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Exercise for individuals with lung cancer: a systematic review and meta-analysis of adverse events, feasibility and effectiveness.

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Abstract

Background: The purpose of this systematic review and meta-analysis was to evaluate the safety (adverse events), feasibility (recruitment, retention and adherence) and effectiveness of exercise among individuals with lung cancer.

Data Sources: Electronic databases (CINAHL, Cochrane, Ebscohost, MEDLINE, Pubmed, ProQuest Health and Medical Complete, ProQuest Nursing and Allied Health Source, Science Direct and SPORTDiscus) were searched for randomised, controlled, exercise trials involving individuals with lung cancer that were published prior to May 1, 2020. The PEDro scale was used to assess risk of bias, and the Common Terminology Criteria for Adverse Events was used to classify adverse event severity. Feasibility was assessed by computing median (range) recruitment, retention and exercise attendance rates. Meta-analyses were performed to evaluate adverse event risk between exercise and usual care, and effects on health outcomes. Subgroup effects for exercise mode, supervision, intervention duration, diagnosis or treatment-related factors and trial quality were assessed.

Results: Thirty-two trials (n=2109) involving interventions ranging between 1 and 20 weeks were included. Interventions comprised of aerobic (n=13, 41%), resistance (n=1, 3%), combined aerobic and resistance (n=16, 50%;) and other exercise (n=2, 6%). There was no difference in the risk of an adverse event between exercise and usual care groups (exercise: n=64 events; usual care: n=61 events]; risk difference: RD: -0.01 [91% CI=-0.02, 0.01]; p=0.31). Median recruitment rate was 59% (9-97%), retention rate was 86% (50-100%) and adherence rate was 80% (44-100%). Significant effects of exercise compared to usual care were observed for quality of life, aerobic fitness, upper-body strength, lower-body strength, anxiety, depression, forced expiratory volume, and sleep (SMD range=0.20-0.59). Subgroup analyses showed that safety, feasibility and effect was similar irrespective of exercise characteristics, stage at diagnosis, treatment (surgery and chemotherapy) and trial quality.

Conclusion: For individuals with lung cancer (stage I-IV), the risk of an adverse event with exercise is low. Exercise can be feasibly undertaken post-diagnosis and leads to improvements in health-related outcomes. Together, these findings add weight behind the importance of integrating exercise into standard cancer care, including for this specific cancer type.

Implications for Nursing Practice: Exercise should be considered as part of the treatment for all patients with lung cancer at any stage. Exercise has been shown to be low

risk and can be feasibly undertaken by patients. The ideal mode, intensity, frequency or duration of exercise for all patients with lung cancer is not known. Nonetheless, these findings support endorsement of cancer-specific physical activity guidelines, as well as referral to an exercise professional, such as an Exercise Physiologist or Physiotherapist, for those diagnosed with lung cancer.

Key words: lung, cancer, neoplasm, aerobic exercise, resistance exercise, exercise oncology.

Introduction

Worldwide, lung cancer is the most commonly diagnosed cancer in males and the third most commonly diagnosed cancer in females¹, accounting for 13% of new cancer diagnoses². Lung cancer is associated with poor prognosis (5-year survival: 19%)^{3,4} and is the leading cause of cancer-related death in both females and males, resulting in more deaths than breast, prostate and colon cancers combined^{2,5,6}. The two main types of lung cancer are Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC), with NSCLC accounting for 70% to 85% of diagnoses⁷. Treatment seeks to mitigate the disease and/or extend life. However, both the disease and its treatment are associated with a range of debilitating side effects, including pain, dyspnoea, fatigue, anxiety, depression, insomnia, pain, anaemia, pneumonitis, weight loss, muscle wasting and reduced physical function.

Disease- and treatment-related side effects contribute to clinically relevant reductions in fitness, lung capacity⁸ and overall quality of life⁹, which in turn increase risk of developing comorbidities and mortality¹⁰⁻¹⁴. Cross-sectional data suggests that impairments in quality of life¹⁵ and presence of respiratory symptoms can persist beyond 5 years post-diagnosis for at least 30% and 60% of lung cancer survivors¹⁶. Further, lung cancer patients report lower physical function and inferior health outcomes compared with healthy age-matched controls¹⁷ and also experience poorer quality of life and a greater number of adverse effects compared with other cancer types (including other common cancers such as colon and prostate¹⁸⁻²⁰).

The respiratory system plays a vital role in the ability to perform any and all daily tasks, as it is responsible for gas exchange (ie, delivers oxygen to the blood and removes carbon dioxide from the body, which is the by-product of aerobic metabolism), with the lungs being the primary organ of the respiratory system. The known benefits of exercise training on the respiratory system include improvements in strength of the breathing muscles, lung capacity

and the efficiency of gas exchange. As such, while a significant evidence base supports the role of exercise for the wider cancer population, exercise is likely particularly useful for those with lung cancer in counteracting the adverse impacts of the disease and its associated treatment on the respiratory system. Further, observational evidence suggests that the benefits of exercise may extend beyond improvements to function and quality of life. Specifically, higher levels of postdiagnosis physical activity is also associated with reduced mortality in lung cancer (HR: 0.76 [95% CI:0.60–0.97])²¹. Unfortunately, over one-third (36%) of lung cancer patients (stage I-IV) reduce, or stop being physically active in the 6 months following diagnosis²².

The effect of exercise for individuals with lung cancer has been evaluated in RCTs and summarised in previous meta-analyses^{23–25}. Findings indicate that exercise interventions lead to improvements in fitness as measured by the 6-minute walk test (mean difference, MD range= 18 to 50 metres, $p < 0.05$ ^{23,24}) and quality of life (standardised mean difference, SMD=0.51, $p < 0.05$ ²⁵). However, to date, reviews have only focused on studies involving patients with NSCLC, which means that previous research has predominantly involved the subgroup of patients who have higher survival (5-year relative survival: NSCLC: 23%; SCLC: 6%²⁶). SCLC represents 25-30% of lung cancer diagnoses and is underrepresented in the body of evidence⁷. Further, thorough assessment of safety and feasibility measures of exercise for those with lung cancer has not been undertaken. Therefore, the purpose of this systematic review was to evaluate the safety, feasibility and efficacy of exercise among individuals with lung cancer (including NSCLC and SCLC). Specifically, this review will evaluate: 1) the number, type and severity of adverse events (safety); and 2) trial recruitment and retention and exercise adherence rates (feasibility). Secondary outcomes of this work included the evaluation of the effect of exercise on health-related outcomes such as quality of life, aerobic fitness, fatigue, upper-body strength, lower-body strength, anxiety, depression,

sleep, forced expiratory volume (FEV 1), forced vital capacity (FVC), dyspnea, pain and length of hospital stay.

