available from: https://doi.org/10.1186/1477-7525-1-79

57. Schmid AB, Elliott JM, Strudwick MW, Little M, Coppieters MW. Effect of splinting and exercise on intraneural edema of the median nerve in carpal tunnel syndrome-an MRI study to reveal therapeutic mechanisms. J. Orthop. Res. [Internet]. 2012 [cited 2021 Mar 4];30:1343–50. Available from: https://pubmed.ncbi.nlm.nih.gov/22231571/

58. Yoshida Y, Satoh A, Yamada T, Aisu N, Matsuoka T, Koganemaru T, et al. The Relationship Between Evaluation Methods for Chemotherapy-Induced Peripheral Neuropathy. Sci. Rep. [Internet]. 2019 [cited 2021 Mar 21];9. Available from: /pmc/articles/PMC6937307/

59. Schwenk M, Grewal GS, Holloway D, Muchna A, Garland L, Najafi B. Interactive sensor-based balance training in older cancer patients with chemotherapy-induced peripheral neuropathy: A randomized controlled trial. Gerontology [Internet]. 2016 [cited 2021 Mar 16];62:553–63. Available from: https://pubmed.ncbi.nlm.nih.gov/26678611/

60. Kneis S, Wehrle A, Dalin D, Wiesmeier IK, Lambeck J, Gollhofer A, et al. A new approach to characterize postural deficits in chemotherapy-induced peripheral neuropathy and to analyze postural adaptions after an exercise intervention. BMC

Neurol. [Internet]. 2020 [cited 2021 Mar 16];20:23. Available from: https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-019-1589-7

61. Kripp M, Heußer AL, Belle S, Gerhardt A, Merx K, Hofmann WK, et al. Does physical activity improve quality of life in cancer patients undergoing chemotherapy? Oncol. Res. Treat. [Internet]. 2015 [cited 2021 Feb 11];38:230–6. Available from: https://pubmed.ncbi.nlm.nih.gov/25966770/

62. Buneviciene I, Mekary RA, Smith TR, Onnela J-P, Bunevicius A. Can mHealth interventions improve quality of life of cancer patients? A systematic review and meta-analysis. Crit. Rev. Oncol. Hematol. [Internet]. 2021 [cited 2021 May 25];157:103123. Available from: https://pubmed.ncbi.nlm.nih.gov/33190065/

63. Drucker AM, Fleming P, Chan A-W. Research Techniques Made Simple: Assessing Risk of Bias in Systematic Reviews. J. Invest. Dermatol. [Internet]. 2016 [cited 2021 Mar 12];136:e109–14. Available from: https://pubmed.ncbi.nlm.nih.gov/27772550/

64. Pachman DR, Qin R, Seisler DK, Smith EML, Beutler AS, Ta LE, et al. Clinical course of oxaliplatin-induced neuropathy: Results from the randomized phase III trial N08CB (Alliance). J. Clin. Oncol. [Internet]. 2015 [cited 2021 Feb 11];33:3416–22. Available from: https://pubmed.ncbi.nlm.nih.gov/26282635/

65. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J. Clin. Oncol. [Internet]. 2014 [cited 2020 Apr 14];32:1941–67. Available from: https://doi.org/10.1200/JCO.2013.54.0914

