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Effectiveness of home-based exercise in older patients with advanced chronic obstructive pulmonary disease: A 3-year cohort study

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9 **The effectiveness of home-based exercise on self-management for advanced COPD**
10 **patients - a 3-year cohort study**
11

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30 **Author Contributions:** Wakabayashi and Kida: study concept and design. Kusunoki, Hattori,
31 Motegi, Furutate, Itoh: acquisition of data. Wakabayashi and Kida: analysis and interpretation
32 of data. Jones and Hyland: preparation of manuscript. Kida had complete access to all data in
33 this study and takes full responsibility for its integrity and the accuracy of data analysis.

34 **Short running title:** Self-management in older COPD patients.

35 **ABSTRACT**

36 **Aim:** To determine whether self-management interventions, including regular home exercise,
37 can offer favorable outcomes for older adults with advanced chronic obstructive pulmonary
38 disease (COPD) using long-term oxygen therapy (LTOT).

39 **Methods:** Information was provided to improve COPD self-management prior to the onset of
40 this prospective three-year cohort study. Patients selected either a home-based exercise
41 intervention using a lower-limb cycle machine (ergo-bicycle) (Group E), or usual exercise
42 (Group U). To assess self-management interventions, the Lung Information Needs
43 Questionnaire (LINQ) was evaluated every 6 months. Clinical outcomes included six-minute
44 walk test (6MWT), pulmonary function tests, the BODE index, St. George's respiratory
45 questionnaire, and the number of exacerbations and hospitalizations.

46 **Results:** A total of 136 patients (Group E = 72; Group U = 64), with a mean age of 74.2 years
47 were enrolled. Total LINQ scores improved over three years for Group E ($p=.003$). The
48 distance of the 6MWT was well maintained in Group E, but significantly decreased in Group
49 U ($p<.001$). Percentage of forced expiratory volume per second at baseline was lower in
50 Group E ($p=.016$) but was maintained over three years, whereas a significant reduction was
51 seen in Group U ($p=.001$). The BODE index significantly worsened in both groups over three
52 years (Group E: $p=.011$; Group U: $p<.001$), while a significant decrease in the number of
53 exacerbations was noted in Group E ($p=.009$).

54 **Conclusions:** Positive outcomes were observed in older COPD patients on LTOT who
55 undertook exercise training with ergo-bicycle machine compared to those who chose usual
56 care at home.

57 **Key words:** COPD; home-based exercise; long-term oxygen therapy; patient education;

58 self-management.

59

60

61 **INTRODUCTION**

62 In an aging population, chronic obstructive pulmonary disease (COPD) is a major cause of
63 morbidity and mortality [1]. Among various COPD symptoms for older adults, dyspnea on
64 exertion is associated with the highest risk of disability and death. Important factors affecting
65 older COPD patients include medication adherence, caregiver involvement, and the incidence
66 of multiple comorbidities, such as cognitive impairment [2,3].

67 Extra-pulmonary manifestations include systemic complications and COPD-associated
68 skeletal muscle dysfunction that includes weakness and atrophy in the lower limbs as a
69 consequence of physical inactivity [4]. Physical exercise is an effective means of managing
70 dyspnea on exertion and preventing sarcopenia, which is prevalent in older patients with
71 COPD [1,5]. Nonetheless, poor physical function has been linked to the incidence of hypoxia
72 in patients with advanced COPD [6]. Insofar, pulmonary rehabilitation offers the best
73 management strategy to rehabilitate patients with COPD [5,7,8]; improvement of muscle
74 strength in the lower extremities is assumed to lead to better exercise tolerance and
75 health-related quality of life [9]. The reduction in muscle power in the lower extremities is
76 likely to be a systemic effect of COPD [9]. However, to our knowledge, little is known
77 regarding the efficacy of self-management interventions for older COPD patients, particularly
78 for those in the advanced stages [1].

79 In our previous study [10], we concluded that the use of patient information for integrative
80 care and patient self-management, as assessed by the Lung Information Needs Questionnaire
81 (LINQ) [11], can improve patient information needs and health outcomes. Recently, Jonkman
82 et al. reported that longer duration of self-management interventions conferred better clinical
83 outcome [12], although sufficient data are still lacking.

