Fluid intelligence in an older COPD sample following short- or long-term exercise

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Abstract:

Purpose: Research supports an association between aerobic fitness and cognitive functioning in chronic obstructive pulmonary disease (COPD) patients. However, the impact of exercise intervention duration has not been satisfactorily examined. Therefore, the purpose of this study was to examine the effects of a 3-month and an 18-month exercise intervention on the cognitive functioning of an older COPD sample. **Methods:** COPD patients (56–80 yr) were given a 3-month exercise program and then were randomly assigned to continue for an additional 15 months (long-term group) or to leave the exercise program (short-term group). Age and education were assessed before involvement in the exercise intervention (baseline). Fluid intelligence, pulmonary function, aerobic fitness, and depression were assessed at baseline, at 3 months, and at 18 months. **Results:** After 3 months of exercise, results indicated that cognitive function and walk distance improved significantly. Results also indicated that the gain in cognitive function was reliably predicted by the decrease in $\dot{V}_E$ at $\dot{V}O_{2peak}$. At 18 months, results indicated that cognitive performance did not differ between the short- and long-term exercise groups, but that walk distance improved significantly for the long-term group, but not for the short-term group. Results of a regression analysis showed that the cognitive performance improvement from 3 months to 18 months was predicted by the gain in walk distance and by the decrease in $\dot{V}_E$ at $\dot{V}O_{2peak}$. **Conclusion:** It is concluded that improvements in aerobic fitness are associated with gains in fluid intelligence after 3 and 18 months of exercise training in COPD patients. However, at 18 months, exercise group was not predictive of the gains in cognitive performance. Therefore, a 3-month exercise program may be a sufficient impetus to foster these cognitive gains in COPD patients.

Keywords: culture fair | cognition | older adults | aerobic fitness | depression

Article:

Aging involves more than the simple advancing of chronologic age; it also involves the initial development and eventual decline of the body across the lifespan, and in many older adults it is associated with concomitant changes in cognition. Aerobic capacity is one of the physical parameters that shows an age-related decline in older years. Aerobic capacity peaks in the late teens or early twenties and declines at the rate of approximately 0.45 $mL \cdot kg^{-1} \cdot min^{-1}$ each year thereafter [23,27]. Cognitive functioning typically exhibits an age-related decline [3,25,37]. Although older adults are able to maintain their performance capacity on crystallized intelligence tasks [25,37], research evidence has shown that as people age beyond 60 yr, most show a pattern of decline in the ability to perform tasks that require problem solving [10,11], assess fluid intelligence [24,40], or have a large emphasis on speed of performance [26].

These coinciding declines in aerobic fitness and cognition have led researchers to contemplate the possibility of a relationship between these systems [13,14]. Cross-sectional studies in which fit older people have been compared to unfit older people generally support the notion of an association between physical fitness and the cognitive parameters that experience age-related declines [7,8,15,21,26,34]. However, longitudinal studies in which fitness has been manipulated in older people have produced mixed results. Positive support for a relationship between fitness and cognition has been found in some studies [13,14,17], but not in others [4,32]. Thus, the research as a whole suggests that the maintenance of fitness is associated with improved cognitive performance, but the efficacy of an exercise intervention for improving cognitive performance has not been clearly established.

Individuals with chronic obstructive pulmonary disease (COPD) are frequently hypoxemic and deconditioned. These individuals exhibit a rapid decline in functional aerobic capacity because of ventilatory limitations and a sedentary lifestyle. Additionally, COPD patients typically display declines in a number of cognitive functions, such as memory [9,35], abstract reasoning skills [35], and reaction time [9,35]. However, as with normal older adults, aerobic fitness levels of COPD patients have been found to be positively related to cognitive functioning [20], and exercise training in COPD patients has been shown to be associated with improvements in cognitive parameters [16,18,19].

Previous investigations into the effects of exercise on cognition in COPD patients have only examined the efficacy of short-term exercise interventions. For example, Emery [16] and Emery et al. [18] report data from the same study, which involved a 30-d exercise intervention, and Emery et al. [19] reported results from a 10-wk exercise intervention. Of obvious interest are the further benefits that might be realized from a longer exercise intervention. The primary focus of this investigation was to examine the effects of formal and structured outpatient exercise programs of different lengths on fitness and cognition in a sample of COPD patients. It was hypothesized that after a short-term formal exercise intervention, all participants would display an improvement in fitness measures and in cognitive measures. Continued improvement was expected in those participants randomly assigned to remain in the formal exercise intervention (long-term group) and subsequent maintenance or declines in aerobic fitness and cognition were expected in those participants randomized to leave the formal exercise intervention (short-term group). It was further hypothesized that cognitive function at baseline would be predicted by measures of age and aerobic fitness and that gains in cognitive function at 3 months and at 18 months would be predicted by age and by gains in aerobic fitness.

METHODS

Participants

Participants were individuals from the Reconditioning Exercise And COPD Trial (REACT) who agreed to participate in cognitive testing for the duration of the study. For the REACT study, the Claude Pepper Older Americans Independence Center of the Wake Forest University School of Medicine recruitment core solicited older participants (55–80 yr) from the local community through physician referral, pamphlet distribution, and advertisements in local newspapers and on local television stations. To qualify for the study, all individuals had to display an expiratory airflow limitation such that the $FEV_{1.0}/FVC$ ratio was less than or equal to 70% and the $FEV_{1.0}$ was greater than or equal to 20% of predicted values. This expiratory airflow limitation could not be reversible by medication. Additionally, inclusion criteria required that participants reported difficulties performing various activities of daily living because of shortness of breath and had not been participating in a regular exercise or pulmonary rehabilitation program for the preceding 6 months. Subjects' age, sex, and years of education were recorded by self-report. A complete list of exclusion criteria is given in Table 1. Subjects were asked not to use inhaled or oral bronchodilators within the 4 h preceding testing.