Figure legends

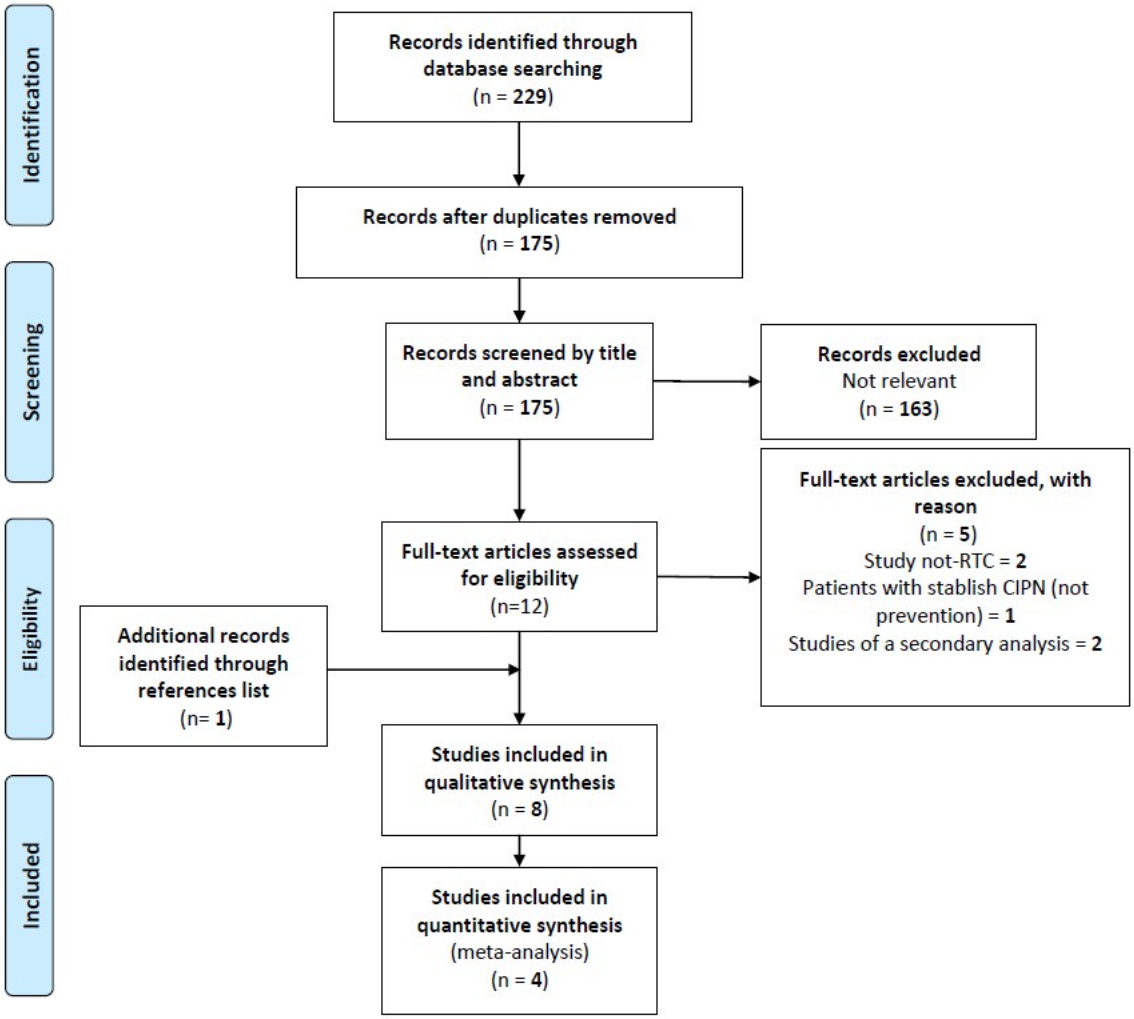
Figure 1. Flow chart according to the PRISMA Statement.