84 We hypothesized that a home-based, lower-limb endurance training program can provide
85 positive outcomes as an adjunctive treatment to long-term oxygen therapy (LTOT) in older
86 and advanced COPD patients.

87 **METHODS**

88 In this prospective cohort study, we recruited patients between January 2008 and
89 December 2012 from the Respiratory Care Clinic, which is a secondary referral clinic
90 affiliated with the Nippon Medical School, Tokyo, Japan. The enrolled patients were over 65
91 years old, and were included if they had the following: dyspnea on exertion, and cough
92 and/or sputum; a history of long-term smoking; a stable condition for at least three months
93 prior to the study; and those receiving LTOT according to the criteria defined by the Japan
94 Respiratory Society [13]. A clinical diagnosis of COPD was derived from the GOLD
95 guidelines [1]. Medication was based on triple therapy [14], which included long-acting
96 muscarinic antagonist, long-acting β 2-agonist, and inhaled corticosteroid. Patients with
97 contraindications, such as cholinergic regimens, or patients with prostate hypertrophy were
98 not included. Continuous oxygen therapy was prescribed for more than 15 hours per day [1],
99 with an oxygen concentrator at the patients' residence to supply oxygen. Patients receiving
100 LTOT were instructed on a monthly basis by their physician, according to the medical
101 insurance regulation in Japan [13]. Patients with cardiovascular diseases, including
102 exercise-related risk factors such as unstable hypertension, severe aortic regurgitation, or
103 comorbid respiratory diseases, such as severe bronchiectasis or lung fibrosis, were excluded
104 by clinical history or appropriate examinations.

105 Cognitive function examinations were performed using the Mini Mental State
106 Examination (MMSE) [15]; patients scoring <26 were excluded from this study. The ethics
107 committee of the Nippon Medical School approved this study, and all patients were required
108 to provide written informed consent prior to enrollment.

109

110 *Study design*

111 The enrolled subjects received equal instruction for comprehensive self-management,
112 regardless of their group, delivered by physicians and other health care professionals [16].
113 Additionally, they were regularly assessed via LINQ [11]. LINQ assesses the patient's
114 information needs on the following six domains: an understanding of COPD; medication;
115 avoidance of exacerbations; smoking cessation; daily exercise; and nutritional support. The
116 medical staff re-evaluated the LINQ scores every six months, and tailored patient instruction
117 were provided to the patients. These instructions were based on the individual's responses,
118 and included additional information or correction of misinformation for self-management.

119 Participants chose either home-based exercises using a lower-limb cycle machine
120 (ergo-bicycle) (Group E), or usual exercises (Group U). Both groups were requested to keep a
121 written diary so that a respiratory nurse could deliver encouragement and advice at each
122 clinic visit.

123 Patients in Group E were obliged to purchase an ergo-bicycle, and asked to follow
124 operating instructions. Group E patients were instructed to use the ergo-bicycle once per day,
125 for at least 20 min, with oxygen inhalation. Exercise was performed at minimum resistance at
126 the beginning of the study with addition of incremental resistance as the study progressed,
127 based on the patient's maximum pulse rate and subjective assessment of dyspnea obtained
128 from their diaries. The patients were requested to increase their pulse rates during exercise to
129 80% of their maximum pulse rate during a six-minute walk test [17].

130 Group U patients were instructed to exercise once a day for at least 20 min [16]. The
131 patients were encouraged to exercise more frequently, and for longer durations, if possible.

132 The exercise intensity was set at either 3 or 4, based on the Borg scale. Patients with portable
133 oxygen cylinders were instructed to use oxygen during exercise.

134 Patients were to suspend training if they experienced the following events: fever ($>37^{\circ}\text{C}$),
135 increased dyspnea, body pain such as lumbago, arthralgia, or a worsening of comorbidities.
136 After each exercise session, approximately 5-10 min of cooling-down time was provided for
137 both groups. Patients could call at the respiratory clinic if they felt concerned during exercise.