Methods

Search strategy and selection criteria

An electronic database search was undertaken using combinations of MeSH and free-text words for “lung”, “cancer”, “physical activity” and “exercise” (see Supplementary content 1 for the full search details for all databases). The following databases were searched: CINAHL, Cochrane, Ebscohost, MEDLINE, Pubmed, ProQuest Health and Medical Complete, ProQuest Nursing and Allied Health Source, Science Direct and SPORTDiscus. Database searches were limited to scholarly journal articles published in English-language peer-reviewed journals prior to May 1, 2020.

The Participant, Intervention, Comparator, and Outcome (PICO) framework²⁷ was used to develop the inclusion criteria as follows: Participants: trials involving female or male participants diagnosed with lung cancer, either awaiting, undergoing or completed surgery, chemotherapy and/or radiotherapy were eligible. Studies that involved samples with mixed cancer types (in addition to lung cancer) were excluded if the results were not reported separately for the participants with lung cancer. Intervention: RCTs designed to evaluate exercise interventions were eligible. An RCT evaluating an exercise intervention was defined as a comparative trial designed to evaluate exercise safety, feasibility and effectiveness with random allocation of participants. Exercise was considered as “any form of planned, structured, and repetitive bodily movements performed to improve or maintain fitness, performance or health”^{28,29}. Eligible trials were categorised into subgroups based on exercise mode (aerobic, resistance, combined aerobic and resistance or other). Any form of exercise that was not specified as aerobic or resistance was considered ‘other’ exercise (e.g., yoga).

Trials were eligible for inclusion irrespective of degree of intervention supervision, intervention length or exercise dose (e.g., exercise intensity). Interventions conducted at any time pre, during or following treatment were eligible. Trials that involved exercise in addition to other interventions (e.g. dietary intervention) were excluded if the results of exercise alone could not be isolated. Comparators: Studies that involved a non-exercise control or usual care group were eligible. Single-group pre-post intervention studies (with no comparison group) were ineligible.

Outcomes of interest

Safety and feasibility: Safety was evaluated by assessing adverse events. Adverse events were defined as any undesirable medical or health-related event that occurred during the trial. Adverse events were classed as either non-exercise adverse events (occurred during the trial but reported as being unrelated to exercise) or exercise-related adverse events (events which occurred during or as a direct result of exercise). Adverse events were categorised by one author (BS) based on severity using the Common Terminology Criteria for Adverse Event (Version 5³⁰) as either: grade 1 (asymptomatic or mild symptoms, clinical or diagnostic observations only and/or intervention not indicated); grade 2 (moderate, minimal, local or non-invasive intervention required and/or limiting age-appropriate activities of daily living); grade 3 (severe or medically significant but not immediately life-threatening; hospitalisation and/or prolongation of hospitalisation indicated; disabling and limiting self-care activities of daily living); grade 4 (life-threatening consequences and urgent intervention indicated), or; grade 5 (death). An adverse event was considered ‘serious’ if it resulted in hospitalisation, significant disability, was life threatening or resulted in death (i.e., grade 3 or higher)³¹. To reduce the potential of under-reporting of adverse events, any withdrawal from a trial that occurred due to a health- or disease-related reason (e.g., illness, or worsening of side effects)

was considered an adverse event³². If an event caused withdrawal from a trial, or if a withdrawal occurred due to a health or medical reason, these events were categorised as grade 3 (if the severity was not specified)³². If a trial did not report adverse events and there were no health-related withdrawals, then it was considered that no adverse events had occurred³².

Health-related outcomes: Meta-analyses of the effects of exercise on health-related outcomes were performed for outcomes that were reported in at least two studies³³. These were quality of life, aerobic fitness, fatigue, upper-body strength, lower-body strength, anxiety, depression, sleep, forced expiratory volume in one second (FEV 1), forced vital capacity (FVC), dyspnea, pain and length of hospital stay.

Data extraction

Screening of the titles and abstracts of all records that were identified during the electronic database search was undertaken by one author (BS). Screening of the reference lists of relevant articles (original studies and reviews) was also undertaken to identify potentially eligible studies. Articles that were considered potentially eligible based on the title or abstract were then retrieved in full-text and screened for eligibility. One investigator (BS) extracted the following data from each trial into tabular format: trial and participant characteristics, intervention details, adverse events, and feasibility information.

Risk of bias assessment of each trial was undertaken using the Physiotherapy Evidence PEDro scale by two investigators (BS, KT) with a third reviewer (SH) assessing conflicts. The scale is a valid and reliable tool for assessing risk of bias in RCTs^{34,35} and each trial was assessed in 11 domains (eligibility criteria, random allocation, concealment, baseline between-group differences, subject blinding, interventionist blinding, assessor blinding,

attrition, intention-to-treat, between-group statistical comparisons and outcome reporting). Trials with a score of six or higher (of a possible score of 10; item one not contributing to the total score) were categorized as high quality, and lower than six as low quality^{35,36}.

Statistical analyses

Meta-analysis of adverse events: The total number of adverse events that occurred in the exercise and usual care groups were analysed using a Mantel-Haenszel random effects model. Adverse events were analysed as a count variable for the meta-analysis and the risk difference (RD) with 95% confidence intervals was calculated as the effect measure. RD was used to ensure that trials with zero adverse events could be included in the analysis^{37,38}. A negative value for RD indicated a lower risk of an adverse event for exercise compared with usual care. Low-grade or low-severity adverse events (i.e., grade 1–2 events) were likely to have not been comprehensively monitored or reported for non-intervention participants due to reduced contact with research staff (compared with the interventions groups). For the intervention groups, grade 1–2 events would also likely include normal responses to exercise (e.g., mild muscle soreness), rather than potentially avoidable or undesirable adverse events³⁹. Therefore, grade 1–2 adverse events were not included in the meta-analysis.

