Title: High-Intensity Interval Training effects in cardiorespiratory fitness of lung cancer survivors: a systematic review and meta-analysis.

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Abstract

Purpose: To assess the exercise intervention focused on HIIT in lung cancer survivors.

Design: We performed a literature search using PubMed, Web of Science, and Science Direct (last search March 2021). Quality assessment and risk of bias were assessed using the Downs and Black scale and the Cochrane tool.

Participants: A total of 305 patients of 8 studies were assessed, with their mean age ranging from 61± 6.3 to 66 ± 10 years in exercise group and from 58.5 ± 8.2 to 68 ± 9 years in control group.

Methods: A systematic review and meta-analysis of randomized controlled trials and pilot randomized controlled trials was performed. We included controlled trials testing the effect of HIIT in lung cancer survivors versus the usual care provided to these patients. The data were pooled and a meta-analysis was completed for cardiorespiratory fitness(VO2peak).

Results: We selected 8 studies, which included 305 patients with lung cancer: 6 studies were performed around surgical moment, one study during radiotherapy´s treatment, and other during target therapy. After pooling the data, exercise capacity was included in the analysis. Results showed significant differences in favour to HIIT when compared to usual care in cardiorespiratory fitness (standard mean difference = 2.62; 95% confidence interval = 1.55, 3.68; p< 0.00001).

Conclusions and implications: The findings indicated a beneficial effect of HIIT for improving cardiorespiratory fitness in lung cancer patients in early stages around oncological treatment moment. Nevertheless, this review has several limitations, the total number of studies was low, and the stage and subtype of lung cancer patients were heterogeneous, that means that the conclusions of this review should be taken with caution.

Keywords. Lung Cancer, Oncological Treatment, High Intensity Interval Training, HIIT, cardiorespiratory fitness.

Introduction

Lung cancer is one of the most common cancer worldwide, in 2018, this cancer was the most diagnosed cancer in men and the third in women [1]. Lung cancer is also the leading cause of cancer mortality [2], nevertheless, the survival of these patients has increased in recent years. As a consequence of the survival gains, there is an increase in comorbidities (e.g., cardiovascular disease and fatigue) which may be linked to treatment intervention and negative changes in lifestyle activities [3,4].

Patients with lung cancer also develop sequelae because of anti-cancer treatment and inactivity [5]. Lung resection surgery has been related to persistent dyspnoea and lower functional outcomes [6], and coadjuvant treatments are associated with an additional impairment that affects all pathways involved in oxygen transport from the lungs to the working muscles [7]. Taken together, these aspects may markedly reduce the patients exercise capacity [8], the ability to function in daily life [7], and health-related quality of life [9].

In this way, oncological prehabilitation, rehabilitation, and palliative care are essential components for the treatment and secondary prevention of cancer and treatment-related impairments [10]. Independent of the treatment phase, exercise has shown to have beneficial effects on exercise capacity, functional activities, and quality of life in patients with cancer [11].

The meta-analysis of Ni et cols published in 2017, demonstrate the positive results of exercise training to improve cardiorespiratory capacity and health-related quality of life after lung resection, in which many of patients underwent adjuvant chemotherapy in addition to lung resection [12]. Furthermore, numerous types of physical training might reduce mortality and recurrence rates of various cancer entities [13,14] among which high-intensity exercise training (HIIT) was found to be highly cost-effective in adult cancer patients compared to other types of training, i.e., by lowering supervision time and overhead costs or by reducing medication use [15].

HIIT may be an efficient exercise modality, inducing positive physiological responses including, improved physical fitness and health outcomes [16]. This type of training induces a protective cardiopulmonary phenotype while enhances the oxygen extraction in skeletal muscle by increasing capillary density and mitochondrial oxidative capacity [17]. As little as 3 sessions per week, with less than 10 min of HIIT in the session, has been shown to improve exercise capacity, markers of disease, and muscle oxidative capacity in healthy people and cardiometabolic patients [18]. Furthermore, a recent systematic review on the impact of high-intensity exercise in cancer patients concluded that HIIT improves exercise capacity in various cancer entities [19].

