Doctor of Philosophy

Smartphone application-based pulmonary rehabilitation in patients with chronic respiratory diseases

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Smartphone application-based pulmonary rehabilitation in patients with chronic respiratory diseases

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ABSTRACT

Background: Pulmonary rehabilitation is well known to improve clinical symptoms including dyspnea, quality of life, and exercise capacity in patients with chronic respiratory disease. However, researchers have reported difficulties in practicing center-based pulmonary rehabilitation. Recently, smartphone application-based pulmonary rehabilitation has become available in clinical practice. We investigated the clinical outcomes of smartphone application-based pulmonary rehabilitation in patients with chronic respiratory disease through literature review and clinical trials.

Methods: A systematic search of the literature published between January 2007 and June 2023 was performed using the PubMed, Embase, Cochrane, and CINAHL databases to identify relevant randomized controlled trials involving patients with chronic obstructive pulmonary disease (COPD). Pulmonary rehabilitation program should provide exercise program on smartphone application. Study outcomes including exercise capacity, symptom score, quality of life, and hospitalization were evaluated. The meta-analysis evaluated mean differences (MDs) in the 6-minute walk test distance (6MWD), COPD Assessment Test (CAT) score, modified Medical Research Council (mMRC) dyspnea scale, St. George's Respiratory Questionnaire (SGRQ), and risk ratio (RR) of hospitalization from exacerbation.

Afterward, we performed a single-center prospective single arm interventional study at Asan Medical Center in 2022. Participants underwent smartphone application-based pulmonary rehabilitation for 12 weeks. Clinical outcomes were compared between the baseline and the end of rehabilitation. The primary outcome was maximal oxygen consumption (VO_2 max) measured by a cardiopulmonary exercise test.

Subsequently, we performed a single-center based single-blind randomized controlled study which recruited 90 participants with chronic respiratory disease from Asan Medical Center in 2023. Participants were randomly allocated into the intervention and control group at the ratio of 2:1 (60 and

30 participants, respectively). The intervention group underwent smartphone application-based pulmonary rehabilitation for 12 weeks. The control group received usual outpatient medical treatment. The primary outcomes were VO_2 max measures by a cardiopulmonary exercise test and the CAT score.

Results: Of the 1,173 screened studies, ten studies were included in the systematic review and nine in the meta-analysis. Six studies were multi-center studies. There were a total of 1,050 participants, and most were aged ≥ 65 years. There were discrepancies in the baseline participant characteristics, smartphone applications, interventions, and study outcomes among the included studies. In the meta-analysis, five studies assessed the 6MWD with an MD of 9.52 (95% confidence interval [CI] –3.05 to 22.08). Six studies assessed the CAT score with an MD of –1.29 (95% CI –2.39 to –0.20). Three studies assessed the mMRC dyspnea scale with an MD of –0.08 (95% CI –0.29 to 0.13). Two studies assessed the SGRQ with an MD of –3.62 (95% CI –9.62 to 2.38). Three studies assessed hospitalization from exacerbation with an RR of 0.65 (95% CI 0.27 to 1.53). These clinical parameters generally favored smartphone application-based pulmonary rehabilitation; however, a statistically significant difference was noted only for the CAT score.

In the subsequent single arm study, a total of 48 participants were recruited, and 41 visited after rehabilitation. Their median age was 67.0 (interquartile range, 62.0–73.0) years, and 32 (78.0%) were men. For patients with chronic respiratory disease (n = 41), VO_2max (median 13.7 to 15.4 ml/kg/min, $P = 0.049$), CAT score (median 14 to 6, $P < 0.001$), Euro-QoL 5-Dimension 5-Level (EQ-5D-5L) index (median 0.795 to 0.862, $P = 0.001$), and Health-related Quality of Life Instrument with 8 Items (HINT-8) index (median 0.784 to 0.855, $P < 0.001$) were significantly improved. In the subgroup analysis, we observed significant improvement in VO_2max only in participants who were compliant to rehabilitation program (n = 17, 41.5%, $P = 0.012$). No participant experienced disease exacerbation or musculoskeletal injury related to rehabilitation activities during the study period.

In the subsequent randomized controlled study, a total of 90 participants were recruited and 70 (46 intervention group and 24 control group) completed follow-up visits. Among the intervention group,

43 were included in the per protocol analysis. Their median age was 65.5 years and 48 (68.6%) were men. In the per protocol analysis, CAT score (median 7.0 vs 10.0, $P = 0.039$) and mMRC dyspnea scale (median 1.0 vs 2.0, $P = 0.010$) were lower and International Physical Activity Questionnaire score (median 1488.0 vs 1164.0, $P = 0.037$) was higher in the intervention group compared with the control group after rehabilitation. In the subgroup analysis, participants who were physically active or compliant to rehabilitation program showed improved clinical parameters. No participant experienced disease exacerbation or musculoskeletal injury related to rehabilitation activities during the study period.

Conclusions: In the systematic review, smartphone application-based pulmonary rehabilitation showed favorable outcomes in exercise capacity, symptom score, quality of life, and hospitalization compared with conventional pulmonary rehabilitation. In the meta-analysis, the CAT score was significantly lower in the smartphone application-based pulmonary rehabilitation group than that of the control group. In the subsequent clinical trials, the smartphone application-based pulmonary rehabilitation program improved clinical outcomes, including exercise capacity, physical activity, quality of life, and dyspnea symptom, in patients with chronic respiratory diseases. Particularly, participants who were physically active or compliant to exercise program, showed significant improvement in clinical parameters. Furthermore, older adult patients with chronic diseases could easily and safely perform smartphone application-based pulmonary rehabilitation. Therefore, in real-world practice, smartphone application-based pulmonary rehabilitation can be a useful treatment option for older adult patients with chronic respiratory diseases when center-based conventional pulmonary rehabilitation is not feasible.

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INTRODUCTION

Globally, chronic respiratory diseases remain important causes of mortality and morbidity [1, 2]. In 2019, lung cancer, chronic obstructive lung disease (COPD), and lower respiratory infections are among the top-ten causes of disability-adjusted life-years among people over 50 years of age [1]. Approximately 3,500,000 people have COPD and it is the third leading cause of total disability-adjusted life years (1,305 per 100,000 population, 6.21%) in South Korea [3, 4]. Individuals with chronic respiratory diseases also experience various problems, including reduced exercise capacity and poor quality of life [5, 6]. Various clinical information is relevant to the mortality of patients with COPD, including physical activity, disability, lung function, long-term oxygen therapy, body-mass index (BMI), quality of life, depressive symptoms, marital status, comorbidity, and hospitalization [7-9]. Pulmonary rehabilitation is a comprehensive intervention to improve the physical and psychological conditions of people with chronic respiratory disease through exercise training, education, and behavior modification [6]. Pulmonary rehabilitation has been shown to improve dyspnea, quality of life, and exercise capacity in patients with chronic respiratory disease, such as COPD [5, 6, 10, 11].

Furthermore, patients with chronic respiratory diseases have decreased respiratory muscle mass and strength, which is accompanied by decreased respiratory function. In this population, pulmonary rehabilitation with exercise training is the only way to improve respiratory function [12].

The pulmonary rehabilitation programs used in previous landmark studies were composed of exercise training for 30–45 min per day, 3–5 days per week for at least 8–12 weeks [13, 14]. However, researchers reported difficulty in practicing center-based pulmonary rehabilitation, including lack of facilities, low health insurance cost, lack of awareness of physicians, lack of motivation, transport barriers, and low levels of social support [3, 15, 16]; thus, alternatives to center-based pulmonary rehabilitation are desperately needed [17]. Recently, the demand for telerehabilitation in pulmonary rehabilitation is increasing owing to advances in telemedicine and challenges with face-to-face rehabilitation during the COVID-19 pandemic [17-19]. Among telerehabilitation, smartphone application-based pulmonary

rehabilitation became used in clinical trials; however, clinical evidence for smartphone application-based pulmonary rehabilitation from these studies has been inconclusive as a result of heterogeneity between participants, study designs, and formats of applications [20-29]. Furthermore, previous systematic reviews have focused on telerehabilitation [30], home telemonitoring [31], or patient support applications [32].

Therefore, we aimed to evaluate the clinical efficacy of smartphone application-based pulmonary rehabilitation programs (without telemonitoring) with exercise programs in patients with chronic respiratory disease, which are key components of pulmonary rehabilitation to improve chronic respiratory diseases and health-enhancing behaviors [6]. Thus, at first, we performed a systematic review and meta-analysis to review previous relevant studies and elucidate the feasibility of smartphone application-based pulmonary rehabilitation in patients with COPD (Chapter 1), and the results has been published previously [33]. Afterward, we developed a smartphone application and aimed to evaluate the efficacy of smartphone application-based pulmonary rehabilitation programs to improve exercise capacity and quality of life of patients with chronic respiratory disease. First, we performed a single-center prospective single arm interventional study to evaluate the feasibility of smartphone application-based pulmonary rehabilitation programs at Asan Medical Center in 2022 (Chapter 2), and the results has been published previously [34]. Subsequently, we performed a single-center single-blind randomized controlled trial study to evaluate the efficacy of smartphone application-based pulmonary rehabilitation programs at Asan Medical Center in 2023 (Chapter 3), and the study protocol has been published previously [35]. In the following text, we will describe the methods, results, discussion, and conclusion of our study per stage, separately.

Chapter 1: systematic review and meta-analysis

METHODS

Data sources and literature search

Literature searches were performed using the PubMed, Embase, Cochrane, and CINAHL databases. The searches were conducted on literature published since 2007 because the iPhone and Android smartphones were released in June 2007 and September 2008, respectively. Databases were searched up to June 30, 2023. Only full-text studies written in English were included. The search strategy was based on a PICOTS-SD list (supplementary material). Briefly, the search algorithm focused on keywords relating to ‘chronic pulmonary disease’, ‘smartphone application’, and various clinical outcomes. If needed, authors were contacted for further information. This study protocol is registered on the PROSPERO (ID=CRD42023466965).[1]

Eligibility criteria and study selection

Each study was reviewed by two authors (Chiwook Chung and Min-Woo Jo) independently according to the inclusion and exclusion criteria. The inclusion and exclusion criteria are presented in Table 1. Screening of titles and abstracts and subsequent full-text review were performed by two authors (Chiwook Chung and Min-Woo Jo) independently. Disagreements during the selection process were resolved through a discussion between three authors (Chiwook Chung, Min-Woo Jo, and Sei Won Lee).