Table 1: Exclusion criteria.

Criteria	Characteristics that Would Result in Exclusion	Screening Methods
Health	Active treatment for cancer, severe congestive heart failure, stroke, peripheral vascular disease, coronary artery disease, valvular heart disease, major psychiatric disease, severe anemia, liver or renal disease, uncontrolled diabetes or hypertension, orthopedic impairment, blindness, or deafness	History, physical exam, graded exercise test, personal physician
COPD with disability	$FEV_{1.0}/FVC > 70\%$, $FEV_{1.0} < 20\%$ of predicted or absence of reported disability, oxygen desaturation during exercise to < 90% at a heart rate < 50% of age-predicted maximum without supplemental O_2	Pulmonary function test, history, graded exercise test
Ability to comply with exercise interventions	Inability to perform exercise because of physical disability or positive exercise stress test	History, physical exam, graded exercise test
Alcohol use	Consumption (current or within proceeding 2 months) > 2 drinks$\bullet d^{-1}$	History
Inability to complete study	Living > 50 miles from center or plans to move	History

Initially, there were 40 volunteers for the study. Of these, 3 dropped out of the REACT before the 3-month session; 8 remained in the study but were unavailable for cognitive testing at both the 3-month session and the 18-month session; 29 were tested at baseline and at 3 months; and 15 were tested at baseline, 3 months, and 18 months. Demographic information and means and standard deviations for the baseline data on cognitive performance, aerobic fitness, oxygen saturation of hemoglobin (Hb) (SpO_2), and pulmonary function for the participants who were available for the baseline session and either subsequent session ($N = 29$) and for those who were only available for the baseline testing ($N = 11$) can be found in Table 2.

Table 2: Demographic, cognitive, aerobic, SpO2, and pulmonary means and standard deviations for study participants.

Sample/Variable	Baseline Measures for Those Who Continued Testing after Baseline (*N* = 29)	Baseline Measures for Those Who Dropped Out after Baseline (*N* = 11)	3-Month Measures for Those Tested at Baseline and at 3-Months and Included in the 3-Month Analysis (*N* = 29)	3-Month Measures for the Short-Term Exercisers Included in the 18-Month Analysis (*N* = 7)	3-Month Measures for the Long-Term Exercisers Included in the 18-Month Analysis (*N* = 8)	18-Month Measures for the Short-Term Exercisers Included in the 18-Month Analysis (*N* = 7)	18-Month Measures for the Long-Term Exercisers Included in the 18-Month Analysis (*N* = 8)
Sex	18 men, 11 women	3 men, 8 women	18 men, 11 women	6 men, 1 woman	5 men, 3 women	6 men, 1 woman	5 men, 3 women
Age range (yr)	58–80	56–80	Same as baseline	59–79	62–74	59–79	62–74
Mean age (yr)	68.10 ± 6.03	68.45 ± 7.54	Same as baseline	69.71 ± 6.32	67.13 ± 3.68	69.71 ± 6.32	67.13 ± 3.68
CESD	9.10 ± 9.17	5.00 ± 3.90	8.48 ± 8.60	5.14 ± 4.14	6.00 ± 8.94	5.43 ± 4.79	6.00 ± 8.85
CF (number correct)	18.52 ± 6.07	19.64 ± 7.02	23.45 ± 5.44	23.43 ± 4.61	25.63 ± 5.60	23.29 ± 4.86	28.13 ± 4.94
$\dot{V}O_{2peak}$ (mL•kg^{-1}•min^{-1})	18.27 ± 3.69	16.86 ± 4.88	19.21 ± 4.19	21.61 ± 3.86	20.69 ± 3.90	19.86 ± 3.60	19.85 ± 4.24
Walk distance (feet)	1614.02 ± 392.43	1500.64 ± 314.23	1821.31 ± 368.50	1959.71 ± 282.26	2041.50 ± 202.34	1883.86 ± 273.98	2081.88 ± 161.64
FVC (L)	2.91 ± 0.81	2.83 ± 1.10	2.93 ± 0.79	3.35 ± 0.78	3.06 ± 0.73	3.14 ± 0.83	3.24 ± 0.88
$FEV_{1.0}$ (L)	1.69 ± 0.55	1.43 ± 0.46	1.69 ± 0.57	2.04 ± 0.45	1.75 ± 0.62	1.92 ± 0.59	1.81 ± 0.72
$FEV_{1.0}$ (% of predicted)	61.41 ± 16.35	58.45 ± 15.03	61.31 ± 17.82	68.43 ± 12.57	61.63 ± 19.42	66.00 ± 15.34	64.13 ± 20.64
$FEV_{1.0}$ /FVC	57.83 ± 9.81	52.45 ± 11.70	57.00 ± 10.10	62.00 ± 9.07	56.63 ± 11.21	61.71 ± 11.74	55.25 ± 10.51
MVV (L•min^{-1})	110.62 ± 23.57	96.00 ± 23.09	73.21 ± 28.83	90.14 ± 24.11	78.38 ± 33.59	84.15 ± 38.95	76.50 ± 30.30
SpO_2 (%) after GXT	93.76 ± 2.56	92.20 ± 4.05	93.41 ± 2.80	93.43 ± 3.55	93.25 ± 1.83	93.00 ± 3.16	92.50 ± 2.67
SpO_2 (%) after 6-min walk	95.03 ± 2.56	92.73 ± 3.69	94.54 ± 2.59	95.00 ± 3.42	94.00 ± 2.45	93.14 ± 3.53	93.00 ± 2.73
$\dot{V}_E$ (L•min^{-1})	52.18 ± 14.76	43.54 ± 19.10	54.08 ± 17.51	63.91 ± 15.98	58.27 ± 21.47	60.59 ± 13.86	55.44 ± 14.49