Despite some studies that have reviewed the effect of HIIT on different types of cancer, no review has yet investigated the effect of High-intensity interval training on exercise capacity in patients with lung cancer. The purpose of the current review was to examine the effects of exercise interventions focus on High-Intensity Interval Training in lung cancer survivors. A systematic review and a meta-analysis were conducted. The research question was: Exercise interventions focus on High Intensity Interval Training are effective in the cardiorespiratory fitness of lung cancer patients?.

Methods

Study registration

The systematic review was conducted and following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20] and the Cochrane Collaboration guidelines for reviewing interventions [21]. The protocol of this systematic review has been registered on PROSPERO 2021 (registration number: CRD42021231229).

Search strategy

We carried out a wide search of the literature for articles indexed on Pubmed, Web of Science and Science Direct of randomized controlled trials databases from their inception to March 2021. We realized a search strategy in MEDLINE using the following steps: 1) development of keywords by examining relevant key terms used in existing systematic reviews, (2) a thorough examination of the MeSH Database in reference to the terms: "lung", "cancer", "exercise interventions with a focus on high intensity interval exercise (HIIT)" and "oncological therapy", (3) and expert guidance and review by a specialist. This search strategy was tested and refined in order to claim it was the most effective strategy for this review. Then, this strategy was adapted in order to index across other databases.

We screened the references of relevant reviews to screen for additional studies that can be potentially included in this review. Non-English language studies, when a translation could be made available, were considered for inclusion too.

We applied the PICOS [22] model (Participants, Interventions, Comparisons, Outcome and Study design) to define the research question. The inclusion criteria were: (1) Lung Cancer survivors; (2) exercise interventions with focus on High Intensity Interval Training; (3) the exercise intervention had to be compared to a control intervention or no-treatment; (4) cardiorespiratory fitness was included in the outcomes; (5) only randomized clinical trials and pilot randomized clinical trials were included.

The inclusion as HIIT intervention was based on the definition proposed by Buchheit and Aursen [23], including repeated short to long bouts of relatively high-intensity exercise alternated with recovery periods of either low-intensity exercise or rest.

To reduce the selection bias potential, two authors (A.H.; C.V.) independently performed the literature search and disagreements were resolved by further consultation from a third author (J.M.). The search process included removing duplicates and screening titles, abstracts, and eligible full texts.

When the articles were selected, Data extraction and Quality assessment were performed. We used the Downs and Black quality assessment method to assess the methodological quality of the included studies [24]. It includes 27 items comprising five subscales (study quality, external validity, study bias, confounding and selection bias, and study power). Quality assessment is classified as follows: Excellent when it reaches a score with more or equal to 26 points, good between 20 and 25, fair between 15 and 19, and poor when it is less or equal to 14. This scale has been ranked as one of the six highest quality assessment scales suitable for use in systematic reviews, due to its high validity and reliability [25,26].

We assessed the risk of bias using The Cochrane Risk of Bias Tool for Randomized Controlled Trials method [27]. It includes 7 elements with 6 subscales (selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias). A study is considered to have high quality when there is low risk for each domain. To have fair quality is considered when one criterion does not meet [28] (i.e. high risk of bias for one domain) or two criteria are unclear, and there is no known important limitation that could invalidate the results. Poor quality is considered, when one criterion does not meet or two criteria are unclear, and there are important limitations that could invalidate the results; and when two or more criteria are listed as high or unclear risk of bias.

Meta-analysis

We used the Review Manager 5 (RevMan 5) software to perform a meta-analysis on all studies that presented cardiorespiratory fitness defined as $VO_{2\ peak}$ [29,30]. When data for $VO_{2\ peak}$ were insufficient for meta-analyses purposes (e.g., no means provided, no standard deviation provided), we contacted trial authors if it was possible.

When p-values or 95% confidence intervals were given and standard deviations were missing, these were calculated via the embedded Review Manager calculator. We used the Q statistic and I2 to examine statistical heterogeneity. Visual inspection of the forest plots for outlier studies was also undertaken. I2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance [31]. We interpreted I2 of over 50–90% as an indicator of substantial heterogeneity [21]. When homogeneity was observed, a fixed-effect model was used [21] and expressed effects as standardized mean differences (SMD) with accompanying confidence intervals.