[1] This study has been previously published as the following article: Chung C, Lee JW, Lee SW, Jo MW. Clinical Efficacy of Mobile App-Based, Self-Directed Pulmonary Rehabilitation for Patients With Chronic Obstructive Pulmonary Disease: Systematic Review and Meta-Analysis. JMIR Mhealth Uhealth. 2024 Jan 4;12:e41753. doi: 10.2196/41753. PMID: 38179689; PMCID: PMC10786334.

Table 1. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Article type	Full-text article	Abstracts, conference posters, and grey literature
Language	English	Not English
Study design	Randomized controlled trials	Non-randomized trials, literature review, and protocol
Participants' age	Adult	Adolescent
Disease	Chronic obstructive pulmonary disease (COPD)	Other respiratory disease, such as asthma
Smartphone application	Conventional or newly developed smartphone application	Cellular phone
Intervention	Pulmonary rehabilitation (PR), including exercise programs, provided by smartphone application	Self-management program, step counter, or peak flow meter, etc.
Control	Conventional PR, including exercise programs (center-based or education).	
Study outcome	At least one of the following outcomes: 6-minute walk test distance (6MWD), COPD assessment test (CAT) score, modified Medical Research Council (mMRC) dyspnea scale, St. George's Respiratory Questionnaire (SGRQ), and hospitalization from exacerbation.	

Data collection and risk of bias assessment

Two authors (Chiwook Chung and Min-Woo Jo) independently collected data regarding (1) general information about the study (authors, year, country, study setting), (2) descriptions of study arms (numbers, sex, age of participants), (3) characteristics of interventions, (4) inclusion and exclusion criteria, (5) results for outcomes, and double-checked them. Two authors (Chiwook Chung and Min-

Woo Jo) independently assessed the risk of bias in the included studies. Discrepancies were resolved in discussions with the third author (Sei Won Lee).

Study outcomes

In the meta-analysis, study outcomes including exercise capacity, symptom score, quality of life, and hospitalization were assessed. Exercise capacity was measured by the 6MWD. The symptom score was measured by the COPD assessment test (CAT) score and the mMRC dyspnea scale. Quality of life was measured by the St. George's Respiratory Questionnaire (SGRQ). Hospitalization was defined as hospitalizations from disease exacerbation. The primary timepoint for the analysis was changes between baseline and the end of the intervention.

Statistical analysis

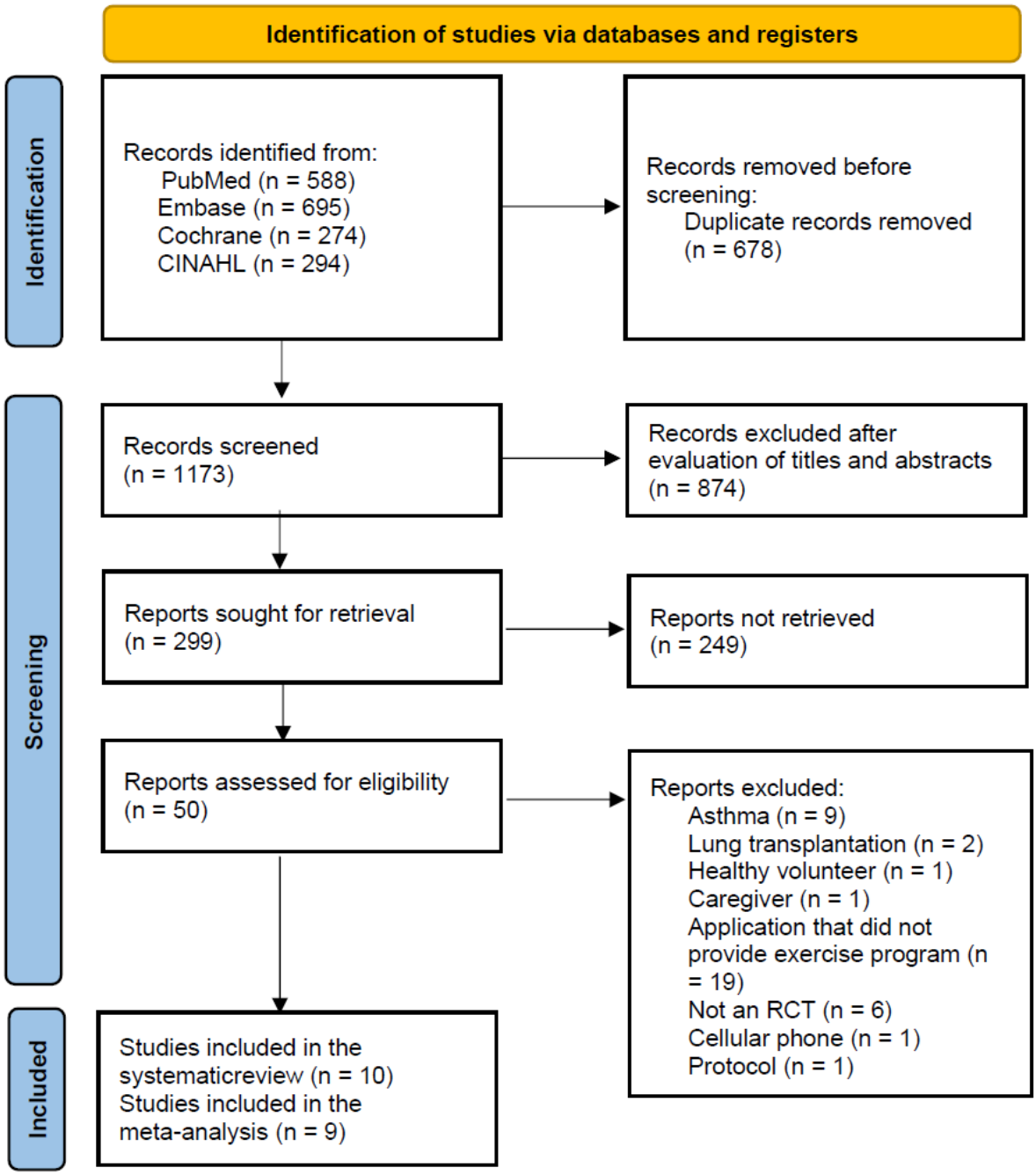
The continuous variables included the 6MWD, CAT score, and SGRQ. The mMRC dyspnea scale was a categorical variable, and it was calculated as a continuous value. Hospitalization from exacerbation was a dichotomous variable. The variables at the time of follow-up were compared between groups. The mean difference (MD) and risk ratio (RR) between the intervention group and the control group were calculated with 95% confidence interval (CI). The χ^2 test and the I^2 statistic were used to assess statistical heterogeneity. If I^2 was < 50%, the fixed effect model was used. Publication bias was visually assessed using a funnel plot analysis because of the limited number of studies on each outcome to perform the Egger test. The meta-analysis was performed using Review Manager (RevMan) Version 5.4. (The Cochrane Collaboration, Copenhagen, Denmark, 2020).

RESULTS

Study selection

An Initial literature search identified a total of 1,851 articles from PubMed, Embase, Cochrane, and CINAHL databases; thereafter, 1,173 articles remained after duplicates were removed. After evaluating titles and abstracts, 299 articles remained eligible for full-text review. A full-text review was performed according to the abovementioned criteria, and ten articles were finally included in the systematic review [20-29]. One study was excluded from the meta-analysis because exercise capacity was evaluated using the incremental shuttle walk test (ISWT) instead of 6MWD [29]. Finally, nine studies were included in the meta-analysis [20-28] (Figure 1).

Figure 1. PRISMA diagram of literature search and selection.



Characteristics of included studies

Characteristics of studies are described in Table 2. Studies were published after 2014, with almost half of them published in 2020 [21, 23, 25, 26]. Six studies were multi-center studies [21, 22, 24, 26-28]. Three studies enrolled fewer than 50 participants and the largest number of participants was 343 [22, 25, 26, 29]. There

were 1,050 total participants, generally aged ≥ 65 years. Male participants were enrolled more than female participants and Wang et al. enrolled only male participants [29]. North et al. recruited participants after hospital admission with acute exacerbation [25]. Vorrink et al. and Wang et al. recruited participants after pulmonary rehabilitation [28, 29]. Kwon et al. recruited two groups of participants in the intervention arm, comprising the fixed regimen group and the fixed-interactive regimen group, according to exercise programs [24]. Various formats of smartphone applications were used for the studies: Two studies in the UK used myCOPD, a digital health care application approved by National Health Service [21, 25], and one in China used WeChat, a popular smartphone messenger in China [23]. The follow-up duration ranged between 3 weeks and 12 months [20, 28].

