Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer

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Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer: A systematic review

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Abstract

This systematic review aimed to examine physical fitness, adherence, treatment tolerance, and recovery for (p)rehabilitation including a home-based component for patients with non-small cell lung cancer (NSCLC). PRISMA and Cochrane guidelines were followed. Studies describing (home-based) prehabilitation or rehabilitation in patients with NSCLC were included from four databases (January 2000–April 2016, N=11). Nine of ten rehabilitation studies and one prehabilitation study (437 NSCLC patients, mean age 59–72 years) showed significantly or clinically relevant improved physical fitness. Three (27%) assessed home-based training and eight (73%) combined training at home, inhospital (intramural) and/or at the physiotherapy practice/department (extramural). Six (55%) applied supervision of home-based...
1. Introduction

Non-small cell lung cancer (NSCLC) concerns 85% of all lung cancer patients (Netherlands Cancer Registry, 2016a). Five-year survival rates remain low ranging from 55%, 41%, 13%, to 2% for stage I, II, III and IV, respectively (Netherlands Cancer Registry, 2016b). Standard curative treatments, including lung resection (Vansteenkiste et al., 2014) and concurrent chemoradiation (Eberhard et al., 2015), lead to adverse events in ≥50% of patients and frequently require hospitalization (Janssen-Heijnen et al., 2004; Schild et al., 2003). High age (Netherlands Cancer Registry, 2016c), smoking-related comorbidities, frailty, poor performance status, and long-term physical inactivity are often present in patients with NSCLC (Janssen-Heijnen et al., 2004; Hsu et al., 2015; Semrau et al., 2014; Granger et al., 2014). These characteristics may affect mobility, independence, treatment tolerance, recovery, and prognosis (Gridelli et al., 2007; Cardenal et al., 2015; Glotzer et al., 2013; Kale et al., 2015; Hoogeboom et al., 2014). Resistance and endurance training can increase the functional and physiological reserve, thereby creating a safety margin to meet potential enlarged demands of cardiac output and other physical capacities at the time of disease and interventions (Hoogeboom et al., 2014; Carli and Zavorsky, 2005). Prehabilitation (therapeutic training before undergoing treatment) (Carli and Zavorsky, 2005) and rehabilitation (therapeutic training during and after treatment) (Spruit et al., 2013) can optimize physical fitness, treatment tolerance, recovery, and survival (Singh et al., 2013; Ni et al., 2016; Bade et al., 2015), even in older cancer patients (Chou et al., 2012; Jack et al., 2011; Kilari et al., 2016). However, intramural training (inpatients) or extramural training (at the physiotherapy practice or department) may counteract compliance of high-risk patients because of commuting problems, accessibility of services, multimorbidity, and vulnerability (Temel et al., 2009; Oosting et al., 2012). A personalized training program in a home-based setting might overcome these barriers and enhance both motivation and adherence, especially for vulnerable and older patients (Bade et al., 2015). Therefore, the aim of this study is to systematically review the literature regarding feasibility and effectiveness of prehabilitation and rehabilitation including a home-based component in patients with NSCLC by evaluating physical fitness, and to describe adherence and treatment tolerance, and recovery.

2. Methods

The Cochrane guidelines for systematic reviews (The Cochrane Collaboration, 2011) and PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009) were followed. Databases Pubmed, Medline, Embase, and PEDro were searched for eligible articles describing patients with NSCLC undergoing prehabilitation or rehabilitation including a home-based component focusing on physical fitness (Table 1). Search terms were explored on free text words to avoid exclusion of recently published articles. Inclusion was limited to studies in English or Dutch language between January 1, 2000 and April 11, 2016. The primary outcome was physical fitness and secondary outcomes were patient adherence, exercise adherence, treatment tolerance, and recovery. Studies were excluded when insufficient training information was available to distinguish prehabilitation and rehabilitation, and when no physical intervention was applied.

2.1. Study selection

All search results were combined and duplicates removed. Assessment of title, abstract and full-texts according to eligibility criteria was performed independently by reviewers MP and ED. Inclusion of eligible studies was discussed until consensus. If no consensus was reached, a third person (BB) determined eligibility. Studies were included when full-text was available. Reference tracking was performed after full-text assessment in order to include additional relevant studies.

2.2. Data collection process and items

For each included article, the following information was independently collected, compared, and combined: first author, publication year, study type (prehabilitation/rehabilitation, country, type of study, randomization), demographics (number of patients with NSCLC, stage of disease, age, sex, treatment, comorbidity, performance status), description of the intervention (exercise content, frequency, intensity, measurement times, exercise time, follow-up, time of delivery, controls), and outcomes (physical fitness, patient adherence, exercise adherence, treatment tolerance, recovery). Physical exercises consisted of resistance and endurance training, and training effects were mainly evaluated by the 6-minute walk test (6MWT) distance. Results were described as mean ± standard deviation, mean (range), or mean difference ± standard deviation. A minimal clinically important gain of ≥42 m or 9.5% change was considered clinically relevant for 6MWT distance (Granger et al., 2015). Patient adherence was described; both patient and exercise adherence (percentage) were considered sufficient above 70%. Treatment tolerance and recovery were displayed by adverse events (numbers, including postoperative complications) and hospitalization time (days, mean ± standard deviation). Differences between outcomes were considered statistically significant if P < 0.05.

2.3. Qualitative and quantitative assessment

Methodological quality was independently assessed by using the domain-based evaluation for systematic reviews by the Cochrane ‘Risk of bias tool’ (Cochrane Statistical Methods Group and Cochrane Bias Methods Group, 2011a). Selection-, performance-, detection-, attrition-, and reporting bias were scored present (+) or absent (−). Low, moderate, or high risk of bias was determined by the percentage of present bias, corresponding to high (≥17%), moderate (18–33%), or low (≥50%) methodological quality, respectively. Therapeutic validity for quality of the training content was assessed by the CONTENT scale (Consensus on Therapeutic Exercise Training) (Hoogeboom et al., 2012; Herbert and Bo, 2005). Nine items regarding patient eligibility, competences and setting, rationale of the study, content of the study, and adherence were scored as performed (+) or not performed
Table 1
Combinations of text words per database of the literature search.

<table>
<thead>
<tr>
<th>Databases</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embase, Pubmed, Medline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Non-small cell lung cancer OR NSCLC OR lung cancer AND (patient OR geriatric OR elderly OR aged OR high-risk OR vulnerable OR frail) NOT (children OR caregiver OR tuberculosis OR aneurysm)</td>
<td>(prehabilitation OR before OR prior to OR presurgical OR preoperative OR during OR undergoing OR rehabilitation OR perioperative OR following OR postoperative OR lung resection OR lobectomy OR physical therapy OR training OR exercise OR physiotherapy OR physical therapy modality) AND (home-based OR living environment OR outpatient OR home OR home-based intervention) NOT (costs OR lung cancer screening OR drug-reimbursement OR homeopathy OR oxygen OR video-assisted)</td>
<td>Physical fitness</td>
</tr>
</tbody>
</table>

PEDro<sup>b</sup> | Lung cancer | Exercise<sup>b</sup> AND home<sup>b</sup> |

<sup>a</sup> Free text words were applied to all search terms; filters were applied to language (English and Dutch included) and publication date (Jan-1-2000 until Apr-11-2016 included); search terms for population, intervention and outcome were all combined by 'AND'.

