Exercise prescription for hospitalized people with chronic obstructive pulmonary disease and comorbidities: a synthesis of systematic reviews

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Introduction: The prescription of physical activity for hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) can be complicated by the presence of comorbidities. The current research aimed to synthesize the relevant literature on the benefits of exercise for people with multimorbidities who experience an AECOPD, and ask: What are the parameters and outcomes of exercise in AECOPD and in conditions that are common comorbidities as reported by systematic reviews (SRs)?

Methods: An SR was performed using the Cochrane Collaboration protocol. Nine electronic databases were searched up to July 2011. Articles were included if they (1) described participants with AECOPD, chronic obstructive pulmonary disease (COPD), or one of eleven common comorbidities, (2) were an SR, (3) examined aerobic training (AT), resistance training (RT), balance training (BT), or a combination thereof, (4) included at least one outcome of fitness, and (5) compared exercise training versus control/sham.

Results: This synthesis examined 58 SRs of exercise training in people with AECOPD, COPD, or eleven chronic conditions commonly associated with COPD. Meta-analyses of endurance (aerobic or exercise capacity, 6-minute walk distance – 6MWD) were shown to significantly improve in most conditions (except osteoarthritis, osteoporosis, and depression), whereas strength was shown to improve in five of the 13 conditions searched: COPD, older adults, heart failure, ischemic heart disease, and diabetes. Several studies of different conditions also reported improvements in quality of life, function, and control or prevention outcomes. Meta-analyses also demonstrate that exercise training decreases the risk of mortality in older adults, and those with COPD or ischemic heart disease. The most common types of training were AT and RT. BT and functional training were commonly applied in older adults. The quality of the SRs for most conditions was moderate to excellent (>.65%) as evaluated by AMSTAR scores.

Conclusion: In summary, this synthesis showed evidence of significant benefits from exercise training in AECOPD, COPD, and conditions that are common comorbidities. A broader approach to exercise and activity prescription in pulmonary rehabilitation may induce therapeutic benefits to ameliorate clinical sequelae associated with AECOPD and comorbidities such as the inclusion of BT and functional training.

Keywords: pulmonary disease, chronic obstructive, comorbidity, exercise, physical fitness

Introduction
Chronic obstructive pulmonary disease (COPD) is the fifth leading cause of death in the world and the mortality rate is expected to increase more than 30% during the next 10 years.1 Acute exacerbations of COPD (AECOPD) are common and are a key predictor of increased morbidity, health care costs, and mortality. The Global Initiative for Lung Disease (GOLD)1 defines a COPD exacerbation as “an event in
the natural course of the disease characterized by a change in the patient’s baseline dyspnea, cough and/or sputum that is beyond normal day-to-day variation, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD. Most patients with COPD have at least one exacerbation per year; a substantial proportion of patients (17%) have three or more episodes per year.2,3

Many exacerbations of COPD are managed on an outpatient basis, but if the patient is hospitalized, the length of stay (LOS) is prolonged: the median LOS in Canadian hospitals is 13 days,4 which translates to an estimated cost of CAD$9500 per hospitalization.5 Premature discharge resulting in shorter LOS, however, is associated with increased readmission and mortality.6

Hospitalization to treat acute illness can have a detrimental effect on muscle performance.7 Muscle impairment and functional decline have been well-documented in older hospitalized patients, and have been attributed to the consequences of hospitalization rather than the admitting illness.8–11 In a previous study on 1181 hospitalized patients with acute medical illnesses (circulatory, 27%; respiratory, 20%; gastrointestinal, 15%; cancer, 6%), 17% of patients required assistance with mobility on discharge, despite being able to walk independently prior to admission.12 Pitta et al reported that patients who are hospitalized with an acute exacerbation of COPD spend the majority of their time sitting, and do not return to their baseline level of activity even after 1 month post-discharge.13

Caring for hospitalized patients with AECOPD can be complicated by the presence of other chronic conditions, which can also influence the severity of the exacerbation and the health outcomes of the patient. Individuals with COPD have a higher risk of multimorbidity14–27 (Table 1) than individuals with other chronic illnesses. Despite this, there has been widespread failure to address the complexities inherent in living with multiple chronic illnesses simultaneously, especially in the hospitalized, acutely ill population. Devising exercise plans for hospitalized AECOPD patients living with multimorbidity is complicated by the limitations imposed by the acute exacerbation and by the synergistic effect of the multiple conditions upon the person. While recent reviews have examined evidence regarding the effectiveness of exercise therapy for people with multimorbidity in community settings,28,29 none have focused on hospitalized patients with COPD who also experience multi-morbidity. National physical activity guidelines fail to address this issue as well.30,31

Systematic reviews (SRs) provide a high level of evidence regarding the efficacy of therapeutic intervention, but the sheer number of available SRs on a given topic can make it difficult for the clinician to distill the important messages. Systematic reviews of systematic reviews have been purported as a way to both evaluate and summarize the key messages on important therapies, and are commonly published in areas of health care.32–36 The aim of the current research was to synthesize the relevant literature on the benefits of exercise for people with multimorbidity who are experiencing an AECOPD. Thus we posed the question: What are the parameters and outcomes of exercise in AECOPD and in commonly associated comorbidities as reported by SRs?

Methods
Search strategy
A systematic review was performed using the methodology outlined by the Cochrane Collaboration protocol.37 Electronic databases were searched up to July 2011 including the Cochrane Controlled Trials Register, Cochrane-Systematic Reviews, MEDLINE, CINAHL (Cumulative Index to Nursing and Allied Health Literature), SPORTDiscus, EMBASE, PEDro (Physiotherapy Evidence Database), PsycINFO, and EBM reviews. Gray literature and reference lists from relevant articles were also reviewed to identify additional articles. Search terms were exemplified by the

| Chronic disease                  | Prevalence in population | Prevalence in COPD |
|----------------------------------|--------------------------|---------------------|
| Heart failure                    | <1% age 50–59; 7% age 80–8922 | 20%24               |
| Ischemic heart disease           | 5%                       | Severe and very severe COPD two-fold risk25 |
| Peripheral arterial disease      | 4.3% at age 40, 14.5% at age 7020 | Smokers OR 4.4620 |
| Hypertension                     | 15%; 50% – 50 years18    | 1.6-fold risk25     |
| Obesity                          | 67% over age 3014        | 54%24               |
| OA                               | 13% at age 50; 40% at age 7523 | 60%–70%27           |
| Osteoporosis/osteopenia          | 15% over age 5021        | Increased relative risk 1.5–1.825 |
| Diabetes mellitus – type 2       | 2.8% in 2000; 6.4% in 2010 with a 10.2% in the Western Pacific14 | Depressive symptoms: 10%–80%25 |
| Depression                       | 4.7% persistent depression or anxiety17 | Depression that requires treatment: 19%–42%25 |
MEDLINE search strategy (Appendix 1) and were modified accordingly to fit the requirements of the other databases.

**Study criteria**
Articles were included if they (1) described participants with AECOPD or COPD, or had one or more of the following conditions that are common comorbidities: anxiety/depression, atherosclerosis, ischemic heart disease, peripheral vascular disease, heart failure, hypertension, diabetes mellitus, human immunodeficiency virus (HIV/AIDS), osteoarthritis (OA), osteoporosis, obesity/overweight, or older adults; (2) were SRs that included at least one randomized controlled trial (RCT); (3) examined an exercise intervention of aerobic training (AT), resistance training (RT), balance training (BT), or a combination thereof; (4) included at least one outcome of fitness; (5) had comparison groups of exercise training versus control/sham (that consisted of usual treatment, no exercise, or attention placebo); (6) were published in English. Articles were excluded if they (1) were published before 2000, or (2) investigated tai chi, yoga, or qi gong due to the multiple forms of these exercises and the difficulty in defining the expected training response to fitness outcomes. If two SRs reported on the same question and the majority of papers included were the same, only the SR with more articles and a more comprehensive review was included. Also, several SRs did not contain meta-analyses. These were reviewed if they met the criteria above, but data were extracted only if other reviews with meta-analyses were not available on the outcomes of interest.

Two individuals independently screened all titles and abstracts retrieved. Any discrepancies were discussed and resolved. From the selected abstracts, one person screened 362 full text articles to determine if they met the inclusion criteria using a screening form. A second person was consulted to confirm agreement on all articles to be excluded. The flow chart of the search strategy and study selection is summarized in Figure 1.

For each condition, one of the coauthors abstracted data and performed the quality assessment, which was double-checked by at least one person. All discrepancies were discussed and reconciled. Data abstracted, when available, included (1) condition, age, and gender of participants, (2) the modality (Mo), frequency (Fr), intensity (I), time of session (T), and duration of program (D) of the exercise intervention, (3) descriptors of the control, placebo, or sham group, and (4) outcomes of fitness, disease control or prevention, quality of life, and function.

Data related to functional training was abstracted. Functional training can be defined as mobility exercises that are functionally- or task-based rather than focused on strength.
training of particular muscle groups or endurance training to improve cardiovascular or aerobic status. Examples are stair climbing, repetitive sit to stand, and transfers. Such training often includes a combination of strength, endurance, and balance.

Quality assessment
All SRs were assessed using the AMSTAR quality assessment tool. Scores for each item and totals are reported. Item 11 was scored as “yes” if the conflict of interest was stated for the authors of the SR.

Data synthesis
Data was synthesized in tables that described the study quality (Table 2), the participants and interventions (Table 3), and outcomes (Table 4). An outcome was assigned to one of two categories based on whether it was measured in several conditions or if it was applied to evaluate a disease specific marker: (1) generic fitness (eg, exercise capacity, strength), quality of life, and functional outcomes (eg, timed up-and-go test, stair climbing), and (2) disease specific fitness, control, and prevention outcomes (eg, dyspnea, mortality, pain, ejection fraction, cholesterol levels).