Table 2. Characteristics of included studies

First author	Year	Setting	Country	Sample size		Age (years)		smartphone application	Follow-up duration
				Intervention	Control	Intervention	Control		
Barata PI [20]	2022	Single center	Romania	M 42 (72.4) F 16 (27.6)	M 54 (75.0) F 18 (25.0)	64.3±4.3	64.9±5.7	Pneumocontrol application (Newly developed)	21 days
Crooks MG [21]	2020	Multi center	UK	M 11 (37.9) F 18 (62.1)	M 20 (64.5) F 11 (35.5)	65.9±7.3	66.4±7.0	myCOPD	90 days
Demeyer H [22]	2017	Multi center	Belgium	M 111 (64.9) F 60 (35.1)	M 108 (62.8) F 64 (37.2)	66±8	67±8	Fitbug application and a project-tailored coaching application.	12 weeks
Jiang Y [23]	2020	Single center	China	M 44 (83.0) F 9 (17.0)	M 43 (81.1) F 10 (18.9)	70.9±6.4	71.8±7.6	WeChat official account based on social media	6 months
Kwon H [24]	2018	Multi center	Republic of Korea	1) M 23 (85.2) F 4 (14.8) 2) M 26 (86.7) F 4 (13.3)	M 21 (75.0) F 7 (25.0)	1) 64±8 2) 65±7	64±8	efil breath (Newly developed)	12 weeks
North M[a] [25]	2020	Single center	UK	M 13 (65.0) F 7 (35.0)	M 11 (52.4) F 10 (47.6)	65.1±6.3	68.1±7.4	myCOPD	90 days
Park SK [26]	2020	Multi center	Republic of Korea	M 19 (86.4) F 3 (13.6)	M 14 (70.0) F 6 (30.0)	70.5±9.4	65.1±11.1	COPD self-management program (Newly developed)	6 months
Spielmanns M [27]	2023	Multi center	Switzerland	M 17 (51.5) F 16 (48.5)	M 17 (50.0) F 17 (50.0)	66.1±6.8	62.7±8.2	Kaia COPD app (newly developed)	6 months
Vorrink SNW[b] [28]	2016	Multi center	Netherlands	M 42(50.0) F 42(50.0)	M 36(49.3) F 37(50.7)	62±9	63±8	Newly developed	12 months
Wang CH[b] [29]	2014	Single center	Taiwan	M 12 (100.0)	M 14 (100.0)	71.4±1.9	71.9±2.7	Newly developed	6 months

Data are presented as the mean ± standard deviation or number (%), unless otherwise indicated.
M: male, F: female.
1) The fixed regimen group. 2) The fixed-interactive regimen group.
[a] Participants were recruited after hospital admission with an acute exacerbation.
[b] Participants were recruited after pulmonary rehabilitation.

Interventions in studies are described in Table 3. Disease education and monitoring were provided in five studies [21, 23, 25-27, 36], and other five studies provided only exercise programs [20, 22, 24, 28, 29]. The level of exercise could be adjusted according to the participants' exercise capacity in five studies [20, 22, 24, 28, 29]. Particularly, Kwon et al. provided two kinds of exercise regimen and walking distances were adjustable in both regimen [24]. In case of exacerbation of COPD or poor compliance to pulmonary rehabilitation, participants could contact healthcare providers in seven studies [21-23, 25-27, 29, 36]. Jiang et al. gave incentives to participants, which could be obtained at the mall using acquired points [23].

Table 3. Interventions of included studies.

First author	Exercise adjustment	Exercise monitoring	Disease education	Disease monitoring	Social support	Contact with healthcare	Incentive
Barata PI [20]	○	○		○			
Crooks MG [21]			○	○		○	
Demeyer H [22]	○	○				○	
Jiang Y [23]		○	○	○	○	○	○
Kwon H [24]	○	○					
North M [25]			○	○		○	
Park SK [26]		○	○	○	○	○	
Spielmanns M [27]		○	○	○		○	
Vorrink SNW [28]	○	○					
Wang CH [29]	○	○				○	

Most studies included adult participants with physician-diagnosed COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [10]. Some studies did not included participants with severe COPD according to the GOLD criteria [26, 28], but others did not set limitations to disease severity. Generally, participants with recent acute exacerbations, long-term home oxygen therapy, or other medical conditions disabling physical exercise were excluded. Meanwhile, North et al. included participants after hospitalization with an acute exacerbation [25] (Supplementary Table 1). Participants were evaluated in various dimensions of outcomes, including exercise capacity, disease severity, qualities of life questionnaire, and acute exacerbation. Wang et al. reported favorable outcomes in exercise capacity and serum inflammatory biomarkers; however, it was excluded from the meta-analysis because exercise capacity was reported in the ISWT and limb muscle strength [29]. Crooks et al. and North et al. reported that inhaler technique was improved in the intervention group, which was beneficial to disease control [21, 25]. Demeyer et al. reported that lung function was not improved during pulmonary rehabilitation in either group, and musculoskeletal events happened more in the intervention group [22]. Barata et al. reported that the maximal inspiratory and expiratory pressures were improved in the intervention group (Supplementary Table 2) [20].

Risk of bias in studies

Overall risk of bias in studies were considered as low risk. Particularly, performance bias was considered inevitably high risk in all studies because participant blinding was impossible owing to the nature of intervention (Figure 2). Funnel plots of comparisons showed fairly symmetrical distribution, which might mean less publication bias (Figure 3).

Figure 2. Risk of bias in the included studies.

A: Risk of bias graph. B: Risk of bias summary.

Kwon (1) denotes the fixed regimen group, and Kwon (2) denotes the fixed-interactive regimen group.

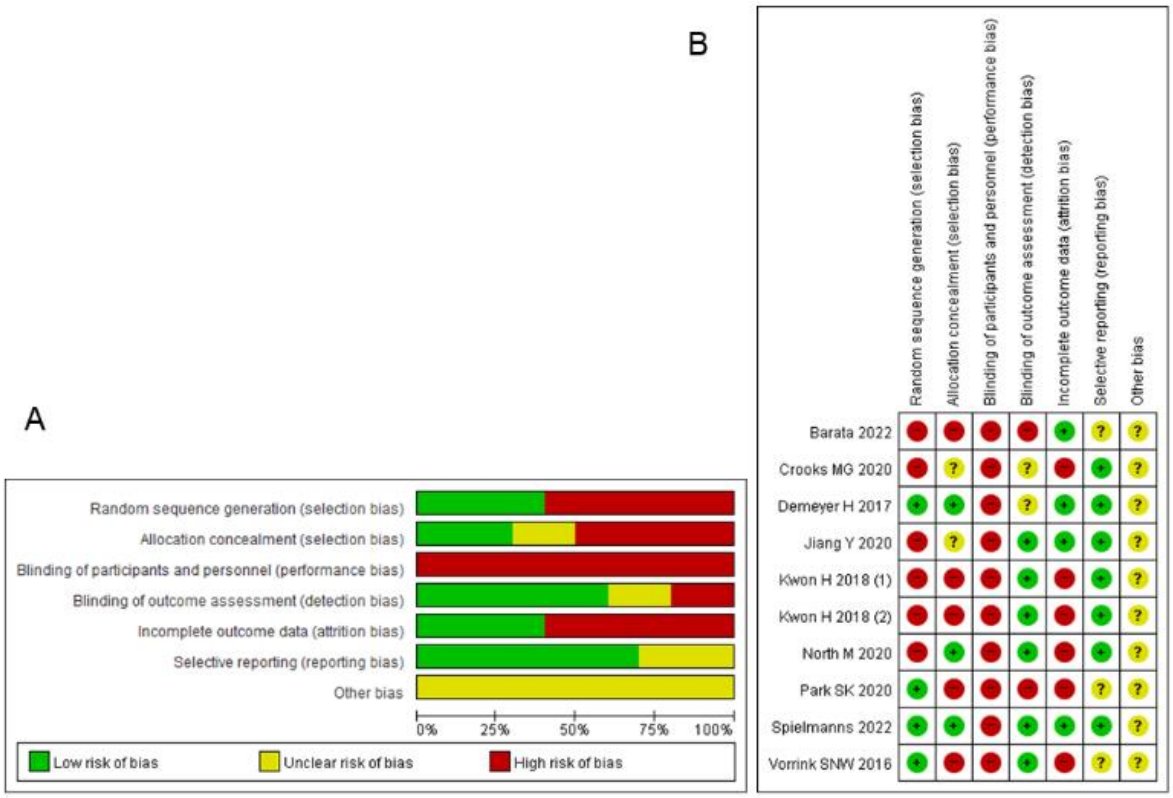
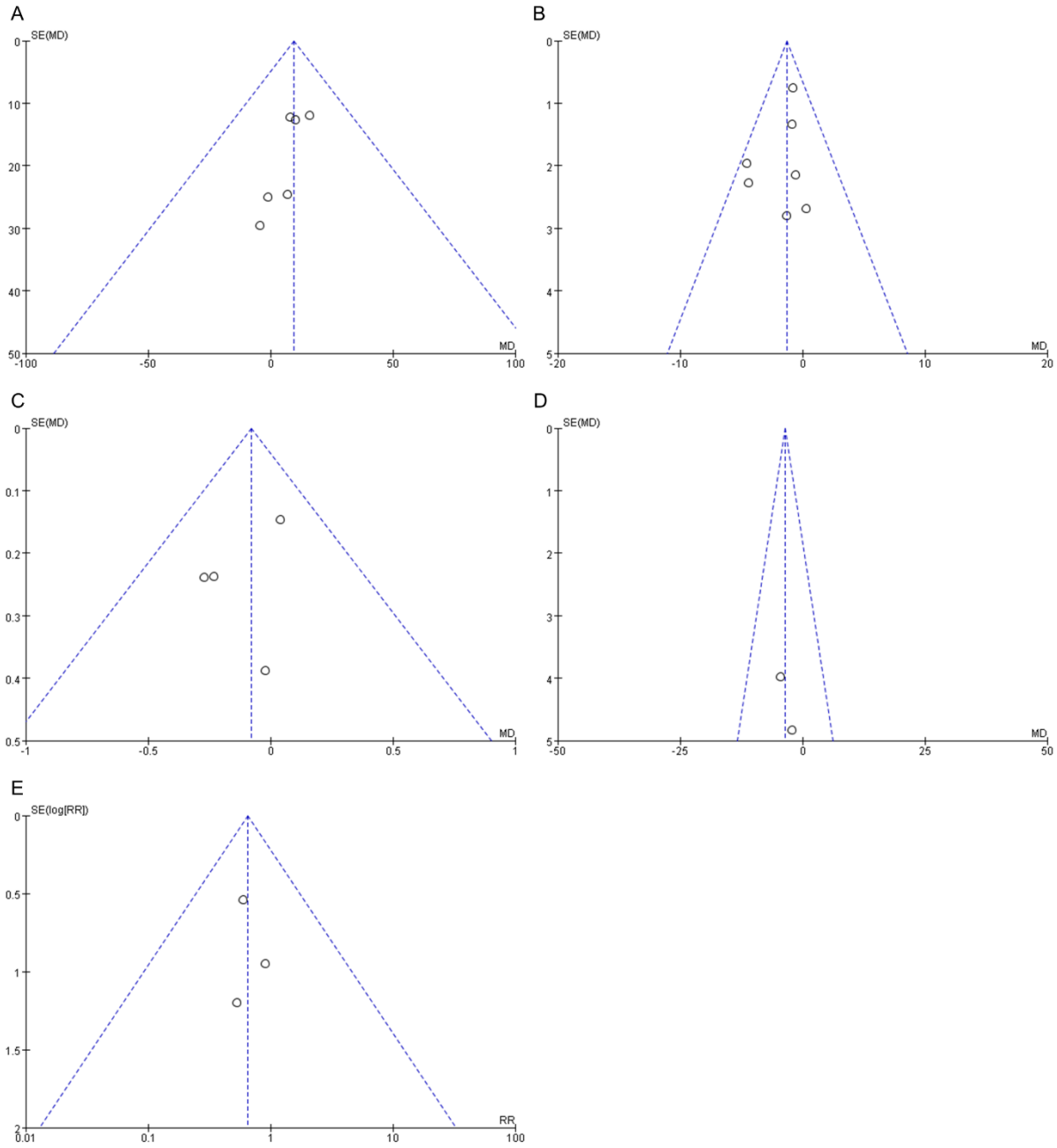


Figure 3. Funnel plots of study outcomes.