Results

Finally, Eight studies were included in the review, 6 of which were included in the meta-analysis.

Please, insert figure 1

This review included 3 RCT [33,38,39], 2 Pilot RCT [32,35] and 3 PROBE [34,36,37] studies. The development of the HIIT program was in 5 studies performed in a Hospital environment [32,33,34,36,37], 2 studies were developed in a Clinic environment [35,39], and 1 study developed his intervention in Fitness centers [38], all of them were in a supervised format. All studies conducted a comparison between an intervention group (High Intensity Interval Training) and a control group (Usual cares) [32-39].

A total of 305 lung cancer survivors were included in the reviewed studies. Seven [32-38] studies recruited Non Small Cells Lung Cancer (NSCLC) patients while one study [39] recruited adenocarcinoma ´s patients; the majority of the disease stage was early stages [32,34-38].

The treatment status of these patients was heterogeneous, 6 studies [32,34-38] included patients in perisurgical resection moment which one of them included also patients after completing chemotherapy treatment [35], another study was carried out during radiotherapy treatment [33] and the last one during targeted therapy [39].

The studies quality scores ranged from 20 to 25, with a mean ± SD score of 22.38 ± 1.68. When Cochrane Risk of Bias Assessment was applied, half of the studies presented poor quality [34,36,37,39] and the other half presented fair quality [32,33,35,38].

Please, insert table 1

Details about applied interventions and obtained results are reported in table 2. High Intensity Interval Training was applied heterogeneously isolated or combined, three studies [34,36,37] applied HIIT isolated, two studies [32,33] combined HIIT with aerobic training, four studies [32,35,37,38] combined HIIT with resistance training and one [38] added a respiratory training. The principal HIIT modality was an aerobic exercise in a treadmill or cycle ergometer, while Messagi-Sator et al. [32] used a HIIT inspiratory and expiratory muscle training.

The components of the usual care in the control groups were heterogenous, these patients received standard medical treatment, routine post-treatment physiotherapy, general information and periodic monitoring from the hospital. Messaggi-Sator et al. [32] added advice to perform physical activity following World Health Organization recommendations, and Hwang et al. [39] gave patient education, social phone calls, and exercise instructions. Licker et al. [37] added advice regarding active mobilization and risk factor management and postoperative care.

The results after intervention were measured with exercise capacity (VO_{2peak}) and accompanied by pulmonary function, quality of life, or activity levels among others. After treatment intervention, most of the studies showed significant improvements in the exercise capacity of the exercise group while the control groups got worse [32,34,37-39]. Additionally, the results betweens groups have shown significant results in favor of exercise groups [32,34,37-39].

In other outcomes like respiratory function, the majority of studies [32,33,35-39] obtained HIIT improvements that in the case of Messaggi-Sator et al. [32] were significant. The quality of life improved after treatment with-in and between groups, moreover, in the study of Edvardsen et al. [38] the exercise group showed significant improvements compared to the control group. Physical Activity levels improved in both groups of the studies [33,35], but there weren´t differences between groups.

Three studies were carried out follow-up assessments. In the studies of Karenovics et al. [36] and Licker et al.[37], the exercise group presented fewer postoperative complications and shorter stays in the intensive care unit compared with the control group, also, the performance improvements were kept one year after pulmonary resection. Messagi-Sator et al. [32] carried out a follow-up of two years where the exercise group had significantly fewer recurrences than the control group.

Six studies reported to have dropouts [32, 35-39], most of them were mainly related to issues of transportation to the program location, recurrences, cerebral metastasis and deaths, but did not significantly. Only Hwang et al. [39] referred a higher-than-average dropout rates were noted, but most of the reasons for non-attendance were mainly personal reasons, such as time limitations and family problems, and none of these reasons were directly related to exercise training. Egegaard et al. [33] referred not have dropouts during the intervention. Most of the included article [33-35, 38, 39] reported to have a high adherence task (>70-80%).