CESD, Center for Epidemiological Studies Depression Scale; CF, Culture Fair Intelligence Test; $\dot{V}O_{2peak}$, peak oxygen consumption; FVC, forced vital capacity; $FEV_{1.0}$, forced expiratory volume in 1 s; MVV, maximum voluntary ventilation; SpO_2, oxygen saturation of hemoglobin; GXT, graded exercise test; $\dot{V}_E$, ventilation at $\dot{V}O_{2peak}$.

Materials

Pulmonary function data. A body plethysmograph (Medical Graphics model 1085; Medical Graphics Corp., Minneapolis, MN) was used to obtain the spirometry and lung volume measurements. These measurements were made following the guidelines of the American Thoracic Society [1,38].

Medication use. Participants were asked to gather all prescription medicines taken during the previous 2 wk and to bring the containers to the testing session. At the testing session, the interviewer verified that these were all of the medicines taken in the last 2 wk and recorded the medication by name, dose, and regimen. The medications were then classified as being respiratory drugs or cardiovascular drugs on the basis of the 49th Edition of the *Physicians' Desk Reference*[33]. The total number of respiratory drugs and of cardiovascular drugs was recorded for each participant at each testing session.

Graded exercise test. In conducting the graded exercise tests (GXTs), the modified Naughton treadmill protocol and the American College of Sports Medicine termination criteria [31] were used. During all GXTs, ventilatory and respiratory gas analysis was performed with a cardiopulmonary exercise system (CPX/D; Medical Graphics Corp.). Peak oxygen consumption ($\dot{V}O_{2peak}$) was defined as the highest $\dot{V}O_2$ that occurred during the GXT. Oxygen saturation of Hb during the GXT (GXT SpO_2) was monitored using a pulse oximeter (Armstrong Medical, BCI International, Waukesha, WI) and was defined as the value that occurred at $\dot{V}O_{2peak}$. Minute ventilation ($\dot{V}_E$) was defined as the value attained at $\dot{V}O_{2peak}$.

6-min walk test. The 6-min walk test has been shown to provide an accurate estimate of $\dot{V}O_{2peak}$ when a traditional GXT may be prohibitive [39]. All participants were asked to walk a measured course for 6 min and to attempt to cover as much distance as possible in the given time. Participants walked at a self-selected pace and were advised to decrease their pace or to stop walking if perceived symptoms became excessive. No feedback was given throughout the test. Just before the end of the 6 min, an exercise technician placed a finger probe on the subject so that SpO_2 (walk SpO_2) could be assessed immediately after the 6-min period. The distance covered during the 6 min was assessed in feet (walk distance). In a sample of 43 patients with chronic lung disease or chronic heart failure, the correlation between 6-min walk distance and time to exhaustion on a maximal exercise test has been reported to be $r = 0.58$ [22].

Fluid intelligence. Fluid intelligence is defined as culture free performance in abstractions and relations, and is differentiated from crystallized intelligence, which is defined as verbal, numerical, spatial, and mechanical abilities [25]. Fluid intelligence is typically considered to represent the abilities of reasoning and problem-solving. To assess fluid intelligence, forms A and B of Scale 3 of the Culture Fair (CF) Intelligence Test (Institute for Personality and Ability testing (IPAT), Champaign, IL) were administered. Scale 3 was chosen because it was designed for use on an educated adult population and thus should not be limited by possible ceiling effects. Following the recommendation of the IPAT, form A was administered before form B to minimize test reactivity and to ensure that premature test sophistication did not occur.

Each form consists of four different subtests including series (13 items), classifications (14 items), matrices (13 items), and conditions (10 items). The series test requires participants to choose a response that best completes progressive series of figures. The classifications test requires participants to identify two figures that are different from three other figures. The matrices subtest requires participants to correctly complete a design or matrix that is missing one figure. The conditions task requires participants to select a figure that mimics the conditions displayed by a dot that is present in the test figure (e.g., the dot is under a diagonal line and inside a square). Each subtest is scored by simply counting the number of correct responses (on the classifications subtest, both answers must be correct). A composite score is calculated by summing the subtest scores.

The recommended time limit for each subtest was doubled. Although this limits our ability to make comparisons between these participants and the general population, it was done to reduce test anxiety, to maximize the amount of data collected, and to minimize the effects of speed of performance on fluid intelligence [2,24]. Even-odd split-half reliability coefficients of the test range from 0.71–0.92 when administered with the extended time limits [29]. Instructions were those provided in the manual and were read to participants. An opportunity to ask questions was allowed at any point during or immediately after instruction. Breaks and verbal encouragement were offered between subsets.