Feasibility: Feasibility was evaluated by calculating recruitment rate, retention rate and exercise adherence rate (as a percentage) and reported as median, minimum and maximum (due to non-normally distributed data). Recruitment, retention and exercise adherence rates were assessed to determine feasibility. Recruitment rates were calculated as the percentage of individuals who were eligible and consented to participate in the trial. Retention rates were the percentage of enrolled participants who completed the trial. Adherence rates were the percentage of scheduled number of exercise sessions that were completed by participants. Feasibility was assessed using the following cut-off values which

were established *a priori* as clinically relevant based on previous studies (recruitment rate $\geq 25\%$ ⁴⁰; retention rate $\geq 75\%$ ⁴¹; and adherence $\geq 75\%$)⁴¹. For subgroup analyses, a difference of $>10\%$ in recruitment, retention and adherence rates between subgroups (exercise mode; intervention supervision; intervention duration; surgery; chemotherapy status; cancer subtype; disease stage; and trial quality) was *a priori* considered clinically relevant.

Meta-analysis of health outcomes: Health-related outcomes were analysed as continuous outcomes by comparing post-intervention means and standard deviations (SDs) for the exercise and usual care groups. To allow comparison of data from different scales, the standardised mean differences (SMDs) were used as the effect measures, calculated using RevMan software (version 5.3). R statistical software (version 3.6.2) was used to create forest plots for each meta-analysis. If means and SDs were not reported in a paper (n=2 trials), the authors were contacted (n=1 responded), or recommended formulas were used to calculate the means and/or SDs using reported data (e.g., using median, range and sample size)⁴². If a trial involved two or more instruments for assessing an outcome, the instrument defined as being the gold standard or with demonstrated validity and reliability was used (n=6).

For each meta-analysis, data were combined at the trial level. Funnel plots were created to evaluate publication bias by plotting RDs or SMDs and standard errors and assessing the presence of asymmetries or missing sections⁴³. The following cut-offs were used to describe the magnitude of effect: less than 0.20 representing a small effect; 0.20–0.50 representing a medium effect; and greater than 0.50 representing a large effect⁴⁴. A p-value of less than 0.05 was considered statistically significant. Cochran's Q test was used to assess for statistical heterogeneity and the proportion of the overall outcome attributed to variability was investigated using the I^2 statistic^{33,45} using the following values: $I^2=0-29\%$, no heterogeneity; $I^2=30-49\%$, moderate heterogeneity; $I^2=50-74\%$, substantial heterogeneity; and $I^2=75-100\%$, considerable heterogeneity³³. Planned subgroup analyses were performed to

assess the effects of: 1) exercise mode (aerobic, resistance, combined and other exercise); 2) intervention supervision (supervised, defined as over half of the exercise sessions involving face-to-face supervision, versus unsupervised, defined as less than half of the exercise sessions involving face-to-face supervision); 3) intervention duration (<12 weeks or \geq 12 weeks); 4) timing of the intervention with respect to surgery (pre-surgery or post-surgery); 5) timing of the intervention with respect to chemotherapy (during or following chemotherapy); 6) cancer subtype (NSCLC, SCLC or mixed [studies involving a mix of participants with different diagnoses]); 7) disease stage (stage I-II, III-IV and mixed [studies involving a mix of participants with different stages]); and 8) trial quality (high- versus low quality) on adverse events, recruitment, withdrawal and adherence rates, and health outcomes.

Results

Literature search: A total of 2503 articles were identified after a search of databases (see Supplementary content 2 for PRISMA flow diagram). Following removal of duplicates, titles and abstracts were screened and 185 full-text publications were retrieved for review. One-hundred and fifty-three (n=153) were subsequently deemed ineligible (see Supplementary content 2 for reasons for exclusion), leaving 32 trials for inclusion. Trials were rated as being of low (n=9, 28%) or high quality (n=23, 72%) (see Supplementary content 3 for trial quality ratings).

Trial and participant characteristics: Sample sizes ranged between 14⁴⁶ and 235⁴⁷ (median=57), and mean age of participants across all trials was 64 years (SD=3). Most trials specifically involved participants with NSCLC (n=21, 66%)⁴⁷⁻⁶⁷, while eleven trials (n=11, 34%) involved participants with NSCLC and SCLC^{46,68-77}. Three trials involved participants with stage I-II disease^{53,54,60}, seven involved participants with stage III-IV

disease^{57,64,65,69,72,74,75}, 22 trials involved a mixed sample with stage I-IV disease^{24,46-52,55,56,58,59,62,63,65,67,68,70,71,73,76,77}. Twenty trials evaluated exercise post-surgery^{46-48,53,55,56,59,61-65,70-77} and 12 trials were pre-operative^{49-52,54,57,58,60,66-69}, with one trial involving inoperable cancer⁶⁹. With respect to chemotherapy, most trials evaluated exercise post-treatment (n=17^{48-50,52-54,56,58-62,66,68,71,72,76}), eight evaluated exercise during chemotherapy^{46,57,64,65,69,74,75,77} and seven trials involved mixed samples of participants who were undergoing or had completed treatment^{47,51,55,63,67,70,73}.

Intervention characteristics: Interventions ranged between one^{49,50,54} and 20 weeks⁶³. Most trials were less than 12 weeks (n=21, 66%)^{49-54,57-61,64-68,70,72-75}, and 11 trials (34%) were 12 weeks or longer^{46-48,55,56,62,63,69,71,76,77}. Combined exercise (aerobic and resistance exercise) was the most common intervention mode (n=16, 50%)^{47,48,52,55,57-59,61,63,68-70,73-76}, while 13 trials involved aerobic only exercise (n=13, 41%)^{49-51,53,54,60,62,64-67,71,72}, two trials evaluated other exercise (n=2, 6%)^{56,77}, and one trial (n=1, 3%) involved resistance exercise only⁴⁶. Most interventions were supervised (n=27, 84%)^{47,49-58,60-70,72,74-77}, and five (16%) interventions were unsupervised (i.e., less than half of the prescribed exercise was supervised face-to-face)^{46,48,59,71,73}. The supervised interventions were most commonly in a hospital setting. Supervision in these trials was from a physiotherapist/physical therapist (n=17)^{47,49-51,53-55,57,58,61,63,65,67,69,70,74,75}, an exercise physiologist (n=3)^{64,66,72}, a Tai chi practitioner (n=2)^{56,77}, an intensive care unit researcher (n=1)⁶², or was not specified (n=4)^{52,60,68,76}. Four of the interventions categorised as unsupervised involved low-levels of supervision from a physiotherapist (n=2)^{48,59} or exercise physiologist (n=2)^{46,73}.