Only Edvardsen et al. [38] reported a dropout for one serious adverse event, a hip fracture during balance training, ptherwise, the intense training was well tolerated. No exercise-related adverse events were reported in the rest of the included articles [32-34, 39]. The studies reported to be feasible, safe and well tolerated [32-34, 37-39].

Please, insert table 2

Results obtained in meta-analysis

Results obtained in Exercise capacity have been analyzed across VO_{2peak} values as shown in Figure 2. The measurements of the VO_{2peak} were analyzed to obtain concrete results on the characteristics of the treatment.

The pooled mean difference (MD) showed significant overall effect of therapeutic exercise: HIIT compared with usual care (MD = 2.62, 95% CI=1.55, 3.68; p< 0.00001). Heterogeneity was high (I2= 50%).

Please, insert figure 2

Discussion

The aim of the current review was to examine the effects of exercise interventions focus on High-Intensity Interval Training in lung cancer survivors. Our results concluded that HIIT aerobic intervention carried out around oncological treatment moment, in Non-Small Cell Lung Cancer (NSCLC) patients; improve the exercise capacity in early stages.

The aerobic HIIT was the most used HIIT modality in this review, only the study of Messaggi-Sator et al. [32] that performed a respiratory training HIIT was different. The application of isolated HIIT or training combinations was varied, as did the intensity and duration of HIIT, and the ratio of High-intensity exercise / rest. However, it was not a barrier to study the HIIT efficacy due to the fact that HIIT encompasses exercise prescriptions that are tailored to individual needs and can be used in almost any exercise setting [40]. Moreover, some scientists have suggested that the rest periods, or the lower intensity exercise intervals, make it possible for risked patients to complete high intensity periods in a good way, providing a great exercise stimulus to the vascular system [41].

The clinical profile of lung cancer survivors, on which HIIT was applied, is so homogeneous, but the clinical timing was unalike, the studies recruited patients during pre-surgical, post-surgical, radiotherapy and target therapy periods. However, other studies in different oncological entities have shown positive effects in the same line of our results [42,43].

The study of Egegaard et al. [33] showed different results to the rest of the studies of this review. This study showed a decrease in the exercise capacity of the intervention group after HIIT was applied. Nevertheless, the clinical timing of these patients may justify the results, in the fact that the reduction may be essentially caused by the radiotherapy´s effects [44], but the applied frequency (5 sessions/week) may cause an overtraining condition in these patients if we look at the other studies where the session´s frequency was 3session per week [32,34-39].

Other reviews [45] have shown the application of HIIT in patients with chronic diseases such as COPD and cardiovascular disorders with similar results to our review. In oncological patients, as in our review, Mugele H. et al [19] concluded an increase of VO_{2peak} in the intervention group when HIIT was compared with usual care; nevertheless this review did not specify the intervention effect in the different oncology stages and the pre-treatment application.

The VO_{2peak} results have great clinic relevance in order to be a strong predictor of decreased cancer-related mortality, and because VO_{2peak} is a strong predictor of morbidity and mortality, the clinicians are interested in the mechanisms associated with how HIIT affects these functional changes [46]. In the fact that 70% of cancer survivors do not engage in the recommended amount of exercise required to achieve health benefits [47], and the benefits observed in HIIT application as treatment strategy, this exercise can be a preferred election of the patients as routine exercise for dodging the barriers that they find during exercise practice [48].

Limitations

This review has several limitations. First, the definition applied for HIIT interventions was the most general one. This can impact the conclusion we obtained due to the differences between interventions, but this definition has been applied in different reviews about HIIT in chronic patients [49,50]. Secondly, the total number of studies and included participants was low, nevertheless previous reviews have been conducted in other populations with a similar number of studies [51]. Also, the stage and subtype of lung cancer patients were not homogeneous, and the oncological treatment timing was in a similar way, making it difficult to categorize the results. Finally, the heterogeneity that appeared in the variables that accompanied exercise capacity in the different studies was a limitation to extrapolate these improvements as a significant clinical change. All this means that the conclusions drawn in this review should be taken with caution for clinical application.