Depression. Research has indicated that depression may impact cognitive performance [28]. Therefore, the Center for Epidemiological Studies Depression Scale (CESD) was used to assess symptoms of depression [36]. The CESD is a self-administered questionnaire that consists of 20 statements regarding a participant's feelings in the past week [36]. Participants ranked the statements on a 4-point scale from "rarely or none of the time" to "most or all of the time." Total scores can range from 20–80, with higher scores indicating greater depression. In a sample of 2846 people randomly selected from the general population, the CESD correlated moderately with interviewer ratings of depression ($r = 0.49$) and with measures of symptoms of depression (Lubin, $r = 0.51$; Bradburn Negative Affect, $r = 0.60$; Bradburn Balance, r = 61) [36]. In a sample of 35 clinically depressed individuals, the correlation between the CESD and another measure of symptoms of depression, the SCL-90, has been reported to be $r = 0.83$ [36].

Testing

Each time that participants were tested, they were tested on three separate days to minimize fatigue. On the first day, participants completed the pulmonary function tests and the CESD. On the second day, participants completed the GXT. On the third day, participants completed the CF before performing the 6-min walk test.

Exercise Training

Exercise sessions were held Monday, Wednesday, and Friday of each week. The exercise training program consisted of walking, upper body strength training, and stretching exercises. Exercise was prescribed using ratings of perceived dyspnea (RPD) [5]. These ratings were described as global ratings of perceived breathlessness and were given on a 1–10 scale. Participants were instructed to walk at a RPD of 3–4 (moderate to somewhat hard). Perceived symptoms as assessed using the RPD scales, heart rate, and SpO_2 measures were taken before exercise, 20 min into exercise, and immediately after cool-down. In the event of a low SpO_2 (≤88%), exercise was suspended and participants returned to exercise after a doctor visit and prescription of oxygen. Participants were asked initially to walk approximately double the walking time they had completed during their GXT and were encouraged to gradually increase to 30 min over the course of 3 months. Resistance training was completed immediately after the aerobic exercise cool-down and consisted of biceps curls, triceps extension, shoulder flexion, shoulder abduction, and shoulder shrugs. Two sets of each exercise were performed, with 15 repetitions in each set. Initial resistance was determined experimentally during the orientation visit for each exercise and was increased as the participants desired.

Procedure

On arrival at the REACT study site, written informed consent forms, which had been approved by the university's institutional review board for research with human subjects, were obtained from the participant. During the initial (baseline) testing days, assessments were made for pulmonary function, CESD, GXT, CF, and walk distance. Additionally, during baseline participants completed a medical health history questionnaire, underwent a medical examination to gauge program eligibility, and provided information relative to medication use. Participants were scheduled for cognitive testing and were randomly assigned to either be tested on fluid intelligence (CF) or to complete computerized tests of inhibition, speed of processing, and memory. This procedure was followed because of time constraints and because of the high testing burden already being placed on the participants. There were inadequate data obtained from the three computerized cognitive measures at 3 months and at 18 months for any meaningful analyses to be conducted. Thus, the present report is limited to the CF.

All participants were initially involved in the exercise intervention for 3 months. After 3 months of exercise, participants were retested on the pulmonary function tests, medication use, CESD, GXT, CF, and walk distance. Participants were then randomized to the long-term group or the short-term group. Participants in the long-term group continued the structured exercise program for an additional 15 months, whereas participants randomized to the short-term group were encouraged to continue exercising; however, no formal structured program was provided. After these 15 additional months, participants were again tested (18-month session) on pulmonary function, medication use, CESD, GXT, CF, and walk distance.

An important consideration of this study is that a no-exercise control group was not included in the study. The REACT study, of which this investigation is a part, was a two-arm randomized clinical trial that was designed to compare the effectiveness of a short-term versus a long-term exercise intervention in terms of physical function, acute exacerbation of chronic obstructive pulmonary disease, health-related quality of life, and cost [12]. Thus, since the primary question of interest in REACT was to examine the relative benefits of a short-term exercise intervention as compared with a long-term exercise intervention, the inclusion of a no-exercise control group was not deemed to be necessary.

Statistical Analysis

All analyses were conducted using the Statistical Package for Social Sciences (SPSS) software for Windows 95 (version 9.0, SPSS, Inc., Chicago, IL). In general, we were interested in testing for changes in the physiological and cognitive variables as a function of involvement in the formal exercise program. We were further interested in determining if the changes in cognitive function were predicted by age or by changes in measures of aerobic fitness. The number of predictors at each session was limited by the sample size available for analyses and, therefore, the fullest analysis possible was chosen given the available sample at that time. Additionally, in interpreting the results of the regression analyses, it is important to recognize the degree to which the expected amount of explained variance could exceed zero when the explained variance in the population is actually equal to zero. For the baseline analysis, there are 40 subjects and 6 predictors and the R^2 attributable to chance is 0.13. For the 3-month analysis, there are 29 subjects and 4 predictors and, therefore, the R^2 attributable to chance is 0.11. For the 18-month analysis, there are 15 subjects and 5 predictors and the R^2 attributable to chance is 0.29.