138

139 *Clinical Examinations and Outcome Measurements*

140

141 *Pulmonary function tests:* The Chestac-55 (Chest Co., Tokyo, Japan) was used to measure the
142 pulmonary function parameters, including post-bronchodilator forced expiratory volume in 1
143 second (FEV1), vital capacity, and forced vital capacity, according to the guidelines of the
144 American Thoracic Society (ATS) [18]. The predicted values were calculated according to
145 the reference values from the Japanese Respiratory Society [19].

146

147 *Dyspnea scale:* The severity of dyspnea was evaluated by the modified Medical Research
148 Council dyspnea scale (MMRC) [20].

149

150 *Exercise capacity:* The six-minute walk test (6MWT) was performed according to standard
151 guidelines as previously reported [21].

152

153 *Body mass index:* The body mass index (BMI) was calculated as the ratio of weight in
154 kilograms to height in square meters.

155

156 *BODE index:* Disease severity of COPD was assessed using the BMI, airflow obstruction,
157 severity of dyspnea, and exercise capacity. The BODE index is a multi-dimensional grading
158 system that predicts mortality, hospitalization, risk of exacerbations, and reflects the
159 detrimental changes that occur during exacerbation in COPD [22]. The total score ranges
160 from 0 to 10 points, and a high BODE score indicates a high risk of death.

161

162 *Lung Information Needs Questionnaire:* The LINQ is a self-completed questionnaire that
163 measures the information needs of patients with COPD [11].

164

165 *Health status:* The disease-specific health status of the patient was assessed using the St
166 George's Respiratory Questionnaire (SGRQ) [23], Japanese version.

167

168 *Comorbidities:* Comorbidities were measured using the Charlson index [24], which is
169 associated with mortality in COPD as previously reported [25].

170

171 *Outcome measurements:* Incidences of exacerbations and hospitalizations were recorded
172 during monthly outpatient clinic visits. Exacerbations were defined as an increase in the
173 severity of the following respiratory symptoms: dyspnea; cough and sputum volume; and
174 sputum purulence that leads to a change in medication, such as antibiotics or systemic
175 corticosteroids, or the admission to hospital [1].

176

177 **Statistical Analysis**

178 To determine the sample size, a power calculation was performed for the outcomes and the
179 total LINQ score. In our preliminary analysis, the distribution of the total LINQ scores had a

180 standard deviation (SD) of 4.28. The required sample size was 100 patients (50 patients per
181 group) for the detection of a difference of 2.80 or larger in the total LINQ score with an alpha
182 level of 0.05, $1-\beta$ 0.90, and the SD. As we anticipated a 25% dropout rate, we initially
183 planned to assign 130 patients.

184 We calculated the mean, SD, and tested differences between Group U and Group E using
185 paired *t*-tests. A p-value $<.05$ was considered significant. Repeated measures of two-way
186 analysis of variance (ANOVA) were used to test the differences over time and between
187 groups. Data were analyzed with the Statistical Package for the Social Sciences, version 22.0
188 for Windows (SPSS Inc., Chicago, Illinois, U.S.A.).

189 RESULTS

190 A detailed flow chart of this study is shown in Figure 1. The total number of patients
191 recruited was 136, out of which 64 patients selected Group U due to economic considerations
192 (16), limited home space for equipment (6), lower joint or back pain (11), or other exercises
193 (31). The patient dropout rate over three years was 25 (39.1%) and 14 (19.4 %) for Groups U
194 and E, respectively, ($p=.007$). The main reasons for patient withdrawal were transference to
195 another hospital or comorbidity. There were no accidental or unexpected events during
196 exercise for either group over the three-year study.

197 The baseline characteristics between the groups are shown in **Table 1**. Group U patients
198 (mean age: 76.1 ± 7.3 years old) were significantly older than those in Group E (mean age:
199 72.5 ± 5.9 years old) ($p=.002$). There were no significant differences evident for the patients'
200 sex, 6MWT distance, MMRC dyspnea score, BMI, SGRQ score or LINQ score at the study
201 baseline. In addition, no significant differences in the prevalence of comorbidities were
202 observed between the patients, as evident from the Charlson Index, which included 33 and 41
203 cases of cardiovascular disease in Group U and Group E, respectively.