Only statistically significant outcomes are reported in Table 4. When available, quantitative data for each meta-analysis was described including the number of studies, the number of participants, the standardized effect size or weighted mean difference, risk ratio, odds ratio, and 95% confidence intervals. If this information was not available, an attempt was made to determine the number of studies that reported a significantly positive change versus the total number of studies that measured the outcome. Nonsignificant findings or trends are not reported.

Results
Study selection
A search of the eight databases yielded 3276 citations and abstracts after duplicates were removed. After independent screening of the citations by two reviewers, 362 full-text articles were selected and reviewed for inclusion. Fifteen additional articles were identified from manual searching of reference lists. The main reasons for excluding articles were that they were not an SR, that participants did not have COPD/AECOPD or one of the other conditions of the search strategy, there was no exercise intervention, the exercise intervention was not clearly described or not differentiated from concurrent treatment, there was no comparison between an exercise group and a control group, the SR reported on similar data but had few articles, the article was not available in English, or the article was published before 2000. No SRs were identified that compared exercise to a control group in people with asthma or bronchiectasis. Fifty-eight SRs met the inclusion criteria.

Quality assessment
The number of RCTs in any of the SRs that related to our question ranged from 4 to 83. The average AMSTAR score was 7.5 out of a potential 11. The most common items not reported were a list of excluded articles (only 26% of SRs provided this list), an examination of publication bias (ie, funnel plot or Egger regression test, which 45% reported), a statement regarding conflict of interest (50% reported), a selection and abstraction of data performed by two reviewers (65% reported), and a search of the gray literature (59% reported). All other items were addressed by 71% of the SRs.

Characteristics of participants
The age of participants ranged between 18 years and the “very elderly”. SRs that described people with HIV or depression had the youngest participants. Gender varied from 100% male to 100% female. SRs that described older adults had the largest sample sizes.

Characteristics of interventions and outcomes in the different chronic conditions
Characteristics of the interventions are detailed in Table 3, while outcomes in the different chronic conditions are shown in Table 4.

AECOPD
One SR investigated the benefits of aerobic and resistance training in people with COPD (AMSTAR of 11). Aerobic and resistance training of the extremities improved walk distance performance and quality of life measures in addition to decreasing dyspnea, compared to the control group. Exercise also reduced admissions to hospital and mortality as demonstrated by meta-analyses of five and three RCTs, respectively. The SR included studies that initiated exercise immediately after or up to 6 weeks after treatment initiation for AECOPD as part of pulmonary rehabilitation on an out- or in-patient basis. Frequency of training ranged from three times a week to twice daily. The intensity of aerobic training was not reported.

COPD (stable)
Six SRs investigated the benefits of AT and RT in people with COPD, and the AMSTAR scores ranged between 5 and 10.
| Condition                        | Author                          | AMSTAR scores |
|---------------------------------|---------------------------------|---------------|
|                                 |                                 | 1 2 3 4 5 6 7 8 9 10 11 Total |
| AECOPD                          | Puhan et al39                   | I I I I I I I I I I I 11 |
| Chronic obstructive             | Lacasse et al42                 | I I I I I I I I I 0 1 10 |
| pulmonary disease               | O'Shea et al43                  | I I 0 0 I I I I 0 1 8  |
|                                 | Salman et al44                  | I 0 I I 0 I I I I 0 8  |
|                                 | Chavannes et al45               | I 0 I I 0 0 0 0 0 5  |
|                                 | Vieira et al46                  | I 0 I I 0 I I I I 0 6  |
|                                 | Janaudis-Ferreira et al41       | I 0 I I 0 I I I I 0 5  |
| Older adults                    | Liu and Latham50                | I I I I I I I I I I 11 |
|                                 | Howe et al50                    | I I I I I I I I 0 1 10 |
|                                 | Gillespie et al50               | I I I I I I I 1 1 1  |
|                                 | Weening-Dijkersterhuis et al51  | I 0 I I 0 I I I I 0 8  |
|                                 | Forster et al50                 | I I I I 0 0 0 0 0 1 5  |
|                                 | Chin et al50                    | I I I I 0 I I 0 0 1 8  |
|                                 | Rydwik et al51                  | I 0 I I 0 I I 0 0 6  |
| Heart failure                   | Davies et al55                  | I 0 I 0 0 0 I I I I 7  |
|                                 | Hwang et al54                   | I I I 0 0 0 0 0 8  |
|                                 | Hwang and Marwick57             | I 0 I 0 0 I 0 0 0 3  |
|                                 | Chien et al53                   | I I I 0 0 I 0 0 7  |
|                                 | Haykowsky et al54               | I I I I 0 I I I 0 8  |
|                                 | van Tol et al58                 | I I I 0 0 I I 0 7  |
|                                 | Spruit et al55                  | I I I 0 0 I I 0 6  |
|                                 | Cahalin et al59                 | I 0 0 0 0 I 0 0 0 2  |
|                                 | Oliveira et al52                | I 0 0 0 0 I 0 0 0 2  |
|                                 | Bentzon59                       | I I I I 0 0 0 0 0 2  |
| Ischemic heart disease          | Haykowsky et al53               | I I I 0 0 I I 0 8  |
|                                 | Valkeinen et al58               | I 0 0 0 0 I 0 0 5  |
|                                 | Cortes et al64                  | I I I I 0 0 0 0 I 9  |
|                                 | Jolliffe et al64                | I I I 0 0 I I 0 10 |
|                                 | Clark et al62                   | I I I 0 0 I I I 0 9  |
|                                 | Cornish et al63                 | I 0 I 0 0 I 0 0 0 3  |
|                                 | Oliveira et al62                | I 0 I 0 0 I 0 0 0 3  |
|                                 | Watson et al59                  | I I I 0 I I 0 1 9  |
|                                 | Wind and Koelemay79             | I I I 0 0 I I 0 7  |
| Hypertension                    | Dickinson et al70               | I I I 0 0 I I I 0 8  |
|                                 | Cornelissen and Fagard72        | I 0 0 0 0 0 0 I 0 4  |
|                                 | Whelton et al74                 | I I I 0 I I 0 1 8  |
|                                 | Kelley et al71                  | I I I 0 I 0 0 0 7  |
| Obesity                         | Shaw et al75                    | I I I I I I 11  |
|                                 | Witham and Avenell75            | I I I 0 0 I I 1 8  |
| Osteoarthritis                  | Devos-Comby et al77             | I 0 I I 0 I I I 0 8  |
|                                 | Lange et al80                   | I I 0 0 0 I I I 0 7  |
|                                 | Ottawa Panel77                  | I I I I I I 0 0 8  |
|                                 | Brosseau et al78                | I I I 0 I I 0 0 7  |
|                                 | Pelland et al81                 | I I I I I I 0 0 9  |
| Osteoporosis                    | Li et al82                      | I 0 I 0 0 0 I I 1 6  |
|                                 | de Kam et al82                  | I 0 I 0 0 I I 0 1 7  |
| Diabetes mellitus               | Chudyk and Petrella83           | I 0 I I 0 I 0 0 1 6  |
|                                 | Umpierre et al80                | I I I 0 0 I I I 10 |
|                                 | Irvine and Taylor86             | I I I 0 0 I I I 0 7  |
|                                 | Thomas et al87                  | I I I I I I I 11  |
|                                 | Kelley and Kelley87             | I I I 0 0 I I I 0 9  |
|                                 | Snowling and Hopkins88          | I 0 I 0 0 I I I 0 6  |
|                                 | Boulé et al84                   | I 0 I I 0 I I 0 0 6  |
| HIV                             | O'Brien et al85                 | I I I I I I 10  |
| Depression                      | Krogh et al89                   | I I I I 0 I I I 1 10 |
|                                 | Herring et al88                 | I 0 I I 0 I I I 1 8  |
|                                 | Mead et al89                    | I I I I I I I 11  |
|                                 | Rethorst et al85                | I I I I 0 I I 0 1 8  |
|                                 | Lawlor and Hopker89             | I I I I 0 I I I 1 9  |
| Tallies for 58 reports          |                                 | 58 38 54 34 15 49 48 41 42 26 29 434 |
| Percentage of total (58 reports)|                                 | 100 66 93 59 26 84 83 71 72 45 50 |
Table 3 Characteristics of participants and interventions