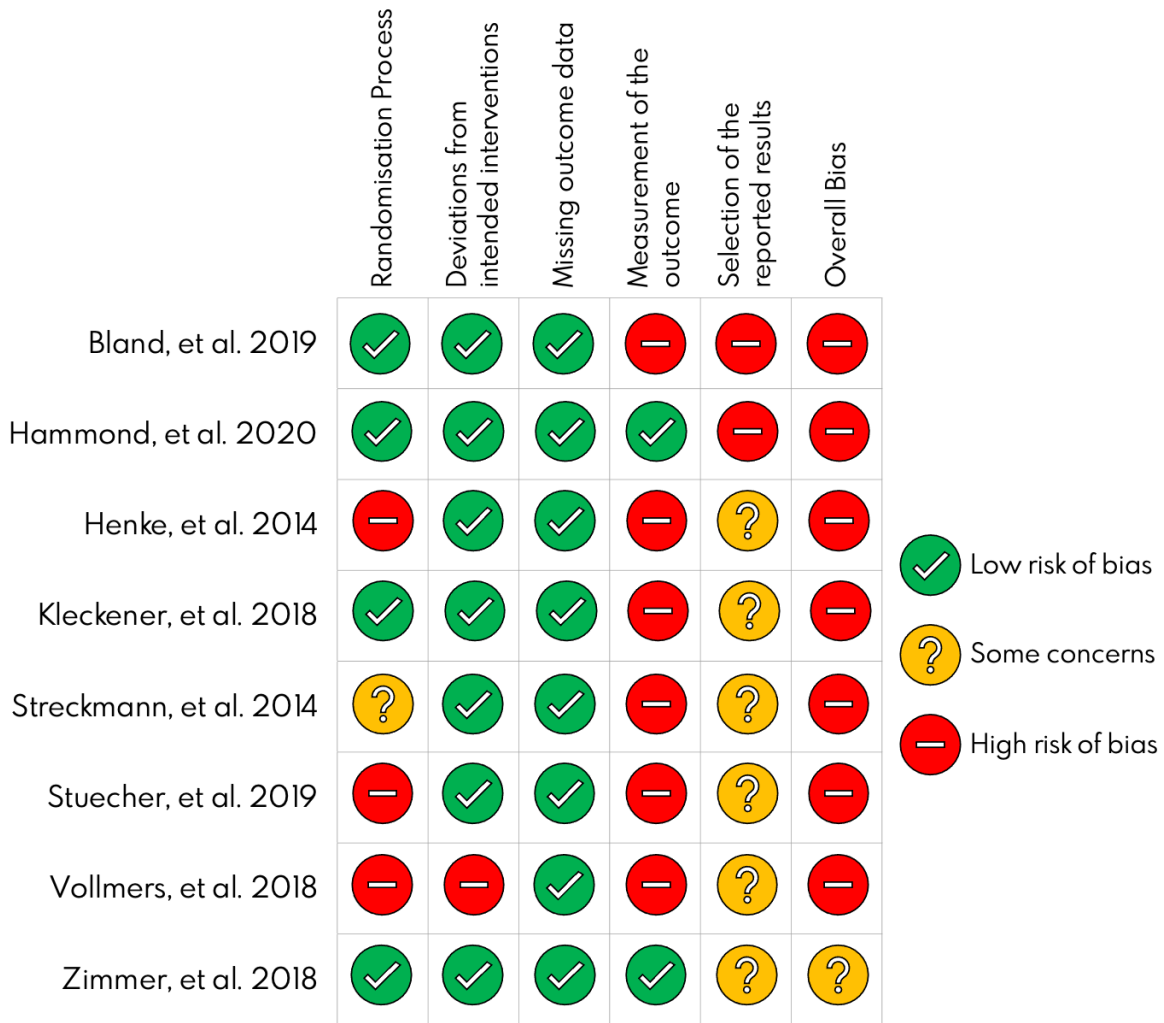
Figure 2. Risk of bias graph: review authors' judgments about each 'Risk of bias' item presented as percentages across all included studies.

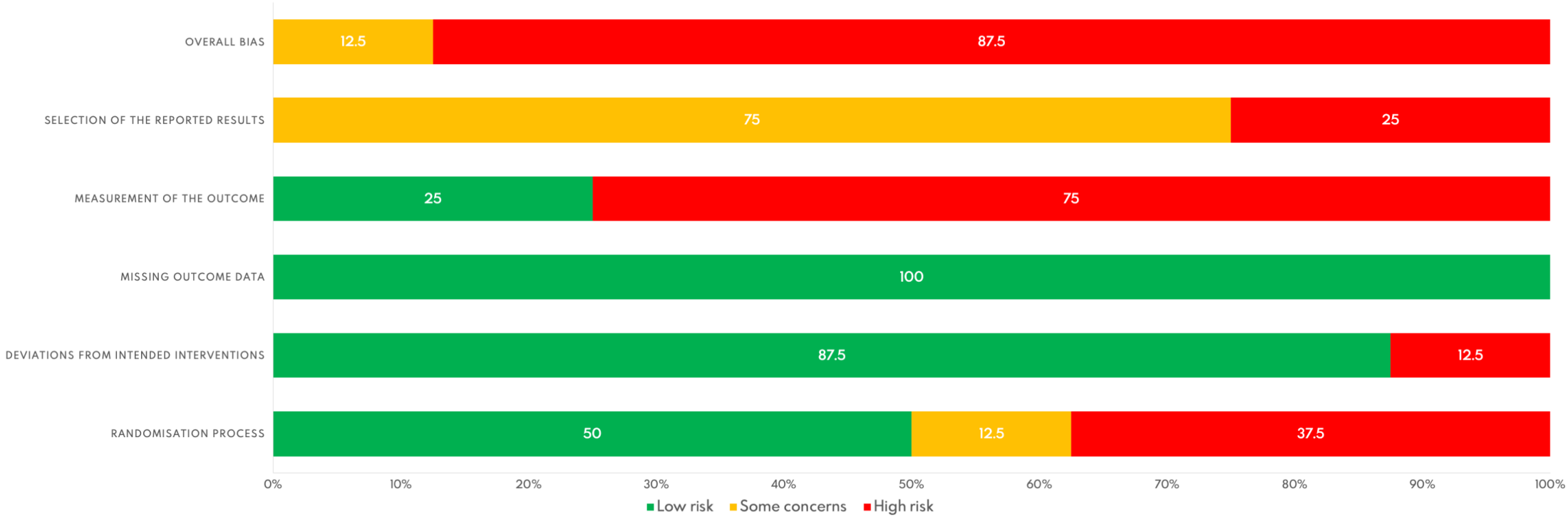
Figure 3. Risk of bias of RCTs included.