204 The total LINQ score in Group E significantly improved over three years ($p=.003$)
205 whereas no change was evident for Group U (**Table 2**). The changes in the total score, and in
206 the six LINQ domains at baseline, and at the first, second, and third year are shown in **Table**
207 **2**. The avoidance of exacerbation domain significantly improved in Group E over three years
208 ($p<.001$). In comparing between groups, a significant difference were seen over three years
209 for the exacerbation domain ($p=.002$). Both groups showed improvements for the exercise
210 domain over three years (Group U and E; $p=.009$ and $p=.017$, respectively).

211 At baseline, the predicted FEV1% was consistently and significantly lower in Group E
212 ($p=.016$) (**Table 3**), whereas a marked decrease was observed for Group U ($p=.001$) (**Fig. 2**).

213 For Group E, the predicted FEV1% decreased by $0.14 \pm 7.59\%$, whereas Group U decreased
214 by $5.01 \pm 7.08\%$ over three years. The predicted Δ FEV1% significantly differed between
215 Groups E and U ($p=.004$).

216 The distance covered by patients in 6MWT differed significantly between the two groups
217 over three years ($p=.014$) (**Fig. 2**); the distance in Group E was maintained, whereas Group U
218 patients showed a significant decrease ($p<.001$). Additionally, a significant decrease
219 (47.7 ± 50.4 m) for 6MWT was also evident between the first and third years for Group U
220 ($p=.006$). Conversely, the distance covered by Group E decreased by 11.5 ± 67.8 m over three
221 years.

222 The MMRC score for each group worsened over three years, but there were no major
223 differences between the groups from baseline to the third year (**Fig. 2**).

224 The patients' BMI showed a gradual decrease but a year-to-year difference was not evident
225 between the groups; however, Group U patients had a significant decrease in the mean BMI
226 until the third year ($p=.006$) (**Table 3**).

227 An increase was noted for the BODE index scores for Groups U and E during the study
228 ($p<.001$ and $p=.011$, respectively), however, no difference was observed between the groups
229 over the three years (**Fig. 2**).

230 The number of exacerbations significantly decreased in Group E ($p=.009$) during the
231 study; however, there was no significant difference evident between the groups over the study
232 period. Furthermore, no differences were seen for the number of hospitalizations between two
233 groups over three years.

234 **DISCUSSION**

235 The present study revealed several interesting observations regarding the self-management
236 of COPD in older adult patients. The concept of LINQ is based on the premise that both
237 information and knowledge are required for self-management interventions for COPD
238 patients [11]. Although the total LINQ scores tended to improve over the first two years, they
239 worsened for Group U over the third year. Furthermore, improvements were noted in the
240 scores of the exercise domain of the LINQ assessment for both groups; however, the distance
241 on the 6MWT decreased sharply in Group U compared to that in Group E. Although the
242 patients in Group U were unable to maintain their baseline exercise capacity, the LINQ scores
243 revealed that the patients improved their information needs on the exercise domain. This
244 discrepancy raises two different possibilities. In a study on the expectancy, adherence, and
245 perceived effort and benefit of medical interventions, Gaitan-Sierra and Hyland
246 [26] concluded that placebo effects were mediated via the affective consequences of
247 performing a motivated ritual, in a therapeutic context. In the present study, the use of the
248 ergo-bicycle may have increased the positive affect during exercise because it is a novel and
249 attractive device. The positive affect would then have increased effort and enjoyment, leading
250 increased exercise as well as non-specific benefits of increased positive affect. Nonetheless,
251 we evaluated neither the motivation nor expectations of the Group E patients towards the use
252 of new therapeutic modalities. Each patient repeatedly received advice from health care
253 professionals, based on their LINQ responses, and were encouraged to continue the
254 self-management interventions, including the use of the home-based bicycle-ergometer for
255 those in Group E. Although selecting the most effective method is important for maximizing
256 the patient's quality of life, healthcare providers are occasionally challenged by older patients.
257 Previously, these difficulties were reported in patients with comorbidities, or those
258 undergoing invasive cardiac surgery [27] or chemotherapy for malignancy [28]. This may be

259 accounted for by the inadequate strategies for disease management and symptoms,
260 maintenance of functional status, and minimization of toxicity for older patients, particularly
261 those over 75 years old.