Safety - overview of adverse events

There were no comments about adverse events in nine (28%) trials, while ten (31%) trials explicitly reported that no adverse events had occurred during the trial, and 13 (41%) trials reported the occurrence of adverse events.

Adverse events among exercise participants: Ninety adverse events occurred among participants allocated to exercise (grade 1: n=16 events; grade 2: n=10 events; grade 3: n=27 events; grade 4: n=20 events; grade 5: n=17 events, Table 1). The most common adverse events among exercise participants were death (n=17 events, grade 5), disease progression (n=12 events, Grade 4) and non-specified respiratory events (n=10 events, grade 2). Of the 90 events, 88 events (98%) were considered unrelated to exercise and 2 events (2%) were reported as exercise-related. Exercise-related adverse events were musculoskeletal soreness/pain (n=1 event, grade 1)⁷² and a hip fracture during balance training (n=1 event, grade 4)⁶³. Of note, one study⁶⁹ reported that during the pre-screening before each supervised exercise session, five participants were excluded from 1-2 exercise sessions due to adverse events (fever, dizziness, pain, and bodily discomfort). These were not considered as exercise-related adverse events, however they resulted in missed exercise sessions.

Adverse events among usual care participants: For participants allocated to usual care, there were 73 adverse events (grade 1: n=6 events; grade 2: n=6 events; grade 3: n=21 events; grade 4: n=22 events; grade 5: n=18 events, Table 1). The most common adverse events were death (n=18 events, grade 5), disease progression (n=13 events, grade 4) and pneumonia (n=10 events, grade 3).

Meta-analysis of adverse events: Meta-analysis of 32 RCTs involving 2109 participants (exercise: n= 1067; usual care: n= 1042) showed no difference in the risk of a grade 3–5 adverse event between exercise and usual care (n=125 adverse events [exercise: n=64 events; usual care: n=61 events], RD= -0.01 [91% CI=-0.02, 0.01]; p=0.31; I^2 =11%, Figure 1). Subgroup analyses showed that adverse event risk was similar irrespective of exercise mode

(aerobic, resistance, combined and other exercise; $\chi^2=4.27$, $p=0.23$), degree of intervention supervision (supervised and unsupervised; $\chi^2=0.12$, $p=0.73$), intervention duration (<12 weeks versus ≥ 12 weeks; $\chi^2=0.05$, $p=0.83$), timing of intervention with respect to surgery (pre-surgery and post-surgery; $\chi^2=0.48$, $p=0.49$), timing of intervention with respect to chemotherapy (during, post- and mixed; $\chi^2=0.26$, $p=0.88$), lung cancer subtype (NSCLC and NSCLC plus SCLC; $\chi^2=2.12$, $p=0.15$), disease stage ($\chi^2=0.32$, $p=0.85$) and trial quality (high and low quality; $\chi^2=0.46$, $p=0.50$).

Feasibility outcomes: Recruitment, retention and adherence rates are shown in Table 2.

Recruitment rates: Overall recruitment rate met the pre-defined criterion of $\geq 25\%$, with a median rate of 59% (range: 9-97%, $n=25$ trials, Table 2). Lower recruitment rates (defined as a difference $>10\%$) were observed for trials that were supervised compared to unsupervised (58% versus 79% respectively), <12 weeks compared to ≥ 12 weeks (54% versus 74%) and high-quality compared to low-quality trials (58% versus 79% respectively). There were no differences in recruitment rates based on exercise mode, timing of intervention with respect to surgery or chemotherapy, lung cancer subtype, disease stage or trial quality.

Retention: Median retention rate for the exercise groups was 86% (range: 50-100%, $n=32$ trials), and therefore met the predefined feasibility criteria of $\geq 75\%$. Retention rate for the usual care groups was 88% (range: 33-100%), with higher (greater than 10% absolute differences) retention rates observed in interventions conducted during chemotherapy compared with post-chemotherapy (88% versus 77%). There were a total of 218 withdrawals (out of 1067 participants) from the exercise groups ($n=65$, 30% due to health-related reasons; $n=153$, 70% due to non-health-related reasons) and 228 (out of 1042 participants) withdrawals from usual care groups ($n=54$, 24% due to health-related reasons; $n=174$, 76% due to non-health-related reasons). Unspecified non-health reasons (i.e., lost to follow-up with no specified reason) were the most common reason for withdrawal in both groups

(exercise groups: n=111 withdrawals; usual care: n=125 withdrawals; see Table 3 for all reasons for withdrawals).

Exercise adherence: Adherence to the scheduled number of exercise sessions met the pre-defined criterion of $\geq 75\%$, with a median rate of 80% (range: 44-100%, n=13 trials). Compared with interventions that were conducted during chemotherapy (69%), higher exercise adherence rates were observed in trials that were post-chemotherapy (79%) or conducted during and post-chemotherapy (87%).

Health Outcomes: An overview of all instruments used to assess quality of life, aerobic fitness, fatigue, upper-body strength, lower-body strength, sleep, anxiety, depression, dyspnoea, pain, FEV 1 and FVC are shown in Supplementary content 4.

Meta-analyses results: exercise versus usual care: Compared with usual care, there were small to large effects (all $p < 0.05$) in favour of exercise for quality of life (SMD=0.31 [95% CI=0.20, 0.42]), aerobic fitness (SMD=0.54 [95% CI=0.32, 0.76]), upper-body strength (SMD=0.59 [95% CI=0.30, 0.88]), lower-body strength (SMD=0.38 [95% CI=0.16, 0.61]), anxiety (SMD=0.26 [95% CI=0.11, 0.42]), depression (SMD=0.49 [95% CI=0.27, 0.72]), FEV1 (SMD=0.28 [95% CI=0.02, 0.54]) and sleep (SMD=0.31 [95% CI=0.01, 0.61]) (Figure 2 and Supplementary material 5-11). No overall effects ($p > 0.05$) of exercise were observed for fatigue, length of hospital stay, FVC, dyspnoea, and pain (Figure 2 and Supplementary material 12-16).