| Author                      | RCTs | n (% M or F) | Age (years) | Characteristics of exercise intervention |
|-----------------------------|------|--------------|-------------|------------------------------------------|
| **AECOPD**                  |      |              |             |                                          |
| Puhan et al                | 9    | 427 (64% M)  | Range 62–70 | Mo: AT and RT; Fr: Twice daily – 3×/week; T: NR except one study stated 2 hours/session; D: 10 days–6 months |
| Lacasse et al              | 31   | 1322         | NR          | Mo: AT and RT, U/E, L/E, and/or respiratory muscle training; Fr and I: NR; D: 4–52 weeks |
| O’Shea et al               | 9 of 18 | 296 of 679 (70% M) | Range 48.5–72 | Mo: RT using free weights, machine, Theraband; Fr: 2×/week–daily; I: variable; T: 5–12 reps, 2–4 sets; D: 6–12 weeks |
| Salman et al               | 20   | 999          | 59–73       | Mo: AT, RT, U/E, L/E, and/or respiratory muscle training; Fr: 3×/week; D: 6 weeks–12 months; other details NR |
| Chavannes et al            | 4 of 5 | 210 (–55% M) | 49–63       | Mo: AT + RT (four studies), AT (one study); Fr: 2–7×/week; D: 8 weeks–18 months; other details NR |
| Vieira et al               | 8 of 12 | 370 of 728 | Range 38–78 | Mo: Home-based AT and RT; Fr: 2×/week – twice daily; I: 90% of velocity of 6 MWD, ≥70% of maximal speed of SWT, cycle ergometer: 30 W, cycling: 70% of work rate; T: 30–60 minutes; D: 4–52 weeks |
| Janaudis-Ferreira et al    | 5    | 157          | NR          | Mo: Arm AT and RT; Fr: 3×/week – 2×/day; I: NR; T: 4–10 reps 1–3 sets; D: 6–8 weeks |
| **Older adults**           |      |              |             |                                          |
| Liu and Latham             | 83 of 121 | 3059 of 6700 | >60         | Mo: RT in gym or against Theraband; Fr: 2–3×/week, except one was daily; I: ranged from low to high intensity; D: most 8–12 weeks but ranged from 2–104 weeks |
| Howe et al                 | 34   | 2883 (<50% M) | 60–75 years | Mo: RT, gait, balance, co-ordination, and functional tasks, tai chi, qi gong, dance, yoga; other details NR |
| Gillespie et al            | 14 of 111 | 55303 (<50% M) | >60         | Mo: AT, RT, gait, balance and functional training, flexibility training, tai chi, and square stepping; general physical activity (walking groups); other details NR |
| Weening-Dijkstra et al     | 27   | 6459         | >70         | Mo: RT (strength, resistance), ROM, balance, functional, gait, tai chi, flexibility; other details NR |
| Forster et al              | 37 of 49 | 3611 (33% M) | Mean 82     | Mo: RT, AT (walking) and general daily living skills eg, eating, dressing, and climbing stairs, flexibility, balance; Fr: mean of 3.5×/week T: ≥30 minutes/week; D: 4 weeks–2 years |
| Chin et al                 | 20   | 2515 (majority F) | 77–88       | Mo: AT, RT, flexibility, balance, tai chi, and/or multi-component training; Fr: usually 3×/week; D: range 10–28 weeks |
| Rydwik et al               | 16   | 1269         | >70         | Mo: RT, gait, and ROM training; Fr: usually 2–3×/week T: variable; D: 9 weeks–2 years |
| **Heart failure**          |      |              |             |                                          |
| Davies et al               | 19   | 3647 (majority M) | 51–72      | Mo: AT or AT + RT; Fr: 2–7×/week; I: 40% max HR or 85% VO2 max; T: 15–120 minutes; D: 24 weeks–3 years |
| Hwang et al                | 4 of 8 | 103 (60% M) | 62–77       | Mo: RT for U/E and L/E; Fr: 2–3×/week; I: 60%–80% 1RM; T: 12–60 minutes; D: 8–22 weeks |
| Hwang and Marwick          | 19   | 1069 (85% M) | 59.05 (95% CI 55–63) | Mo: AT or AT + RT: cycle ergometer, walking, calisthenics, ball games, strength training; Fr: NR; I: AT; –10% of AT, 60%–80% HRmax, 70% VO2 max RT: 80% 1RM, 70% HRmax; T: 40–400 minutes/week; D: 8–52 weeks |

(Continued)
| Author            | RCTs  | n (% M or F)          | Age (years) | Characteristics of exercise intervention |
|-------------------|-------|-----------------------|-------------|------------------------------------------|
| Chien et al53     | 10    | 648 (79% M)           | 52–81       | Mo: Home based AT (walking program, and/or cycle ergometer) and RT (added in 3/10 studies); Fr: 2–5×/week; I: 40%–70% HRmax, or 70% HR at VO2 max; T: 20–60 minutes; D: 6–52 weeks. All home programs |
| Haykowsky et al56 | 9 of 14 | 538 of 812 (83% M)    | 52–61       | Mo: AT: cycle ergometer, rowing, swimming, walking, arm ergometer, treadmill, interval training; Fr: 2–7 days/week; I: 50%–80% VO2 peak, 60%–85% HRpeak, or 50%–70% max work load; T: 20–60 minutes; D: 2–14 months |
| van Tol et al58   | 35    | 1486 (76% M)          | Mean 60.6 (SD 7.5) | Mo: AT + RT; Fr: range 1–7×/week, mean 3.7×/week; I: 50%–80% VO2 peak, 60%–80% HRmax, 60%–80% HRR; T: 15–96 minutes, 50 minutes (mean); D: 3–26 weeks, 13.0 weeks (mean) |
| Spruit et al61    | 4 of 10| 114 (72% M)           | Mean 57–77  | Mo: RT alone Fr: 2–3×/week; I: 40%–80% 1 RM; T: 15–60 reps in 1–3 sets; D: 8–20 weeks; progression described in some reports |
| Cahalin et al60   | 11 of 22 | 387 of 633 (70% M)   | 30–80       | Mo: RT: variety of strength exercises either alone or with short or long bursts of AT; Fr: 2–5×/week; I: RT: 20%–80% 1RM; AT: up to 80% VO2 peak, or 70% HRpeak, or 50% peak workload; T: 5–60 minutes; D: 4–26 weeks |
| Benton59          | 4 of 16| 115 of 379 (80% M)    | Mean 30–76  | Mo: RT: chair stands, heel lifts, weights, pulleys, hydraulic fitness; Fr: 2–3×/week; I: 60% 1 RM; AT: cycling, arm ergometer, stair climbing, walking; T: 2–60 minutes; D: 2–5 month study duration; reps and progression: variable |
| Ischemic heart disease |       |                       |             |                                            |
| Haykowsky et al65 | 12    | 647                   | 55          | Mo: AT: Cycle, walk, jogging, calisthenics; Fr: 3–7×/week; I: 60%–80% VO2 max or peak HR; T: 30–180 minutes; D: 1–6 months |
| Valkeinen et al68 | 18    | 922 (majority M)      | 59.9 ± 4.9  | Mo: AT: walking, jogging, cycling, and arm cranking; Fr: 3.1 ± 0.4×/week; I: 70%–80% HRmax, HRR, HR of anaerobic threshold or 25%–70% VO2 max; T: 20–60 minutes; D: 14.2 ± 13.5 weeks |
| Cortes et al64    | 11 of 14 | 3148 (≥70% M)        | 55–65       | Mo: Early mobilization: sitting on bed/chair, walking, moving legs, climbing stairs, any movement out of bed, dangling legs, progressive activity while in hospital; settings descriptions: CCU, hospital wards, in-hospital |
| Jolliffe et al66  | 32    | 8440 (majority M)     | 55          | Mo: AT: walking, running, cycling, skipping, swimming, stairs, and rowing; Fr: 1–5×/week; I: 70%–85% HRmax or predicted HRmax, other 75% max work capacity; T: 20–60 minutes; D: 4 weeks to 30 months |
| Clark et al62     | 41 of 63 | 8460 of 21295 (majority M) | Mean 49–71 | Mo: AT: interval training; aerobic dance movements, upper/lower body exercises, cycle ergometer, or treadmill walking/running; Fr: 2–3×/week; I: 3 intervals of 5–10 minutes at RPE 15–18 in one study and 3 minutes at 60%–70% HRmax + 4 minutes at 90%–95% HRmax in another; T: 50–60 minutes; D: 16–26 weeks |
| Cornish et al63   | 2 of 7 | 120 of 213            | 57 ± 14–71.5 ± 7.8 | Mo: AT: no details on intervention |

(Continued)
| Author | RCTs | n (% M or F) | Age (years) | Characteristics of exercise intervention |
|--------|------|--------------|-------------|------------------------------------------|
| Oliveira et al67 | 4 of 11 | 126 | most <60 | Mo: RT: free weights in one study, NR in others; I: 40%–60% MVC or 50%–80% 1 RM; D: 10 weeks to 6 months; Other details NR |
| PVD | Watson et al69 | 16 of 22 | 783 of 1200 (>50% M) | 45–89 | Mo: AT, RT: polestriding, cycling, and U/E and L/E exercises. Fr: 2–7×/week; T: 30–120 minutes; D: 3–12 months |
| Wind and Koelemay70 | 10 of 15 | 625 of 761 (>50% M) | 60–76 | Mo: AT: crank exercise, walking, others not detailed. Fr: 2–3×/week; T: 30–60 minutes; D: 12–26 week except one study was 104 weeks |
| Hypertension | Dickinson et al73 | 21 of 105 | 1518 of 6805 (~57% M) | 52 (30–67) | Mo: AT: brisk walking, jogging, cycling; Fr: 3–5×/week; T: 30–60 minutes; D: 8–52 week (median 12). 2 trials received RT, but details NR; 1 trial offered advice to participants |
| Cornelissen and Fagard72 | 28 of 72 | 492 in exercise group | 52.7 ± 11.8 | Mo: AT: walking, jogging, running, cycling; Fr: 2–7×/week (median 3); I: 30%–87% HRR (median 65); T: 25–60 minutes (median 40); D: 4–52 weeks (median 12) |
| Whelton et al74 | 15 of 54 | 872 (majority M) Mean 40–69 Range 18–86 | Mo: AT: biking, walking, jogging; Fr: 1–7×/week; I: 40%–70% VO2 max, 60%–85% HRmax, 40%–70% Wmax; T: 20–60 minutes; D: 3–26 weeks |
| Kelley et al71 | 47 | 2543 >50% M | 48 | Mo: AT: walking, jogging, cycling, aerobic dance, and swimming; Fr: 1–5×/week; I: 45%–86% VO2 max; T: 15–60 minutes; D: 360–9360 minutes |
| Obesity | Shaw et al76 | 4 of 41 | 440 of 3476 (majority M) | 30–64 | Mo: AT: walking/jogging, circuit training; Fr: 2–3×/week; I: 60%–80% HRmax; T: 30–60 minutes; D: 26–52 weeks |
| Whitham and Avenell75 | 2 of 9 | 173 (100% F) | 60 | Mo: supervised AT, no details; Fr: 3×/week; I: aiming for 70% VO2 max; T: NR; D: 3 months; Transition to home: exercise 4×/week plus weekly supervised exercise |
| OA | Devos-Comby et al79 | 16 | 2154 Mean 65.8, range 29–89 | Mo: AT + RT: knee muscles strength training, low/medium intensity exercise, and light physical activity (walking, aerobic exercise, balance or flexibility exercises); Fr: 2–5×/week (sometimes 2×/day); I: AT: 50%–85% HRR; RT: 6 set × 5 max contraction (others NR); T: 20 minutes – 1.5 hour; D: 4–12 weeks (different follow-up periods) |
| Lange et al80 | 18 | 2723 Range 55–74 | Mo: RT: dynamic or isotonic training mainly targeting the quadriceps using resistance machines, free weights, or Theraband; Fr: 2–7×/week; I: light to maximal; T: 10–60 minutes, 5–12 reps, 1–10 sets (most 3 sets); D: 1–30 months |
| Ottawa Panel77 | 26 | 2486 >18 | Mo: AT: walking or cycle ergometer; RT: strengthening (eg, isometric, isokinetic, eccentric, concentric, aerobic), general physical activity, combination of exercises; Fr: 1×/week–10×/day (depends on phase); I: AT: 50%–70% HRR when described, RT: variable. T: 5 minutes–1.5 hours; D: 4 weeks–18 months |
| Brosseau et al78 | 9 of 12 | 1363 | 57–69.4 | Mo: AT: walking, stationary bike; Fr: 1–4 ×/week; I: 50%–85% HRR or 60%–80% HRmax. T: 30–90 minutes when reported; D: 5–12 weeks. Some changed to home-based program up to 15 months. Some studies included strengthening exercises |