<sup>b</sup> Truncation of search terms.

\(\rightarrow\), where >6 times 'performed' indicated high therapeutic validity. The interobserver agreement was calculated by Cohen’s Kappa, with poor (<0.20), reasonable (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) or very good (>0.80) agreement (Petrie and Sabin, 2009). A meta-analysis could not be performed due to clinical and statistical heterogeneity in patient samples, exercise design, study execution, and reporting of physical outcomes.

3. Results

The literature search identified 141 hits, leading to 107 unique studies of which 74 did not meet inclusion criteria. Thirty-three studies were selected for full-text assessment and 24 of them were excluded (conference paper with no available full-text version, \(n = 16\)), no physical outcome \((n = 3)\), no home-based intervention \((n = 2)\) or other reasons \((n = 3)\). Reference tracking identified two additional articles. Eventually, 11 studies were included (Andersen et al., 2011, 2013; Arbane et al., 2011, 2014; Brocki et al., 2014; Cheville et al., 2013; Coats et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014; Quist et al., 2012). The PRISMA flow diagram is shown in Fig. 1 (Moher et al., 2009).

3.1. Study characteristics

Fourhundred-fiftyone lung cancer patients were included (97% NSCLC) with various stages of disease and treatment regimens. Ranges for sample size and mean age were 5–131 participants and 59–72 years, respectively. In Table 2, characteristics of included studies are displayed.

Only one study described prehabilitation (Coats et al., 2013) and ten studies described rehabilitation (Andersen et al., 2011, 2013; Arbane et al., 2011, 2014; Brocki et al., 2014; Cheville et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014; Quist et al., 2012). Home-based training alone was examined in three studies (27%) (Cheville et al. 2013; Coats et al., 2013; Hoffman et al., 2014). One study (9%) combined home-based and extramural training (Brocki et al., 2014), six studies (55%) combined home-based and intramural training (Andersen et al., 2011, 2013; Arbane et al., 2011, 2014; Kuehr et al., 2014; Quist et al., 2012), and one study (8%) combined all three (Granger et al., 2013). The intervention period lasted four to 16 weeks. The home-based training component mainly consisted of resistance exercises (muscle strength) and endurance exercises (cardiorespiratory fitness) (Arbane et al., 2011; Brocki et al., 2014; Cheville et al., 2013; Coats et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014), or mere walking (Andersen et al., 2011, 2013; Arbane et al., 2014; Quist et al., 2012). Only four interventions (36%) were personalized (Andersen et al., 2013; Arbane et al., 2011; Granger et al., 2013; Hoffman et al., 2014). Supervision was performed by telephone calls (Arbane et al., 2014; Cheville et al., 2013; Coats et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014), home visits (Arbane et al., 2014; Granger et al., 2013; Hoffman et al., 2014), or during intramural sessions (Andersen et al., 2011, 2013; Arbane et al., 2014; Brocki et al., 2014; Kuehr et al., 2014; Quist et al., 2012). The number of home-based training sessions varied between twice a week (Brocki et al., 2014; Cheville et al., 2013) and once a day (Andersen et al., 2013; Arbane et al., 2014; Brocki et al., 2014; Granger et al., 2013), and moderate intensity was mainly applied. Intramural and extramural training consisted of supervised endurance training combined with resistance exercises. The number of sessions varied from twice a day postoperatively (Arbane et al., 2011; Granger et al., 2013) to once a week (Brocki et al., 2014), from 10 to 30 min (Granger et al., 2013) up to 1.5 h (Andersen et al., 2011, 2013) at moderate or high intensity. These sessions took place during hospitalization after surgery followed by home-based training alone (Arbane et al., 2011, 2014; Brocki et al., 2014), intramural training combined with concurrent home-based exercises (Andersen et al., 2011, 2013; Kuehr et al., 2014; Quist et al., 2012), or intramural training with home-based exercises in between (Andersen et al., 2013; Granger et al., 2013). Five studies (45%) included a control group that received regular care (Arbane et al., 2011, 2014; Granger et al., 2013), home-based exercises (Brocki et al., 2014), or no exercises (Cheville et al., 2013).

Physical fitness was mainly measured by cardiorespiratory fitness (6MWT distance) (Arbane et al., 2011; Brocki et al., 2014; Coats et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014; Quist et al., 2012) and muscle strength (kilogram of resistance per muscle group) (Arbane et al., 2011, 2014; Coats et al., 2013; Kuehr et al., 2014; Quist et al., 2012). All studies (100%) reported patient adherence (percentage) and most described reasons for drop-out. Six studies (55%) reported on compliance of home-based exercises (percentage) (Brocki et al., 2014; Cheville et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014; Quist et al., 2012). Treatment tolerance and recovery were
Table 2
Description of demographics and results of included (home-based) prehabilitation studies.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study type</th>
<th>Demographics (IG/CG)</th>
<th>Intervention exercise (IG/CG)</th>
<th>Intervention</th>
<th>Outcomes (IG/CG)</th>
</tr>
</thead>
</table>
| Andersen, 2011     | 1. Rehabilitation  
2. Denmark  
3. PCT  
4. NA | N = 24  
NSCLC N = 19  
Age mean (range)  
Men 64 (55–77)  
Women 67 (48–76)  
Treatement N  
Surgery 5, CT 19, RT 8, TKI | Home-based  
5/wk for 7 weeks unsupervised  
diary-based aerobic  
(walking) + breathing  
Intramural (simultaneously)  
2/wk for 7 weeks supervised  
group sessions, aerobic  
(walking, <83)  
VO2max) + breathing  
Control NA | 1. T0 1st supervised training  
2. Home training  
3. Wk1–10/11  
4. After surgery; during CT, RT, or TKI | 1. ISWT med diff (range) +9% (−77; 39%)  
P = 0.021  
ESWT med diff (range) +109% (−70; 432%)  
P = 0.002  
FEV1 (L) mean ± SD T0 14 ± 3 T1 14 ± 3 P = 0.763  
P = NS  
2. Drop-out with reasons (N) home-based  
NR; intramural  
28%, <55% of sessions present (3),  
incomplete data ISWT (4)  
Compliance (N) NR; continued after intervention (7)  
3. NR |
| Andersen, 2013     | 1. Rehabilitation  
2. Denmark  
3. PCT  
4. NA | N = 51  
NSCLC N = 39  
Age mean ± SD  
Men 65 ± 8, women 65 ± 7  
Treatement N  
Surgery 10, CT 26, RT 3, TKI 2 | Intramural  
2/wk for 3 weeks aerobic  
(cycling and walking) (Borg RPE  
16–18) + breathing  
Repetition of this design after  
home training  
Home-based  
7/wk for 3 weeks (between  
intramural sessions)  
personalized unsupervised  
diary instructed  
aerobic + breathing  
Intramural  
2/wk for 3 weeks intramural  
regimen  
Control NA | 1. T0 1st supervised training  
2. Home training  
3. Wk1–13  
4. Unclear (after surgery);  
during or after CT, RT, and TKI | 1. VO2max (ml/O2/kg/min) mean ± SD T0  
14 ± 3 T1 14 ± 3 P = 0.763  
FEV1 (L) mean ± SD T0 2.0 ± 0.6 T1 2.0 ± 0.5  
P = NS  
2. Drop-out with reasons (N) 43%,  
withdrawal after first session  
(7), withdrawal after home sessions (9),  
<65% present at second session (6); After intervention, not  
continuing physical activity (8), LFU (3)  
Compliance (N) NR; continued after intervention (18)  
3. NR |
| Arbane, 2011       | 1. Rehabilitation  
2. UK  
3. RCT  
4. Block randomization | N = 26/25  
NSCLC N = 26/25  
Stage N  
II 115/10, III 6/6, IV 2/0, IV 0/5, NR  
3/4  
Age mean (range)  
62.6 (32–47)/65.4 (47–82)  
Sex NR  
Treatement N  
Surgery 26/25 | Intramural  
2/day for 5 days postoperative  
mobility + resistance (seated  
leg raise) + aerobic (walking,  
cycling 60–80% HRmax)  
Home-based  
12 weeks personalized (based  
on hobbies) aerobic  
(walking) + strength (not  
specified) with monthly  
supervision/home visit  
Control  
Monthly check-up calls and  
usual care including  
breathing + mobilization | 1. T0 preoperative  
2. Postoperative  
3. Wk7  
4. After surgery | 1. 6MWIT (m) mean ± SD T0 466.6 ± 1021/  
4557 ± 980.0  
T1 336.7 ± 308.7/124.8; T2  
480.2 ± 110.0/448.2 ± 95.1  
P = 0.89; P < 0.00  
Quads strength (kg) mean ± SD T0  
33.2 ± 15.2/29.1 ± 10.9  
T1 37.6 ± 27.1/21.5 ± 7.7; T2  
34.2 ± 9.4/26.4 ± 9.7; P = 0.04  
P = 0.70  
2. Drop-out with reasons (N) 15% (32%), IG:  
palliative care (1), no surgery (1), refused  
measurement (1), no reason (1);  
CG: ITU admission (1), no reason (1),  
palliative care (1), withdrawal (1), refused  
Compliance (N) 2/3 P = NR  
3. Length of hospital stay (days) mean ± SD  
8.9 ± 9.3/11.0 ± 8.9  
P = NR; A priori post-operative  
complications (N) 2/3 P = NR |
Intramural
1/day for 5 days postoperative supervised strength (ankle lift 10-15°)+ aerobic cycling (max 60% heart rate reserve), intensity increases daily
Home-based
7/wk for 4 weeks unsupervised walking by pedometer and weekly calls
Control
Monthly check-up calls and usual care including pain relief by breathing and mobilization exercises