Because of the decrease in sample size between baseline and 3 months and between 3 months and 18 months, one-way analysis of variance (ANOVA) was performed to test for possible differences between those individuals who were tested only at baseline ($N = 11$) and those who were tested at baseline and either 3 months or 18 months ($N = 29$). Differences were tested for age, CESD score, and education level and for baseline measures of respiratory drugs, cardiovascular drugs, $\dot{V}O_{2peak}$, $\dot{V}_E$, walk distance, CF, $FEV_{1.0}$, FVC, $FEV_{1.0}$/FVC, maximum voluntary ventilation (MVV), predicted MVV, and predicted $FEV_{1.0}$. At baseline, a hierarchical regression analysis was applied with CF as the criterion. The predictor variables of CESD and education were forced into the model first and then the remaining predictor variables of age and the measures of aerobic fitness ($\dot{V}O_{2peak}$, $\dot{V}_E$, walk distance) were entered stepwise.

At 3 months, repeated measures ANOVAs were used to test for changes in CF, walk distance, $\dot{V}O_{2peak}$, respiratory drugs, cardiovascular drugs, $\dot{V}_E$, walk SpO_2, and GXT SpO_2 as a function of time (baseline, 3 months). Repeated measures MANOVAs were used to test for changes in the pulmonary function variables as a function of time (baseline, 3 months). Since all participants were involved in exercise from baseline to the 3-month session, examination of the group variable was not relevant. Regression analysis was then used to see if the change in CF from baseline to 3 months could be predicted by age or by changes in walk distance, $\dot{V}O_{2peak}$, or $\dot{V}_E$ from baseline to 3 months.

At 18 months, repeated measures ANOVAs were used to test for changes in CF, walk distance, $\dot{V}O_{2peak}$, respiratory drugs, cardiovascular drugs, $\dot{V}_E$, walk SpO_2, and GXT SpO_2 as a function of time (3 months, 18 months) and group (short-term, long-term). Repeated measures MANOVAs were used to test for changes in the pulmonary function variables as a function of time (3 months, 18 months) and group (short-term, long-term). Regression analysis was then used to determine whether changes in CF from 3 months to 18 months could be predicted from age, from group, or from changes in walk distance, $\dot{V}O_{2peak}$, or $\dot{V}_E$ from 3 months to 18 months.

When appropriate, the Huynh-Feldt epsilon was used to check the sphericity assumption. When the sphericity assumption was not met (i.e., $\varepsilon < 0.75$), multivariate tests of significance were used. For all effects, eta-squared (η^2) values were reported as an index of the magnitude of the effect size. Means and standard deviations for the samples included in the 3-month and 18-month analyses can be found in Table 2. A power analysis was conducted using effect size (ES) estimates calculated using Cohen's d and derived from the most similar cognitive parameters reported in the literature on cognition and exercise in COPD patients [16,18,19]. The ES for the within-subjects analysis at 3 months was estimated as 0.34 on the basis of an average of reported pre-post changes [16,18,19]. Using this effect size and assuming that the correlation between the repeated measurements was 0.50, the power for the time effect at 3 months with 29 subjects available was estimated to be 0.53 [30]. The ES for the between-subjects analysis at 18 months was estimated as 0.54 on the basis of the reported differences in cognitive performance between treatment and control groups [19]. Using this effect size, the power for the group effect at 18 months with 15 subjects available was estimated to be 0.23 [30]. Because of the low power at these time points, main effects and interaction effects that were critical to the interpretation of the results and that did not reach significance were further examined so that effect sizes could be presented.

RESULTS

Participant Demographics

Sample sizes differed at baseline ($N = 40$), 3 months ($N = 29$), and 18 months ($N = 15$) because of both the complete departure of participants from the REACT study ($N = 3$) and the participant missing either the 3-month session ($N = 8$) or the 18-month session ($N = 22$). No significant differences (F values = 0.04–3.47, P values > 0.05) were found on any of the dependent variables between those individuals who had sufficient data to be included in the 3-month or 18-month analysis ($N = 29$) and those who were omitted from both the 3-month and 18-month analyses because of missing data ($N = 11$).

Before Exercise Intervention (Baseline)

Prediction of CF by CESD, education, age, and aerobic fitness measures. CESD score was entered into the regression and explained 14% of the observed variance in CF performance ($F(1,37) = 6.02$, $P < 0.02$). Education level was also entered into the regression and explained an additional 15% of the observed variance in CF performance ($F_{change}(1,36) = 7.30$, $P < 0.02$). Walk distance was stepped into the equation next and added significantly to the prediction of CF performance ($F_{change}(1,35) = 12.62$, $P < 0.001$, $r^2_{change} = 0.19$). Age was stepped into the equation next and accounted for a further significant increase in the explained variance in CF performance ($F_{change}(1,34) = 5.40$, $P < 0.03$, $r^2_{change} = 0.07$). Thus, after statistically controlling for depression and education level, participants who walked farther during the 6-min walk test and were younger in age performed better on the CF test at baseline.

After 3 Months of Exercise Intervention for All

Tests of changes from baseline to 3 months. A significant increase in CF from baseline (mean = 18.52, SD = 6.07) to 3 months (mean = 23.45, SD = 5.44) was found (Wilk's $\lambda = 0.38$, $F(1,28) = 45.09$, $P < 0.001$, $\eta^2 = 0.62$). Significant increases in walk distance (Wilk's $\lambda = 0.65$, $F(1,28) = 15.40$, $P < 0.001$, $\eta^2 = 0.36$) from baseline (mean = 1614.03, SD = 392.43) to 3 months (mean =

1821.31, SD = 368.50) and in $\dot{V}O_{2peak}$ (Wilk's $\lambda = 0.78$, $F(1,28) = 8.15$, $P < 0.01$, $\eta^2 = 0.23$) from baseline (mean = 18.27, SD = 3.69) to 3 months (mean = 19.21, SD = 4.19) were found.