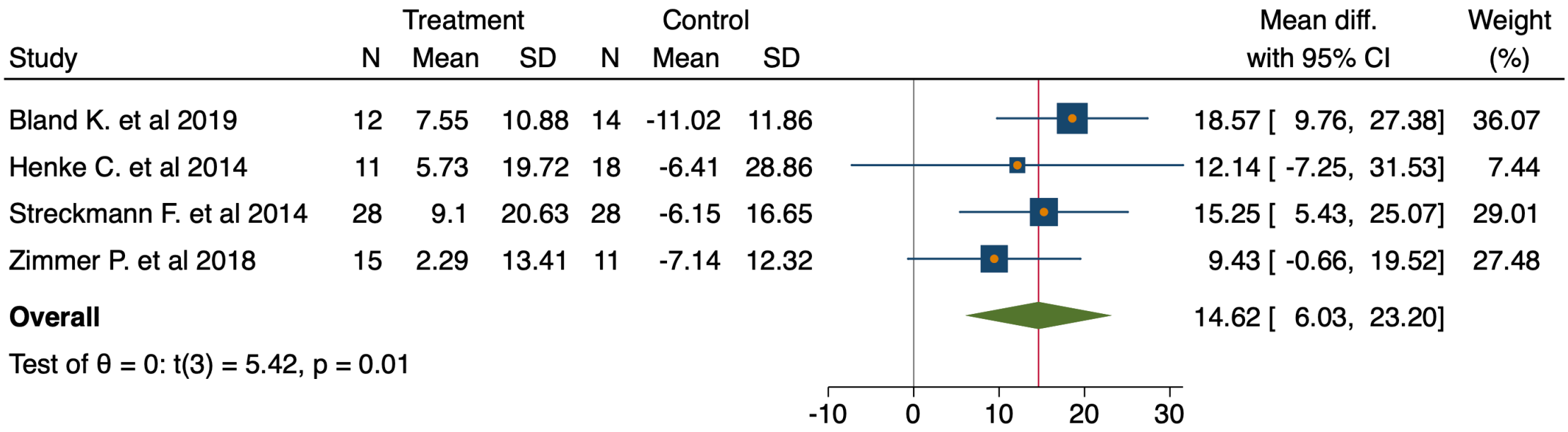
Figure 4. Forest plot of studies analysing effects of physical exercise versus usual care on the quality of life (X axis – standardised mean difference and Y axis – studies included).

Figure 5. Forest plot of studies analysing effects of physical exercise versus usual care on the quality of life (X axis – effect size (Hegdes' g) and Y axis – studies included).