Extramural
1/wk for 10 weeks starting wk3 postoperative supervised group aerobic (walking with increasing intensity)+ strength+ breathing
Home-based (simultaneously)
2/wk strength + 7/wk aerobic (walking, cycling BORG RPE 11–12)) diary based at home
Control
2/wk strength + 7/wk aerobic (walking, cycling BORG RPE 11–12) diary based at home
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study type</th>
<th>Demographics (IG/CG)</th>
<th>Intervention exercise (IG/CG)</th>
<th>Intervention</th>
<th>Outcomes (IG/CG)</th>
</tr>
</thead>
</table>
| Coats, 2013        | 1. Prehabilitation | N = 13  
NSCLC N = 13  
Stage N 1, IIB 4, III 0, IV 2  
Age mean ± SD 59 ± 9  
Sex N Female 5  
Treatment N  
Awaiting surgery; CT 1, CT palliative 1, RT + CT palliative 1  
Comorbidities N  
COPD 5, hypertension 5, dyslipidemia 3, DMH II 2, anxiety 2 | Home-based  
3-5/wk for 4 weeks diary  
Based aerobic (cycling (Borg BS ≥ 6)) + strength and weekly check-up calls  
Control NA | 1. T0 baseline  
T1 wk4  
2. Home training 30  
3. Wk1-4  
4. Before treatment | 1. VO2max (ml/kg/min) mean ± SD T0  
21.6 ± 7.9; T1 23.3 ± 7.5 P < 0.05  
VO2max (l/min) mean ± SD T0 1.63 ± 7.8; T1 1.75 ± 0.71 P > 0.05  
CWS (s) mean ± SD T0 264 ± 79; T1 421 ± 241 P < 0.05  
6MWT (m) mean ± SD T0 540 ± 98; T1 568 ± 101 P > 0.05  
Muscle strength (kg) mean increase (SD); ± SD  
m. detoides: 1.82 ± 2.83; 18 ± 31; ± P < 0.05  
m. triceps: 1.32 ± 1.75; 14 ± 25; ± P < 0.05  
m. hamstrings: 3.41 ± 3.7; 27 ± 40; ± P < 0.05  
Hand grip; m. biceps and m. quadriceps NS  
Drop-out with reasons (N)  
Compliance (%) Aerobic (125); strength (84); recruitment (50) | 2. No adverse events |
| Granger, 2013      | 1. Rehabilitation  
2. Australia  
3. RCT  
4. Computer-generated randomization tables | N = 7/8  
NSCLC N = 2/5  
Age mean ± SD 57 ± 16.2/72.4 ± 12.4  
Sex N Female 57.1/37.5  
Treatment N  
Surgery 7/8 | Intramural  
From postoperative until discharge aerobic (walking (Borg BS 4)) 2/day, cycling 1/day + strength (Borg RPE 13) 1/day  
Home-based  
7/wk for 2 weeks after discharge personalized aerobic (walking (Borg BS 4)) + strength 1/wk check-up calls + 3 home visits  
Extramural  
2/wk for 8 weeks after home training aerobic (walking and cycling (Borg BS 4)) + strength (Borg RPE 13)  
Control Standard care + breathing | 1. T0 preoperative-wk2  
T1 postoperative wk2  
T2 postoperative wk12  
2. Home training 30  
Intramural 10-30  
Extramural 30  
3. Preoperative-wk12  
4. After surgery | 1. 6MWT (m) mean ± SD T0  
677.0 ± 435.8/435.8 ± 98.2;  
T1 647.5 ± 51.3/264.0 ± 64.3; T2 705.7 ± 65.3/458.2 ± 38.6  
P < 0.024  
T2; others NR  
TUG(s) mean ± SD T0 6.3 ± 1.6/9.0 ± 2.6; T1 4.4 ± 2.6/6.0 ± 3.2;  
T2 4.9 ± 0.8/6.8 ± 1.5 = 0.041  
at T2; others NR  
Drop-out with reasons (N) 433/386  
Compliance (%) Intramural (71); extramural (81)  
Length of hospital stay (days) mean(range) 4(3-9)/6(3-17) | 3. No adverse events |
| Hoffman, 2014      | 1. Rehabilitation  
2. United States  
3. PCT  
4. NA | N = 5  
NSCLC N = 5  
Stage N IIA 1, IIB 2, IIIA 2  
Age mean ± SD 63.4 ± 7.3  
Sex N Female 3  
Treatment N  
Surgery + CT 5  
Karnofsky PS N 70% 2, 90% 3  
Comorbidities mean N (range) 5.4 (2-12) | Home-based  
5/wk for 16 weeks from day 4 post-operative personalized aerobic (walking (≥ 3MET)) + balance by Nintendo Wii Fit. Two home visits and weekly check-up calls  
Control NA | 1. T0 preoperative  
T1 postoperative wk5  
T2 postoperative wk16  
2. Home-training 5 + daily 5 increase  
3. Baseline-wk16  
4. After surgery and during CT | 1. 6MWT (m) mean ± SD T0 413 ± 32; T1 382 ± 108; T2 463 ± 62 P = NR  
Walking time (min) mean ± SD T0 NR; T1 24.0 ± 4.3; T2 31.0 ± 6.5 P = NR | 2. Drop-out 0%  
Compliance ± SD(range) Walking 92.6 ± 4.6 (87.0-98.1); Balance 94.7 ± 7.0 (82.5-100)  
Length of hospital stay (days) mean ± SD(range) 8.4 ± 2.6/5.12 P = NR |
Kuehr, 2014
1. Rehabilitation
2. Germany
3. PCT
4. NA