There was not a significant change in either the total number of respiratory drugs taken (Wilk's $\lambda = 0.96$, $F(1,27) = 1.00$, $P > 0.05$, $\eta^2 = 0.04$) or the total number of cardiovascular drugs taken (Wilk's $\lambda = 1.00$, $F(1,27) = 0.00$, $P > 0.05$, $\eta^2 = 0.00$). The change in $\dot{V}_E$ was not significant (Wilk's $\lambda = 0.93$, $F(1,27) = 1.93$, $P > 0.05$, $\eta^2 = 0.07$). There were not significant changes in SpO_2 walk (Wilk's $\lambda = 0.91$, $F(1,27) = 2.72$, $P > 0.05$, $\eta^2 = 0.09$) or SpO_2 GXT (Wilk's $\lambda = 0.97$, $F(1,28) = 0.83$, $P > 0.05$, $\eta^2 = 0.03$). There also was not a significant change in the pulmonary function variables from baseline to 3 months (Wilk's $\lambda = 0.83$, $F(6,23) = 0.81$, $P > 0.05$, $\eta^2 = 0.17$).

Prediction of change in CF from baseline to 3 months from changes in aerobic fitness and from age. Results from the regression analysis indicated that the change in CF performance from baseline to 3 months could be reliably predicted from the change in $\dot{V}_E$ ($F(1,26) = 8.71$, $P < 0.01$, $r^2 = 0.25$). Age was also a significant predictor and accounted for the explanation of an additional 12% of the variance ($F_{change}(1,25) = 4.81$, $P < 0.04$). Thus, a decrease in the $\dot{V}_E$ obtained at $\dot{V}O_{2peak}$ and older age were predictive of greater improvement in CF performance.

After 15 Additional Months of Exercise or of Normal Lifestyle

Tests of changes from 3 months to 18 months. With regards to CF, neither the main effect for time (Wilk's $\lambda = 0.89$, $F(1,13) = 1.66$, $P > 0.05$, $\eta^2 = 0.11$) nor the main effect for group ($F(1,13) = 2.08$, $P > 0.05$, $\eta^2 = 0.14$) was significant. The interaction of group by time was also not significant (Wilk's $\lambda = 0.86$, $F(1,13) = 2.08$, $P > 0.05$, $\eta^2 = 0.14$). Examination of the effect sizes for the groups indicated that there was essentially no change in CF from 3 months to 18 months for the short-term group (ES = −0.03), whereas the long-term group had a moderate improvement in CF (ES = 0.47) from 3 months to 18 months. Furthermore, the ES for the comparison of CF performance at 18 months between the long-term group and the short-term group was 0.99, which indicated that the long-term group was performing better than the short-term group at this time point.

The main effect for time on walk distance was not significant (Wilk's $\lambda = 0.96$, $F(1,13) = 0.61$, $P > 0.05$, $\eta^2 = 0.05$), nor was there a main effect for group ($F(1,13) = 1.41$, $P > 0.05$, $\eta^2 = 0.10$). However, there was a significant interaction effect for group by time (Wilk's $\lambda = 0.67$, $F(1,13) = 6.52$, $P < 0.03$, $\eta^2 = 0.33$). The nature of this interaction was such that walk distance decreased from 3 months (mean = 1959.71, SD = 282.26) to 18 months (mean = 1883.86, SD = 273.98) for the short-term group, whereas walk distance increased from 3 months (mean = 2041.50, SD = 202.34) to 18 months (mean = 2081.88, SD = 161.64) for the long-term group.

A main effect for time was found for $\dot{V}O_{2peak}$ (Wilk's $\lambda = 0.55$, $F(1,13) = 10.68$, $P < 0.01$, $\eta^2 = 0.45$) and indicated that across groups, $\dot{V}O_{2peak}$ decreased from 3 months (mean = 21.12, SD = 3.77) to 18 months (mean = 19.85, SD = 3.81). However, there was not a significant effect for group ($F(1,13) = 0.06$, $P > 0.05$, $\eta = 0.004$), nor was there a significant interaction effect (Wilk's $\lambda = 0.91$, $F(1,13) = 1.34$, $P > 0.05$, $\eta^2 = 0.09$) for group by time.

For the respiratory drugs taken, neither the main effect for time (Wilk's $\lambda = 0.97$, $F(1,13) = 0.43$, $P > 0.05$, $\eta^2 = 0.03$), nor the main effect for group ($F(1,13) = 3.39$, $P > 0.05$, $\eta^2 = 0.21$), nor the interaction of group by time (Wilk's $\lambda = 0.97$, $F(1,13) = 0.43$, $P > 0.05$, $\eta^2 = 0.03$) was significant. For the cardiovascular drugs taken, neither the main effect for time (Wilk's $\lambda = 0.93$, $F(1,13) = 0.93$, $P > 0.05$, $\eta^2 = 0.07$), nor the main effect for group ($F(1,13) = 1.13$, $P > 0.05$, $\eta^2 = 0.08$), nor the interaction of group by time (Wilk's $\lambda = 1.00$, $F(1,13) = 0.004$, $P > 0.05$, $\eta^2 = 0.00$) was significant.