Conclusions and implications

In conclusion, the exercise interventions focused on aerobic HIIT, which had been applied around oncological treatment moment in NSCLC patients with early stage, improved the exercise capacity of the patients. However, this review could not show any conclusion about HIIT application in advanced stages, other lung cancer subtypes, or a specific clinical moment. Future studies need to be developed in which these patients´ conditions are carried out, in order to improve the personalised approach of lung cancer patients.

As exercise is systematically recognized as a part of the treatment of cancer patients, HIIT application could open new therapeutic clinical lines, and therefore based in our results, support units for oncology patients could present therapeutic lines that include exercise intervention focused on HIIT in lung cancer survivors around the oncological treatment moment.

Declarations

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- **Conflicts of interest:** The Author(s) declare(s) that there is no conflict of interest.
- **Availability of data and material:** Not applicable.
- **Code availability:** Not applicable.
- **Author contributions:** The author Valenza Marie Carmen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Heredia-Ciuró Alejandro and Fernández-Sánchez Manuel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Martín-Núñez Javier, Calvache-Mateo Andrés, Rodríguez-Torres Janet, and López-López Laura contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.
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Table 1. Characteristics of studies and Quality Assessment

Study (year)	Design	Anthropometrical Profile		Lung Cancer Profile		Quality Assessment Downs and Black (Risk of Bias)
		Sample N (% Men)	**Sample Age** Years ± SD	**TNM Cancer Stage**	**Treatment Status**	
Messaggi-Sartor, et al. (2019) [32]	Pilot RCT	37 (70.3%)	**EG:** 64.2 ± 8.1 **CG**: 64.8 ± 8.9	I or II NSCLC	Post-resection	21 (Fair Quality)
Egegaard. Et al. (2019) [33]	RCT	15 (33.33%)	**EG**: 64 ± 5.8 **CG**: 65 ± 4.7	Advanced NSCLC	During radiotherapy	23 (Fair quality)
Bhatia, et al. (2019) [34]	RCT (PROBE)	151 (60.26%)	**EG**: 64 ± 13 **CG**: 64 ±10	I-IIIA NSCLC	Pre-resection	21 (Poor quality)
Cavalheri, et al. (2017) [35]	Pilot RCT	17 (29.41%)	**EG**: 66 ± 10 **CG**: 68 ± 9	I-IIIA NSCLC	Post-resection Post-chemotherapy	20 (Fair quality)
Karenovics, et al. (2017) [36]	RCT (PROBE)	151 (60.26%)	**EG**: 64 ± 13 **CG**: 64 ±10	I-IIIA NSCLC	Pre-resection	23 (Poor quality)
Licker, et al. (2016) [37]	RCT (PROBE)	151 (60.26%)	**EG**: 64 ± 13 **CG**: 64 ± 10	I-IIIA NSCLC	Pre-resection	24 (Poor quality)
Edvardsen, et al. (2015) [38]	RCT	61 (69.72%)	**EG**: 64.4 ± 9.3 **CG**: 65.9 ± 8.5	NSCLC	Post-resection	25 (Fair quality)
Hwang, et al. (2012) [39]	RCT	24 (50%)	**EG**: 61.0 ± 6.3 **CG**: 58.5 ± 8.2	Adenocarcinoma	During targeted therapy	22 (Poor quality)

RCT: Randomized Controlled Trial; PROBE: Prospective randomized open blinded end point controlled trial; NSCLC: Non-Small cell lung cancer; SD: Standard Deviation; EG: Exercise Group; CG: Control Group.