(Continued)
### Table 3 (Continued)

| Author                  | RCTs | n (% M or F) | Age (years) | Characteristics of exercise intervention |
|-------------------------|------|--------------|-------------|------------------------------------------|
| **Osteoporosis**        |      |              |             |                                          |
| Li et al                | 5 groups in 4 papers | 256 (100% F) | NR          | Mo: RT or combined stretch/strength/balance programs; strengthening of extremities and trunk (1 study), “agility” training (1 study), combined exercise (stretching, strengthening, balance, posture) (2 studies), trunk flexor/extensor strengthening (1 study); Fr: 3 studies 2 days/week, 1 study 7 days/week; I: NR; T: 40–60 minutes; D: 10–25 weeks |
| De Kam et al            | 28   | 1707, some reports used the same subjects | Mean 57–82 | Mo: fast walking; aerobic exercise; weight-bearing aerobic exercise; strengthening exercises; balance exercises; posture and gait exercises; trunk extensor exercises; heel drops with impact; heel drops with no impact; whole body vibration; jumping; agility training including ball games, relay races and obstacle courses; tai chi, home-based walking, strengthening and stretching; Fr: 3–7×/week; I: not described – only one study described progression by increasing step count by 30%; T: 4–90 minutes; D: 10–104 weeks |
| **Diabetes**            |      |              |             |                                          |
| Chudyk and Petrella     | 30 of 34 | NR             | NR          | Mo: AT; Fr: most 3×/week but range of 1–7×/week; I: 50%–85% VO2max or 35%–85% HRmax; T: 40–75 minutes; D: 2–24 months. RT: variable |
| Umpierre et al         | 23 of 47 | 1513 of 8538 | Range of means 52–69 | Mo: AT, RT; Fr: 2–5×/week T: AT: 30–150 minutes/week and RT: 9–27 sets; D: 12–52 weeks |
| Irvine and Taylor       | 7 of 9 | 162 of 256   | 47–68       | Mo: RT: free weights or weight machines; Fr: 2–3×/week; I: 55%–85% 1RM or to moderate on Borg; T: 8–15 reps, 1–3 sets, 5–10 exercises; D: 8–26 weeks |
| Thomas et al            | 14   | 377          | 45–65       | Mo: qi gong, RT, AT: cycle ergometer, walking cycling, skiing, swimming; Fr: 3–7×/week; I: AT: 50%–85% VO2peak, 65%–75% HRR or 85% HRmax; T: 30–120 minutes; if PRT, 2–3 sets of 10–12 reps; D: 8 weeks–1 year |
| Kelley and Kelley       | 7    | Both         | 40–75       | Mo: cycle ergometer, walking, jogging, cycling, swimming, skiing; Fr: 3–7×/week; I: 60%–75% VO2max; T: 30–75 minutes; D: 10–26 weeks |
| Snowling and Hopkins    | 27   | 1003         | 55 ± 7      | Mo: AT; Fr: 3–7×/week; I: 50%–85% VO2max, HR 110–140 bpm, 40%–80% HRR; T: 30–120 minutes; D: 6–104 weeks |
| Boulé et al             | 27   | 266          | 55.7        | Mo: AT, RT; Fr: 3–5×/week; I: 50%–80% of 1 RM; T: 10–20 reps, 2–3 sets, 5–10 ext; D: 5–16 weeks |
| **HIV**                 |      |              |             |                                          |
| O’Brien et al          | 7 of 14 | 306 of 454 (70% M) | 18–58       | Mo: AT: interval or continuous aerobic, walking, jogging, stair stepping, ski machine, stationary bike, cross country machine; Fr: 3×/week I: AT: usually 50%–85% VO2max and 60%–80% HRmax or RT: 60%–80% 1 RM; T: 20–60 minutes; D: 5–24 weeks |

(Continued)
AT and RT of the extremities improved maximal exercise capacity, walk distance performance, and quality of life measures in outpatient COPD compared to a control group as described by a high quality SR with an AMSTAR score of 10. Whether people with mild-to-moderate COPD with AECOPD benefit from exercise training is equivocal, as summarized by two SRs with AMSTAR scores of 5 and 8. Exercise training that focused on RT improved leg strength and cycling endurance as described by one review with an AMSTAR of 8. Unsupported and supported arm exercise showed improvement in half of the studies evaluated by one SR. Home exercise demonstrated improvement in exercise capacity in all studies that assessed this attribute and half of the studies that assessed quality of life. Dyspnea was significantly improved by aerobic and resistance trainings in two reports.

Walking and cycling were the most common AT whereas free weights and Theraband™ were the most common resistance used during RT. Frequency of training ranged from twice weekly to twice daily. The intensity of aerobic training was either not described in the SRs or, in one report, was quantified as a percentage of walk test distance. RT intensity ranged from one-third of a (repetition maximum) RM to near maximal intensity for the number of repetitions. The time for each session varied between 30 and 120 minutes, or was defined in terms of repetitions and sets for RT. Durations of studies ranged between four weeks and 18 months. There was an obvious focus on AT and RT in the SRs, and no reports described the outcomes from balance or functional training in people with COPD.

### Older adults

Overall, exercise training results in improved physical and functional performance for older adults, as demonstrated by seven SRs, although initial health status influenced both the ability to participate in certain programs as well as the outcomes of the training. Most SRs and many RCTs included a mix of RT, BT, and functional training rather than focusing on a single type of training. Thus, evidence for the most part is provided from multifaceted training rather than a singular approach. Many other aspects of the training varied widely, with a training frequency most often of two to three times a week, total duration that ranged from 2 to 104 weeks, and a variable intensity level (Table 3). SRs, which had AMSTAR scores ranging from 5 to 11, showed that mixed training improved balance and strength, reduced falls, and improved functional measures such as the 6-minute walk distance (6MWD).

### Heart failure

Six meta-analyses investigated the benefits of AT and/or RT in patients with chronic heart failure. Most of these papers...
| Author | Condition and severity | Type of training: | Generic fitness, quality of life and functional outcomes | Disease specific fitness, control and prevention outcomes |
|--------|------------------------|------------------|-------------------------------------------------------------|-------------------------------------------------------------|
|        |                        |                  | # RCTs/difference [95% confidence intervals]                  | # trials/difference [95% confidence intervals] |
| Puhan et al<sup>39</sup> | COPD after AECOPD | AT, RT | 6MWD: 6/NR/WMD: 77.7 m [12.2, 143.2]; Shuttle walk test: 3/NR/WMD: 64.4 M [41.3, 87.4]; QoL: SGRQ: 3/NR/WMD: 9.88 [−14.40, −5.37] | Dyspnea: 5/NR/OR: 0.97 [0.35, 1.58]; Admission to hospital: 5/250/OR: 0.22 [0.08, 0.58]; Mortality: 3/110/OR: 0.28 [0.08, 0.84] |
| Lacasse et al<sup>42</sup> | COPD | AT, RT | Maximal exercise capacity on cycle ergometer: 13/51/WMD: 8.4 watts [3.45, 14.31]; 6MWD: 16/669/WMD: 48.5 m [31.6, 65.3]; QoL: Fatigue of CRQ: 11/619/WMD: 0.92 [0.71, 1.13] | | |
| O’ Shea et al<sup>43</sup> | Mild to severe COPD | RT | Walking distance: 20/979/SWS: 0.71 [0.43, 0.99] | Shortness of breath: 12/723/SWS: 0.62 [0.26, 0.91] |
| Chavannes et al<sup>44</sup> | Mild to severe COPD | AT, RT | | |
| Vieira et al<sup>45</sup> | COPD | Home based | Exercise capacity: 2 of 2 studies show ↑ in 6MWD or constant work rate test; QoL: 3 of 6 studies showed ↑ compared to control | |
| Janaudis-Ferreira et al<sup>41</sup> | Mod. to severe COPD | Arm AT, RT | Unsupported and supported arm exercise capacity: 2 (of 4) studies and 1 (of 2) showed ↑ compared to control | |
| Liu and Latham<sup>50</sup> | Elderly | RT | Lower limb strength: 73/3059/SWS: 0.84 [0.67, 1.00]; VO<sub>2</sub> max: 18/710/WMD: 1.50 mL/kg/min [0.49, 2.51]; 6MWD: 11/325/WMD: 52.37 m [17.38, 87.37]; Gait speed: 24/1179/WMD: 0.08 m/s [0.04, 0.12]; Timed up and go: 12/691/WMD: −0.69 s [−1.11, −0.27]; Time to stand from a chair: 11/384/SWS: −0.94 [−1.49, −0.38]; Stair climbing: 8/268/MD: −1.44 s [−2.51, −0.37]; Vitality: (SF-36) 10/611/SWS: 1.33 [−0.89, 3.55]; Main function: 33/2172/SWS: 0.14 [0.05, 0.22] | Death: 13/1125/RR: 0.89 [0.52, 1.54]; Pain: 6/503/SWS: −0.30 [−0.48, −0.13] |
| Howe et al<sup>49</sup> | Improving balance | Balance, gait, functional task | Single leg stance time, eyes open: 4/164/MOD: 0.33 s [0.02, 0.64]; Berg Balance Scale: 3/126/MD: 2.72 [0.94, 4.50] | Rate of falls: 3/461/RR: 0.73 [0.54, 0.98] 0.036; Number of fallers: 17/2492/RR: 0.83 [0.72, 0.97] 0.018 |
| Gillespie et al<sup>50</sup> | Falls prevention | Balance, gait, functional | | |
| Weening-Dijksterhuis et al<sup>51</sup> | Institutionalized frail elderly | AT, RT, balance and functional training | Strength: ↑ in 8 of 9 studies; 6MWD: ↑ in 3 of 3 studies; Balance: ↑ in 10 of 10 studies; Psychological function/perceived health: some effect; Function: ↑ in 4 of 4 on depression and activity measures | |