N = 40
NSCLC N = 40
Stage N
IA 2, IIA 3, IIB 8, IV 27
Age mean = SD(range) 60 ± 12(22–75)
Sex N(%): female 16(40)
Treatment N
Surgery 3, concurrent CHRT 4, sequential CHRT 1, CT 33

Intramural
5/wk for 8 weeks of which 3 times supervised aerobic (walking, cycling (Borg RPE 12–14)) + strength (resistance (Borg RPE 14–16))

Home-based
3/wk for 8 weeks diary based aerobic (walking) (Borg RPE 14–16) + strength (resistance (Borg RPE 14–16)) and weekly check-up calls

Control NA

1. T0 baseline
T1 wk8
T2 wk16
2. Home training NR
Intramural NR
3. Baseline-wk16
4. After surgery, during CHRT and CT

1. 6MWT(m) mean ± SD T0 493 ± 100; T1 525 ± 95 P < 0.01; T2 543 ± 120 P = 0.46
Knee flexion (Newton) mean ± SD T0 140 ± 41; T1 177 ± 61 P < 0.01; T2 192 ± 57 P < 0.01
Knee extension (Newton) mean ± SD T0 201 ± 86; T1 279 ± 71 P < 0.01; T2 327 ± 116 P < 0.01

Other muscle strengths reported but NS
2. Drop-out with reasons (N) 50%; T0 fatigue (4), pneumonia (1), deceased (1), pain (1), infection (1), stroke (1); T1 stress (4), moved (1), metastases (1), dyspnea (1), pneumonia (1), stopped treatment (1); T2 no time (4), LFU (5)

Compliance (3) overall (82), home-based (77), intramural (95)

3. NR

Quist, 2012
1. Rehabilitation
2. Denmark
3. PCT
4. NA

N = 29
NSCLC N = 19
Age mean(range) 63(45–80)
Sex N(%): female 16(55.2)
Treatment N
CT 27, CHRT 2

Physical activity before diagnosis N
Sedentary (2), <3 h/wk 14, ≥3 h/wk 12, >4 h/wk 1

Intramural
2/wk for 6 weeks supervised strength (resistance (70–90% 1RM)) + aerobic (cycling (85–95% max HR)) + stretching

Home-based
3/wk for 6 weeks unsupervised diary based aerobic (walking) + relaxation

Control NA

1. T0 baseline
T1 wk6
2. Home training 20–60
Intramural 90
3. Baseline-wk6
4. During CT and CHRT

1. VO2max(L/min) mean ± SD T0 1.48 ± 0.41; T1 1.57 ± 0.41 P = 0.014
6MWT (m) mean ± SD T0 524.7 ± 88.5; T1 564.0 ± 88.6 P = 0.006
FEV1 (L) mean ± SD T0 1.76 ± 0.70; T1 1.96 ± 0.63 P = 0.061

Muscle strength(kg) mean ± SD Leg press: T0 70.34 ± 26.9; T1 86.9 ± 28.8 P = 0.000; Chest press T0 30.8 ± 13.2; T1 40.3 ± 16.3

P = 0.000; Lat machine: T0: 35.8 ± 13.8; T1 39.2 ± 17.6 P = 0.049
Abdominal crunch: T0 24.9(10.7); T1 29.5(11.3) P = 0.000
Lower back: T0 35.3 ± 14.1; T1 43.1 ± 16.2 P = 0.000
Leg extension: T0 38.6 ± 15.5; T1 45.1 ± 18.9 P = 0.000

2. Drop-out with reasons (N) 21% Loss of motivation (3), worsened PS (3)

Compliance (3) home-based 8.7%, intramural 73.3%

3. No adverse events

Abbreviations: 6MWT=6-Minute Walking Test; Borg BS=Borg CR 10 Breathlessness Scale; BORG RPE=Borg Rating of Perceived Exertion Scale; CG=Control Group; CHRT=Chemotherapy; CI=Confidence Interval; COPD=Chronic Obstructive Pulmonary Disorder; CR=Category Ratio; CT=ChemoTherapy; CVD=CardioVascular Disease; CWCE=Constant Workrate Cycle Exercise; diff=difference; DM=Diabetes Mellitus; ESWT=Endurance Shuttle Walk Test; FEV1=Forced Expiratory Volume in 1 second; HR=Heart Rate; IG=Intervention Group; ISWT=Incremental Shuttle Walk Test; kg=kilogram; IQR=Inter Quartile Range; L=Liter; LFU=Lost to Follow Up; max=maximal; m= meter; med=median; MET=Metabolic Equivalents; min= minute; ml=milliliter; N=Number; NA=Not Applicable; NR=Not Reported; NS=Not Significant; NSCLC=Non-Small Cell Lung Cancer; O2=oxygen; PCT=Patient Cohort Trial; PS=Performance Status; RCT=Randomized Controlled Trial; RM=Repeat Maximum; RT=RadioTherapy; s=second; SD=Standard Deviation; subj=subjects; TKI=Tyrosin Kinase Inhibitor (targeted therapy); UK=United Kingdom; VO2max=maximal oxygen uptake; WHO=World Health Organization; wk=week.

1 Within subjects group time effect.
2 Between subjects group time effect.
3 Between groups.
Table 3  
Physical outcomes including significance and clinical relevance of changes of included studies according to measuring instruments.