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 229)
Records after duplicates removed (n = 175)
Records screened by title and abstract (n = 175)
Records excluded Not relevant (n = 163)
Full-text articles assessed for eligibility (n=12)
Full-text articles excluded, with reason (n = 5) Study not-RTC = 2 Patients with stablish CIPN (not prevention) = 1 Studies of a secondary analysis = 2
Additional records identified through references list (n= 1)
Studies included in qualitative synthesis (n = 8)
Studies included in quantitative synthesis (meta-analysis) (n = 4)


Randomisation Process
Deviations from intended interventions
Missing outcome data
Measurement of the outcome
Selection of the reported results
Overall Bias
Bland, et al. 2019
Hammond, et al. 2020
Henke, et al. 2014
Kleckener, et al. 2018
Streckmann, et al. 2014
Stuecher, et al. 2019
Vollmers, et al. 2018
Zimmer, et al. 2018
Low risk of bias
Some concerns
High risk of bias


OVERALL BIAS
12.5
87.5
SELECTION OF THE REPORTED RESULTS
75
25
MEASUREMENT OF THE OUTCOME
25
75
MISSING OUTCOME DATA
100
DEVIATIONS FROM INTENDED INTERVENTIONS
87.5
12.5
RANDOMISATION PROCESS
50
12.5
37.5
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Low risk
Some concerns
High risk


Treatment
Control
Mean diff.
Weight
Study
N
Mean
SD
N
Mean
SD
with 95% CI
(%)
Bland K. et al 2019
12
7.55
10.88
14
-11.02
11.86
18.57 [9.76, 27.38]
36.07
Henke C. et al 2014
11
5.73
19.72
18
-6.41
28.86
12.14 [-7.25, 31.53]
7.44
Streckmann F. et al 2014
28
9.1
20.63
28
-6.15
16.65
15.25 [5.43, 25.07]
29.01
Zimmer P. et al 2018
15
2.29
13.41
11
-7.14
12.32
9.43 [-0.66, 19.52]
27.48
Overall
14.62 [6.03, 23.20]
Test of θ = 0: t(3) = 5.42, p = 0.01
-10
0
10
20
30

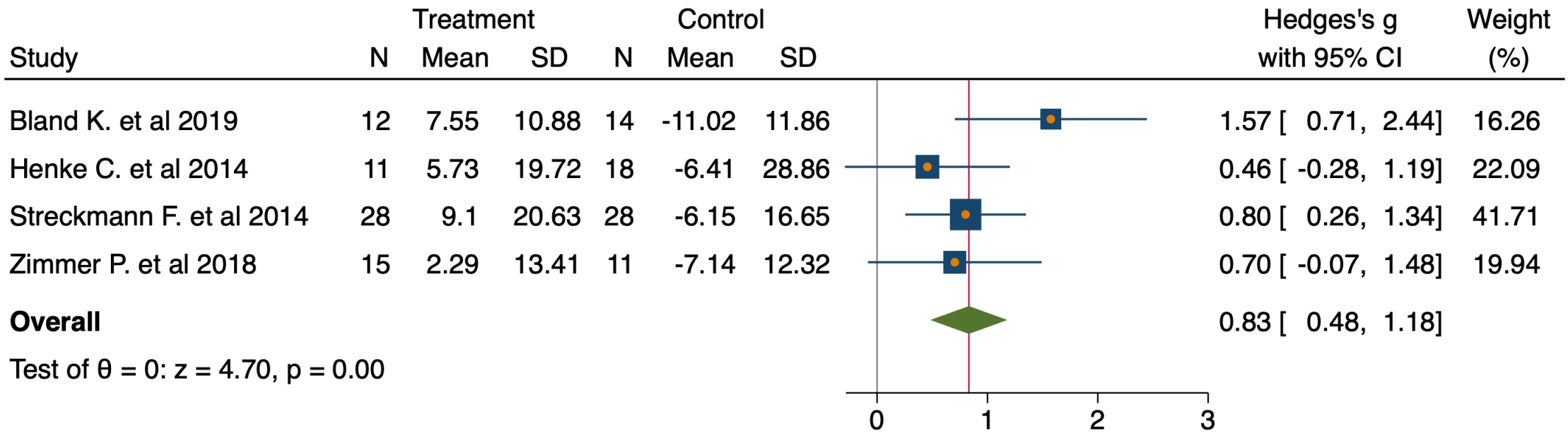

Treatment
Control
Study
N
Mean
SD
N
Mean
SD
Hedges's g with 95% CI
Weight (%)
Bland K. et al 2019 12 7.55 10.88 14 -11.02 11.86 1.57 [0.71, 2.44] 16.26
Henke C. et al 2014 11 5.73 19.72 18 -6.41 28.86 0.46 [-0.28, 1.19] 22.09
Streckmann F. et al 2014 28 9.1 20.63 28 -6.15 16.65 0.80 [0.26, 1.34] 41.71
Zimmer P. et al 2018 15 2.29 13.41 11 -7.14 12.32 0.70 [-0.07, 1.48] 19.94
Overall 0.83 [0.48, 1.18]
Test of θ = 0: z = 4.70, p = 0.00
0
1
2
3