(Continued)
| Author          | Condition and severity                      | Type of training | Generic fitness, quality of life and functional outcomes # RCTs/n/difference [95% confidence intervals] | Disease specific fitness, control and prevention outcomes # trials/n/difference [95% confidence intervals] |
|-----------------|---------------------------------------------|------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Forster et al   | Elderly in long term care                   | AT, RT and balance | Mobility (variety of tests): ↑ in 24 of 35 trials; Strength: ↑ in 18; Balance: ↑ in 12 of 16 studies | Hospital admissions related to heart failure: 7/569/RR: 0.72 [0.52, −0.99]; QoL using Minnesota Living with Heart Failure Questionnaire: 6/700/WMD −10.3 [−15.9, −4.8]; QoL using all scales: 9/779/SMD: −0.57 [−0.83, −0.31] |
| Chin et al      | Frail, Elderly                              | AT, RT and balance | Physical Performance Test: ↑ in 3 of 4 studies; 6MWD: ↑ in 9 of 17 studies                      |                                                                                                  |
| Rydwik et al    | Institutionalized elderly, multiple diagnoses | AT, RT, balance, mobility, gait, ADL | Strength: ↑ in 6 of 9 studies; Mobility: ↑ in 8 of 12 studies; Range of motion: ↑ in 2 of 3 studies; Gait: ↑ in 4 of 8 studies; Activities of daily living: ↑ in 3 of 6 studies |                                                                                                  |
| Davies et al    | HF, severity not an inclusion criterion      | AT, RT            |                                                                                                  |                                                                                                  |
| Hwang et al     | HF, diagnosis based on clinical signs or LVEF < 40% | RT                | 6MWD: 2/40/52 m [19, 85]                                                                        |                                                                                                  |
| Hwang and Marwick | HF, diagnosis based on clinical signs or LVEF < 40% | AT (15) or AT + RT (4) | VO₂ max: 16/733/2.86 mL/kg/min [1.43, 4.29]; Exercise duration: 7/241/2.00 min [1.43, 2.57]; 6MWD: 6/628/30.4 m [6.1, 54.7] | Hospitalization due to cardiac events: 2/143/OR 0.75 [0.19, 2.92] |
| Chien et al     | HF, diagnosis based on clinical signs or LVEF < 40% | Mostly AT, home-based. RT added in 3/10 studies | VO₂ max: 7/355/MD 2.71 mL/kg/min [0.67, 7.74]; 6MWD: 5/320/MD 41.09 m [19.12, 63.06] | Ejection fraction: 9/538/WMD 2.59% [1.44, 3.74]; End-diastolic volume: 5/371/WMD −11.49 mL [−19.95, −3.02]; End-systolic volume: 5/371/WMD −12.87 mL [−17.80, −7.93] |
| Haykowsky et al | HF, severity not a criterion, clinically stable | AT                | VO₂ max: 9/538/WMD 2.98 mL/kg/min [2.47, 3.49]                                                   | End-diasstolic volume at rest: 9/527/WMD −3.13 mL; Cardiac output during maximal exercise: 3/104/WD 2.51 L/min |
| Spruit et al    | HF, severity not a criterion for inclusion   | AT, RT            | VO₂ max: 31/1240/MD 2.06 mL/kg/min; Watts on maximal test: 19/715/MD 14.3 W; Anaerobic threshold: 13/511/MD 1.91 mL/kg/min; 6MWD: 15/599/MD 46.2 m; HR during maximal exercise: 18/683/MD 3.5 bpm; SBP during maximal exercise: 10/382/MD 5.4 mmHg; QoL: 9/463/MD −9.7 points |                                                                                                  |
| Authors          | Condition                          | Intervention | Findings                                                                 |
|------------------|------------------------------------|--------------|---------------------------------------------------------------------------|
| Cahalin et al.   | HF, severity not a criterion        | RT, with short or long bursts of AT | Muscle strength, muscle endurance, daily activity, forearm blood flow, performance of heel lift, and QoL increased and resting HR decreased, but no synthesis of data from more than one RCT was provided |
| Benton           | HF, severity not a criterion        | AT, RT       | Muscle strength, muscle endurance, QoL, heart rate during exercise, and forearm blood flow improved, but no synthesis of data from more than one RCT was provided |
| Haykowsky et al. | Post-MI                             | AT           | Left ventricular ejection fraction, left ventricular fractional shortening, and insulin-stimulated glucose uptake improved, but no synthesis of data from more than one RCT was provided |
| Valkeinen et al. | Ischemic heart disease (MI, angina, CABG, PTCA, angioplasty, percutaneous intervention) | AT (majority), RT | VO<sub>2</sub> max for aerobic training: 15/807/SMD 0.67 mL/kg/min [0.39, 0.94]; Longer exercise training period (>6 months) starting soon after a cardiac event (<3 months) had a significant effect on VO<sub>2</sub> max in patients with CHD: 7/406/SMD 0.94 mL/kg/min [0.38, 1.50] and 11/647/SMD 0.77 mL/kg/min [0.44, 1.10, P < 0.001] respectively |
| Cortes et al.    | Acute myocardial infarction         | In hospital early mobilization | VO<sub>2</sub> max for aerobic training: 15/807/SMD 0.67 mL/kg/min [0.39, 0.94]; Longer exercise training period (>6 months) starting soon after a cardiac event (<3 months) had a significant effect on VO<sub>2</sub> max in patients with CHD: 7/406/SMD 0.94 mL/kg/min [0.38, 1.50] and 11/647/SMD 0.77 mL/kg/min [0.44, 1.10, P < 0.001] respectively |
| Jolliffe et al.  | Coronary heart disease              | AT (majority), RT | VO<sub>2</sub> max for aerobic training: 15/807/SMD 0.67 mL/kg/min [0.39, 0.94]; Longer exercise training period (>6 months) starting soon after a cardiac event (<3 months) had a significant effect on VO<sub>2</sub> max in patients with CHD: 7/406/SMD 0.94 mL/kg/min [0.38, 1.50] and 11/647/SMD 0.77 mL/kg/min [0.44, 1.10, P < 0.001] respectively |
| Clark et al.     | Ischemic heart disease              | AT, RT (no details) | Trend towards decreased total mortality and non-fatal re-infarction, but n.s |
| Cornish et al.   | Ischemic CAD (narrative review)     | AT (interval training) | Exercise capacity: 2 studies (of 2) showed ↑ in either 6MWD, cycle test time, VO<sub>2</sub> max, time to fatigue and HRrest, while both showed increase in workload |
| Oliveira et al.  | Post-MI, CABG (narrative review)    | RT           | Exercise capacity: 2 of 2 studies showed ↑ in 6MWD; Muscle strength: 2 studies (of 2) showed ↑ in muscle strength |

Meta-regression analysis shows that exercise training had beneficial effects on LV remodeling in clinically stable post-MI patients with greatest benefits occurring when training starts earlier following MI (from one week) and lasts longer than 3 months.