Table 2. Characteristics of interventions

Study	Timming	Outcomes	Interventions	Experimental Intervention Description Exercise: Intensity (Duration)	Training duration and frequency Weeks Days x week Minutes session	Main Results
Messaggi-Sartor, et al. (2019) [29]	6-8 weeks Post-resection	·Exercise capacity (CPET) ·Quality of life (EORTC QLQ-C30) ·Respiratory Function (Spirometry) ·Insulin growth factor (Levels IGF-I and IGFBP-3)	**EG:** HIIT (IEMT) + Aerobic + Resistance training **GC:** Usual Care	Warm-up: 5min HIIT: IEMT 50% PI_{max} / PE_{max} (15min) Aerobic training: Cycle ergometer 60% W_{peak} (30min) Resistance training: Upper limb press 0.5kg (NR) Cool down: 5min	8 weeks 3 x week 60 min	After intervention, EG improved significantly exercise capacity respect to baseline moment. EG had significant improvement in exercise capacity, respiratory function and Insulin growth factor compared to CG.
Egegaard. Et al. (2019) [30]	Immediately before radiotherapy seasons	·Exercise Capacity (CEPT ; 6MWT) ·Quality of Life (FACT-L) ·Respiratory Function (Spirometry) ·Depression and Anxiety (HADS) ·Physical Activity levels (IPAQ-L, activity monitor) ·Feasibility, safety, adherence	**EG:** HIIT (Aerobic) + Aerobic training **GC:** Usual Care	Warm-up: 5min HIIT: Cycle ergometer 80–95%iPPO (10min) Aerobic training: Cycle ergometer 80%iPPO (5min) Cool down: NR	7 weeks 5 x week 20 min	No significant differences were observed within or between groups from baseline to post intervention in any outcomes. EG intervention demonstrated to be feasible, safe and well tolerated.

Bhatia, et al. (2019) [31]	Between the decision for resection and its realization (2-3 weeks)	·Exercise capacity (CPET; 6MWT)	**EG:** HIIT (Aerobic) **GC:** Usual Care	Warm-up: 5min HIIT: Cycle ergometer 100% W_{peak} (20min) Cool down: 5min	2-3 weeks 3 x week 30min	After intervention, EG improved significantly exercise capacity respect to baseline moment. EG had significant improvement in exercise capacity compared to CG.
Cavalheri, et al. (2017) [32]	6-10 weeks post-resection 4-8 weeks post-chemotherapy	·Exercise capacity (CPET; 6MWT) ·Quality of life (EORTC QLQ-C30, FACT-L, SF-36) ·Respiratory Function (Spirometry) ·Anxiety and Depression (HADS) ·Physical Activity levels (activity monitors) and sedentary behaviours ·Muscle strength (Quadriceps and handgrip) ·Fatigue (FACIT-L)	**EG:** HIIT (Aerobic) + Resistance training **GC:** Usual Care	Warm-up: NR HIIT: Walking 70/80% 6MWT speed (20min) / Cycle ergometer 80% W_{max} (10min) Resistance training: Step-ups and Hand weights 1.5kg women / 2 kg men (NR) Cool down: NR	8 weeks 3 x week 60 min	After intervention, EG had significant improvement in daily steps, light activity and sedentary behaviour respect to baseline moment. EG had significant improvement in exercise capacity compared to CG.
Karenovics, et al. (2017) [33]	Between the decision for resection and its realization (2-3 weeks)	·Exercise Capacity (CPET) ·Respiratory Function (Spirometry) ·Mortality and morbidity score (TMM) ·Physical Activity (Zebra questionnaire) ·Dyspnoea (MRC questionnaire)	**EG:** HIIT (Aerobic) **GC:** Usual Care	Warm-up: 5min HIIT: Cycle ergometer 100% W_{peak} (20min) Cool down: 5min	2-3 weeks 3 x week 30min	1 year after lung cancer resection, EG didn´t have significant improvement compared to preoperative values. 1 year after lung cancer resection, EG didn´t have significant changes compare to CG.