Subgroup analyses: An overview of all subgroup effects is shown in Supplementary material 17. *Mode:* Combined exercise (SMD=0.69) had a larger effect on upper-body strength than aerobic exercise (SMD=0.14; $\chi^2=4.66$, $p=0.03$). Combined exercise (SMD=0.41) also showed a larger benefit on length of hospital stay compared with aerobic exercise (SMD=-0.33; $\chi^2=5.44$, $p=0.02$). For fatigue, larger effects were observed for

combined (SMD=0.41) and other exercise (SMD=0.62) compared with aerobic exercise (SMD=-0.11; $\chi^2=14.61$, $p<0.001$). *Supervision*: Supervised interventions had a larger effect on quality of life (SMD=0.36) compared with unsupervised interventions (SMD=-0.02; $\chi^2=4.73$, $p=0.03$). Greater effects were observed for sleep following unsupervised interventions (SMD=0.64) compared with supervised interventions (SMD=0.14; $\chi^2=5.05$, $p=0.02$). *Intervention length*: Interventions that were 12 weeks or longer showed a larger effect on fatigue (SMD=0.44) compared with shorter interventions (SMD=0.01; $\chi^2=6.63$, $p=0.01$). *Treatment*: With respect to treatment, interventions that were conducted during treatment (SMD=0.69) had greater effects on dyspnoea compared with post-treatment (SMD=-0.12) or combined exercise trials (SMD=0.06; $\chi^2=8.30$, $p=0.02$). *Disease stage*: Trials involving participants with stage 1-4 (SMD=0.11) showed a small effect on FVC, while moderate and large effects were observed in trials involving participants with stage 1-2 (SMD=1.21) and stage 3-4 (SMD=0.65; $\chi^2=11.72$, $p=0.003$) disease, respectively. *Timing of surgery*: No subgroup effects were observed for surgery. *Diagnosis*: Cancer subtype had an effect on sleep ($\chi^2=4.94$, $p=0.03$), with trials involving participants with NSCLC showing no effect (SMD=0.04) and trials involving mixed samples (NSCLC and SCLC) showing a moderate effect (SMD=0.46). *Trial quality*: Trial quality had an effect on upper-body strength ($\chi^2=6.25$, $p=0.01$); low quality studies showed a large effect (SMD=1.64) and high-quality studies showed a moderate effect (SMD=0.47).

Discussion

Findings from this review support the safety and feasibility of exercise for individuals with lung cancer (NSCLC and SCLC). Exercise was safe and feasible, with similar findings

observed irrespective of exercise mode, degree of intervention supervision, intervention length, diagnosis, and whether exercise was performed pre- or post-surgery, or during or following chemotherapy. Benefits through exercise were observed for a range of physical and psychosocial outcomes including quality of life, aerobic fitness, upper-body strength, lower-body strength, anxiety, depression, FEV1 and sleep.

There was no difference in adverse event risk between exercise and usual care, and the proportion of adverse events related to exercise was extremely low (n=2, 3% of all adverse events reported) and comparable to rates previously observed in studies involving other cancer types (e.g., 5% of adverse events reported in trials involving women with stage II+ breast cancer were exercise-related adverse events)³². However, the rates of total adverse events observed here (7.7%, 163 events in 2109 participants), as well as the proportion of grade 3 or higher adverse events (76% of all adverse events, with death accounting for 25% of these) is more than double that reported in a review of exercise and breast cancer trials (3%, 156 events in 5200 participants)³². These figures are reflective of the known higher morbidity and mortality associated with lung cancer, compared with other common cancers. However, they also underscore the complexities of intervening with exercise in this cohort, and the importance of exercise professionals (such as Exercise Physiologists or Physiotherapists) working with lung cancer patients to have a deep understanding of the pathophysiology of the disease and treatment-related side effects. For example, all of the grade 2 adverse events reported were non-specified respiratory events, and although clearly associated with the disease and its treatment, require consideration and accommodation in any exercise prescription. Further, given the high rate of disease progression and death, there is a clear need to ensure exercise prescription is based on patient-directed goals, with reducing disease-related morbidity and maintaining independence likely to be common short-term goals.

Despite dealing with a cancer type with poorer prognosis than other common cancers, average recruitment (59%), retention (86%) and exercise adherence rates (80%) were similar to those previously found in breast³², prostate⁷⁸ and colorectal⁷⁹ cancer cohorts. However, since 34% (n=11) of trials excluded participants with comorbidities, 31% (n=10) excluded participants with advanced stage cancer, no trials specifically involved individuals with SCLC, and the mean age of participants in included studies was 64 years compared with the mean age at lung cancer diagnosis being 70 years⁴, it is plausible that these rates overestimate exercise feasibility for the wider lung cancer population. Further, more work is required to better understand the ability for those with lung cancer to adhere to exercise prescription. This review identified that only 40% of trials reported on adherence (participant attendance to exercise sessions) and no trial reported on exercise compliance. The lack of adherence and compliance data makes it difficult to determine realistic exercise prescription guidelines (including session frequency, mode, intensity and duration) with confidence and prevents a clear understanding of the relationship between exercise dose (prescribed and completed) and safety and response. These feasibility data highlighted the importance of a referral to an exercise professional who are trained to work with patients on an individualised basis to maximise gains while reducing risk of adverse events, and the subsequent positive efficacy findings of this review suggest it's important to do so.

Our efficacy findings, which showed improvements (of medium to high effect) in quality of life, aerobic fitness, upper-body strength, lower-body strength, anxiety, depression, FEV1 and sleep ($p < 0.05$), confirm and strengthen findings from previous meta-analyses which showed improved measures of aerobic fitness^{23,61,80}, quality of life⁸⁰ and lower-body strength. However, in contrast to findings reported in previous reviews of lung cancer and exercise studies we did not show beneficial effects of exercise on FVC and dyspnoea⁸⁰. However, differences in the inclusion criteria between the reviews (in particular patient

characteristics with previous reviews conducted on studies that only involved NSCLC) may explain the differences in these findings. Further, while we did not show a benefit in these outcomes, exercise was not associated with detriment, indicating that exercise may prevent worsening in these outcomes typically observed overtime.