<table>
<thead>
<tr>
<th>Outcome unit</th>
<th>First author, year</th>
<th>Measurement times (IC/GC)</th>
<th>Mean ± SD (range)</th>
<th>1. Absolute change [percentage] (IC/GC)</th>
<th>2. Mean ± SD of change (range) (IC/GC/IC/GC)</th>
<th>3. P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Postoperative</td>
<td>End iv</td>
<td>Post iv</td>
<td>T0–T1</td>
</tr>
<tr>
<td>Prehabilitation – cardiorespiratory fitness</td>
<td></td>
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<tr>
<td>VO(_{2}\max) mL/kg/min</td>
<td>Coats, 2013</td>
<td>21.6 ± 7.8</td>
<td>23.3 ± 7.5</td>
<td>1. +1.7 [7.8%]</td>
<td>2. No</td>
<td>3. &gt; 0.05</td>
</tr>
<tr>
<td>VO(_{2}\max) L/min</td>
<td>Coats, 2013</td>
<td>1.63 ± 7.8</td>
<td>1.75 ± 0.7</td>
<td>1. +0.12 [+7.4%]</td>
<td>2. No</td>
<td>3. &gt; 0.05</td>
</tr>
<tr>
<td>6MWT m</td>
<td>Coats, 2013</td>
<td>540 ± 98</td>
<td>548 ± 101</td>
<td>1. +28 [+5.2%]</td>
<td>2. +28 ± 29</td>
<td>3. No</td>
</tr>
<tr>
<td>CWCE s</td>
<td>Coats, 2013</td>
<td>264 ± 79</td>
<td>421 ± 241</td>
<td>1. +571 [55.5%]</td>
<td>2. +157 ± 195</td>
<td>3. No</td>
</tr>
<tr>
<td>Rehabilitation – cardiorespiratory fitness</td>
<td></td>
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</tr>
<tr>
<td>VO(_{2}\max) mL/kg/min</td>
<td>Andersen, 2013</td>
<td>1.4 ± 3</td>
<td>1.4 ± 3</td>
<td>1. +0.0 [+0.0%]</td>
<td>2. No</td>
<td>3. &gt; 0.05</td>
</tr>
<tr>
<td>VO(_{2}\max) L/min</td>
<td>Quist, 2012</td>
<td>1.48 ± 0.41</td>
<td>1.57 ± 0.41</td>
<td>1. +0.9 [+6.1%]</td>
<td>2. +0.09 [0.02;0.16]</td>
<td>3. No</td>
</tr>
<tr>
<td>FEV(_1) L</td>
<td>Andersen, 2013</td>
<td>2.0 ± 0.6</td>
<td>2.0 ± 0.5</td>
<td>1. +0.0 [±0.0%]</td>
<td>2. No</td>
<td>3. &gt; 0.05</td>
</tr>
<tr>
<td>FEV(_1) L</td>
<td>Brocki, 2014</td>
<td>1.73 ± 0.5/1.9 ± 0.6</td>
<td>Mean diff 0.14 ± 0.3/0.1 ± 0.4</td>
<td>Mean diff 0.1 ± 0.4/0.06 ± 0.4</td>
<td>1. +0.14/0.1 [±0.13/0.53]</td>
<td>2. 0.02/0.1 [±0.14/0.17]</td>
</tr>
<tr>
<td>6MWT m</td>
<td>Quist, 2012</td>
<td>1.76 ± 0.7</td>
<td>1.96 ± 0.6</td>
<td>1. +0.2 ± 0.1 [±0.16/0.41]</td>
<td>2. 0.02/0.1 [±0.01/0.41]</td>
<td>3. No</td>
</tr>
<tr>
<td>6MWT m</td>
<td>Arbane, 2011</td>
<td>466.6 ± 102.1/ 457.7 ± 98.0</td>
<td>Mean diff 482 ± 110.0/ 448 ± 95.1</td>
<td>Mean diff 61 ± 52/55 ± 45</td>
<td>1. +0.13 ± 0.7 [±27.5/—32.2]</td>
<td>2. +0.05 ± 0.4 [±12.1/—1.8]</td>
</tr>
<tr>
<td>6MWT m</td>
<td>Brocki, 2014</td>
<td>427 ± 124/407 ± 102</td>
<td>Mean diff 65 ± 70/65 ± 45</td>
<td>Mean diff 61 ± 52/55 ± 45</td>
<td>1. +0.13 ± 0.7 [±27.5/—32.2]</td>
<td>2. +0.05 ± 0.4 [±12.1/—1.8]</td>
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<tr>
<td>6MWT m</td>
<td>Granger, 2013</td>
<td>677 ± 89.3/ 415.8 ± 98.2</td>
<td>Wk2 647.5 ± 53.1/429± 64.3</td>
<td>Wk5 382 ± 108 (202—480)</td>
<td>1. +0.2 ± 0.1 [±0.13/0.17]</td>
<td>2. +0.05 ± 0.4 [±12.1/—1.8]</td>
</tr>
<tr>
<td>6MWT m</td>
<td>Hoffman, 2014</td>
<td>413 ± 32 (367—452)</td>
<td>Wk5 382 ± 108 (202—480)</td>
<td>Wk16 149 ± 85</td>
<td>1. +0.2 ± 0.1 [±0.13/0.17]</td>
<td>2. +0.05 ± 0.4 [±12.1/—1.8]</td>
</tr>
<tr>
<td>6MWT m</td>
<td>Kuehr, 2014</td>
<td>493 ± 100</td>
<td>Wk5 382 ± 108</td>
<td>Wk16 149 ± 85</td>
<td>1. +0.2 ± 0.1 [±0.13/0.17]</td>
<td>2. +0.05 ± 0.4 [±12.1/—1.8]</td>
</tr>
<tr>
<td>6MWT m</td>
<td>Quist, 2012</td>
<td>524.7 ± 88.5</td>
<td>564.0 ± 88.6</td>
<td>1. +0.3 ± 0.0 [±6.1/6.1]</td>
<td>2. +0.05 (7.7/39)</td>
<td>3. Yes</td>
</tr>
<tr>
<td>ISWT m</td>
<td>Andersen, 2011</td>
<td>NR</td>
<td>Med diff 0.05 [±0.05]</td>
<td>2. +0.05 (7.7/39)</td>
<td>3. Yes</td>
<td>4. &gt; 0.05</td>
</tr>
<tr>
<td>ISWT m</td>
<td>Arbane, 2014</td>
<td>290/180—440/300/290—450</td>
<td>D5 110/135</td>
<td>350/290</td>
<td>1. +0.06/0.15 [±62/—53]</td>
<td>2. +0.05 [±0.05]</td>
</tr>
<tr>
<td>ESWT m</td>
<td>Andersen, 2011</td>
<td>NR</td>
<td>Med diff 0.72/3.82 [±6.8/13.5]</td>
<td>2. +0.05 [±0.05]</td>
<td>3. Yes</td>
<td>4. &gt; 0.05</td>
</tr>
<tr>
<td>Steps/day n</td>
<td>Cheville, 2013</td>
<td>1200</td>
<td>1200</td>
<td>1. +0.05 [±0.05]</td>
<td>2. +0.05 [±0.05]</td>
<td>3. Yes</td>
</tr>
<tr>
<td>Walking time min</td>
<td>Hoffman, 2014</td>
<td>NR</td>
<td>Wk 5 249 ± 43</td>
<td>310.0 ± 4.5</td>
<td>1. +0.05 [±0.05]</td>
<td>2. +0.05 [±0.05]</td>
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<tr>
<td>T2G s</td>
<td>Granger, 2013</td>
<td>6.1 ± 1.6/9.0 ± 2.6</td>
<td>Wk2 4.4 ± 2.6/6.0 ± 3.2</td>
<td>4.9 ± 0.8/6.8 ± 1.5</td>
<td>1. +0.05/0.8 [±11.4/13.3]</td>
<td>2. +0.05 [±0.05]</td>
</tr>
<tr>
<td>Mobility likert scale</td>
<td>Cheville, 2013</td>
<td>NR/NR</td>
<td>NR/NR</td>
<td>NR/NR</td>
<td>1. +0.05 [±0.05]</td>
<td>2. +0.05 [±0.05]</td>
</tr>
<tr>
<td>Activity likert scale</td>
<td>Cheville, 2013</td>
<td>NR/NR</td>
<td>NR/NR</td>
<td>NR/NR</td>
<td>1. +0.05 [±0.05]</td>
<td>2. +0.05 [±0.05]</td>
</tr>
<tr>
<td>Prehabilitation – muscle strength</td>
<td>Coats 2013</td>
<td>NR</td>
<td>1. ±1.82 ± 2.83</td>
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<tr>
<td>m. delto-ideus kg</td>
<td>NR</td>
<td>NR</td>
<td>±18.0% ± 31.0</td>
<td></td>
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<tr>
<td>m. triceps kg</td>
<td>NR</td>
<td>NR</td>
<td>±1.32 ± 1.75</td>
<td></td>
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<tr>
<td>m. ham-strings kg</td>
<td>Coats 2013</td>
<td>NR</td>
<td>±14.0% ± 25.0</td>
<td></td>
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<td></td>
<td></td>
<td>NR</td>
<td>±1.34 ± 2.7</td>
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<td>±27.0% ± 40.0</td>
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<tr>
<td>Rehabilitation – muscle strength</td>
<td>Coats 2013</td>
<td>NR</td>
<td>1. ±0.05</td>
<td></td>
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<tr>
<td>m. quadriceps kg</td>
<td>Arhane 2011</td>
<td>33.2 ± 15.2/29.1 ± 10.9</td>
<td>34.2 ± 9.4/26.4 ± 9.7</td>
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<td></td>
<td></td>
<td>D5 37.6 ± 27.1/21.5 ± 7.7</td>
<td>1. ±4.4–7.6</td>
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<td></td>
<td>±13.1–26.1</td>
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<tr>
<td>Extension knee N</td>
<td>Kuehr 2014</td>
<td>201 ± 86</td>
<td>279 ± 71</td>
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<td></td>
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<td>1. ±78[38.8%]</td>
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<td></td>
<td>±120[62.7%]</td>
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<td></td>
<td>±48[17.2%]</td>
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<tr>
<td>Extension leg kg</td>
<td>Quist et 2012</td>
<td>38.6 ± 15.5</td>
<td>45.1 ± 18.9</td>
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<td>±6.5[18.8%]</td>
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<td></td>
<td>±2.6[4.1–8.9]</td>
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<tr>
<td>Press leg kg</td>
<td>Quist 2012</td>
<td>70.34 ± 26.9</td>
<td>86.9 ± 28.8</td>
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<td></td>
<td>±16.5[23.5%]</td>
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<td></td>
<td>±2.16[11.5–21.7]</td>
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<tr>
<td>Extension elbow N</td>
<td>Kuehr 2014</td>
<td>124 ± 44</td>
<td>136 ± 44</td>
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<td></td>
<td>1. ±12[9.7%]</td>
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<td></td>
<td></td>
<td>±5[4.0%]</td>
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<tr>
<td>Flexion knee N</td>
<td>Kuehr 2014</td>
<td>140 ± 41</td>
<td>177 ± 61</td>
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<td></td>
<td></td>
<td></td>
<td>±3[23.6%]</td>
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<td>±52[37.1%]</td>
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<td>±15[8.5%]</td>
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<tr>
<td>Flexion elbow N</td>
<td>Kuehr 2014</td>
<td>144 ± 52</td>
<td>152 ± 55</td>
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<td>±8[5.8%]</td>
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<td></td>
<td></td>
<td>±14[9.7%]</td>
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<td></td>
<td>±6[3.9%]</td>
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<tr>
<td>Hip flexion N</td>
<td>Kuehr 2014</td>
<td>133 ± 48</td>
<td>137 ± 54</td>
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<td>±5[3.8%]</td>
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<td>±2[1.5%]</td>
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<td></td>
<td>±2[1.5%]</td>
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<tr>
<td>Hip abduction N</td>
<td>Kuehr 2014</td>
<td>153 ± 45</td>
<td>164 ± 48</td>
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<td></td>
<td>±11[7.2%]</td>
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<td>±8[5.2%]</td>
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<td></td>
<td>±3[1.8%]</td>
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<tr>
<td>Chest press kg</td>
<td>Quist 2012</td>
<td>30.8 ± 13.2</td>
<td>40.4 ± 16.3</td>
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<td></td>
<td>±9.6[31.2%]</td>
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<td></td>
<td>±2.9[6.4–12.7]</td>
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<tr>
<td>Lat ma-chine kg</td>
<td>Quist 2012</td>
<td>35.8 ± 13.8</td>
<td>39.2 ± 17.6</td>
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<td></td>
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<td></td>
<td>±3.4[8.5%]</td>
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<td></td>
<td></td>
<td>±2.3[0.0–6.7]</td>
<td></td>
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</tr>
<tr>
<td>Abdominal crunch kg</td>
<td>Quist 2012</td>
<td>24.9 ± 10.7</td>
<td>29.5 ± 11.3</td>
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<td></td>
<td></td>
<td></td>
<td>±4.8[18.5%]</td>
<td></td>
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<tr>
<td>Lowerr back kg</td>
<td>Quist 2012</td>
<td>35.3 ± 14.1</td>
<td>43.1 ± 16.2</td>
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<td></td>
<td>±4.8[2.2–6.0]</td>
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<td></td>
<td>±7.8[4.8–10.8]</td>
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</tbody>
</table>