Licker, et al. (2016) [34]	Between the decision for resection and its realization (2-3 weeks)	·Exercise Capacity (CPET; 6MWT) ·Respiratory Function (Spirometry) ·Mortality and morbidity score (TMM) ·Length of stay and admission to the intensive care unit	**EG:** HIIT (Aerobic) + Resistance Training **GC:** Usual Care	Warm-up: 5min HIIT: Cycle ergometer 100% W_{peak} (20min) Resistance Training: NR (NR) Cool down: 5min	2 - 3weeks 3 x week 30min	After intervention EG improved significantly exercise capacity respect to preoperative moment. After surgery, EG had significant shorter stay in the intensive care unit compared to CG.
Edvardsen, et al. (2015) [35]	5-7 weeks post-resection	·Exercise Capacity (VO_{2peak} protocol test) ·Quality of Life (SF-36) ·Respiratory function (Spirometry) ·Muscle strength, (RM Concentric leg strength, Handgrip) ·Physical performance (chair stand test, maximum stair steps, static balance test) ·Dyspnoea (QLQ-C30 subscale) ·Total muscle mass (X-ray absorptiometry)	**EG:** HIIT (Aerobic) + Resistance + Respiratory training **GC:** Usual Care	Warm-up: NR HIIT: Walking uphill on a treadmill 80–95% HR_{max} (NR) Resistance training: Lower limb, Upper limb and Back weights/press 6-12RM (NR) Inspiratory muscle training: NR (NR) Cool down: NR	20 weeks 3 x week 60min	After intervention, EG improved significantly exercise capacity and TIco levels compared to baseline moment. EG had significant improvement in exercise capacity, TIco levels, muscle strength, total muscle mass, physical performance and quality of life compared to CG.
Hwang, et al. (2012) [36]	During targeted therapy	·Exercise Capacity and muscle oxygenation (CPET) ·Quality of Life (QLQ-C30, L13) · Muscle Strength and Endurance (Quadriceps Isokinetic dynamometer) ·Insulin resistance (HOMA-	**EG:** HIIT (Aerobic) **GC:** Usual Care	Warm-up: 10min HIIT: Treadmill or Cycling ergometer 80% $VO2_{peak}$ / RPE 15-17 (25min) Cool-down: 5min	8 weeks 3 x week 40 min	After intervention, EG improved significantly exercise capacity and muscle oxygenation compared to baseline moment. In both group muscles strength and endurance had a significant improvement too.

		IR) ·Inflammatory response (CRP levels)				EG showed significant improvement in exercise capacity but not in Quality of Life or other outcomes compared to CG.

HIIT: High Intensity Interval Training; Wpeak: Peak work rate; IEMT: Inspiratory and expiratory muscle training; Kg: Kilograms; VO2peak: peak oxygen uptake; IGF-I:serum insulin growth factor I; IGFBP-3: IGF binding protein 3, EORTCQLQ-C30: European Organization for Research and Treatment of Cancer questionnaire; 6MWT: 6 Minutes Walking Test; CPET: perform cardiopulmonary exercise testing SF-36: Short-Form 36 general health survey, FACT-L: Functional Assessment of Cancer Therapy - Lung scale; HADS: Hospital Anxiety and Depression Scale; FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue subscale; FACIT-L: Functional Assessment of Chronic Illness Therapy - Lung subscale; MRC: Medical Research Council questionnaire; TMM: Modified thoracic mortality and morbidity classification system; HRMax: Maximum Heart rate; TIco: Carbon Monoxide transfer factor; 1RM: One-repetition maximum; iPPO: patient's peak power; IPAQ-L: Long International Physical Activity Questionnaire ; HOMA-IR: homeostatic model assessment of insulin resistance; CRP: C-reactive protein; RPE: Rate of Perceived Exertion; EG: Exercise Group; CG: Control Group; NR: Non-reported.

Fig. 1 Flow chart of literature search and study selection [20]