Ejection fraction: Q = 25.48, df = 2, P < 0.01
End systolic volume: Q = 23.89, df = 2, P < 0.005
End diastolic volume: Q = 27.42, df = 2, P < 0.01
| Author                  | Condition and severity | Type of training: | Generic fitness, quality of life and functional outcomes | Disease specific fitness, control and prevention outcomes |
|-------------------------|------------------------|------------------|----------------------------------------------------------|----------------------------------------------------------|
|                         |                        |                  | # RCTs/difference [95% confidence intervals]              | # trials/difference [95% confidence intervals]            |
| Watson et al⁶⁹          | PVD                    | AT, RT           | Maximal walking time: 7/255/MD: 5.1 [4.5, 5.7]            | Pain-free walking time: 3/150, MD: 2.9 min [2.5, 3.3]    |
|                         |                        |                  | Maximal walking distance: 6/391, MD: 11.3/20 M [9.50, 13.14] | Pain-free walking distance: 6/322, MD: 8.2 M [7.17, 9.27] |
| Wind and Koelemay⁷⁰     | PVD                    | AT               | Walking distance: 9/499, WMD: 155.8 M [80.8, 230.7]      | Pain-free walking distance: 8/409, WMD: 81.3 M [35.5, 127.1] |
| Dickinson et al⁷³       | Hypertension           | AT               | SBP: 21/1346/MD: 4.4 mmHg [3.7, 5.1]; DBP: 23/340/MD: 4.4 mmHg [3.7, 5.1] | Triglycerides: 3/348/WMD: 0.18 mmol/l [0.31, −0.05]; Fasting glucose: 2/273/WMD: 0.17 mmol/l [−0.30, −0.05]; HDL: 3/348/WMD: 0.06 mmol/l [0.03, 0.09] |
| Cornelissen and Fagard⁷²| Hypertension           | AT               | VO₂ max: 17/279/WMD: 4.4 mL/kg/min; HR: 23/340/WMD: −4.5 bpm [−6.5, −2.6]; SBP: 30/492/WMD: −6.9 mmHg [−9.1, −4.6]; DBP: 30/492/WMD: −4.9 mmHg [−6.5, −3.3] |                      |
| Whelton et al⁷⁴         | Hypertension           | AT               | SBP: 15/NR/ES: −4.54 mmHg [−7.17, −2.70]; DBP: 13/NR/ES: −3.73 mmHg [−5.69, −1.77] |                |
| Kelley et al⁷¹          | Hypertension           | AT               | SBP: 15/NR/ES: −4.54 mmHg [−7.17, −2.70]; DBP: 13/NR/ES: −3.73 mmHg [−5.69, −1.77] |                |
| Shaw et al⁷⁶            | Obesity                | AT               | DBP: 2/259/WMD: −2.09 mmHg [−3.68, −0.51] |                |
| Witham and Avenell⁷⁵    | Obese postmenopausal women | AT, RT         | VO₂ max: increase by 11.7% in the intervention group and 0.7% in the control group at 12 months (P < 0.001) | Combined physical outcomes (Scales of physical disability, discomfort, pain, function, mobility ie, AIMS): 12/80/8/SSE: 0.29 [0.23, 0.36] |
| Devos-Comby et al⁷⁹     | OA                     | AT, RT, and balance | Direct measures of impairment (walking distance test, timed chair rise, time getting out of a car, balance tests, or gait): 1/740/SES 0.15 [0.08, 0.23] | Pairs: ↑ in 10 of 18 studies; Physical disability: ↑ in 11 of 14 studies; Physical self efficacy: ↑ in 2 of 2 studies |
| Lange et al⁸⁰          | Knee OA                | RT               | Strength: ↑ in 9 of 14 studies; Maximal gait speed: ↑ in 4 of 4 studies; Maximal stair climb/descent: ↑ in 3 of 5 studies | Pairs: ↑ in 10 of 18 studies; Physical disability: ↑ in 11 of 14 studies; Physical self efficacy: ↑ in 2 of 2 studies |
| Ottawa Panel⁷⁷          | OA                     | AT, RT           | Strength, aerobic capacity, and functional status: different levels of evidence support various types of strengthening, mobility and flexibility exercises based on RCTs but no synthesis of data from more than one RCT was provided | Pairs: different levels of evidence from RCTs show that different types of exercise decrease pain. No synthesis of data from more than one RCT was provided |
| Brosseau et al⁸⁰       | OA                     | AT               | Aerobic capacity, timed walk distance, walk velocity: ↑ in RCTs but no synthesis of data from more than one RCT was provided | Pairs: decreases, but no synthesis of data from more than one RCT was provided |
| Pelland et al⁸¹        | OA – most knee or hip  | Mainly RT        | Strength, function and QoL: improves, but no synthesis of data from more than one RCT was provided | Pairs: decreases, but no synthesis of data from more than one RCT was provided |
| Li et al⁸³             | Osteoporosis or osteopenia; severity not an inclusion criteria | RT or combined stretch/strength/balance programs | QoL: All domains of SF36 were significantly improved for all 4 studies. Scores out of 100. | Pairs: decreases, but no synthesis of data from more than one RCT was provided |
|                       |                        |                  | Physical function: 5/288/WMD 2.77 [2.27, 3.37]; Pain: 5/288/WMD 4.95 [3.52, 8.70]; |                  |
| Study                          | Intervention | Outcome Measures                                                                 |
|-------------------------------|--------------|----------------------------------------------------------------------------------|
| De Kam et al (32)             | Osteoporosis or osteopenia | AT, RT, Balance, Gait. Improvements in: TUG, standing up and walking around cones, U/E strength, posturegraphy; figure 8 walking; L/E strength; trunk strength; step test; lateral reach; walking velocity; balance performance |
| Chudyk and Petrella (35)      | Type 2 DM    | AT 21 RCT, AT + RT. Improvements in: spine BMD, hip BMD, femur BMD, fall-related fractures; radius BMD, calcaneus BMD, fall risk reduction; tibia BMD, falls incidence; vertebral height |
| Improvements in: TUG, standing up and walking around cones, U/E strength, posturegraphy; figure 8 walking; L/E strength; trunk strength; step test; lateral reach; walking velocity; balance performance |
| Umpierre et al (30)           | Type 2 DM    | AT, AT + RT. Strength: 4/NR/SES: 0.95 [0.58, 1.31] |
| Irvine and Taylor (66)        | Type 2 DM    | RT. VO2 max: 3/95/MD: 4.8 mL/kg/min [2.6, 7.1] |
| Thomas et al (39)             | Type 2 DM    | AT or RT. VO2 max: 5/276/WMD: 2.6 mL/kg/min [1.2, 4.1]; Strength: ↑ in 5 of 6 studies |
| Kelley and Kelley (37)        | Type 2 DM    | AT, AT, or RT. Strength: 2/65/WMD: −13.5, 7.7 |
| Snowling and Hopkin (38)      | Type 2 DM    | AT, RT, or A + RT. DBP: 5/276/WMD: −5.5 mmHg [-9.9, −1.1]; |
| Boulé et al (34)              | Type 2 DM    | AT. VO2 max: 9/266/SES: 0.53 [0.18, 0.88] |
| O’Brien et al (31)            | HIV – range of severity | AT. VO2 max: 5/276/WMD: 2.6 mL/kg/min [1.2, 4.1]; |
| Krogh et al (33)              | Depression   | 9 AT; 3 RT; 1 A + RT. |
| Herring et al (39)            | Anxiety and chronic illness | AT, RT, Balance |
| Mead et al (36)               | Depression   | AT, RT, A + RT. |
| Rethorst et al (35)           | Depression   | AT, RT, AT + RT. Depression scores: 5/2982/ES: −0.80 [0.92, 0.67]. |
| Lawlor and Hopker (32)        | Depression   | AT. Depression symptoms: 9/461/SES: −1.1 [-1.5 to −0.6]. |

**Notes:** WMD (weighted mean difference) is a calculation that provides an average mean difference of studies by weighting the means more highly when the n is larger and the variance is smaller. If the WMD is provided, the unit value for the measure is shown. SES (standardized effect size) is usually calculated by determining the difference between the pre-post values for the intervention and control groups and dividing this difference by the respective standard deviation of differences for the intervention group or the average SD of the differences for both groups.

**Abbreviations:** AT, aerobic training; BMD, bone mineral density; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; MD, mean difference; OR, odds ratio; QoL, quality of life; RR, rate ratio; RT, resistance training; SES, standardized effect size; 6 MWD, six-minute walking distance; SBP, systolic blood pressure; TUG: timed up-and-go; WMD, weighted mean difference.
and had AMSTAR scores ranging from 6 to 8, although one had a score of 3. Based on these papers, it can be concluded that AT and RT significantly improved numerous cardio-pulmonary exercise outcomes, including increasing VO₂max, 6MWD, maximal workload, and anaerobic threshold. It also improved several cardiac system factors, including increasing the heart rate and cardiac output during maximal exercise, improving left ventricular ejection fraction, and the end-diastolic and end-systolic ventricular volume. Two meta-analyses also reported that exercise significantly improved quality of life in these patients.

There were no meta-analyses that investigated the role of AT and/or RT on muscle strength or endurance. Three reviews without meta-analyses investigated the benefits of exercise on a large number of outcomes, including several that are specific to muscle performance. Exercise improved upper and lower extremity strength and muscle endurance, increased oxidative enzyme activity in the quadriceps muscle, and increased forearm blood flow. However, these results must be interpreted with caution as these reports were SRs without meta-analyses, and the AMSTAR scores were relatively low (2 to 6), with few details quantifying the magnitude of the effect.

The AT was relatively consistent across all the studies, in terms of frequency, mode, and intensity. Subjects exercised 2–7 days per week, with most trials within each SR providing the exercise intervention for 3 days per week. Cycle ergometry and treadmill walking were the most commonly used modalities. Most studies prescribed an AT intensity based on a maximal cardiopulmonary exercise test, with exercise intensities ranging from 50% to 80% of VO₂ max. The time per session and the durations of the programs were very variable, ranging from 12 to 100 minutes and 1 to 14 months, respectively. Where described, the resistance training prescription tended to be based on 40% to 80% of one RM.

Ischemic heart disease

Seven SRs investigated the benefits of early mobilization, anaerobic training, and/or RT in ischemic heart disease patients. The AMSTAR scores ranged from 3 to 10, with two reviews having a score of 3 and one a score of 5. The remaining reviews had AMSTAR scores exceeding 8.

The study populations were predominantly male. There was variation in the specific type of intervention (both AT and RT), and differing endpoints were utilized to evaluate benefit and responses. Five reviews examined the effects of AT, three reported the effects of both AT and RT, and one examined the sole effect of early in-hospital mobilization, and one examined the sole effect of RT. Some work focused on reporting disease-specific outcomes (ie, recurrent myocardial infarction, cholesterol and triglyceride levels, ejection fraction, and end-systolic and end-diastolic volumes), while others studied indices of overall activity and fitness (ie, walking distance, maximal aerobic capacity, exercise duration, and muscle strength) in these populations with ischemic heart disease. Quality of life and health care utilization were not studied or specifically reported, and significant variation was evident in the duration of follow-up.