**Abbreviations:** 6MWT = 6-Minute Walking Test; CG = Control Group; CI = Confidence Interval; CWCE = Constant workrate Cycle Exercise; D = day; diff = difference; ESWT = Endurance Shuttle Walk Test; FEV = Forced Expiratory Volume in 1 second; IG = Intervention Group; ISWT = Incremental Shuttle Walk Test; iv = intervention; kg = kilogram; L = Liter; m = meter; MCID = Minimal Clinically Important Difference; med = median; ml = milliliter; min = minutes; n = Number; N = Newton; NA = Not Applicable; NS = Not Significant; NR = Not Reported; s = seconds; SD = Standard Deviation; T0 = baseline; T1 = first measurement time; T2 = last measurement time; VO2max = maximum oxygen uptake; wk = week.

* MCID-values for aerobic outcomes: VO2max increase of 3.5 ml/min/kg (Myers et al., 2002); 6MWT increase of ≥24 m or 9.5% change (Granger et al., 2015); CWCE increase of ≥100 s (Redelmeier et al., 1997); FEV1 increase of 0.23 L (Lavoilette et al., 2008); ISWT increase of 70 m (Santangelo et al., 1999); ESWT increase of 154–164 m (Houchen-Wolloff et al., 2015); TUG (s) decrease of ≥0.8 s (Altenburg et al., 2015); MCID-values not found for: Steps/day (N); Walking time (min); Mobility (Likert scale); Activity (Likert scale) and muscle strengths.

*1 Within subjects group time effect.
*2 Between subjects group time effect.
*3 Between groups.
*4 Between measurement times.
described as adverse events (including post-operative pulmonary complications) (Cheville et al., 2013; Coats et al., 2013), or hospitalization days (Arbane et al., 2011, 2014; Brocki et al., 2014; Granger et al., 2013; Hoffman et al., 2014). Other results of physical outcomes are displayed according to measuring instruments in Table 3 (Myers et al., 2002; Redelmeier et al., 1997; Laviolette et al., 2008; Santanello et al., 1999; Houchen-Wolloff et al., 2015; Altenburg et al., 2015; Wright et al., 2011).

