Effects of Exercise Training on Cognition in Chronic Obstructive Pulmonary Disease: A Systematic Review

Laura Desveaux[1,2,3], Samantha L Harrison[1,4,5], Jean-François Gagnon[6,7], Roger S Goldstein[1,4], Dina Brooks[1,4], Véronique Pepin[6,8].

[1]West Park Healthcare Centre, Toronto, Canada; [2]Institute of Health Policy, Management, and Evaluation, University of Toronto; [3]Women's College Research Institute, Women's College Hospital, Toronto, Canada; [4]Rehabilitation Sciences Institute and Departments of Physical Therapy and Medicine, University of Toronto, Toronto, Canada; [5]School of Health and Social Care, Teesside University Middlesbrough, UK, [6]Centre de recherche de l'Hôpital du Sacré-Cœur de Montréal, Montreal, Canada; [7]Department of Psychology, Université du Québec à Montréal, Montreal, Canada; [8]Department of Exercise Science, Concordia University, Montreal, Canada.

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Address for correspondence and reprint requests:

Véronique Pepin

Department of Exercise Science, Concordia University

7141 Sherbrooke Street West, SP165.29

Montreal, Quebec, H4B 1R6

Phone: 514-848-2424 ext. 5806

Fax: 514-848-8681

E-mail: veronique.pepin@concordia.ca

ABSTRACT

Background: As exercise may mitigate cognitive decline in individuals with chronic obstructive pulmonary disease (COPD), its effect has been evaluated in a number of clinical trials. The objective of the present systematic review was to describe the impact of exercise training on cognition in COPD.

Methods: Electronic searches of four databases were performed from inception until March 24, 2015 and last updated 23rd October 2017. Included studies reported on at least one cognitive outcome before and after a formal exercise-training program in individuals with COPD. Two reviewers independently rated study quality using the Downs and Black checklist. The protocol was registered on PROSPERO (CRD42015017884).

Results: Seven articles, representing six exercise interventions in 293 individuals with COPD (55% males, mean age 67 ± 2 year) were included. Although each study documented a significant pre-post training improvement in at least one cognitive domain, the heterogeneity in study design, exercise intervention and cognitive outcome measures among studies precluded a meta-analysis. The only randomized controlled trial available reported an improvement on a letter verbal fluency task in the exercise group only.

Conclusions: Exercise training may positively impact cognition in COPD patients, but current evidence is limited by the heterogeneity of study design, exercise intervention and cognitive outcome measures. Future studies should emphasize comprehensive reporting of intervention parameters, including program length, type(s) of exercise, and duration of individual sessions, in order to facilitate applied insights to inform replication and/or program development.

Introduction

Cognitive impairment is increasingly documented as a comorbidity of chronic obstructive pulmonary disease (COPD) [1-4]. The reported prevalence of cognitive impairment amongst COPD patients has ranged widely (10- 77%), depending on which cognitive measurements and diagnostic criteria for cognitive impairment have been reported [4]. In a recent systematic review and meta-analysis of observational studies, the pooled prevalence of cognitive impairment in COPD was 25% and 32% for mild and any cognitive impairment, respectively [5]. In studies that have used validated diagnostic criteria and a well-matched comparison group, cognitive impairment was noted two to three times more frequently in individuals with COPD than in healthy controls [2,6]. Impaired cognitive domains in individuals with COPD include; attention, executive functions, learning and memory, and motor functions [1,2,7]. Mild cognitive impairment is a known risk factor for dementia [8] and has been associated with reduced adherence to treatment [9] as well as increased mortality in COPD patients [10].

Proposed mechanisms for the increased prevalence of cognitive impairment in COPD include smoking, hypoxemia, systemic inflammation, oxidative stress, arterial stiffness and reduced exercise capacity [1,4]. Both socio-demographic factors, such as lower education, and other comorbidities, such as cardiovascular disease, depression and sleep disorders, may also contribute [1,4]. Given the suspected role of hypoxemia in the development of cognitive impairment in this patient population, long-term oxygen therapy is considered a potential intervention for the preservation of cognition, but its effects are unclear [11,12].

As in healthy older adults, cardiorespiratory fitness has been positively associated with cognitive functioning in COPD patients [13-15]. In a crossover experimental trial, strenuous exercise acutely improved verbal fluency compared to video watching [16]. Although longer-term trials of exercise on cognition in COPD have been reported [17-23], the heterogeneity of exercise training as well as cognitive outcome used makes it difficult to draw clear conclusions. Therefore, the objectives of the present systematic review were to: i) describe the exercise training interventions designed to improve cognition in COPD, and ii) document their impact.