Neither the main effect of time (Wilk's $\lambda = 0.79$, $F(1,12) = 3.28$, $P > 0.05$, $\eta^2 = 0.21$), nor the main effect for group ($F(1,12) = 0.39$, $P > 0.05$, $\eta^2 = 0.03$), nor the interaction of group by time (Wilk's $\lambda = 1.00$, $F(1,12) = 0.003$, $P > 0.05$, $\eta^2 = 0.00$) was significant for $\dot{V}_E$.

For the SpO_2 walk data, the main effect for time was significant (Wilk's $\lambda = 0.47$, $F(1,13) = 14.75$, $P < 0.01$, $\eta^2 = 0.53$). Examination of the means for time indicated that both groups showed a slight decrease in SpO_2 from 3 months (mean = 94.47, SD = 2.88) to 18 months (mean = 93.07, SD = 3.01). Neither the main effect for group ($F(1,13) = 0.14$, $P > 0.05$, $\eta^2 = 0.01$) nor the interaction of group by time (Wilk's $\lambda = 0.91$, $F(1,13) = 1.33$, $P > 0.05$, $\eta^2 = 0.09$) was significant. For the GXT SpO_2 data, neither the main effect for time (Wilk's $\lambda = 0.95$, $F(1,12) = 0.69$, $P > 0.05$, $\eta^2 = 0.05$), nor the main effect for group ($F(1,12) = 0.02$, $P > 0.05$, $\eta^2 = 0.002$), nor the interaction of group by time (Wilk's $\lambda = 0.98$, $F(1,12) = 0.28$, $P > 0.05$, $\eta^2 = 0.02$) was significant.

Neither the main effect of time (Wilk's $\lambda = 0.65$, $F(6,8) = 0.72$, $P > 0.05$, $\eta^2 = 0.35$), nor the main effect for group (Wilk's $\lambda = 0.60$, $F(6,8) = 0.89$, $P > 0.05$, $\eta^2 = 0.40$), nor the interaction of group by time (Wilk's $\lambda = 0.30$, $F(6,8) = 3.16$, $P > 0.05$, $\eta^2 = 0.70$) was significant for the pulmonary function variables.

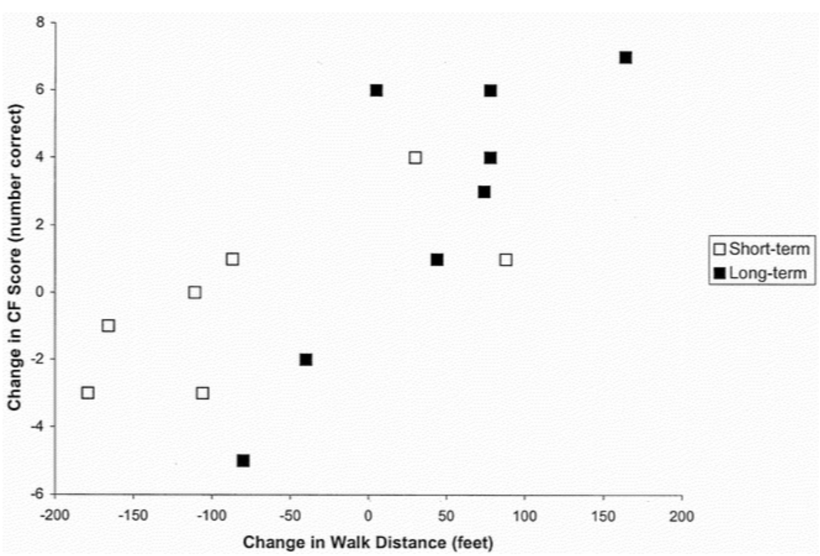

Figure 1. Scatterplot of the change scores for Culture Fair (CF) and walk distance from 3 months to 18 months as a function of exercise group.

Prediction of change in CF from 3 months to 18 months from changes in aerobic fitness and from age and group. The regression analysis indicated that 57% of the variance in the change in CF from 3 months to 18 months could be reliably predicted ($F\,(1,12) = 16.19$, $P < 0.002$) from the change in walk distance from 3 months to 18 months. The change in $\dot{V}_E$ at $\dot{V}O_{2peak}$ from 3 months to 18 months accounted for an additional 26% of the variance ($F_{change}(1,11) = 17.23$, $P < 0.002$). Thus, the improvement in CF from 3 months to 18 months could be reliably predicted from the increase in walk distance (Fig. 1) and from the decrease in $\dot{V}_E$ at $\dot{V}O_{2peak}$.

DISCUSSION

Before addressing the primary findings, it is worthwhile to mention that the exercise intervention in this study did not have a significant impact on depression as self-reported by the participants. That is, at 3 months, the decrease in depression from baseline was negligible (ES = 0.07) and nonsignificant. At 18 months, neither time, group, nor the interaction of time by group had a significant effect on self-reported depression and, again, the ESs were negligible. These findings were not anticipated, but are not remarkable in light of the low depression levels reported by the participants (see Table 2).

The results with respect to cognitive performance at baseline indicated that depression, education, age, and aerobic fitness as assessed by a 6-min walk test are predictive of fluid intelligence. These findings replicate those reported previously with all REACT participants who completed baseline testing [(20)]. This replication is not surprising, because these subjects are merely a subset of those included in the previous study; however, it is important because it suggests that the participants who agreed to participate in the longitudinal portion of the study are representative of those who agreed to only participate in baseline testing.