Early in-hospital mobilization demonstrated nonsignificant trends towards decreased total mortality and nonfatal re-infarction. The results suggest that anaerobic and RT reduces the risk of total cardiac death, recurrent myocardial infarction, as well as cholesterol and triglyceride levels. Improvements were also demonstrated in peak oxygen uptake, exercise duration, exercise workload, and 6MWD. The findings suggest that benefits were greater when exercise programming was initiated soon after an ischemic event (as early as 1 week post-myocardial infarction), and when exercise program duration exceeded either 3 or 6 months (rather than <3 months).

Peripheral vascular disease

Exercise training significantly improved the walking distance and pain-free walking distance in patients with peripheral vascular disease (PVD) when compared to standard care as evidenced by two meta-analyses with relatively high AMSTAR scores of 9 and 7. Exercise training was generally supervised. The optimal intensity was not clear, although it was suggested that patients exercised until near maximal pain. The majority of the studies applied an exercise regimen of two to three times per week for 30–60 minutes, with these usually incorporating walking, leg exercises, or treadmill training. Some encouraged additional home exercise.

Hypertension

Exercise training (mainly aerobic exercise) significantly lowered the systolic (SBP) and diastolic blood pressure (DBP) in people with hypertension, as supported by four meta-analyses. Two of the SRs had AMSTAR scores of 8 of 11 while two others had scores of 7 and 4. VO₂max increased significantly and resting heart rate (HR) decreased after exercise training. Exercise training also demonstrated significant improvement in cardiovascular risk factors as shown by an increase in high density lipoprotein levels.
exercise interventions lasted 3–6 months, though some were education or usual care with no additional treatment. Most included. Control interventions primarily included patient education or usual care with no additional treatment. Most exercise interventions lasted 3–6 months, though some were as short as 4 weeks and as long as 24 months. Some studies required daily exercise, while others included only two or three sessions per week. Individual sessions were typically 45–60 minutes in length and complied with usual dosage characteristics for exercise in healthy populations (ie, three sets of ten repetitions for resistance training, and 50% to 80% of maximum heart rate for aerobic interventions).

Pain and physical function were consistently improved following exercise, but no particular type of exercise was found to be superior. Studies examining RT found improvements in strength compared to control interventions,\textsuperscript{77,81} while studies examining the effects of AT found improvements in aerobic capacity, walking speed, and walking distance.\textsuperscript{77–80} All studies found exercise to be a safe and feasible intervention with minimal side effects for patients with OA.

Osteoporosis
Most of the SRs identified in this study investigated the benefits of exercise in the prevention of osteoporosis or osteopenia in healthy, pre- or post-menopausal women. Two SRs investigated the impact of exercise in women diagnosed with osteoporosis or osteopenia, and these had AMSTAR scores of 7\textsuperscript{82} and 6,\textsuperscript{83} indicating moderate quality overall. One of these was an SR without a meta-analysis that evaluated the benefits of AT, RT, BT, and gait on numerous exercise- and disease-related outcomes. It was reported that exercise resulted in improvements in balance measures such as the timed-up-and-go, upper extremity strength, and walking velocity, as well a reduction in fall incidence and fall-related fractures.\textsuperscript{82} The other paper included a meta-analysis investigating the benefits of RT with or without balance exercise, and reported that exercise improved several quality-of-life domains including physical function, pain, and vitality.\textsuperscript{83}

Type 2 diabetes mellitus
Seven meta-analyses investigated the benefits of RT and or AT in people with type 2 diabetes with AMSTAR scores that ranged from 6 to 11.\textsuperscript{84–90} Aerobic exercise improved VO\textsubscript{2} max as evidenced by two SRs with AMSTAR scores of 6 and 11.\textsuperscript{84,89} Two SRs with AMSTAR scores of 6 also demonstrated reductions in SBP and DBP after AT, RT, or a combination of AT and RT.\textsuperscript{85,88} Strength measures improved after RT, as described by one SR with an AMSTAR of 7.\textsuperscript{86} Glycosylated hemoglobin (HbA\textsubscript{1c}), a measure of blood sugar levels, was the most consistent outcome reported in all of the included SRs, with a reduction in this seen in all reviews regardless of the type of exercise training.\textsuperscript{84–90}

Osteoarthritis
Results from the five SRs examining the effects of exercise on patients with knee or hip OA consistently show beneficial results for fitness levels and functional performance, though emphasis was primarily on disease-specific outcomes such as joint pain or physical dysfunction.\textsuperscript{77–81} AMSTAR scores were between 7 and 9, and most studies failed to report publication bias or conflicts of interest.

Isotonic RT targeting the quadriceps or hamstrings muscle groups was the most common exercise intervention, though AT and range of motion exercises were also included. Control interventions primarily included patient education or usual care with no additional treatment. Most exercise interventions lasted 3–6 months, though some were

Obesity
Data on the effect of physical activity on fitness outcomes in this population were limited. In post-menopausal obese women, an exercise-based program improved VO\textsubscript{2} max as shown in one RCT reported by one SR.\textsuperscript{75} A Cochrane review with an AMSTAR score of 11 did not report the effect of physical activity on VO\textsubscript{2} max but found a decrease in DBP, reduced triglycerides and glucose, and increased HDL levels.\textsuperscript{76} The majority of trials in the two SRs consisted of AT, usually two to three times per week, at 60%–80% of VO\textsubscript{2} max or HRmax, with different durations utilized.

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The exercise interventions described were quite varied across the SRs. AT consisted of stationary cycling, outdoor cycling, walking, jogging, swimming, rowing, or skiing. RT was performed using a Theraband, free weights, or weight machines. AT intensity ranged 50%–85% of VO₂max, 35%–85% of HRmax, or 40%–80% of HRR. RT intensity ranged 50%–85% of one RM. The exercise sessions were between 30 and 120 minutes, and the duration of the program ranged from 5 to 52 weeks. The SRs primarily focused on the benefits of AT, RT, or a combination of these interventions. However, no studies focused on balance or functional training, or reported functional or quality-of-life outcomes.

**HIV/AIDS**

Interval and continuous AT improved VO₂max in patients living with HIV, as evidenced by a Cochrane review with an AMSTAR score of 10.91 This SR also described improved strength in five of the six studies that reported this measure. Additional benefits from exercise training include no change in the viral load, an increase in CD4 cell counts after interval AT, and improved Profile of Moods scores after AT. A summary of the interventions applied is shown in Table 3.

**Depression**

The five SRs relating to depression were moderate-to-high quality (AMSTAR 8-11).92–96 Exercise programs (AT, RT, or a combination of these) for people diagnosed with major or minor depression were found to result in improved scores on depression and mood, particularly in the short term.92,93 Medium- to long-term effects were less clear.92,93 As a group of studies, the interventions were not well described. Most examined both AT, RT, and mixed AT plus RT, except one92 that focused on AT. The intensity of AT, if described, was moderate to high.93,95 Each session was 30 to 60 minutes in length, with these performed one to five times per week, and the duration of the programs was between 10 days and 52 weeks.

**Discussion**

This synthesis examined 58 systematic reviews of exercise training in people with AECOPD, COPD, or eleven chronic conditions commonly associated with COPD. Overall, this review provides Level 1A evidence that exercise training improves generic or disease-specific measures of fitness in several disease populations. Markers of endurance (aerobic capacity, 6MWD) were shown to improve in all conditions except depression, whereas strength was shown to improve in most conditions with the exception of PVD, hypertension, obesity, and depression. In addition, several studies in different disease populations also reported improvements in quality of life, function, control, or prevention outcomes. Depression was the only condition where SRs exclusively focused on disease-specific outcomes (measures of depression and anxiety).92–96 Exercise training also decreases the risk of mortality in older adults,50 and in those with COPD or ischemic heart disease.66

Overwhelmingly, the most common types of training provided to people with all conditions reviewed were AT and RT. Balance and functional training were less commonly applied SRs of exercise training. However, these interventions had widespread application in most SRs that examined older adults.96–99 and in one SR that examined OA patients99 and one that examined osteoporosis patients.82

The quality of the SRs for most conditions was moderate to excellent (>65%) as evaluated by AMSTAR scores. However, SRs that examined training outcomes in heart failure, ischemic heart disease, hypertension, and osteoporosis scored moderately poorly on the AMSTAR (>51% but ≤61%). The listing of articles that were excluded from in the review was the most common item omitted from most SRs, which may have been due to page constraints. Even with this item excluded, the AMSTAR scores remained relatively low for heart failure (56%) whereas scores for the other conditions were ≥66%. In addition to the SR design and strength of AMSTAR scores, the number of participants and RCTs for each condition, including COPD, were large. These numbers further strengthen the foundation of evidence and recommendations for exercise training as an intervention that produces positive outcomes for COPD and commonly associated conditions.98

Although COPD patients often have one or more comorbidities, no information is available, on prescription parameters of exercise training for patients with multimorbidity. Training parameters from studies examining conditions that are common comorbidities might be applicable, however, consideration should be give to similarities of patient demographics and details of training, especially intensity. Given that the most common conditions associated with COPD are obesity (prevalence of 54%),26 osteoporosis (60%–70%)23 and osteoarthritis (increasing prevalence to 40% at age 75)27 (see Table 1), data from SRs describing these conditions may have the greatest relevance. The pertinence of these data is further strengthened by the similarity in age of participants from SRs that examined exercise training in people who were obese, had osteoporosis or osteoarthritis to those affected by COPD. In contrast, subjects were somewhat younger in...
some of the RCTs that examined obesity. Gender was mixed in all of these conditions, except in the case of the SRs on osteoporosis in which predominantly women were studied.52,83

The modalities of AT and RT for obesity, osteoporosis, and osteoarthritis were similar to those typically applied for COPD patients, although exercise training for these conditions utilized more diverse types of training. The intensity of AT appeared to be much higher for obese individuals and those with arthritis compared to that prescribed for COPD patients; intensity was commonly based on aerobic or HR parameters for the former compared to walk distance or dyspnea measures used in COPD patients. This raises the notion that a broader spectrum approach to exercise training in order to improve fitness in patients with COPD and comorbidities such as obesity, osteoporosis, and osteoarthritis may be effective. However, exercise training of the more complex COPD patient (with multiple comorbidities) may result in smaller gains of disease-specific outcomes due to the inability to achieve comparable AT and RT intensities (compared to those achieved in patients with a single condition). These issues merit further study.