Methods

Study Design

This review was conducted according to the PRISMA and Cochrane Guidelines for Systematic Reviews [24,25]. The protocol was registered on PROSPERO (CRD42015017884).

Data Sources

Electronic databases (MEDLINE, PubMed, EMBASE, and CINAHL) were searched from inception until March 24, 2015 and last updated October 23, 2017. The full search strategy was developed in collaboration with a professional librarian, with search terms derived using MeSH headings (Supplement 1). Secondary searches were conducted by hand searching reference lists of included studies. ~~Corresponding authors were contacted as needed to provide clarification regarding the delivery of exercise interventions.~~

Inclusion Criteria

One member of the research team (LD) initially performed the search and two members (LD and VP) reviewed the titles and abstracts for inclusion. Inclusion criteria for studies were defined according to PRISMA guidelines as follows: (1) Population: intervention participants formally diagnosed with COPD; (2) Intervention: a structured exercise program delivered across two or more sessions; (3) Comparison Group: none required, but may include a control group, secondary intervention, or attention control; (4) Outcomes: any measure of cognitive performance; (5) Study Design: any study design that includes outcome measurements pre- and post-intervention. Included articles were restricted to those available in English or French.

Exclusion Criteria

Exclusion criteria included: (1) article not available in English or French; (2) study not evaluating a formal exercise program; (3) study including participants with diagnoses other than COPD; and (4) only available in abstract form and therefore insufficient data available to assess eligibility.

Quality Assessment

Two members of the review team (SH and VP) assessed the quality of both randomized and non-randomized studies using the Downs and Black checklist for measuring study quality [26], which includes 27 items related to reporting, external validity, internal validity – bias, internal validity – confounding (selection bias), and power. Scores were completed independently and discrepancies between reviewers were resolved by consensus to ensure complete agreement.

Data Extraction & Analysis

Data were extracted by one member of the review team (LD) using a standardized form and verified by a second member (JFG). Data extracted included: the target population; program duration; frequency (number of times per week); session duration (in minutes); exercise components; specific outcome measures collected; and the key findings of the study, including both within- and between-group differences. Variability in study design, interventions and outcome measures precluded the ability to conduct a meta-analysis. The outcome measures utilized across included studies were organized according to the general constructs of cognitive domains and subsequently described according to the specific cognitive tests. Data describing intervention delivery and significant findings were synthesized in a table format.

Results

Search Results

The study selection process is outlined in Figure 1. A total of 881 titles were screened, resulting in the retrieval of 17 full-text articles for review. Seven of the 17 articles met the inclusion criteria, representing six different exercise interventions and 293 individuals with COPD. The characteristics of the included trials are outlined in Table 1. Participants had a mean age of 67 ± 2 year and were 55% male. Two studies from Emery and colleagues [17,18] reported on the same intervention on the same cohort with findings analyzed according to gender [17] and age[18]. The results for the population as a whole were not reported. A study by Etnier and Berry [20] reported outcomes of a three month exercise intervention on a single cohort of patients, followed by a randomized controlled trial where participants either continued with the intervention for 15 months or were assigned to a control group receiving usual care.

Risk of bias was assessed across the five aforementioned categories from the Downs and Black's checklist for measuring study quality [26]. Initially, discrepancies between reviewers occurred for 21 (11%) of the 189 items scored (27 items x 7 articles). After consensus, reviewers came to an agreement across all aspects of the quality assessment (Table 2). Total scores on the checklist ranged from 9 to 20 out of a possible maximum of 28. Willems and colleagues [27] used a cut-off of 19 to identify high-quality studies as scores ≥ 19 met at least two-thirds of the quality items. Based on this approach, only Aquino et al.'s study [23] would be considered high quality. All but the earliest two studies by Emery et al. [17,18] would meet the high-quality criterion for reporting. Internal validity bias was well addressed, given that those participating in exercise cannot be fully blinded, but no information on compliance with the intervention was provided. Selection bias was an issue in the nonrandomized trials and missing information limited the understanding of external validity. Statistical power was only mentioned in one study [20].

[Figure 1 about here]

[Table 1 about here]

[Table 2 about here]

Intervention Delivery

A description of the exercise interventions can be found in Table 1. All six interventions included supervised aerobic exercise, resistance training, and education. Psychosocial support and stress management was included in all but two studies [20,23]. All studies evaluated a short-term exercise intervention, ranging in length from three-four weeks [17,18,21,23] to two-three months [19,20,22]. All but one program [23] were delivered on an outpatient basis and involved a frequency of 3-5 sessions per week. Only two programs specified exercise intensity [20,23].