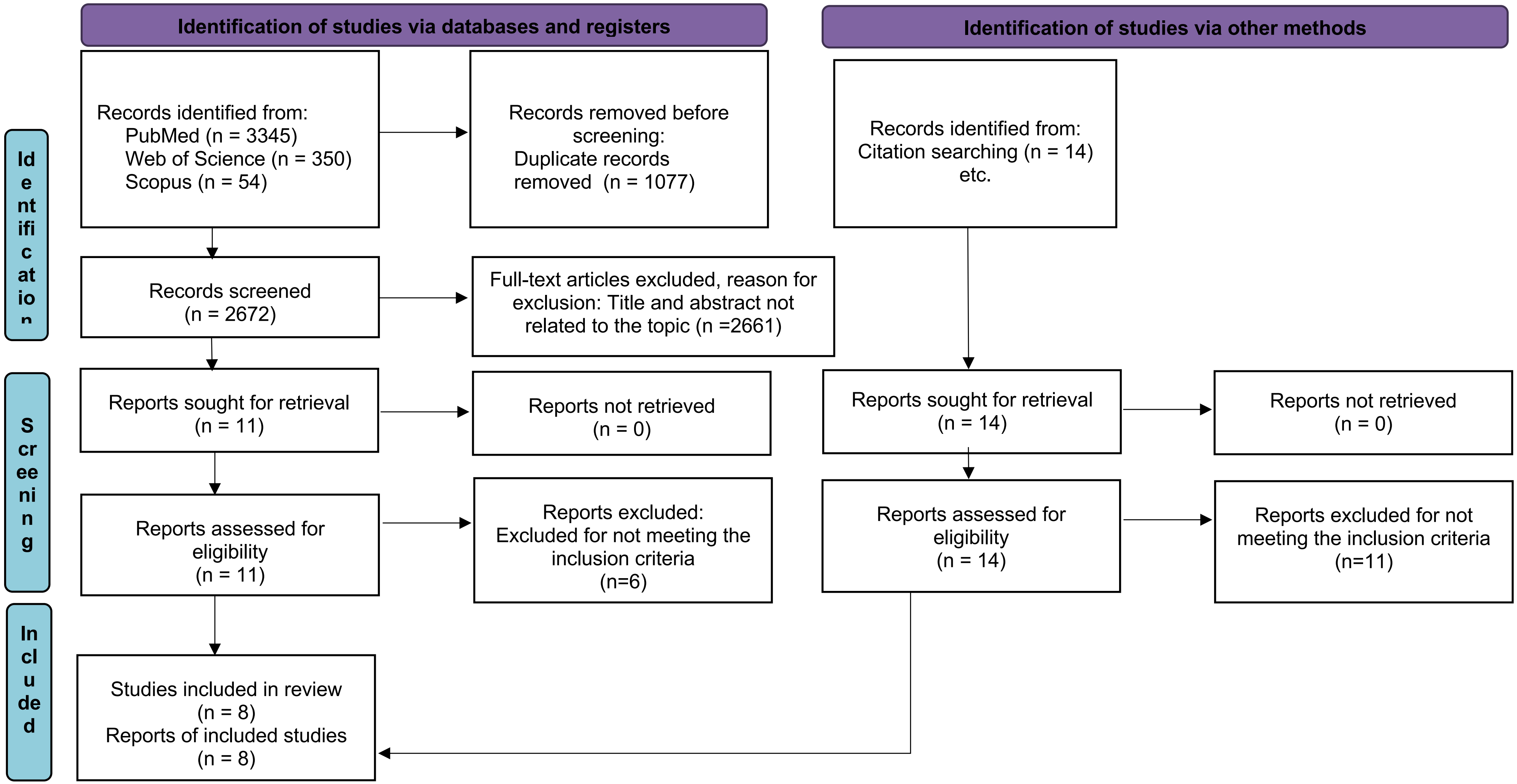

Fig. 2 Meta-analysis: Forest plot illustrating changes in Exercise Capacity (VO_{2peak})

	Experimental			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Messagi-Sartor 2019	16.7	2.14	11	13.7	2.5	13	33.2%	3.00 [1.14, 4.86]
Egegaard 2019	18.7	2.8	8	23.8	6.6	5	3.1%	-5.10 [-11.20, 1.00]
Bhatia 2019	21.1	8.33	74	19.1	5.37	77	22.7%	2.00 [-0.25, 4.25]
Cavlheri 2017	17	2.5	6	13.3	2.1	8	18.7%	3.70 [1.23, 6.17]
Edvardsen 2015	23.3	5.5	30	19	6	31	13.7%	4.30 [1.41, 7.19]
Hwang 2012	16.8	4.1	13	16.3	4.6	10	8.7%	0.50 [-3.12, 4.12]
Total (95% CI)			**142**			**144**	**100.0%**	**2.62 [1.55, 3.68]**

Heterogeneity: $Chi^2 = 9.95$, df = 5 ($P = 0.08$); $I^2 = 50\%$

Test for overall effect: $Z = 4.80$ ($P < 0.00001$)