A: 6-minute walk test distance. B: COPD assessment test score. C: modified Medical Research Council dyspnea scale. D: St. George's Respiratory Questionnaire. E: hospitalization from exacerbation.



Meta-analysis of clinical outcomes

Figure 4 shows the meta-analysis of study outcomes. In terms of statistical heterogeneity, the χ^2 and I^2 test on each meta-analysis showed no important heterogeneity. Exercise capacity was reported in eight studies in various forms, including the 6MWD, ISWT, number of steps per day, and metabolic equivalents [20-22, 24, 26-29]. Wang et al. reported the ISWT only [29], and Crooks et al. and Spielmanns et al. reported the number of steps per day only [21, 27]; thus, the 6MWD, which was used in five studies, was included in the meta-analysis [20, 22, 24, 26, 28]. There was no statistically significant difference between groups (MD 9.52 m, 95% CI −3.05 to 22.08, $P = 0.14$).

The CAT score was reported in seven studies [20-25, 27]; however, Demeyer et al. reported the CAT score as the median and interquartile range [22]. Thus, the CAT scores from six studies were analyzed [20, 21, 23-25, 27]. The CAT score was significantly lower in the intervention group than that of the control group (MD –1.29, 95% CI –2.39 to –0.20, $P = 0.02$). Dyspnea was measured using the mMRC dyspnea scale in three studies [23-25], and it did not differ between groups (MD –0.08, 95% CI –0.29 to 0.13, $P = 0.45$). The quality of life was assessed in six studies using various questionnaires [21-23, 25, 26, 28], and the SGRQ was reported in two trials [23, 25]. No statistical difference was shown between groups (MD –3.62, 95% CI −9.62 to 2.38, $P = 0.24$).

The exacerbation of COPD was reported as outpatient clinic visit, emergency room visit, or hospitalization in four studies [21, 22, 25, 26]. Among them, hospitalizations were reported in three studies [21, 25, 26]. The frequency of hospitalization was not statistically different between groups (RR 0.65, 95% CI 0.27 to 1.53, $P = 0.32$).

We subsequently performed a subgroup analysis for the 6MWD and CAT score based on the baseline study results (6MWD ≥ 400 m vs. < 400 m, and CAT ≥ 20 vs. < 20) [20-28]. The subgroup analysis did not show statistically significant differences. Furthermore, we performed a subgroup analysis for the CAT score based on the rehabilitation program (exercise program only vs. exercise and self-management program) [20, 21, 23-25, 27]. Among studies offering both exercise and self-management program, the CAT score was significantly lower in the intervention group than that of the control group (MD –2.16, 95% CI –3.93 to –0.39, $P = 0.02$) (Figure 5).

Figure 4. Forest plots of study outcomes between the intervention and control groups.

A: 6-minute walk test distance. B: Chronic obstructive pulmonary disease assessment test score. C: modified Medical Research Council dyspnea scale. D: St. George's Respiratory Questionnaire. E: hospitalization from exacerbation.

Kwon (1) denotes the fixed regimen group, and Kwon (2) denotes the fixed-interactive regimen group.

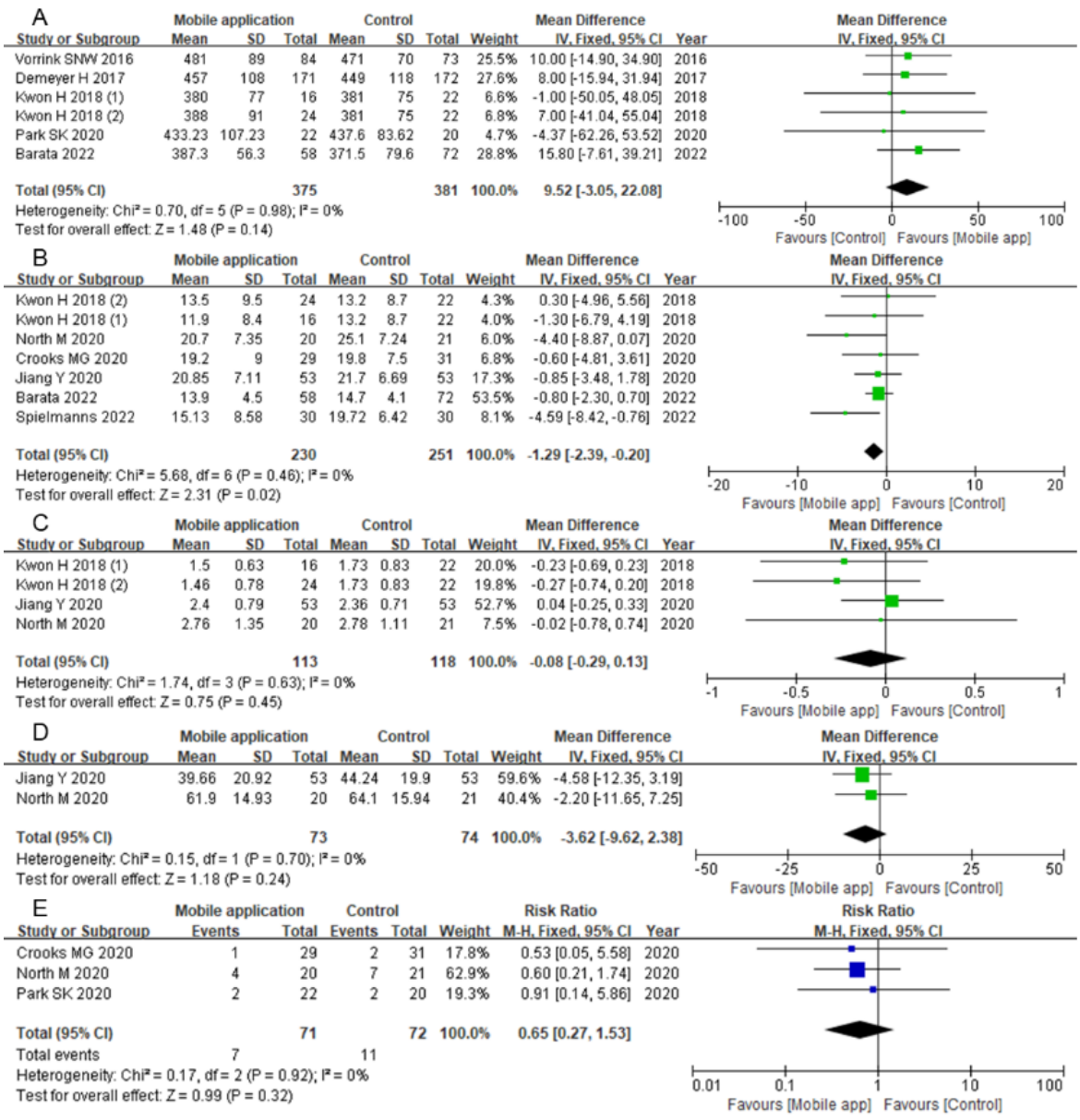
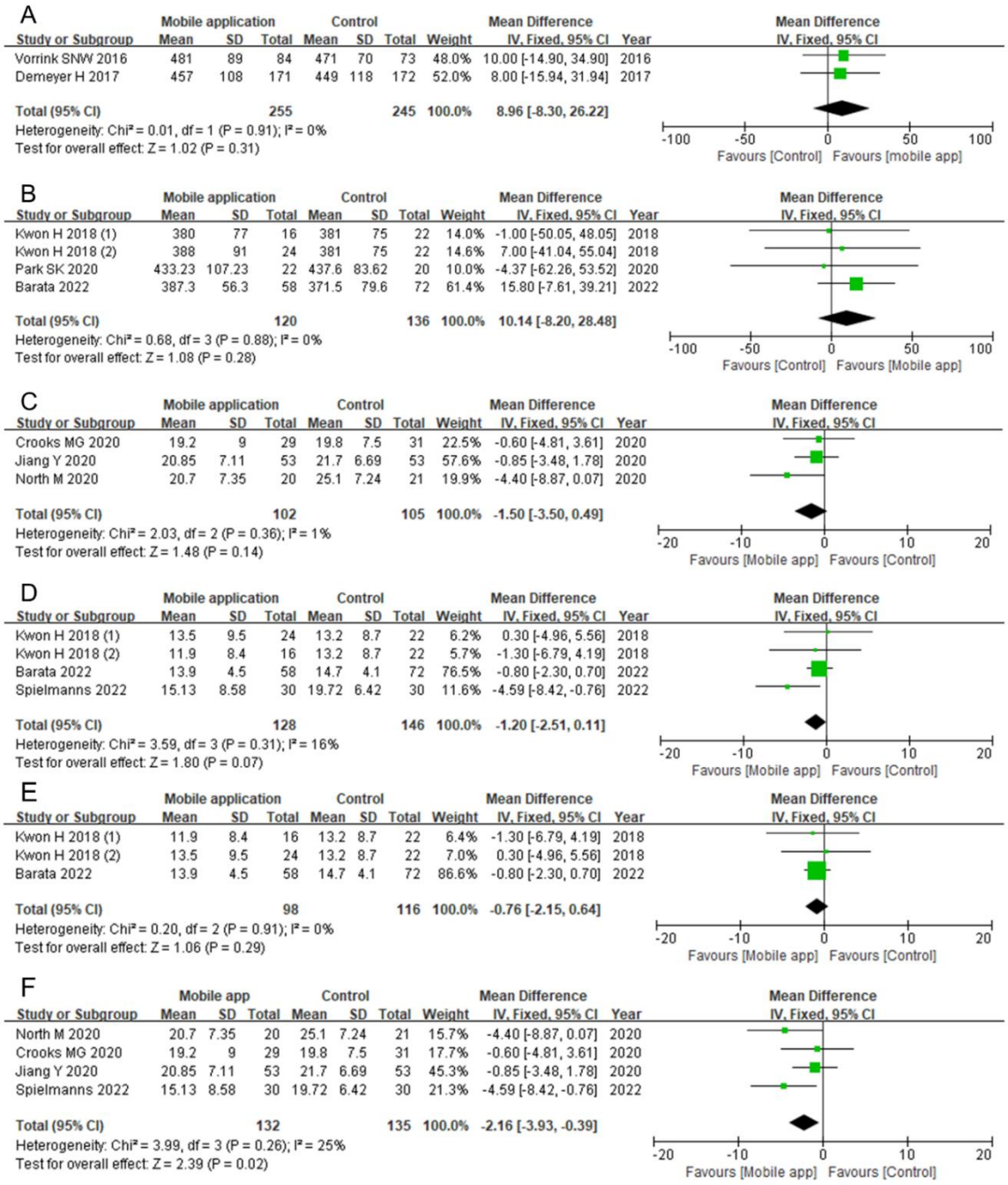