Measures of Cognition

A total of 22 cognitive tests (or subtests), representing five cognitive domains, were used to measure cognition (Table 3). The domains most frequently evaluated were processing speed, attention and executive functions, with all but one study [20] evaluating this domain and ten unique tests utilized to assess it. Of these, eight were used across multiple studies: the Finger Tapping test [17-19], Digit Vigilance [19,21], Digit Span [17,18,21,22], Digit Symbol [17-19,21], Trail Making Test part A [17-19] and part B [17-19,21], Verbal Fluency – letter category [19,21,22], and Verbal Fluency – semantic category [21,23]. A more detailed description of these tests can be found in supplement 2.

The remaining cognitive domains measured included learning and memory (Rey Auditory Verbal Learning Test [RAVLT] [22,23] and subtests of the Wechsler Memory Scale-Revised [21]), visuo-spatial abilities (Clock Drawing [21] and Drawing Copy Test [23]), language denomination (Boston Naming Test [21]), and fluid intelligence (Culture Fair Intelligence Test [20] and Raven Test [23]).

Effect of Exercise Training on Cognition

Table 3 summarizes pre- to post-exercise training changes observed across the six interventions reviewed. Significant within-group improvements after training (or correlations between participation in rehabilitation and change in cognitive scores [22]) were reported for processing speed/ attention/ executive functions [17-19,21-23], verbal learning and memory [21-23], visuospatial abilities [21,23], and fluid intelligence [20,23]. For the domain of processing speed/ attention/ executive functions, participation in exercise-based rehabilitation was associated with gains in the following sub-constructs: psychomotor speed (Finger Tapping Test [17]), psychomotor speed/ sequencing ability/ implicit memory functions (Digit Symbol [17,18]), selective visual attention (Stroop Colour Word Test [22]), processing speed/ visual attention/ working memory/ mental flexibility (Trail Making Test part B [17]), organized verbal processing/ mental flexibility (Verbal Fluency Test [19,23]), and selective and sustained attention (Attentive Matrices Test [23]). For the learning and memory domain, significant within-group improvements were noted for verbal episodic memory as measured by the RAVLT (sum of trials 1 to 5 [22], immediate recall [22], and delayed recall [22,23]) and subtest Logical Memory from the Wechsler Memory Scale-Revised [21]. Of note, these tests also require good attention (for encoding) and executive functions (for retrieval strategies) to adequately learn the verbal material presented.

Emery et al.[17] noted greater scores in males for certain tests of processing speed/ attention/ executive functions despite both males and females having a similar response to the exercise program. The same authors [18] subsequently reported significant age by time interactions with greater improvements in verbal attention/ verbal working memory (Digit Span) observed in the younger-old (≤ 67.5 years) and an increasing trend in psychomotor speed (Finger Tapping Test, nondominant hand) was noted in the older-old (> 67.5 years). Etnier and Berry [20] noted that older age was associated with greater gains in fluid intelligence (Culture Fair Intelligence Test). Lastly, although Perreira et al.[22] found that being a male and being aged < 65 years were each associated with greater verbal memory pre- and post-rehabilitation, the analysis model precluded them from examining the interaction effect on pre- to post-rehabilitation change in cognition.

Three studies examined the effects of exercise training versus usual care [19-21]. A randomized controlled trial by Emery et al.[19] noted significant between-group difference in a letter verbal fluency task in favour of the exercise group. Two others [20,21] found no significant between-group differences in cognitive measures. Recently, a randomized trial by Aquino et al. [23] compared the effects of combined aerobic and resistance training to those of aerobic training alone. The combined aerobic-resistance training group showed greater gains in verbal episodic memory (RAVLT delayed recall), visuospatial abilities (Drawing Test II), and fluid intelligence (Raven Test).

Discussion

This systematic review is the first to describe the impact of exercise training on cognition in patients with COPD. The evidence is limited to seven published articles reporting on six intervention trials. Study heterogeneity in design, exercise intervention and outcome measures prevented a quantitative synthesis of the evidence.