TABLE 1

Table 1. Research strategy using PICOS strategy

Research idea	PICOS					Research question
	Participants	**I**ntervention	**C**omparation	**O**utcomes	**S**tudy design	
Physical exercise in patients undergoing chemotherapy could prevent CIPN	Patients with cancer undergoing chemotherapy	Any kind of exercise or physical activity modalities	No restriction was applied	CIPN development	Randomized controlled trials (RCT)	What kind of physical exercise program has the greatest effect on prevention CIPN?

TABLE 2

Table 2. Search strategy in Medline database

COMPONENTS OF SEARCH STRATEGY	
P	(Chemotherapy[Mesh] OR Chemotherap*[All fields] OR Chemotherapy Adjuvant[Mesh terms] OR Chemotherapy Adjuvant[All fields] OR Drug Therapy Adjuvant[tiab] OR Neoadjuvant Therapy[Mesh terms] OR Neoadjuvant Therap*[All fields] OR Treatment* Neoadjuvant[tiab])
I	(Exercise[Mesh] OR exercise*[All fields] OR Activit* Physical[tiab] OR Exercise* Physical[tiab] OR Exercise* Acute[tiab] OR Exercise* Isometric[tiab] OR Exercise* Aerobic[tiab] OR Exercise Training[tiab] OR exercise movement techniques[tiab] OR Breathing exercise[tiab] OR Dance therapy[tiab] OR Tai Ji[tiab] OR Yoga[tiab] OR Exercise therapy[Mesh] OR exercise therapy[tiab] OR Endurance training[tiab] OR Motion therapy continuous passive[tiab] OR muscle stretching exercise[tiab] OR Plyometric exercise[tiab] OR Resistance training[tiab])
C	-
O	(Peripheral Nervous System Diseases[Mesh terms] OR Peripheral Nervous System Disease*[All fields] OR Disease* PNS[tiab] OR Neuropath* Peripheral[tiab] OR Nerve Disease* Peripheral[tiab] OR Peripheral Nervous System Disorder*[tiab] OR Small Fiber Neuropathy[Mesh] OR Neuropath* Small Fiber[All fields] OR Polyneuropathies[Mesh] OR Polyneuropath*[All fields] OR Polyneuropath* Motor[tiab] OR Neurotoxicity Syndromes[Mesh] OR Neurotoxicity syndrome*[all fields] OR Neurotoxin Disorder*[tiab] OR Neurotoxic disorder*[tiab] OR Neurotoxin disease*[tiab] OR Chemotherapy induced peripheral neuropath*[tiab] OR CIPN[tiab] OR Chemotherapy Induced Polyneuropath*[tiab] OR Chemotherapy induced peripheral neurotoxicit*[tiab] OR Chemotherapy Induced Neuropathic Pain[tiab] OR Platinum induced peripheral neurotoxicit*[tiab] OR Bortezomib induced peripheral neuropath*[tiab] OR BIPN[tiab] OR Taxane induced peripheral neurotoxicit*[tiab] OR TIPN[tiab] OR Cancer treatment induced neurotoxic*[tiab] OR Platinum drugs induced peripheral neurotoxicit*[tiab] OR chemotherapy induced painful peripheral neuropath*[tiab] OR Bortezomib Induced Neuropathic Pain[tiab] OR Chemotherapy induced neuropath*[tiab] OR platinum induced peripheral neuropath*[tiab] OR neuropathy induced by bortezomib[tiab] OR Bortezomib induced polyneuropath*[tiab] OR Taxane induced neurotoxic*[tiab] OR bortezomib induced neurotoxic*[tiab] OR taxane induced neuropath*[tiab] OR taxane induced peripheral neuropath*[tiab] OR bortezomib related chemoneuropathy patients[tiab] OR chemoneuropath*[tiab] OR Therapy related peripheral neuropath*[tiab] OR cancer neuropath*[tiab])
S	(Randomized controlled clinical trial*[tiab] OR randomised controlled clinical trial*[tiab] OR randomized controlled trial*[Publication Type] OR randomised controlled trial*[Publication Type] OR randomized controlled trials as topic[MeSH Terms] OR randomized controlled trial*[All Fields] OR randomised controlled trial*[All Fields] OR clinical controlled trial*[tiab] OR controlled clinical trial*[tiab] OR clinical trial*[tiab] OR random allocation[tiab] OR randomly allocated[tiab] OR allocated randomly[tiab])

TABLE 3

Table 3. Characteristics of eight randomized controlled trials (RCTs) regarding physical exercise for outcomes in chemotherapy-induced peripheral neuropathy (CIPN).