3.2. Results of individual studies

The prehabilitation study and six rehabilitation studies (64%) described significantly improved physical fitness after (home-based) training (Andersen et al., 2011; Arbane et al., 2011; Coats et al., 2013; Granger et al., 2013; Kuehr et al., 2014; Quist et al., 2012). Three additional rehabilitation studies (27%) indicated improved physical fitness as well, although significance was not reported (Brocki et al., 2014; Cheville et al., 2013; Hoffman et al., 2014). Specific outcomes are displayed in Table 2. The 6MWT distance was described in seven studies (64%), including the prehabilitation study, and showed a significant improvement of 28–65 m (5.2–43%) (Arbane et al., 2011; Brocki et al., 2014; Coats et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014). In five of them, this gain was clinically relevant (Arbane et al., 2011; Brocki et al., 2014; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014). Muscle strength increased significantly during training sessions for most muscle groups (Arbane et al., 2014; Coats et al., 2013; Kuehr et al., 2014; Quist et al., 2012). All studies described patient adherence and varied from 50% (Kuehr et al., 2014) to 100% (Coats et al., 2013; Hoffman et al., 2014). Main reasons for dropout were clinical deterioration, incomplete data-assessment, dying, and withdrawal from study-protocol. In all three studies examining home-based training alone, patient adherence was sufficient (72%, 100%, and 100%, respectively) (Cheville et al., 2013; Coats et al., 2013; Hoffman et al., 2014). In three of eight studies combining home-based with extramural and/or intramural training, patient adherence was sufficient (71%, 72%, and 79%, respectively) (Andersen et al., 2011; Brocki et al., 2014; Quist et al., 2012), and varied from 50 to 68% in the remaining five studies (Andersen et al., 2013; Arbane et al., 2011, 2014; Granger et al., 2013; Kuehr et al., 2014). Reported exercise adherence for the home-based component varied from 9% (Quist et al., 2012) to 125% (Coats et al., 2013) and was sufficient in four of six studies (Cheville et al., 2013; Coats et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014). Six studies included adverse events or hospitalization time (55%). For surgical patients, hospitalization varied in the intervention group from four (Granger et al., 2013) to nine days (Brocki et al., 2014), compared to six (Granger et al., 2013) to eleven days (Arbane et al., 2011) in the control group. Adverse events were absent (Coats et al., 2013; Kuehr et al., 2014).
Table 4: Results of methodological quality according to ‘the Cochrane risk of bias tool’.

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<tr>
<th>First author year</th>
<th>Randomization (selection bias)</th>
<th>Equal groups (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Selective drop-out (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Methodological quality</th>
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<td>Andersen 2011</td>
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et al., 2013; Quist et al., 2012) or occurred infrequently during the postoperative period (Arbane et al., 2011).

3.3. Qualitative assessment

Only one study (9%) had a high methodological quality and was at risk for performance bias as participants or personnel were blinded (Table 4; Cochrane Methodology Group and Cochrane Bias Methods Group, 2011a; Brocki et al., 2014). Therapeutic validity was low in this study due to insufficient eligibility criteria for therapist and setting, rationale for the training program, and monitoring or personalization of the intervention (Table 5; Hoogeboom et al., 2012). A moderate methodological quality was found in two rehabilitation studies and one prehabilitation study (45%), where especially selection bias could influence study outcomes (Andersen et al., 2011; Coats et al., 2013; Hoffman et al., 2014). Additionally, therapeutic validity was high in all studies. In the seven remaining rehabilitation studies, a low methodological quality was found due to selection (Andersen et al., 2013; Arbane et al., 2014; Cheville et al., 2013; Granger et al., 2013; Kuehr et al., 2014; Quist et al., 2012), reporting (Arbane et al., 2011, 2014; Cheville et al., 2013; Granger et al., 2013; Quist et al., 2012), and attrition bias (Andersen et al., 2013; Arbane et al., 2011, 2014; Cheville et al., 2013; Granger et al., 2013; and Quist et al., 2012). Of these seven studies, three had a low therapeutic validity due to lack of eligibility criteria (Arbane et al., 2011, 2014; Kuehr et al., 2014; Quist et al., 2012), lack of rationale for the content and intensity of the program (Arbane et al., 2011; Quist et al., 2012), or no personalized exercises (Arbane et al., 2014; Kuehr et al., 2014; Quist et al., 2012). The three studies assessing home-based training alone had a high therapeutic validity, and a moderate (Coats et al., 2013; Hoffman et al., 2014), and low (Cheville et al., 2013) methodological quality. The interobserver agreement for methodological quality was very good (kappa 0.80) and for therapeutic validity good (kappa 0.76).

Across included studies, only one described specific demands for therapist and setting (Hoffman et al., 2014) and four did personalize exercises (Andersen et al., 2013; Arbane et al., 2014; Granger et al., 2013; Hoffman et al., 2014). Selective dropout in six studies could have led to attrition bias (Andersen et al., 2013; Arbane et al., 2011, 2014; Granger et al., 2013; Kuehr et al., 2014; Quist et al., 2012). Five studies did not display results entirely or did not report on significance, thereby inducing reporting bias (Arbane et al., 2011, 2014; Cheville et al., 2013; Granger et al., 2013; Quist et al., 2012). The included randomized controlled trials did not perform blinding for randomization, participants, or personnel. Therefore, these studies were at risk for performance and detection bias (Arbane et al., 2011, 2014; Brocki et al., 2014; Cheville et al., 2013; Granger et al., 2013).

4. Discussion

The aim of this systematic review was to evaluate feasibility and effectiveness of prehabilitation and rehabilitation including a home-based component for patients with NSCLC and to describe physical fitness, adherence, treatment tolerance, and recovery.