Figure 5. Forest plots of study outcomes between the intervention group and the control group.

A: baseline 6-minute walk test distance ≥ 400 m. B: baseline 6-minute walk test distance < 400 m. C: baseline COPD assessment test score ≥ 20. D: baseline COPD assessment test score < 20. E. COPD assessment test score among studies offering exercise program only. F. COPD assessment test score among studies offering both exercise and self-management program.

Kwon (1) denotes the fixed regimen group and Kwon (2) denotes the fixed-interactive regimen group.



Chapter 2: prospective single arm interventional study

METHODS

Study design

This was a single-center prospective single arm interventional study designed to evaluate the clinical efficacy of smartphone application-based rehabilitation in patients with chronic respiratory disease. In 2022, 50 patients with chronic respiratory disease were recruited from Asan Medical Center. Participants were screened at outpatient clinics of the pulmonology departments. Subsequently, they were assigned to the pulmonary rehabilitation program.

Participants were provided with the smartphone application and performed an application-based self-directed rehabilitation program for the entire intervention duration of 12 weeks. They were evaluated at the baseline and at the end of the rehabilitation.

The study protocol was approved by the Institutional Review Board of Asan Medical Center (Approval number: 2022-0562). Written informed consent was obtained from all participants prior to inclusion. This study complied with the guidelines stipulated in the Declaration of Helsinki and all methods were performed in accordance with the relevant guidelines. Finally, this study was registered in the ClinicalTrials.gov database (NCT05383950, https://clinicaltrials.gov/ct2/show/NCT05383950, 20/05/2022).[2]

[2] This study has been previously published as the following article: Chung C, Kim AR, Kim D, Kwon H, Lee SH, Jang IY, Jo MW, Kang DY, Lee SW. Smartphone application-based rehabilitation in patients with chronic respiratory and cardiovascular diseases. Sci Rep. 2024 Feb 6;14(1):3018. doi: 10.1038/s41598-024-53583-2. PMID: 38321153; PMCID: PMC10847123.

Study participants

Patients with a clinically diagnosed chronic respiratory disease were recruited at the outpatient clinic of Asan Medical Center. The inclusion criteria were as follows: (1) aged 20–80 years; (2) dyspnea score ≥1 in the mMRC; and (3) had a chronic respiratory disease and underwent regular medications. Chronic respiratory diseases included (1) obstructive lung disease, such as asthma and COPD (defined as exhibiting a forced expiratory volume in one second [FEV_1] < 80% of the predicted value or a FEV1/forced vital capacity [FVC] < 0.7), (2) bronchiectasis (defined as bronchiectasis visualized in more than one lobe of the lungs via chest computed tomography), or (3) restrictive lung disease, such as tuberculous lung destruction and interstitial lung disease (defined as an FVC or diffusing capacity for carbon monoxide [DL_{CO}] < 80% of the predicted value) [37]. The exclusion criteria were as follows: (1) an acute exacerbation of underlying disease within four weeks immediately before enrollment; (2) inability to perform the rehabilitation program due to disability; and (3) inability to run the smartphone application.

Smartphone application and rehabilitation program

The smartphone application (SENIORS) was developed by LifeSemantics Corp. (Seoul, Republic of Korea). Briefly, investigators reviewed existing smartphone applications, the relevant scientific literature, and rehabilitation guidelines to design an application and related rehabilitation programs [5, 6, 19, 38, 39]. The application was developed on the Android platform (requiring at least Android 8.0). The application provides exercise programs, records, and partners, and disease education (Figure 6). Pulmonary rehabilitation comprises one level of the exercise program. Each exercise program consisted of two 30-min periods of aerobic and anaerobic exercise, respectively. Participants practiced various core and limb muscle exercises, and the exercise level increased weekly (Table 4). Finally, participants could earn rewards that depended on their exercise records.

Figure 6. Screenshots of the "SENIORS" application.

Shown are: (A) Opening screen (B) Home menu, which displays daily and total exercise records of the user and an exercise partner. (C) Each exercise program could be selected in a daily exercise schedule menu. (D) Rating of perceived exertion (RPE) scale, which were evaluated after each exercise. (E) Instructions for walking exercises. (F) Step counter and timer for walking exercises.

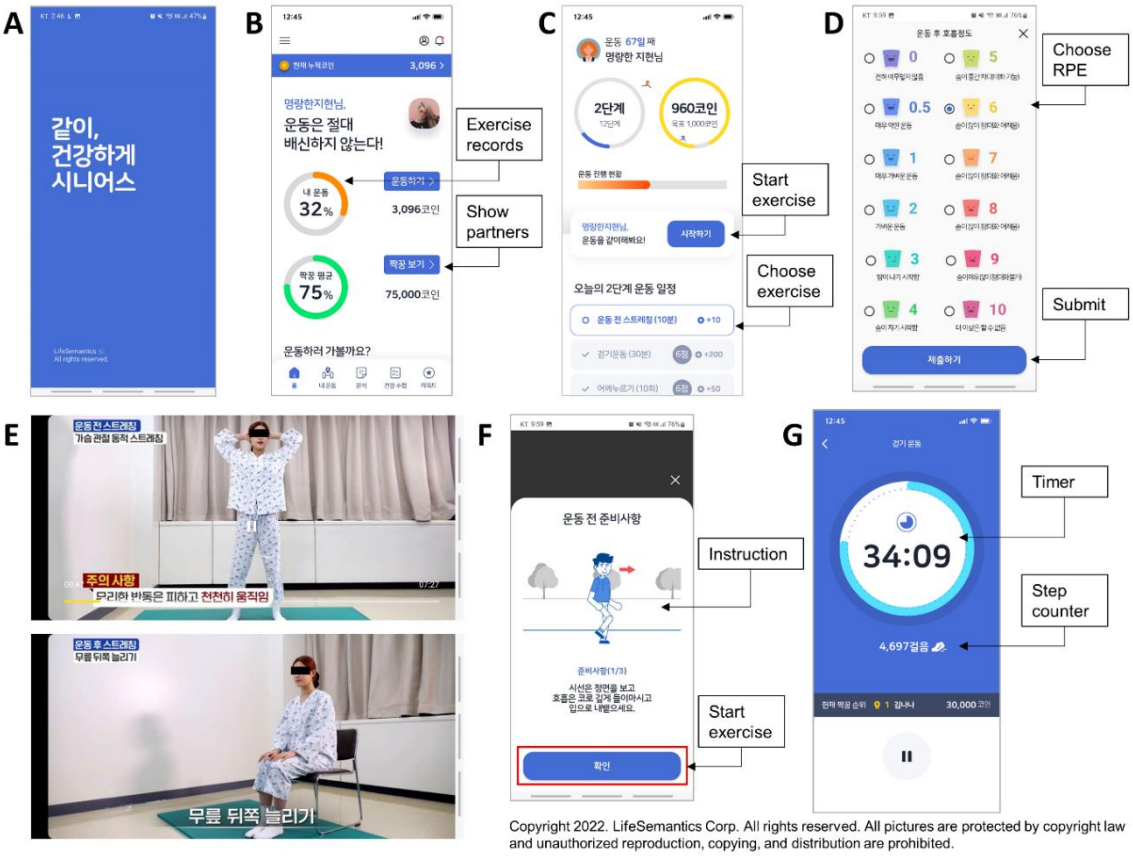


Table 4. Content of anaerobic exercise program

Warm-up stretching	Active ROM exercise	Latex resistance band exercise
Scapulothoracic joint	Hand clap	Band press
Shoulder joint	Wall push-up	Upper back exercise
Elbow joint	Wall lateral pull-down	Lower back exercise
Wrist joint	Knee assisted push-up	Monster walk
Hip joint flexion	Push-up	
Hip joint extension	Ankle dorsiflexion	
Hip joint external rotation	Ankle plantarflexion	
Knee joint	Knee extension	
Ankle joint	Hip adduction	
	Glute bridge	
	Clamshell	
	Wall squat	
	Squat	
	Lunge	
Dumbbell exercise	Cool-down stretching	Aerobic exercise
Biceps exercise	Wrist and elbow	Walking exercise
Triceps exercise	Shoulder	
Pectoralis exercise	Neck	
Deltoid exercise	Hamstring and calf	
	Quadriceps	

ROM: range of motion

Study outcome

The primary outcome was maximal oxygen consumption (VO_2max) as measured by the cardiopulmonary exercise test after the end of rehabilitation [40]. A cardiopulmonary exercise test was performed based on incremental protocol [40], using cycle ergometer (VIAsprint 150P; Carefusion, San Diego, CA, USA) and metabolic cart (Vmax 29; SensorMedics, Yorba Linda, CA, USA). Secondary outcomes after the end of rehabilitation included dyspnea scores, responses to quality of life questionnaires, lung function, and a limb muscle test. Dyspnea symptoms were assessed using the

mMRC dyspnea scale. Quality of life questionnaires included the Euro-QoL 5-Dimension 5-Level (EQ-5D-5L) [41, 42], Health-related Quality of Life Instrument with 8 Items (HINT-8) questionnaire [43-45], and CAT [46]. EQ-5D-5L and HINT-8 index scores were calculated based on previous studies [44, 45, 47]. Lung function was quantified by FVC, FEV1, and DL_{CO} [37]. The limb muscle tests included hand grip strength and limb muscle mass as measured by bioelectrical impedance analysis [48, 49].