1st Author (year)	Groups (numbers of participants)	Type of cancer (stage)	Program duration (frequency)	Intensity	Measured time points	Measured tools	Results	Adherence	Adverse effects
Multimodal physical exercise: endurance, resistance, and balance									
Bland (2019)[39]	IE: immediate physical exercise during chemotherapy (n=15) DE: delayed exercise after chemotherapy (n=16)	BC (I-III)	8-12 weeks (supervised 3 days per week and after 3 weeks 2 days per week of home-based)	Endurance: 50-75% of HRR Resistance: 50-65 % of RM	Baseline Mid-chemotherapy After chemotherapy Follow-up	Quality of life (EORTC QLQ-C30) Neurotoxicity (EORTC QLQ-CIPN20) Vibration senses (present or absent)	**Quality of life** *Intergroup:* p = .05 (after chemotherapy, IE>DE, $g = 1.57^{\#}$) p > .05 (follow-up) *Intragroup*: P < .01 (baseline to follow-up, both groups combined increase. **Neurotoxicity** *Intergroup*: p > .05 (any time points, IE vs DE)	IE: 80.66%; DE 89.33% †	Reported (follow-up cancer recurrence in IE n=1)

							Vibration sense *Intergroup*: p < .01 (at mid-chemotherapy, IE > DE)		
Streckmann (2014)[42]	IG (n=30) CG: Usual care (n=31)	Lymphoma (any stage)	36 weeks (twice per week)	Endurance: 60-80% HR max Resistance: Maximal force or theraband in inpatients	Baseline Twice during chemotherapy (12 and 24 weeks) After intervention (36 weeks)	Quality of life (EORTC QLQ-C30) Vibration sense Sway area on static and dynamic surface	**Quality of life** *Intergroup*: p = .03 (at 12 weeks, IG > CG, g = .80[#]) p > .05 (after intervention) *Intragroup*: p = .03 (baseline to after intervention, IG increase) p > .05 (CG) **Vibration sense** *Intergroup over time:* p = .07 (IG > CG, after intervention average incidence of PNP) p < .001 (after IG > CG reduction of PNP once	65 %	Reported (none)

							develop) p = .002 (after, IG reduction PNP>CG) **Sway area static surface** *Intergroup:* P = .035 (after intervention, IG > CG) ***Sway area dynamic surface*** *Intergroup:* P = .007 (after intervention, IG > CG)		
Vollmers (2018)[38]	IG (n=17) CG: Usual care (n=19)	BC (not reported)	18 weeks (twice per week)	13–15 on the Borg Scale	Baseline After intervention Follow up (6 weeks)	Quality of life (EORTC QLQ-C30) Balance (Fullerton Advanced Balance Scale) Sway area (monopedal and bipedal stance)	**Quality of life** *Intergroup*: p > .05 **Balance** *Intergroup:* *p = .004 (after intervention, IG > CG).* *Intragroup:* *p < .001 (after intervention, IG increase, CG decrease)*	Not reported	Not reported

							Sway area monopedal *Intergroup*: p < .001 (after intervention, IG > CG) p < .01 (follow up, IG > CG) **Sway area bipedal** *Intergroup*: p = .039 (after intervention, IG > CG)		
Zimmer (2018)[43]	IG (n=17) CG: Usual care (n=13)	CRC (any stage)	8 weeks (twice per week)	Endurance: 60-70% HR max Resistance: 60-80% of H1rm	Baseline After intervention Follow up (4 weeks)	Quality of life (TOI of FACT/GOG-NTX) Balance (GGT-Reha)	**Quality of life** *Intergroup*: p = .028 (after, IG>CG, *g* = .70[#]) p = .031 (follow-up, IG>CG) *Intragroup time effects*: p = .077 (baseline to after, IG decrease) p = .037 (baseline to follow-up, CG decrease) **Balance** *Intergroup:* *p > .05 (over time)*	80%	Reported (IG death n=2)