262 Bourbeau et al. [29] indicated that when patient knowledge and skills improve,
263 self-efficacy can play a part in determining which activities or situations an individual will
264 perform or avoid. Although the patients in Group U understood the importance of daily
265 exercise for the self-management of COPD, they were either unable or unwilling to continue
266 usual exercise training, which may account for their higher rate of exacerbations compared to
267 those in Group E. Further, Group E patients had lower information needs on the LINQ
268 domain for the avoidance of exacerbation. Therefore, they may have been better adapted to
269 integrate self-management skills into their daily life, and differ in their perception of
270 self-efficacy. Additionally, the patients who selected ergo-bicycle therapy were significantly
271 younger, and had a lower dropout rate; however, these patients also had more severe airflow
272 obstruction. Although we did not study the patient's rationale for selecting ergo-bicycle
273 therapy in detail, it was likely that the patients in Group U were less motivated, more
274 depressive, or had difficulty predicting the treatment outcome. This may be due to the
275 functional decline associated with aging and/or the reduction in overall motivation
276 characteristic of older adults, which may warrant further study.

277 The total LINQ scores improved, particularly for the exercise domain, over three years for
278 both groups. Nonetheless, the mean distance covered by the patients of Group U for the
279 6MWT decreased significantly by 47.7 m over three years,. This indicated that the use of the
280 ergocycle significantly benefitted the patients in Group E. Intriguingly, the scores for the
281 BODE index declined over the clinical course. The mean BODE index score significantly
282 worsened for both groups over three years. Nonetheless, it was noted that the rate of change

283 in the BODE index scores for Group E was more gradual compared to that of Group U. The
284 main factors that influenced this observation are attributable to the increase in the MMRC
285 scores of the patients, which was indicative of increased dyspnea on daily movements. Thus,
286 the relief of dyspnea during daily movements necessitates a viable treatment option,
287 particularly for older patients with COPD, as current medications have shown limited
288 therapeutic efficacy for COPD [1].

289 There were several limitations in this study. First, we were unable to precisely establish the
290 patient's intensity as they used the home-based, lower-limb training machine unsupervised.
291 Second, the patients were not randomly allocated into groups. Nonetheless, this study design
292 may have been more representative of real world circumstances.

293 In conclusion, patients undertaking exercise training were able to maintain pulmonary
294 function and exercise capacity, and experienced fewer exacerbations over the three-year study
295 period. Positive outcomes were also observed in older patients with COPD who were using
296 LTOT and exercise training with an ergo-bicycle machine as an adjunctive treatment at home.

297

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299 Conflict of Interest: The authors declare no conflict of interest.

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380 Table 1. Patient characteristics at baseline

	Group U n=64	Group E n=72	p-value
Age	76.13±7.27	72.49±5.94	.002
Male / Female	57 / 7	66 / 6	.772
Smoking Ex / Current	59 / 5	71 / 1	.099
COPD / ACOS / CPFE	48 / 12 / 4	51 / 16 / 5	.859
Cardio diseases	33	41	.606
Charlson Index (range 0-33)	3.33±1.33	2.97±1.34	.124
Pulmonary function			
VC, L	2.84±0.80	2.97±0.73	.337
%VC, %	87.26±19.07	87.51±19.40	.941
FVC, L	2.79±0.80	2.90±0.72	.389
FEV1, L	1.38±0.56	1.27±0.46	.198
FEV1 %, %	50.85±17.83	43.41±10.45	.004
FEV1, %predict, %	56.34±21.77	48.16±16.15	.016
6MWT			
Distance, m	403.69±106.86	425.04±91.99	.214
Minimum SpO2, %	87.13±6.25	85.89±5.33	.216
Δ SpO2	8.56±5.68	9.35±4.83	.384
Maximum pulse rate	113.48±17.82	118.23±16.36	.110
Δ Pulse	28.48±13.77	30.68±13.50	.353
Borg scale	4.00±2.29	4.43±2.06	.253
MMRC (range 0-4)	1.60±1.02	1.64±1.02	.796
BMI	21.12±3.34	21.45±4.17	.627
SGRQ (range 0-100)	38.10±15.85	39.04±14.03	.772
LINQ (range 0-25)	7.78±3.12	7.25±3.28	.437
Number of exacerbations / year	1.23±1.10	1.35±1.28	.584
Number of hospitalizations / year	0.19±0.59	0.19±0.43	.937