Sample size calculation

The sample size was calculated to determine the significance of improvements in the primary outcome between baseline and after rehabilitation based on previous studies. A previous study demonstrated that baseline and after rehabilitation VO_2max measurements had mean values of 13.2 ± 3.0 and 14.8 ± 4.1 ml/kg/min, respectively [50]. We assumed that the participants' mean baseline VO_2max was 13.2 ± 3.0 ml/kg/min, and therefore resulted in a 10% increase after rehabilitation. To achieve an alpha of 0.05 and a power of 80%, at least 41 participants were required. Moreover, to allow a 20% drop-out, 50 participants were required.

Statistical analysis

Continuous variables were presented as medians [interquartile range] and were compared using Wilcoxon signed rank tests. Categorical variables were presented as counts (percentages). All *P*-values were two-tailed, with the threshold of statistical significance set to $P < 0.05$. All statistical analyses were performed using SPSS version 26.0 (Statistical Package for the Social Sciences, IBM SPSS Corporation, Armonk, NY, USA).

RESULTS

Participant baseline characteristics

Figure 7 shows the flowchart of the study process. A total of 48 participants were recruited, and 46 started rehabilitation. Finally, 41 visited after rehabilitation, resulting in 20% withdrawal rate [51, 52]. Table 5 shows the baseline characteristics of the study participants. Their median age was 67.0 (IQR, 62.0–73.0) years and 32 (78.0%) were men. Twenty-nine (70.7%) participants had a history of smoking. Of the 41 participants with chronic respiratory disease, 33 had obstructive lung disease and eight had bronchiectasis.

Figure 7. Study flowchart.

One patient in the chronic respiratory disease group experienced a leg fracture; however, this was unrelated to the rehabilitation.

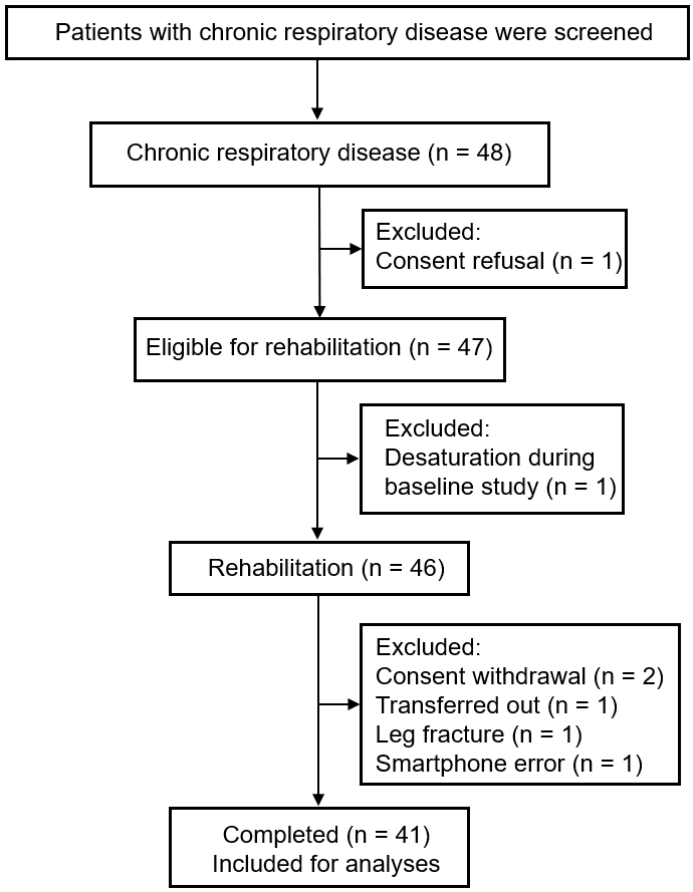


Table 5. Baseline characteristics of participants

	Chronic respiratory disease (n = 41)
Age (years)	67.0 [62.0–73.0]
Male	32 (78.0)
Body weight (kg)	64.8 [54.3–72.6]
Height (cm)	167.0 [159.5–171.0]
BMI (kg/m^2)	23.7 [20.2–26.2]
Ever-smoker	29 (70.7)
Underlying disease	
Diabetes mellitus	3 (7.3)
Hypertension	15 (36.6)
Dyslipidemia	12 (29.3)
Malignancy	4 (9.8)

Data are presented as median [interquartile range] or count (%), unless otherwise indicated.

BMI, body mass index.

Clinical parameters of participants

Among participants with chronic respiratory diseases, their VO_2max was significantly improved (P = 0.049). Moreover, we observed significant improvement in CAT score (P < 0.001), EQ-5D-5L index (P = 0.001), and HINT-8 index (P < 0.001; Table 6, Figure 8). No participants experienced disease exacerbation or musculoskeletal injury related to rehabilitation activities during the study period.

Table 6. Clinical parameters of participants with chronic respiratory disease

n = 41	Baseline	After rehabilitation	P value
*VO_2max (ml/kg/min, n = 38)	13.7 [10.1–16.3]	15.4 [12.0–19.2]	0.049
mMRC dyspnea scale	2 [1–2]	1 [1–2]	0.062
CAT score	14 [10–20]	6 [3–9]	<0.001
EQ-5D-5L index	0.795 [0.724–0.862]	0.862 [0.808–1.000]	0.001
HINT-8 index	0.784 [0.711–0.825]	0.855 [0.803–0.895]	<0.001

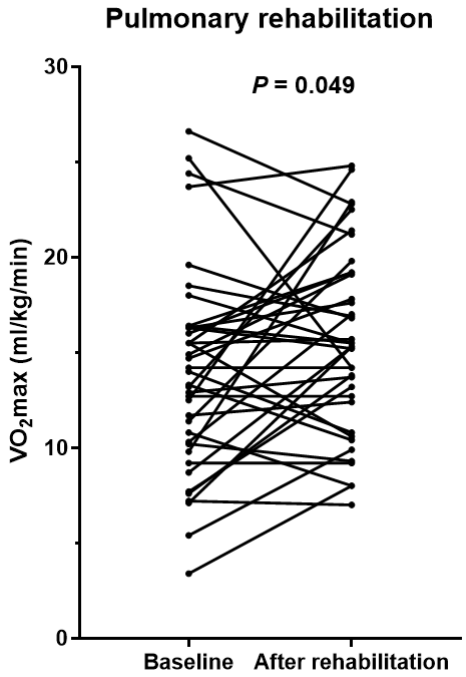
FEV1 (%predicted)	61.0 [32.0–72.0]	50.0 [33.0–71.5]	0.031
FVC (%predicted)	77.0 [64.5–90.0]	75.0 [64.5–85.0]	0.021
DL_{CO} (%predicted, n = 40)	56.5 [40.3–73.5]	55.5 [41.3–68.5]	0.265
Hand grip strength (kg)	39.0 [31.0–46.0]	40.0 [34.0–46.0]	0.442
Limb muscle mass (kg)	19.3 [17.0–22.2]	20.2 [17.5–22.3]	0.081
Upper limb	4.7 [3.8–5.7]	5.1 [4.1–5.9]	<0.001
Lower limb	14.8 [12.7–16.5]	14.9 [12.7–16.6]	0.510

Data are presented as median [interquartile range].

*VO_2max was measured using a cardiopulmonary exercise test.

VO_2max, maximal oxygen consumption; mMRC, mMRC Modified Medical Research Council; CAT, COPD Assessment Test; EQ-5D-5L, Euro-QoL 5-Dimension 5-Level; HINT-8, Health-related Quality of Life Instrument with 8 Items; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide.

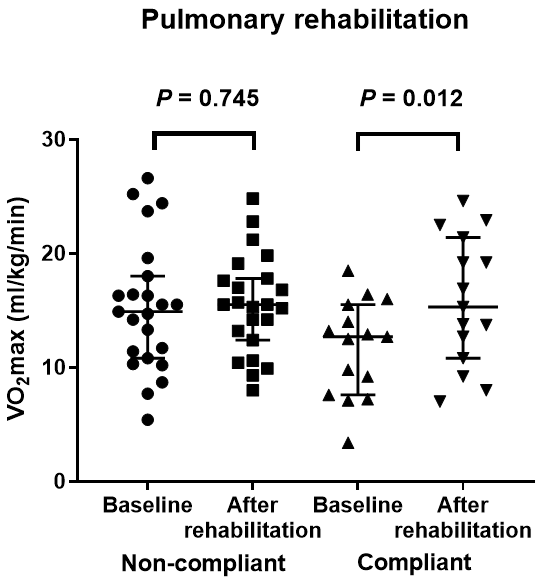
Figure 8. Change in maximal oxygen consumption (VO_2max) of participants.