4.1. Summary of evidence

Ten rehabilitation studies and one prehabilitation study were included (451 patients with NSCLC). Patients included in this review were diagnosed with stage I–IV disease, and most underwent surgery with or without (neo)adjuvant treatment (308 of 496 (62%)). However, studies in which patients received radiotherapy, chemotherapy, chemoradiotherapy, or palliative care were also included. Rehabilitation studies including a home-based component showed significantly or clinically relevant increased physical fitness. Home-based prehabilitation may increase physical fitness as well, although only one published study was found. Patient adherence and exercise adherence were generally higher and sufficient in home-based interventions compared to combinations of home-based, intramural- and/or extramural training. It remains unclear whether home-based prehabilitation can lead to less adverse events or hospitalization time, while rehabilitation including a home-based component might improve recovery after treatment. Highest patient adherence and/or exercise adherence together with significant or clinically relevant improvements in physical fitness can be reached by home-based interventions, as was seen in three studies including home-based interventions only (Cheville et al., 2013; Coats et al., 2013; Hoffman et al., 2014). However, it should be mentioned that these were two pilot studies (Coats et al., 2013; Hoffman et al., 2014) and one randomized controlled trial (Cheville et al., 2013), and other included studies with a home-based component did not always report compliance of home-based exercises (Andersen et al., 2011, 2013; Arbane et al., 2011, 2014; Granger et al., 2013). Still, physical fitness did not differ between home-based training alone and those with additional extramural sessions (Brocki et al., 2014). Probably, newly diagnosed lung cancer patients show interest and motivation for exercise programs, in which home-based training during treatment was preferred (Karvinen et al., 2016). As patients with NSCLC are often older and frail (Hsu et al., 2015; Semrau et al., 2014; Hoogeboom et al., 2012), commuting and accessibility to in- and outpatient facilities hin-
der participation in clinic-based exercise programs (Oosting et al., 2012). Therefore, exercise programs should be delivered at the patient’s own living situation to optimize adherence (Oosting et al., 2012). Furthermore, regular supervision (Dalal et al., 2010), and a personalized training program (Spruit et al., 2013; Royal Dutch Physiotherapy Society, 2008; Netherlands Cancer Registry, 2011; Pouwels et al., 2015) can further increase adherence rates by facilitating motivation and a physically active lifestyle, as is recognized by the CONTENT scale (Hoogeboom et al., 2012; Herbert and Ba, 2005). At the time of cancer diagnosis, patients are more susceptible to pursue a healthy lifestyle to optimize treatment outcomes and general health (Westmaas et al., 2015). In two included studies, increased physical fitness maintained several weeks (Kuehr et al., 2014), and ten months (Brocki et al., 2014) after the intervention without additional exercise instructions. This was previously found in surgical patients with NSCLC receiving prehabilitation and/or rehabilitation ((p)rehabilitation), although home-based exercises were not included in these studies (Ni et al., 2016; Cavalieri et al., 2014). Despite the fact that improvement of treatment tolerance or recovery is the driving force behind the concept of (p)rehabilitation, it was either not reported or reported by diverse parameters (number of complications or hospitalization days). Trials mainly included fit and selected patients without comorbidities, leaving older and high-risk patients underrepresented (Kilari et al., 2016).

Most rehabilitation studies combine intramural and/or extramural training with home-based exercises. Also, there is heterogeneity in the contents of training sessions, and their planning and sequences. Higher training intensity and use of devices such as bicycles and treadmills were more present in intramural and extramural sessions, whereas home-based sessions included lower intensity and more simple instruments. The broad patient population provided in our review included different stages of disease, treatment options, age groups, and physical fitness. This heterogeneity reflects everyday clinical care and probably explains the observed wide range of effect sizes and maximal capable improvements in treatment outcomes. However, it hinders the interpretation of summarized results, and effects of interactions between training contents and patient characteristics are warranted. Furthermore, natural physical recovery comes into play as increased physical fitness cannot be explained by the intervention solely, emphasizing the importance of control groups in studies.

4.2. Strengths and limitations

Strengths of this study are the independent literature search, selection, and data extraction by two reviewers with good agreement, thereby preventing errors in study and data selection, and limiting reporting bias (Cochrane Statistical Methods Group and Cochrane Bias Methods Group, 2011b). Also, therapeutic validity was assessed, providing more insight in reported study outcomes, as a low therapeutic quality might explain decreased effectiveness of the intervention compared to what was expected (Hoogeboom et al., 2012). Nevertheless, the outcomes of this systematic review should be interpreted carefully due to several constraints. Only three studies incorporated home-based training alone for (p)rehabilitation. The eight remaining studies included home-based, intramural- and/or extramural components and as a result, separate effects of a home-based training component could not be attributed. Also, several pilot studies were included. This means that evidence is still lacking and powered randomized controlled trials are required. Especially for home-based prehabilitation, not all potential eligible studies were available. As negative and non-significant outcomes are less likely to be published, publication bias could lead to a more positive scope of outcomes. Regarding methodological quality, cut off values were not present and categories were arbitrarily chosen. This could lead to an over-

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estimation of methodological quality as some types of bias are determined by more than one study characteristic (The Cochrane Collaboration, 2011). Moreover, some components did apply to randomized controlled trials only. Since clinical and statistical heterogeneity impeded the interpretation of patient characteristics and exercise contents, the internal validity of summarized effect sizes for the 6MWT distance is questionable. Therefore, a meta-analysis could not be performed despite the vast number of studies and patients included (Herbert and Ba, 2005). Furthermore, the goal of (p)rehabilitation will be different for patients receiving surgery, radiotherapy, chemoradiotherapy, chemotherapy, and palliative treatment. As the included patient group was heterogeneous with different prognoses and applied treatment regimens, various effects can be expected which cannot be explained by (lack of) effectiveness of (p)rehabilitation.

Several types of bias could influence methodological quality. Selection bias in non-randomized studies and omission of blinding participants or personnel could lead to increased motivation and more positive study results. Although it is almost impossible to perform blinding during physical interventions, one study was able to apply this on outcome assessors and patients (Granger et al., 2013). Attrition bias could have influenced results, although most patients indicated a reason for withdrawal. Nevertheless, some were unknown and could disguise potential negative treatment effects such as worse physical functioning or fatigue (Ni et al., 2016; Pouwels et al., 2015). Selective reporting is a concern as data regarding statistical significance were not always displayed for the home-based component specifically. Yet, evaluating whether there was a clinically relevant improvement in cardiorespiratory fitness after (p)rehabilitation was possible for all studies using the 6MWT distance. As only physical fitness was included in the search strategy, missing values for adherence treatment tolerance, and recovery were foreseen.

With regard to therapeutic validity, small sample sizes and patient cohort studies allow researchers to provide a flexible training scheme which can be easily monitored and adapted, thereby increasing patient and exercise adherence (Dalal et al., 2010; Pouwels et al., 2015). As a result, effect rates could be based on individually optimized, but slightly incomparable exercise programs (Hoogeboom et al., 2012; Herbert and Ba, 2005). Mainly larger studies disregard components like personalization of exercises and supervision for increasing quality and effectiveness of the intervention. Absolute training effects are more easy to compare in non-personalized fully structured training sessions (Thorsen et al., 2005), resulting in higher methodological quality. However, the main goal of home-based (p)rehabilitation should be to enhance and preserve wellbeing and everyday life in patients with NSCLC (Salander and Lilliehorn, 2016). Therefore, a patient tailored program with a necessity-based design should be at best interest, together with the highest therapeutic and methodological quality (Griddelli et al., 2007; Kilari et al., 2016). Furthermore, all patients with NSCLC can benefit from increasing endurance and muscle strength in order to optimize treatment outcomes by home-based (p)rehabilitation. However, the selection of patients should mainly focus on older and high-risk patients and how to increase accessibility to home-based, supervised, and personalized sessions in order to maximize training, physical fitness, adherence, treatment tolerance, and recovery (Kilari et al., 2016).

In conclusion, this systematic review showed positive and encouraging results of (home-based) (p)rehabilitation on physical fitness for patients with NSCLC. Although included studies varied in quality, and quantity, results of this review indicate that combining (home-based) resistance and endurance training, as well as supervision and personalization, seem necessary to optimize physical fitness, adherence, treatment tolerance, and recovery. Although different training contexts have been included in this review, home-based training alone has not been studied extensively and several studies were underpowered. Therefore, additional randomized controlled trials are required. This sets priority for prospective trials including older and high-risk patients with NSCLC, in which supervision, personalization, and high methodological and therapeutic quality in a home-based context are investigated. Ultimately, more evidence for home-based (p)rehabilitation can be gathered leading to improved physical fitness, patient adherence, exercise adherence, and especially recovery and treatment tolerance in this predominantly high-risk patient group.

Conflict of interest
None.

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