Results at 3 months are also of interest because they replicate the findings of past research with relatively short-term exercise interventions [(16,18,19)]. That is, results suggest that aerobic fitness, as assessed by $\dot{V}O_{2peak}$ and walk distance, and cognitive functioning, as assessed by CF performance, increased significantly after participation in a 3-month exercise intervention. Results also indicated that the gain in CF performance from baseline to 3 months was reliably predicted by the decrease in $\dot{V}_E$ at $\dot{V}O_{2peak}$ from baseline to 3 months. Thus, the improvements in one of the measures of aerobic fitness were predictive of the improvements in cognitive performance. It is, however, important to qualify these results somewhat because of the fact that there was not a control group at this testing session and the comparison being made is a within-subjects comparison relative to baseline measures. Thus, the results may only be interpreted to indicate an *association* between involvement in a 3-month exercise program and enhanced $\dot{V}O_{2peak}$, walk distance, and cognitive performance. It remains possible that the improvements in these variables are not caused by the exercise intervention itself, but rather are caused by confounding variables such as test reactivity, the social nature of the intervention, exposure to 3 months of attention by health professionals, or a placebo effect.

After 15 additional months of either continued participation in the exercise program or a departure from the formal exercise program, there was a further significant increase in walk distance for the long-term exercisers and a concomitant significant decrease in walk distance for the short-term exercisers. These results suggest that the long-term exercise intervention can result in increases in aerobic fitness (as assessed by walk distance) that exceed those obtained after the initial short-term exercise intervention. It is important to note that at this time point, a stronger case can be made for cause-and-effect because participants were randomly assigned to either the short-term or the long-term exercise intervention and the independent variable of exercise program duration was manipulated.

Of further importance is the fact that the regression analysis indicated that increases in walk distance and decreases in $\dot{V}_E$ at $\dot{V}O_{2peak}$ from 3 months to 18 months are predictive of increases in CF performance from 3 months to 18 months. That is, participants who gained the most in terms of aerobic fitness (as assessed by both walk distance and the decrease in $\dot{V}_E$) also showed the biggest gains in CF performance. This is especially important when one considers that 83% of the variance in CF performance gain was predicted by the gain in walk distance and the decrease in $\dot{V}_E$ at $\dot{V}O_{2peak}$.

The interpretation of the results of this study is difficult for several reasons. The first difficulty is related to the fact that $\dot{V}O_{2peak}$ did not continue to improve in the long-term exercise group as a result of the 15-month exercise intervention. This result is not surprising, however, given that a review of the literature has shown that exercise training in COPD patients has an inconsistent effect on $\dot{V}O_{2peak}$[(6)]. The second difficulty in interpretation arises from the lack of a significant difference in cognitive functioning between the long-term and short-term groups at 18 months. However, we have acknowledged that our statistical power at this point is low and suggest that the effect sizes are actually indicative of meaningful changes in CF from 3 months to 18 months for the long-term group. That is, whereas the short-term group showed essentially no change, the long-term group showed a gain in CF performance from 3 months to 18 months that was equal to almost one half of a standard deviation. Furthermore, at 18 months the long-term exercise group was performing a full standard deviation better on the CF test than was the short-term group. Thus, the expected continued improvement in CF did occur for the long-term group and the expected maintenance of CF performance did occur in the short-term group, and statistical significance might have been reached had our sample size been larger. The third difficulty in interpretation arises from the fact that the group variable (short-term, long-term) did not obtain significance in the prediction equation at 18 months. Examination of Figure 1 provides an explanation for this, as there were two subjects in each group who did not exhibit the same pattern of change in walk distance or in CF as did the rest of their group. Thus, the results suggest that regardless of group assignment, those who gained the most in aerobic fitness (as assessed by walk distance and by $\dot{V}_E$) after 18 months were those who gained the most in cognitive performance. Although it is clear then that the exercise duration manipulation was somewhat effective at the group level (because the long-term group increased their average walk distance whereas the short-term group decreased their average walk distance), the results of the regression analysis suggest that at the individual level there may be other explanations for subsequent changes in cognition.

One of these alternative explanations is that individual differences may be such that a person may be predisposed to gain the most aerobically (as assessed by the increase in walk distance and the decrease in $\dot{V}_E$ at $\dot{V}O_{2peak}$) and to gain the most cognitively, and these individual differences may not be related to the exercise stimulus in a dose-response fashion. Another related explanation is that the initial formal exercise stimulus may have been sufficiently motivating, informative, and habit-forming that some of those previously sedentary COPD patients who were randomized to the short-term exercise group made lifestyle changes that impacted their subsequent performance on the CF test. Thus, the results suggest that although the ultimate increase in aerobic fitness (as assessed by walk distance and by $\dot{V}_E$ at $\dot{V}O_{2peak}$) is predictive of cognitive gains, a long-term formal exercise program may not be required to realize these increases. Obviously, in terms of practical value this is an encouraging finding because it suggests that 3 months of formal exercise results in gains in cognitive performance for COPD patients. However, in terms of understanding the mechanisms underlying exercise-related differences and improvements in cognitive performance, our lack of success at clearly manipulating aerobic fitness after an 18-month exercise intervention limits our ability to pinpoint the mechanism. Future research should continue to examine aerobic fitness and cognition in search of the mechanisms that explain their relationship.

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