Participant compliance during rehabilitation

Participants who performed both aerobic and anaerobic exercises ≥ 30% of the entire study period of 84 days, based on the log data of application, were considered to be compliant participants. Among participants with chronic respiratory disease, 17 (41.5%) were compliant (aerobic exercise, median 19.0 days [IQR, 1.0–47.3] and anaerobic exercise, median 36.0 days [IQR, 2.8–56.3]). We observed significant improvement in VO_2peak only in these compliant participants ($P = 0.012$).

Figure 9. Change in maximal oxygen consumption (VO_2max) of participants according to compliance.



HINT-8 distribution

To evaluate which dimensions of quality of life improved during rehabilitation, we subsequently analyzed the distribution of HINT-8 results by item and level. Participants with chronic respiratory disease reported significant improvements in all dimensions measured by HINT-8 except for climbing stairs (Table 7).

Table 7. HINT-8 distribution by item and level in participants.

HINT-8 item	Chronic respiratory disease (n = 41)		
	Baseline	After rehabilitation	*P* value
Climbing stairs	2 [2-3]	2 [2-3]	0.072
Pain	1 [1-2]	1 [1-1]	0.005
Vitality	2 [2-3]	1 [1-2]	<0.001
Working	2 [1-2]	1 [1-2]	0.001
Depression	1 [1-2]	1 [1-1]	0.022
Memory	2 [1-2]	1 [1-2]	0.002
Sleep	1 [1-2]	1 [1-1]	0.008
Happiness	2 [2-3]	1 [1-3]	0.003

Data are presented as median [interquartile range].

HINT-8, Health-related Quality of Life Instrument with 8 Items.

Ease-of-use of the application

Approximately 80% of participants indicated that they perceived the application as easy to use (i.e., "very easy," 78.0% of participants; "easy," 4.9% of the participants) and were accustomed to using the application within three days (i.e., 65.9% and 12.2% within one and three days, respectively). Moreover, approximately two-thirds (65.9%) of the participants indicated that they wanted to use the application if it were commercially available. The most attractive point of the application was that it was a physician-designed exercise program (as indicated by 63.4% of respondents, Table 8).

Table 8. Application service evaluation questionnaire.

Question	N = 41
How easy and convenient was the application service provided to you?	
Very easy	32 (78.0%)
Easy	2 (4.9%)
Difficult	5 (12.2%)
Very difficult	2 (4.9%)
How long did it take to adapt to using the app after installation?	

Within 1 day	27 (65.9%)
Within 3 days	5 (12.2%)
Within 1 week	3 (7.3%)
Within 2 weeks	1 (2.4%)
Difficult to use	5 (12.2%)
Do you want to use the application service if it is commercialized?	
Yes	27 (65.9%)
No	14 (34.1%)
If yes, why do you want to use it? (Multiple choice)	
I think the app would be easy and fun to use.	2 (7.4%)
If I have the app, I think I'll exercise more often.	18 (66.7%)
I think exercising with others would be more effective than doing it alone.	6 (22.2%)
I can get a reward if I exercise.	1 (3.7%)
If no, why do you want not to use it (Multiple choice)	
I think that the app is difficult and complex to use.	2 (14.3%)
I don't need it because I'm still receiving rehabilitation and hospital treatment.	2 (14.3%)
I prefer to exercise alone and not with others.	6 (42.9%)
I can’t use my phone app very well.	4 (28.6%)
What was the most attractive point of the application?	
It is easier to use and understand than other apps.	4 (9.8%)
It's fun to choose a partner to exercise with.	0 (0.0%)
It's good to be able to check how much I've exercised.	3 (7.3%)
Being able to get a reward helps me motivate myself.	8 (19.5%)
It is good that the physicians designed the exercise and adjusted it for my condition.	26 (63.4%)

Data are presented as count (%).

Chapter 3: randomized controlled trial study

METHODS

Study design

This single-center single-blind randomized controlled trial study evaluated the efficacy of smartphone application-based rehabilitation programs in patients with chronic respiratory diseases. Altogether, 90 participants were recruited from Asan Medical Center in 2023. Participants were recruited from the outpatient clinic of the pulmonology departments. Participants were randomly allocated to the intervention or control groups at the ratio of 2:1 (60 for the intervention group and 30 for the control group).

The study duration was 12 weeks. The intervention group was provided with a smartphone application and undergo the application-based pulmonary rehabilitation for 12 weeks. They were provided by daily one pack of protein supplement drink during study period. The control group received the usual outpatient medical treatment without rehabilitation. All participants were evaluated twice at baseline and at the end of rehabilitation (after 12 weeks).[3]

The study protocol was approved by the Institutional Review Board of Asan Medical Center (Approval number: 2022-1460). The detailed study protocols were described previously [35)]. Written informed consent was obtained from all participants prior to inclusion. This study complied with the guidelines stipulated in the Declaration of Helsinki and all methods were performed in accordance

[3] This study protocol has been previously published as the following article: Chung C, Kim AR, Jang IY, Jo MW, Lee S, Kim D, Kwon H, Kang DY, Lee SW. Smartphone application-based rehabilitation in patients with chronic respiratory and cardiovascular diseases: a randomised controlled trial study protocol. BMJ Open. 2023 Sep 20;13(9):e072698. doi: 10.1136/bmjopen-2023-072698. PMID: 37730392; PMCID: PMC10514628.

with the relevant guidelines. This study was registered in the ClinicalTrials.gov database (NCT05610358, https://clinicaltrials.gov/ct2/show/NCT05610358).

Study participants and randomization

Adult patients with a physician-diagnosed chronic respiratory disease were screened at the outpatient clinic by attending physicians. The inclusion criteria were as follows: (1) aged 20–80 years; (2) dyspnea symptom score ≥ mMRC dyspnea scale 1; (3) with chronic respiratory disease; and (4) provided written informed consent. Chronic respiratory diseases include (1) obstructive lung disease, such as COPD and asthma (defined as [1] $FEV_1/FVC < 0.7$ or [2] $FEV_1 < 80\%$ predicted in PFT), (2) restrictive lung disease, such as interstitial lung disease, tuberculous destroyed lung, and history of lung resection (defined as [1] $FVC < 80\%$ predicted or [2] $DL_{CO} < 80\%$ predicted in PFT), or (3) bronchiectasis (defined as bronchiectasis in more than one lobe on chest computed tomography regardless of lung function).[37] The exclusion criteria were be as follows: (1) history of an acute disease exacerbation within 4 weeks prior to enrolment; (2) having disabilities which disable them to participate in the rehabilitation program; (3) unable to run smartphone applications or iPhone users; (4) pregnant or breastfeeding; (5) unsuitable to participate in the study per assessment by the physician on duty; and (6) consent refusal.

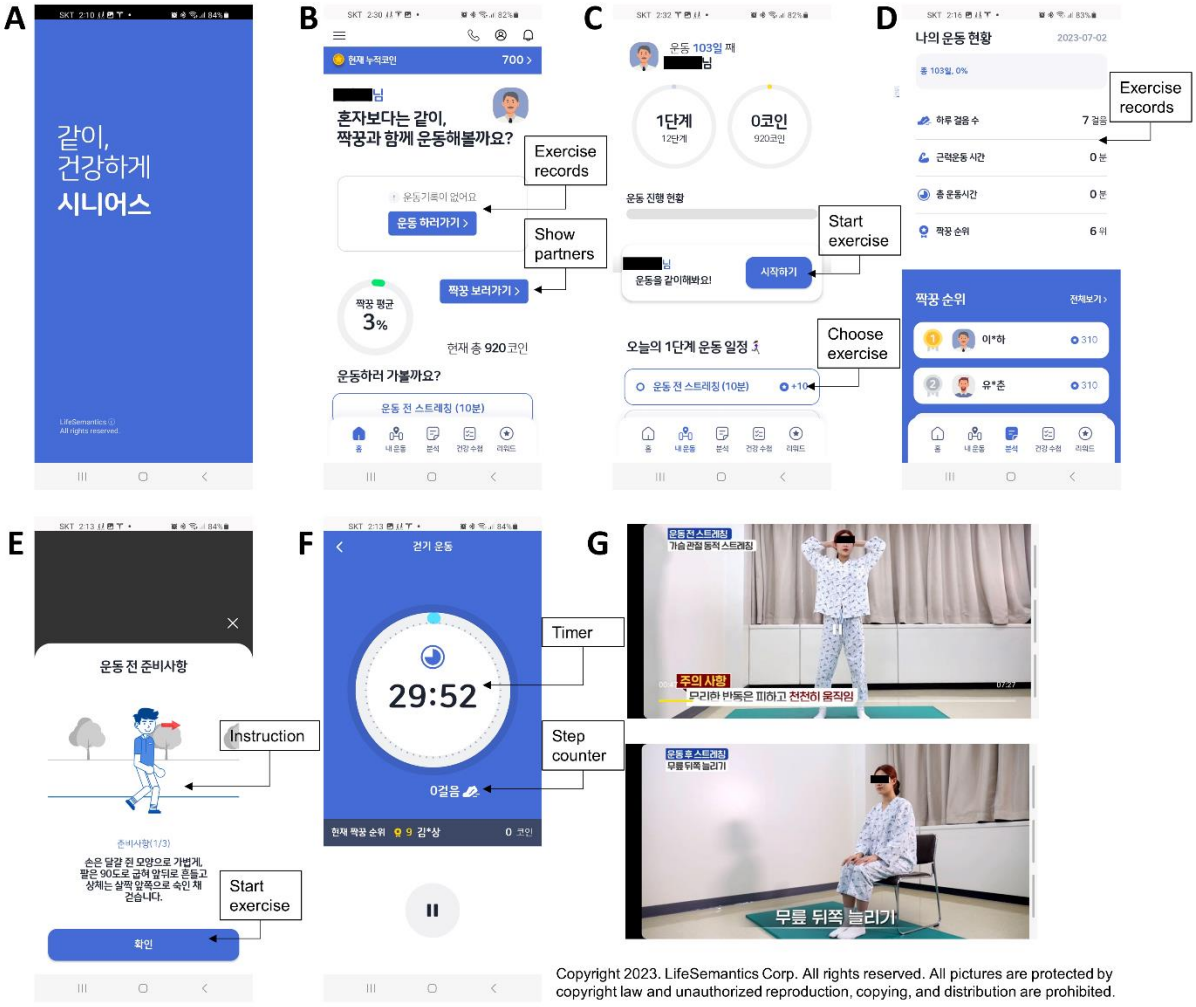
At enrolment, participants were allocated to the intervention or control group at the ratio of 2:1 (60 and 30 in the intervention group and control groups, respectively). The random sequence was prepared with varying block sizes of 3, 6, or 9 using Microsoft 365 Excel (Microsoft, Redmond, WA, USA). Clinical research coordinators conducted the group allocation using a list of random numbers. Then, participants practiced their rehabilitation program. The investigators were blinded to the group allocation until the end of the study.