Because obesity is a major cause of morbidity and a significant risk factor for other comorbidities such as heart disease and diabetes,26,75,76 SRs addressing exercise fitness outcomes other than body composition are needed in order to determine the overall impact of exercise training in this particular group. Although altering body composition may be the primary outcome for people who are obese, understanding the training and physiologic determinants to achieve that goal are essential; thus fitness outcomes such as aerobic capacity and strength measures should be reported in order to better evaluate the type and intensity of training that results in improvement. Moreover, it has also recently been demonstrated that some obese COPD patients have better fitness outcomes than non-obese COPD patients.99 Determining how physical activity interventions can attenuate obesity, reduce cardiovascular risk factors, and improve overall fitness in people with COPD needs further attention.

Depression is a common comorbidity in COPD with estimates of prevalence ranging between 10% and 80%.25 SRs that examined the effect of exercise on depression had participants with an age range similar to those with COPD, and the interventions were similar to many of the other conditions in this review. A major contrast to the other SRs was that only disease-specific outcomes and no generic fitness measures were reported. All five SRs demonstrated significant decreases in depression or anxiety scores.92–96 These benefits were reported regardless of whether AT, RT, or a combination of AT and RT were applied. Of interest is the finding that the benefits decreased in response to longer training programs. More RCTs are needed to examine clinical sub-groups (minor, moderate, major depression), to compare different forms of exercise, and to clarify the appropriate dose/intensity of physical exercise in addition to the mechanism of improvement. Designing a training program that might result in gains related to self-efficacy would be very different from a regimen that requires improved aerobic fitness or an endorphin response to induce a therapeutic benefit. A better understanding of the type of depression most commonly experienced by COPD will also provide further insight into if and how exercise training can reduce the clinical severity of these two conditions.

Exercise training for older adults showed the greatest contrasts to interventions applied to COPD and other associated conditions in this review. This is especially important given that many individuals with COPD who present for health care interventions are 65 or older. Major foci appeared to be on balance and functional training rather than predetermined intensities of AT or RT.46–49,51,52 In addition, frequently reported outcomes by the SRs on the elderly included balance/falls, and physical performance measures that were functional (ie, timed up-and-go, stair climbing) as opposed to more physiologic measures of strength and endurance. Exercise training for older adults may provide an excellent model to further broaden exercise prescription for COPD patients because, as with the elderly,49,49 people with COPD have a high relative risk of falls.100 In addition, the physical activity level of COPD patients is often comparable to much older, healthier adults. Thus, a greater focus on balance and functional training may not only reduce falls in COPD patients but might also result in greater gains in daily physical activity outside of pulmonary rehabilitation.101

Limitations

Although this synthesis of systematic reviews examined several conditions commonly associated with COPD, the participants within each of the SRs most often had a homogeneous presentation of the condition of interest. Only SRs of the elderly appeared to include participants with diverse and multiple morbidities. For this reason, it might be challenging to apply modalities in a sufficient dose in order to induce both generic and disease-specific benefits that address a complex patient with COPD and multimorbidities. The more functional approach of physical activity training, even in the frail elderly, did result in functional gains, and this approach may also prove to be beneficial to the AECOPD patients with multimorbidities.
Many SRs included lengthy training programs but did not compare the benefits of shorter versus longer programs, with the exception of SRs that evaluated those with hypertension\(^2,7,4\) and depression.\(^2,9,3\) These SRs indicated a slightly diminished response with longer training programs, which may have resulted in a blunting of the physiologic benefits of exercise, decreased adherence to the exercise training program, or a continued onslaught of inciting factors that could no longer be countered by the benefits of exercise training.

**Conclusions**

In summary, this systematic review showed evidence of significant benefits from exercise training in AECOPD, COPD, and many conditions that are common comorbidities associated with COPD. Exercise training, primarily consisting of AT and/or RT, leads to meaningful generic and disease-specific benefits in these conditions. Meta-analyses of endurance (aerobic or exercise capacity, 6MWD) were shown to improve in most conditions whereas meta-analyses of strength were shown to improve in five of the 13 conditions (that is, COPD, older adults, heart failure, ischemic heart disease, and diabetes). Additional research is required to determine the added benefit of RT plus AT in several conditions that are common comorbidities associated with COPD.

A broader approach to exercise and activity prescription in pulmonary rehabilitation for AECOPD may induce therapeutic benefits to ameliorate clinical sequelae associated with COPD and comorbidities. For example, BT and functional training, similar to that applied in older adults, could potentially be very effective in improving functional outcomes including fall risk, and may have a greater impact on daily physical activity than recently demonstrated.\(^10\)

**Disclosure**

The authors report no conflicts of interest in this work.

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Appendix 1
Search strategy for Medline Ovid

Most of the numbered items are entered as keywords or phrases in the search box on the main page of Medline OvidSP. However, some line items at the end of each concept (eg, line 7) are commands to combine previous items in a particular fashion for the main concept. Asterisks indicate truncated terms in Medline. As well, abbreviations (ie, adj3) can be used to link words together.

Similar search terms were used in all databases. However, the preferred term could differ and the user needed to determine if the alternate term provided in a database was suitable. In addition, the manner of truncation, labeling for title or abstract, and combining of terms differed amongst databases.

Concept: COPD
1. lung diseases, obstructive/or exp pulmonary disease, chronic obstructive/or bronchitis, chronic/
2. exp Pulmonary Emphysema/
3. (obstruct* adj3 (pulmonary or lung* or airway* or air-flow* or bronch* or respirat*)).ti,ab.
4. ((chronic airflow or chronic airway*) adj2 (disease* or disorder* or obstruct* or limitation*)).ti,ab.
5. (COPD or COAD or chronic bronchi* or emphysema* or hyperlucent lung*).ti,ab.
6. (chronic adj3 obstructive).ti,ab.
7. or/1–6

Concept: comorbidities
8. bronchial diseases/or asthma/or bronchial hyperreactivity/or bronchial spasm/or bronchiectasis/or bronchopneumonia/
9. (bronchial disease* or asthma* or bronchial asthma* or bronchial hyperreactivity* or bronchospasm*).ti,ab.
10. (bronchiectasis* or bronchitis or bronchopneumonia* or bronchial pneumonia*).ti,ab.
11. exp Pneumonia/
12. (pneumonia* or pneumoniti* or pulmonary inflammation* or lung inflammation* or lobar pneumonia*).ti,ab.
13. Influenza, Human/
14. ((influenza adj3 human*) or human flu or influenza* or grippe).ti,ab.
15. respiratory insufficiency/
16. (respiratory insufficiency or respiratory failure or respiratory depression).ti,ab.
17. heart diseases/or arrhythmias, cardiac/or heart failure/or myocardial ischemia/or myocardial infarction/or pulmonary heart disease/
18. (arythmia or arrhythmia or cardiac arrhythmia* or cardiac dysrhythmia*).ti,ab.
19. (heart failure or cardiac failure or myocardial failure or heart decompensation or myocardial infarction).ti,ab.
20. (pulmonary heart disease* or cor pulmonale).ti,ab.
21. Hypertension/
22. (hypertension or high blood pressure).ti,ab.
23. Diabetes Mellitus/
24. (diabetes mellitus or diabetes).ti,ab.
25. Obesity/or Overweight/
26. (obesity or overweight).ti,ab.
27. Sleep Apnea, Obstructive/
28. (sleep apnea or obstructive sleep apnea or obstructive sleep apnea syndrome).ti,ab.
29. Depression/
30. (depression* or depressive symptoms or emotional depression*).ti,ab.
31. Anxiety/
32. (anxiety* or nervousness or anxious).ti,ab.
33. Anemia/
34. (anaemia).ti,ab.
35. Osteoporosis/
36. (osteoporosis or senile osteoporosis or bone-loss*).ti,ab.
37. Osteoarthritis/
38. (osteoarthritis or osteoarthritides or osteoarthroses or degenerative arthritis).ti,ab.
39. osteopenia.mp.
40. exp aged/or frail elderly/
41. (aged or elderly or frail elderly or frail elder* or frail older adult*).ti,ab.
42. or/8–41
43. 7 or 42

Concept: hospitalized patients
44. exp Inpatients/
45. Hospitalization/
46. (inpatient* or in-patient* or hospitalized or hospitalised or hospitalization*).ti,ab.
47. or/44–46
48. 43 and 47

Concept: exercise
49. exp exercise/or exp walking/
50. exp Exercise Therapy/
51. Physical Fitness/
52. Exercise Movement Techniques/
53. (exercise* or physical exercise* or exercise therap* or walk* or ambulat* or physical fitness or physical activity).ti,ab.
54. (exercise* adj5 train*).mp.
55. (strength* adj5 train*).mp.
56. exp "Physical Therapy (Specialty)"
57. (physiother* or physical therap*).mp.
58. Rehabilitation/
59. rehabilitat*.mp.
60. or/49–59
61. 48 and 60
62. animals/not humans/
63. 61 not 62
64. limit 63 to English