Findings from the subgroup analyses conducted as part of this review suggested that the effect of exercise may differ for some outcomes based on specific intervention characteristics. For example, supervised interventions had a larger effect on quality of life than unsupervised interventions (SMD=0.36 vs. -0.02, respectively); longer duration interventions had a larger effect on fatigue than shorter interventions (SMD=0.44 vs. 0.01, respectively); and interventions conducted during treatment showed benefits to dyspnoea, whereas interventions conducted post-treatment did not (SMD=0.69 vs SMD=-0.12, respectively). While findings from such exploratory analyses may assist in informing precision exercise medicine in the future, caution must be applied in the interpretation at this stage. No clear trends emerged between outcomes and intervention or patient characteristics. Further, most outcomes improved with exercise, irrespective of exercise mode, degree of supervision, intervention duration, timing of intervention with respect to timing of surgery or chemotherapy, stage of disease at diagnosis, lung cancer type or study quality. When effect sizes were negligible (that is, <0.2) and/or results were not supported statistically or confidence intervals were wide, this was most likely due to having only between 2-5 studies, with small sample size overall, contributing to these results. Nonetheless, the key implication of these findings to date is that when prescribing exercise for patients with lung cancer, exercise professionals should pay close attention to patient exercise preferences.

There were several limitations to the findings of this review that need to be considered. Overall, reporting of safety and feasibility findings in exercise trials involving lung cancer patients needs improving. Most trials in this review did not describe adverse event monitoring

procedures and for about one-third (29%, n=9) there was no mention of whether adverse events occurred or not. Further, it is also plausible that consenting participants were likely to have higher function and less morbidity compared with the wider lung cancer population. Consequently, while results suggest exercise is safe and feasible for patients with lung cancer, caution needs to be applied to these findings and future research can aid practice through more comprehensive reporting of safety and feasibility (including exercise compliance) outcomes. There remains a scope for more translational exercise intervention research that seeks to transition patients from shorter-term highly supervised exercise to longer-term exercises in unsupervised conditions. This type of research will determine whether exercise is safe, feasible and effective for subgroups who may find it more difficult to access supervised exercise services, either due to place of residence (e.g., live in more rural/regional areas), disease- or treatment-related factors, patient preferences (e.g., prefer home-based interventions) or due to other factors (e.g., lack of carer support). Nonetheless, findings from this review suggest that exercise is beneficial for improving health outcomes among those diagnosed with lung cancer at any stage. These are important findings as they highlight that despite lung cancer being associated with poorer prognosis compared with other common cancers, promotion of physical activity guidelines and referral to exercise services remains relevant for this specific cancer group.

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Table 1. Adverse events categorised by grade of severity for participants allocated to exercise and usual care.

AE grade	Exercise (90 adverse events, 1067 participants) Exercise-related adverse events / total number of adverse events ¹	Usual care (73 adverse events, 1042 participants) Total number of adverse events ¹
1	Grade 1 adverse events: 1/16 Minor (non-specified) events: 0/9 Fatigue: 0/1 Musculoskeletal soreness or pain: 1/5	Grade 1 adverse events: 6 Minor (non-specified) events: 6
2	Grade 2 adverse events: 0/10 Non-specified respiratory events: 0/10	Grade 2 adverse events: 6 Non-specified respiratory events: 6
3 ²	Grade 3 adverse events: 0/27 Pneumonia: 0/6 Atelectasis: 0/2 Cardiac events: 0/4 Weakness and weight loss ^a : 0/1 Too unwell/fever: 0/4 COPD exacerbation ^a : 0/1 Hospitalisation: 0/3 Anaemia: 0/1 Musculoskeletal pain or injury ^a : 0/2 Dizziness: 0/1 Chemotherapy side effects: 0/2	Grade 3 adverse events: 21 Pneumonia: 10 Leucopenia: 1 Too unwell: 4 Atelectasis: 1 Anemia: 2 Required palliative care: 1 Knee pain: 1 Post-surgery complications: 1
4	Grade 4 adverse events: 1/20 Disease progression: 0/12 Pleural effusion needing tube: 0/1 Diagnosed with a primary cancer other than lung: 0/2 Empyema: 0/1 Stroke: 0/1 Hip fracture: 1/1 Brain metastasis: 0/1	Grade 4 adverse events: 22 Disease progression: 13 Chylothorax: 1 Pleural effusion needing tube: 2 Empyema: 1 ICU admission: 2 Pulmonary embolism: 1 Myocardial infarction: 1 ARDS or respiratory failure: 1
5	Grade 5 adverse events: 0/17 Death: 0/17	Grade 5 adverse events: 18 Death: 18

AE: adverse events.

¹ Adverse events were classified using the Common Terminology Criteria as; grade 1: asymptomatic or mild symptoms; grade 2: moderate, minimal, local or non-invasive intervention indicated and limiting age-appropriate instrumental activities of daily living; grade 3: severe or medically significant but not immediately life-threatening; grade 4: life-threatening consequences and urgent intervention indicated, or; grade 5: death.

¹ Includes all adverse events (both exercise- and non-exercise related).

² Adverse events in which the severity was not reported were considered Grade 3 or higher if the event led to trial withdrawal.

³ Not reported individually.

⁴ Reported as “cancer” with no further detail provided on whether the withdrawals were due to cancer progression, recurrence or development of other cancer.

^a Event led to trial withdrawal

Table 2. Trial recruitment rate, withdrawal rate and exercise adherence by exercise mode, treatment status, intervention supervision and intervention length.