Concurrent physical exercise: endurance and resistance									
Henke (2014)[44]	IG concurrent training + breathing exercise (n=18) CG: Usual care (n=11)	Inoperable lung cancer (III-IV)	During three cycles of chemotherapy (endurance training and breathing techniques 5 sessions per week, strength once per week)	Endurance: 55-70 % HRR Resistance: 50% of maximal capacity.	Baseline After intervention	Quality of life (EORTC QLQ-C30)	**Quality of life** *Intergroup:* p > .05 (after intervention, *g* = .46[#]) *Intragroup:* p > .05 (after intervention, in both groups)	Not reported	Reported (not related to the program death n=6)
Kleckner (2018)[41]	IG (n=170) CG: Usual care (n=185)	BC, lymphoma, CRC and lung cancer (any stage)	6 weeks (daily)	Endurance: 60–85% HRR Resistance: 3-5 rated perceived exertion scale	Baseline After intervention	Numbness and tingling (VAS) Hot and coldness (VAS)	**Numbness and tingling** *Intergroup:* p = .061 (after intervention, IG > CG, *d* = .42) *Intragroup:* p = .027 (IG + .38 points) p = .003 (CG + .58 points) **Hot and coldness** *Intergroup:* p = .045 (after intervention, IG > CG, *d* = .46) *Intragroup:*	77% for resistance proposals	Reported (lymphopenia, neutropenia, multiorgan failure n=5)

							p = .022 (after intervention, IG + .38 points) p < .0001 (after intervention, CG +.77 points)		
Other modalities									
Hammond (2020)[40]	IG (n=22) home-based nerve gliding exercises CG: Usual care (n=26)	BC (I-III)	Until symptoms disappear (3 times daily)	-	Baseline Mid-chemotherapy Post-chemotherapy Follow-up (3 and 6 months)	Pain (VAS) Vibration sense (amplitudes µm/s)	**Pain** *Intergroup:* p = .053 (IG less pain than CG) *Intragroup:* p = .002 (IG less pain over time, OR .85) **Vibration sense** *Intergroup:* p > .05 (any time points)	Not reported	Not reported
Stuecher (2019)[45]	IG (n=13) home-based walking exercise CG: Usual care (n=15)	Gastrointestinal cancer (III–IV)	12 weeks (until complete 150 minutes per week)	Endurance: 46 to 63% of VO2peak	Baseline Mid-chemotherapy (4-6 weeks) After intervention	Functional status (SPPB) Sway area (bipedal static surface)	**SPPB** *Intergroup:* p > .05 (any time points) *Intragroup:* p < .05 (mid-chemo to baseline, CG decrease) **Sway area**	81.3%	Reported (not related to the program, hospitalization due to infection or severe fatigue n=3)

		<u>Intergroup</u>: *p = .001 (mid-chemo, IG > CG, d = .59†)* *p = .003 (after intervention, IG > CG, d = .95†)*

Abbreviations: BC: breast cancer; CG: control group; CRC: colorectal cancer; H1rm: hypothetic one-repetition maximum; HR: Heart rate; HRR: heart rate reserve; OR: Odds ratio; RM: repetition maximum; VO2 max: maximal oxygen consumption; †: indirectly calculated; #: effect size reported from meta-analysis of quality of life versus usual care.

TABLE 4

Table 4. Sensitivity/precision analysis for each database

Databases	Total hits retrieved	Relevant hits retrieved	NNR	Unique hits	Sensitivity	Precision
Medline	68	3	23	-	33.33	4.41
Scopus	119	3	40	-	33.33	2.52
Web of Science	34	2	17	-	22.22	5.88
Cochrane	8	0	-	-	0	0
TOTAL	**229**	**8***				

Number asterisked (*) include total number of hits after duplicates removed.

NNR: Number Needed to Read (total hits retrieved/ relevant hits on a database).

Unique paper: relevant study retrieved from one database only.

Sensitivity: relevant hits retrieved / relevant hits retrieved TOTAL (%).

Precision: relevant hits retrieved / total retrieved (%).