The domain most often assessed was processing speed/ attention/ executive functions, which is known to be impaired in COPD [2,7]. The verbal learning and memory domain is also noted to respond to exercise [21-23] but is likely associated with the former, as the tasks used to assess learning and memory (RAVLT [28] and Logical Memory from the Wechsler Memory Scale-Revised [29]) require preserved attention and executive functions for encoding as well as retrieval strategies for learning. In general, the neuropsychological batteries used in the studies were limited in the number of cognitive domains assessed, with the exception of two studies [21,23]. Thus, future investigations should include test batteries covering several cognitive domains, with a specific focus on those that have been used successfully thus far (processing speed/ attention/ executive functions/ verbal learning and memory).

Moreover, we cannot exclude the presence of practice effects due to repeated testing. Indeed, changes in cognitive test performance can occur due to increasing familiarity with and exposure to test instrument, items, and paradigms. Practice effects are frequent in clinical trials on individuals with cognitive impairment, and can manifest across a range of cognitive measures, including speed processing, episodic learning and memory, executive functions, and working memory. All these cognitive domains showed improvement after exercise intervention in COPD population. Goldberg al. [30] proposed three complementary approaches to attenuating practice effects: 1) massed practice in a prebaseline period; 2) tests designed to reduce practice-related gains, and 3) well-matched alternate forms on cognitive tests.

The exercise interventions were heterogeneous in their design and included variable program length, type of exercise, and session duration. It remains unclear whether and which features of exercise interventions are necessary to optimize cognitive function. The mechanisms underlying how exercise positively influences cognition are not fully understood. This is particularly true in individuals with COPD as most of the research in the area of exercise and cognition has focused on healthy aging. Proposed mechanisms include physiological changes, such as increased cerebral blood flow, shown to be linked with cognitive function; psychological changes, such as increased arousal and mood, known to affect cognitive performance; and direct effects on brain function through the performance of motor skills involving a cognitive component (i.e., executive functioning and information processing speed) [31]. Given this, it may be that the exercise protocols associated with such physiological, psychological, and motor skills improvements are those that would optimize improvements in cognition.

In keeping with the international guidelines for pulmonary rehabilitation [32] a combination of aerobic and resistance training, as used across reviewed studies, may be sufficient. However, approaches to education and self- management as well as program adherence might need to be modified in those with cognitive impairments, especially if there is a reduction in short term memory. In a recent study by Cleutjens et al. [33], patients with cognitive impairment were at a heightened risk of dropping out from pulmonary rehabilitation, although response in terms of improved functional exercise capacity, disease-specific health status, and psychological wellbeing was comparable to those without cognitive impairment.

In the only randomized controlled trial [19], greater improvements in a verbal fluency (letter) task was noted after 10 weeks of training in the exercise group compared with the non-training comparison groups. The authors suggest that improvement may be associated with improved frontal lobe function enabling increased executive functions (mental flexibility). The inclusion of comparison groups reduce the likelihood of exercise-related gains occurring only through repeated cognitive testing, and active control conditions of education or attention[19] minimize the confounding effect of attention time and other social interactions on cognitive function.

Consistent with the diminution of the gains in dyspnea and quality of life following exercise training in COPD [34-36], the improvement in cognitive function identified after 3 months of exercise did not meet criteria for statistical significance at 18 months [20]. Moreover in a 1-year follow-up study of their earlier randomized controlled trial, Emery and colleagues[37] demonstrated that only patients who adhered to their exercise routine maintained the cognitive benefits. This may be a key observation, as the non-exercise group did not experience alterations in anxiety, depression or cognitive function.

This review presents a number of limitations that ought to be considered, namely the heterogeneity of study designs, interventions and outcome measures used, which prevented a quantitative synthesis of the evidence. Only one included trial was assessed as being 'high quality' and only one reported being adequately powered. No studies commented on compliance to the exercise interventions; it may be that individuals with cognitive impairment are less likely to adhere to an exercise program, making the delivery of exercise to this population challenging. That said, the review was performed rigorously with two reviewers included at each stage of the process, the participation of experts in exercise training and cognition, and the contribution of clinician-researchers with extensive experience in COPD assisting in the interpretation of the results.

In summary, exercise training may have a role in the mitigation of cognitive decline in COPD patients. However, heterogeneity in study design, exercise intervention and outcome measures, prevents a clear synthesis of existing trials. Future studies should emphasize comprehensive reporting of exercise intervention parameters (program length, exercise type(s), individual session duration, etc.) and should seek to minimize practice effects on cognitive tests in order to facilitate applied insights to inform replication and/or program development. The impact of program attendance, exercise adherence, and knowledge retention may potentially mediate the impact of exercise on cognition and should be explored further.

Figure Legends

Figure 1: Study flow from identification of articles to final inclusion

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