	Recruitment rate (%) Median (minimum, maximum)	Retention rate (%) ¹ Median (minimum, maximum)		Exercise adherence rate (%) Median (minimum, maximum)
		Exercise	Usual care	
Overall	59 (9, 97), n=25	86 (50, 100), n=32	88 (33, 100), n=32	80 (44, 100), n=13
Exercise mode				
Aerobic	55 (34, 97), n=9	90 (67, 100), n=13	93 (33, 100), n=13	79 (60, 90), n=6
Combined	58 (9, 81), n=14	83 (50, 100), n=16	81 (55, 100), n=16	81 (44, 100), n=6
Resistance	NA, n=1	NA, n=1	NA, n=1	NA, n=1
Other	NA, n=1	83 (79, 88), n=2	78 (75, 71), n=2	NA, n=0
Supervision				
Unsupervised	79 (9, 97), n=5	86 (63, 100), n=5	81 (57, 100), n=5	79 (60, 81), n=3
Supervised	58 (13, 87), n=20	88 (50, 100), n=27	88 (33, 100), n=27	87 (44, 100), n=10
Length				
<12 weeks	54 (9, 87), n=16	87 (50, 100), n=21	88 (33, 100), n=21	84 (64, 100), n=8
≥12 weeks	74 (40, 97), n=9	86 (60, 100), n=11	87 (59, 100), n=11	79 (44, 88), n=5
Chemotherapy				
During	58 (13, 97), n=12	88 (50, 100), n=18	88 (57, 100), n=18	69 (44, 100), n=6
Post	67 (44, 97), n=6	77 (58, 100), n=7	75 (33, 100), n=7	79 (70, 90), n=3
Mixed	58 (9, 87), n=7	86 (63, 96), n=7	93 (59, 95), n=7	87 (81, 88), n=4
Surgery				
Pre-surgery	67 (13, 87), n=8	91 (50, 100), n=12	93 (60, 100), n=12	87 (44, 100), n=5
Post-surgery	58 (9, 97), n=17	84 (58, 100), n=20	81F (33, 100), n=20	88 (60, 100), n=8
Cancer dx				
NSCLC	59 (13, 87), n=16	88 (50, 100), n=21	85 (33, 100), n=21	87 (64, 90), n=6
NSCLC+SCLC	62 (9, 97), n=9	85 (58, 100), n=11	88 (55, 100), n=11	79 (44, 100), n=7
Cancer stage				
I-II	58 (9, 87), n=3	77 (58, 100), n=3	75 (33, 100), n=3	79 (70, 90), n=3
III-IV	52 (13, 97), n=7	88 (50, 100), n=7	88 (57, 100), n=7	69 (44, 100), n=6
Mixed	60 (44, 97), n=15	86 (63, 96), n=27	93 (59, 95), n=27	87 (81, 88), n=5
Trial quality		1		

Low	79 (9, 97), n=5	77 (58, 100), n=3	72 (55, 88), n=3	79 (60, 81), n=3
High	58 (13, 87), n=20	87 (50, 100), n=29	88 (33, 100), n=29	87 (44, 100), n=10

¹ Reported by intervention groups because n=2 studies involved multiple intervention groups.

Dx: Diagnosis; NA: Not applicable.

Table 3. Overview of withdrawals reported separately based on intervention length and health- or non-health-related.

	Withdrawals from exercise groups 218 withdrawals out of total 1067 participants		Withdrawals from usual care groups 228 withdrawals out of 1042 participants	
	<12-week interventions, n=104	≥12-week interventions, n=114	<12-week interventions, n=94	≥12-week interventions, n=134
Reason for withdrawals	<p>Health-related reasons, n=38</p> <ul style="list-style-type: none"> Death, n=12 Change of cancer treatment, n=5 Non-malignant disease, n=4 Too unwell, n=3 Knee pain, n=3 Required further treatment, n=3 Hospitalisation, n=1 Acute COPD exacerbation, n=1 Anaemia, n=1 Myalgia, n=1 Asthenia, n=1 Pneumonia, n=1 Neoadjuvant therapy, n=1 Non-resectable tumour, n=1 <p>Non-health-related reasons or other, n=66</p> <ul style="list-style-type: none"> Lost to follow-up or reason not reported, n=48 Did not receive intervention, n=11 Refused to continue, n=3 Personal reason, n=1 Transferred out of area, n=1 Perceived a lack of benefit, n=1 Lack of motivation, n=1 	<p>Health-related reasons, n=27</p> <ul style="list-style-type: none"> Disease progression, n=13 Death, n=5 Chemotherapy-related side effects, n=2 Bone pain, n=2 Referred to palliative care, n=1 Cancelled surgery, n=1 Brain metastasis, n=1 Hip fracture, n=1 Ankle injury, n=1 <p>Non-health-related reasons or other, n=87</p> <ul style="list-style-type: none"> Lost to follow-up or reason not reported n=63 Refused to continue, n=14 Loss of interest or motivation, n=7 Travelling, n=1 Caring for family, n=1 Moved away, n=1 	<p>Health-related reasons, n=30</p> <ul style="list-style-type: none"> Death, n=9 Change of cancer treatment, n=5 Too unwell, n=4 Inoperable cancer, n=3 Anemia, n=2 Received chemotherapy, n=2 Disease progression, n=2 Further surgery required, n=1 <p>Post-surgery complications, n=1</p> <p>Leucopenia, n=1</p> <p>Non-health-related reasons or other, n=64</p> <ul style="list-style-type: none"> Lost to follow-up or reason not reported, n=41 Did not receive allocated usual care, n=18 <p>Personal reason, n=2</p> <p>Not NCLS, n=2</p> <p>Transferred out of area, n=1</p>	<p>Health-related reasons, n=24</p> <ul style="list-style-type: none"> Disease progression, n=12 Death, n=9 ITU admission, n=1 Required palliative care, n=1 Change of cancer treatment, n=1 <p>Non-health-related reasons or other, n=110</p> <ul style="list-style-type: none"> Lost to follow-up or reason not reported, n=84 Refused to continue, n=11 Loss of interest or motivation n=10 Too busy, n=2 Change in study eligibility status, n=2 Transportation difficulties n=1

Figure 1. Meta-analysis results of all grade 3 to 5 adverse events in exercise compared to usual care presented as overall with subgroup analyses for i) exercise mode, ii) supervision, iii) intervention length, iv) surgery, v) treatment status, vi) diagnosis, vii) stage, and viii) trial quality (n=22 trials, n=24 exercise intervention arms). Negative Risk Difference (RD) value favours exercise.