381

382 Definition of abbreviations: COPD = chronic obstructive pulmonary disease, ACOS =
383 asthma-COPD overlap syndrome, CPFE = combined pulmonary fibrosis and emphysema, VC
384 = vital capacity, FVC = forced vital capacity, FEV1 = forced expiratory in 1 second, 6MWT
385 = 6-minute walk test, MMRC = modified Medical Research Council scale, BMI = body mass
386 index, SGRQ = St. George's respiratory questionnaire, LINQ = Lung Information Needs
387 Questionnaire. Values are represented as mean \pm standard deviation.

388 Table 2 The LINQ domains and the total scores for each domain over three years
389

LINQ domain	Group	Baseline	Year 1	Year 2	Year 3	p-value
Understanding	U	1.06±0.68	1.13±0.50	1.06±0.57	1.25±0.58	.664
COPD (range 0-4)	E	1.32±0.68	1.15±0.61	1.15±0.61	1.21±0.88	.547
	U vs E	0.234	0.812	0.643	0.907	.710
Medication (range 0-5)	U	0.75±0.93	0.31±0.60	0.44±0.73	0.38±0.62	.068
	E	0.53±0.71	0.41±0.74	0.50±0.75	0.47±0.71	.786
	U vs E	0.490	0.620	0.782	0.633	.083
Avoid exacerbation (range 0-6)	U	2.81±1.76	3.38±1.82	2.31±1.74	2.44±2.00	.115
	E	3.00±2.09	2.38±1.71	2.50±1.67	1.71±1.24	.000***
	U vs E	0.752	0.070	0.717	0.183	.002**
Smoking cessations (range 0-3)	U	0.00±0.00	0.00±0.00	0.00±0.00	0.06±0.25	.047*
	E	0.00±0.00	0.00±0.00	0.00±0.00	0.03±0.17	.325
	U vs E	-	-	-	0.617	.587
Exercise (range 0-5)	U	1.50±0.89	0.87±0.50	0.94±0.44	0.94±0.44	.009**
	E	1.29±0.87	1.03±0.52	0.88±0.48	0.91±0.57	.017*
	U vs E	0.459	0.318	0.699	0.963	.465
Nutrition (range 0-2)	U	1.00±0.55	1.00±0.52	0.81±0.40	0.81±0.54	.024*
	E	1.13±0.50	0.91±0.45	0.91±0.51	0.97±0.30	.654
	U vs E	0.335	0.552	0.501	0.173	.036*
Total score (range: 0-25)	U	7.31±2.27	6.75±2.70	5.63±2.22	5.94±2.91	.067
	E	7.21±3.02	5.94±2.37	6.00±2.58	5.35±2.10	.003**
	U vs E	0.901	0.289	0.619	0.423	.458

390

391 Definition of abbreviations: COPD = chronic obstructive pulmonary disease, LINQ = Lung

392 Information Needs Questionnaire, Group U = usual care, Group E = exercise with ergo-cycle,

393 U vs E = comparison between groups.

394 Values are represented as mean \pm standard deviation.

395 * $p < .05$, ** $p < .01$, *** $p < .001$

396

397 Table 3 Group comparisons over three years

	Group	Baseline	Year 1	Year 2	Year 3	p-value
FEV1%	U	55.7±19.2	54.6±21.1	53.0±20.3	50.4±18.8	.001**
predict, %	E	48.3±14.5	48.2±16.4	48.1±17.9	47.9±17.1	.945
	U vs E	0.048	0.124	0.243	0.522	.016*
6MWT Distance, m	U	441.3±90.2	420.6±85.3	402.5±94.8	392.5±96.6	.000
	E	441.2±86.7	444.2±76.1	438.6±92.6	429.6±95.3	.265
	U vs E	0.996	0.219	0.116	0.110	.014*
MMRC (range 0-4)	U	1.4±1.0	1.5±1.1	1.7±1.3	1.9±1.2	.114
	E	1.5±1.0	1.6±0.7	1.6±0.9	1.7±1.0	.560
	U vs E	0.726	0.901	0.698	0.369	.543
BMI	U	21.1±3.5	20.7±3.3	20.6±3.1	20.4±3.4	.006**
	E	22.2±3.6	21.8±2.9	21.7±3.0	21.5±2.8	.083
	U vs E	0.178	0.137	0.116	0.098	.940
BODE index (range 0-10)	U	2.0±1.5	2.3±1.8	2.8±1.9	3.1±1.7	.000***
	E	2.6±1.4	2.6±1.5	2.8±1.6	3.0±1.7	.011*
	U vs E	0.124	0.431	0.835	0.889	.118
SGRQ (range0-100)	U	36.0±17.5	37.7±15.5	36.0±16.3	35.9±17.1	.805
	E	36.6±11.2	35.2±11.8	39.5±14.6	38.4±14.2	.177
	U vs E	0.908	0.530	0.443	0.579	.289
Number of exacerbations / year	U	1.2±0.8	1.0±0.8	1.0±0.8	1.1±0.9	.510
	E	1.0±0.8	0.6±0.8	0.8±0.8	0.9±0.8	.009**

	U vs E	0.532	0.057	0.436	0.229	.742
Number of hospitalization / year (Respiratory)	U	0.1±0.4	0.1±0.3	0.0±0.0	0.2±0.5	.054
	E	0.2±0.4	0.1±0.2	0.1±0.4	0.1±0.4	.344
	U vs E	0.482	0.982	0.047	0.186	.066
Number of hospitalization / year (Other)	U	0.1±0.4	0.2±0.5	0.2±0.5	0.1±0.3	.614
	E	0.1±0.3	0.1±0.4	0.1±0.4	0.2±0.4	.226
	U vs E	0.186	0.880	0.746	0.028	.295

398

399 Definition of abbreviations: FEV1 = forced expiratory in 1 second, 6MWT = 6-minute walk
400 test, MMRC = modified medical research council scale, BMI = body mass index, BODE
401 index = body mass index, airflow obstruction, dyspnea and exercise capacity, SGRQ = St.
402 George's respiratory questionnaire, Group U = usual care, Group E = exercise with
403 ergo-cycle, U vs E = comparison between groups.

404 Values are represented as mean ± standard deviation.

405 * p< .05, **p< .01, ***p< .001

406

407 **Figure Legends**

408

409 Figure 1. Flow chart showing the distribution of participants throughout the study.

410

411 Figure 2. Changes in the variables and total score of the BODE index over three years.

412 A) At baseline, predicted FEV1 % was significantly lower in Group E ($p=.016$), and was

413 maintained over the study period, whereas a marked decrease was observed in Group U

414 ($p=.001$). B) Six-minute walking test distance (6MWT) was significantly lower for Group

415 U ($p<.001$) and worsened dramatically from baseline to the second year ($p=.001$), and the

416 third year ($p<.001$). There was also a significant difference between the first year and the

417 third year for Group U ($p=.006$). A significant difference was noted between Groups U and E

418 from baseline to the third year ($p=.014$). C) The modified medical research council scale

419 (MMRC) in each group worsened over three years, but there was no major difference

420 between the groups from baseline to the third year. D) An increase was noted for the BODE

421 index scores for Groups U and E from baseline to completion of the study, ($p<.001$ and

422 $p=.011$, respectively); however, no difference was evident between the groups over three

423 years.