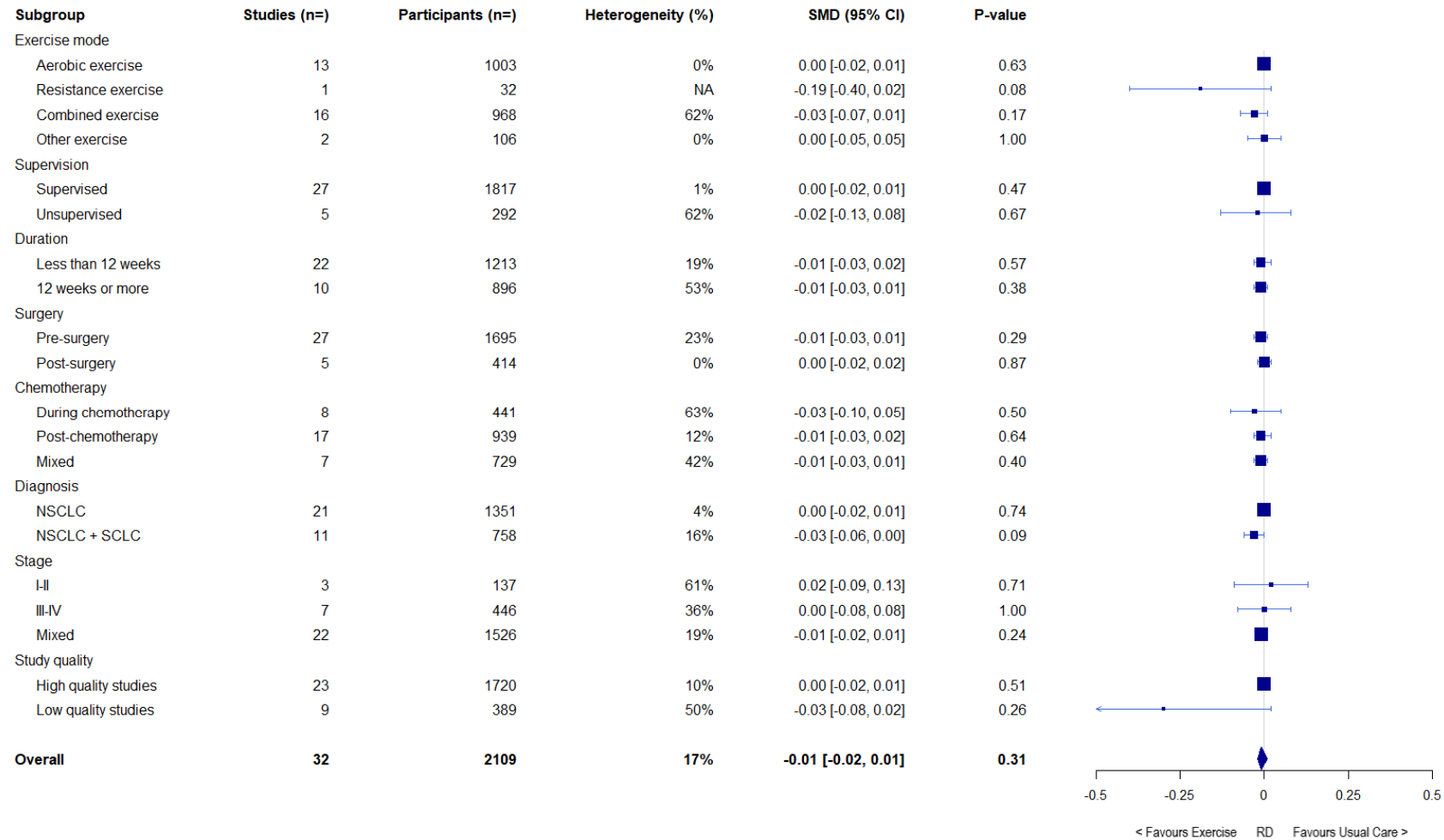
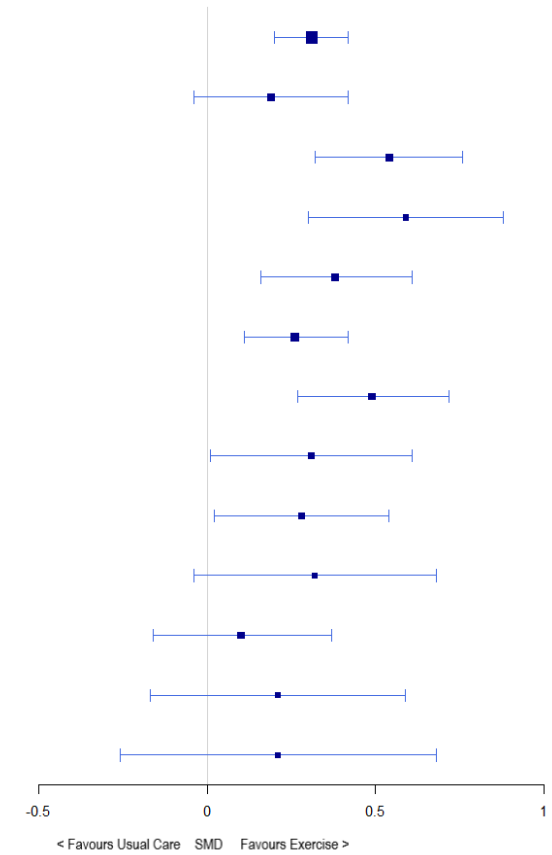


Figure 2. Meta-analysis results of all health outcomes presented as overall effects.

Outcome	Studies (n=)	Participants (n=)	Heterogeneity (%)	SMD (95% CI)	P-value
Quality of life	20	1293	0%	0.31 [0.20, 0.42]	<0.001
Fatigue	11	726	50%	0.19 [-0.04, 0.42]	0.10
Aerobic Fitness	26	1778	78%	0.54 [0.32, 0.76]	<0.001
Upper-body strength	9	721	66%	0.59 [0.30, 0.88]	<0.001
Lower-body strength	10	660	48%	0.38 [0.16, 0.61]	<0.001
Anxiety	6	695	0%	0.26 [0.11, 0.42]	0.001
Depression	6	695	54%	0.49 [0.27, 0.72]	<0.001
Sleep	4	467	55%	0.31 [0.01, 0.61]	0.04
Forced Expiratory Volume (FEV 1)	17	1257	78%	0.28 [0.02, 0.54]	0.04
Forced vital capacity (FVC)	9	561	74%	0.32 [-0.04, 0.68]	0.08
Dyspnea	15	1006	73%	0.10 [-0.16, 0.37]	0.45
Pain	7	435	65%	0.21 [-0.17, 0.59]	0.28
Length of hospital stay	5	321	71%	0.21 [-0.26, 0.68]	0.37



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