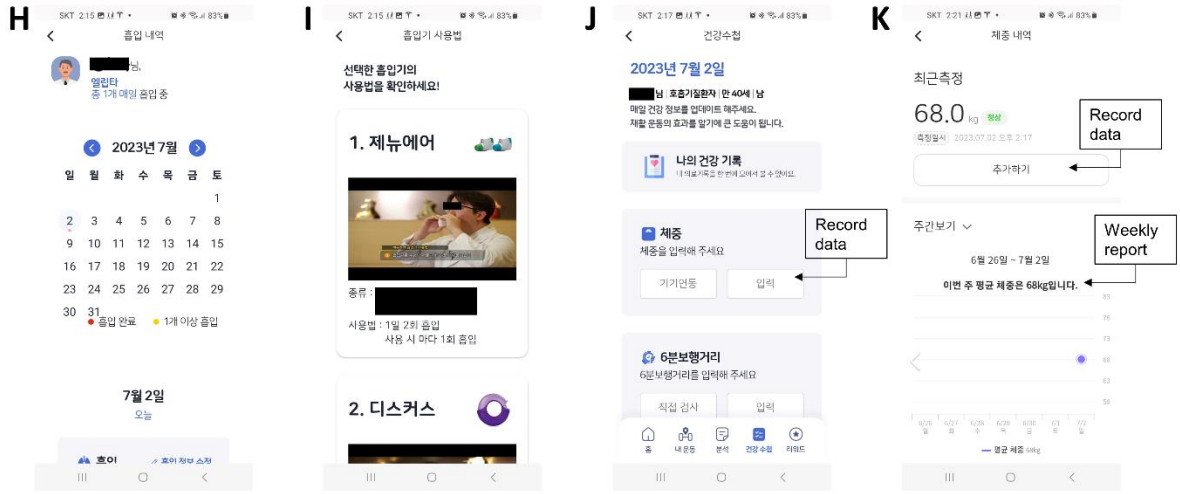
Smartphone application development

The smartphone application (SENIORS) was newly developed for our study by investigators and LifeSementics Corp. (Seoul, Republic of Korea). The investigators reviewed the existing smartphone applications for healthcare management, relevant literature, rehabilitation programs and guidelines, and patient educational resources to determine the content and design of the application.[5, 6, 19, 38, 39] The content and design were discussed throughout many meetings between investigators and professional developers. The application was developed on an Android platform (minimum required version: Android 8.0). The font size and user interfaces were designed for comfortable viewing in consideration of the old age of potential participants. The investigators tested a prototype application and submitted bug reports several times. Additionally, several potential participants with chronic respiratory diseases tested a prototype application and gave their feedback. After system refinements and bug repairs, the final version of the application was uploaded to Google Play Store and prepared for field testing. The application provided exercise program, exercise records, disease education, medication diary, and health data diary (Figure 10). Particularly, instruction videos for inhaler use, medication diary, and health data diary menu were updated from the previous version (Figure 6).

Figure 10. Screenshots of the "SENIORS" application.

(A) Opening screen (B) Home menu displays the exercise records of the user and exercise partners. (C) Exercise menu displays the exercise level and daily exercise program. (D) Exercise report displays the exercise records of the user and exercise partners. (E) Instructions for walking exercises. (F) Timer and step counter for walking exercises. (G) Instruction videos for anaerobic exercise. (H) Medication diary displays the monthly medication records. (I) Instruction videos for inhaler users. (J) Health diary, in which users can record their anthropometric data. (K) Health dairy displays users' anthropometric data.





Rehabilitation program

The investigators reviewed the existing rehabilitation program in Asan Medical Center and relevant guidelines to design the rehabilitation programs.[38, 39] After many meetings, the investigators designed 12-week pulmonary rehabilitation programs and recorded instruction videos. Pulmonary rehabilitation provided one level of exercise program according to the participant's baseline exercise capacity and symptom scores. Each exercise program consisted of 30 minutes of aerobic exercise and 20–30 minutes of anaerobic exercise. During the aerobic exercise, participants walked outdoors with their smartphone application turned on; thus, the exercise duration and step counts were monitored and recorded in real time. Thereafter, participants performed indoor anaerobic exercise following the instruction video on the smartphone application. Anaerobic exercise consisted of warm-up stretching, main exercise, and cool-down stretching. Participants performed various limb and core muscle exercises, and the intensity of exercise increased weekly. Participants were able to compare their exercise records with those of the other participants on the bulletin of application. The detailed exercise programs are listed in Table 4.

Data collection and study outcome

At the time of enrolment, the clinical research coordinators collected data on the participants' baseline characteristics and demographics, including sex, age, weight, height, body mass index, smoking history, underlying disease, and history of lung resection surgery. Participants were evaluated for their study outcomes twice according to the abovementioned schedule. The study outcomes were measured twice, before and after the rehabilitation. Furthermore, the cost questionnaire were collected twice at baseline and after the 12-week rehabilitation program to evaluate the cost distribution on intervention. Additionally, the intervention group submitted their feedback to the application service via questionnaire for further development after the end of the study.

The primary outcomes were exercise capacity, such as VO_2 max measured by cardiopulmonary exercise test after the 12-week rehabilitation program.[40] A cardiopulmonary exercise test was

performed based on incremental protocol using cycle ergometer (VIAsprint 150P; Carefusion, San Diego, CA, USA) and metabolic cart (Vmax 29; SensorMedics, Yorba Linda, CA, USA) [40]. In case of severely impaired lung function (e.g., FEV_1 < 30% predicted), resting desaturation (e.g., oxygen saturation by pulse oximetry < 88%), or long term oxygen therapy, the 6-minute walk test distance could replace the VO_2max considering participants' safety.[53] Additionally, the primary outcomes included the CAT [46]. To evaluate the long-term effects of rehabilitation, CAT of the intervention group was measured again at 12 weeks after the end of rehabilitation.

The secondary outcomes included quality of life questionnaires, symptom scores, and PFT and limb muscle test findings after the 12-week rehabilitation program. Quality of life was evaluated using the EQ-5D-5L,[41, 42, 54] and HINT-8 questionnaires.[43, 44] The EQ-5D-5L and HINT-8 index scores were calculated based on previous studies.[44, 47, 55] Symptom scores included the mMRC dyspnea scale. PFT evaluated the patients' FVC, FEV_1, and DL_{CO}.[37] The limb muscle test included handgrip strength and limb muscle mass as measured by bioelectrical impedance analysis.[48, 49] The timeline of data collection is presented in Table 9.

Table 9. Timeline of data collection.

	Visit 1 Baseline	Visit 2 12 weeks later
Medical history	●	
Informed consent	●	
Body measurements	●	
Symptom score	●	●
Exercise capacity test	●	●
Pulmonary function test	●	●
Limb muscle test	●	●
Quality of life questionnaire	●	●
Cost questionnaire	●	●

Data management and monitoring

All discriminable data were removed from the original data, and each participant was assigned an anonymized study identification number prior to reporting to the principal investigator. Trained clinical research coordinators collected the participants' data. Cost questionnaire data were analyzed by specialists in preventive medicine. Access to the study data was limited to only the attending investigators and clinical research coordinators approved by the IRB of Asan Medical Center. During the study period, the process of data collection was periodically monitored by the principal investigator. A research meeting involving the principal investigator, attending investigators, and clinical research coordinators was held weekly to monitor the study process and data collection. The study protocol could be modified in the research meeting and each modification was granted approval from the IRB.

Sample size calculation

Participants were randomly allocated to the intervention or control groups at the ratio of 2:1. The sample size was estimated to determine a clinically significant improvement in the exercise capacity from baseline to follow-up based on previous reports. As for the pulmonary rehabilitation, a previous study showed that the baseline and follow-up VO_2 max had mean values of 13.2 ± 3.0 and 14.8 ± 4.1 ml/kg/min, respectively.[50] We assumed that the participants' mean baseline VO_2max as 13.0 ± 4.0 ml/kg/min, indicating a 20% increase after the rehabilitation. To achieve an alpha of 0.05 and a power of 80%, at least 42 and 21 patients were required for the intervention and control groups, respectively. To allow a 20% drop-out rate, 81 participants (54 for the intervention group and 27 for the control group) were considered necessary for rehabilitation program.

Trial status

Enrolment began in January 2023 with the aim of completing enrolment in 2023. The 12 weeks of follow-up and the final data collection completed in 2024. This study is registered in the ClinicalTrials.gov (NCT05610358, https://clinicaltrials.gov/ct2/show/NCT05610358).

Patient and public involvement

No patient was involved.

Statistical analysis

Study outcomes at the end of 12-week rehabilitation were compared with those at baseline to assess the efficacy of the intervention. Continuous variables were presented as mean ± standard deviation or median [interquartile range] and compared using the Student's t-test or the Mann-Whitney test. Categorical variables were presented as numbers (percentages) and compared by using the χ^2 or Fisher's exact test. All *P*-values were two-tailed, with statistical significance set at $P < 0.05$. All statistical analyses were performed using SPSS software (version 26.0; Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA) and MedCalc® Statistical Software version 22.021 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2024).

RESULTS

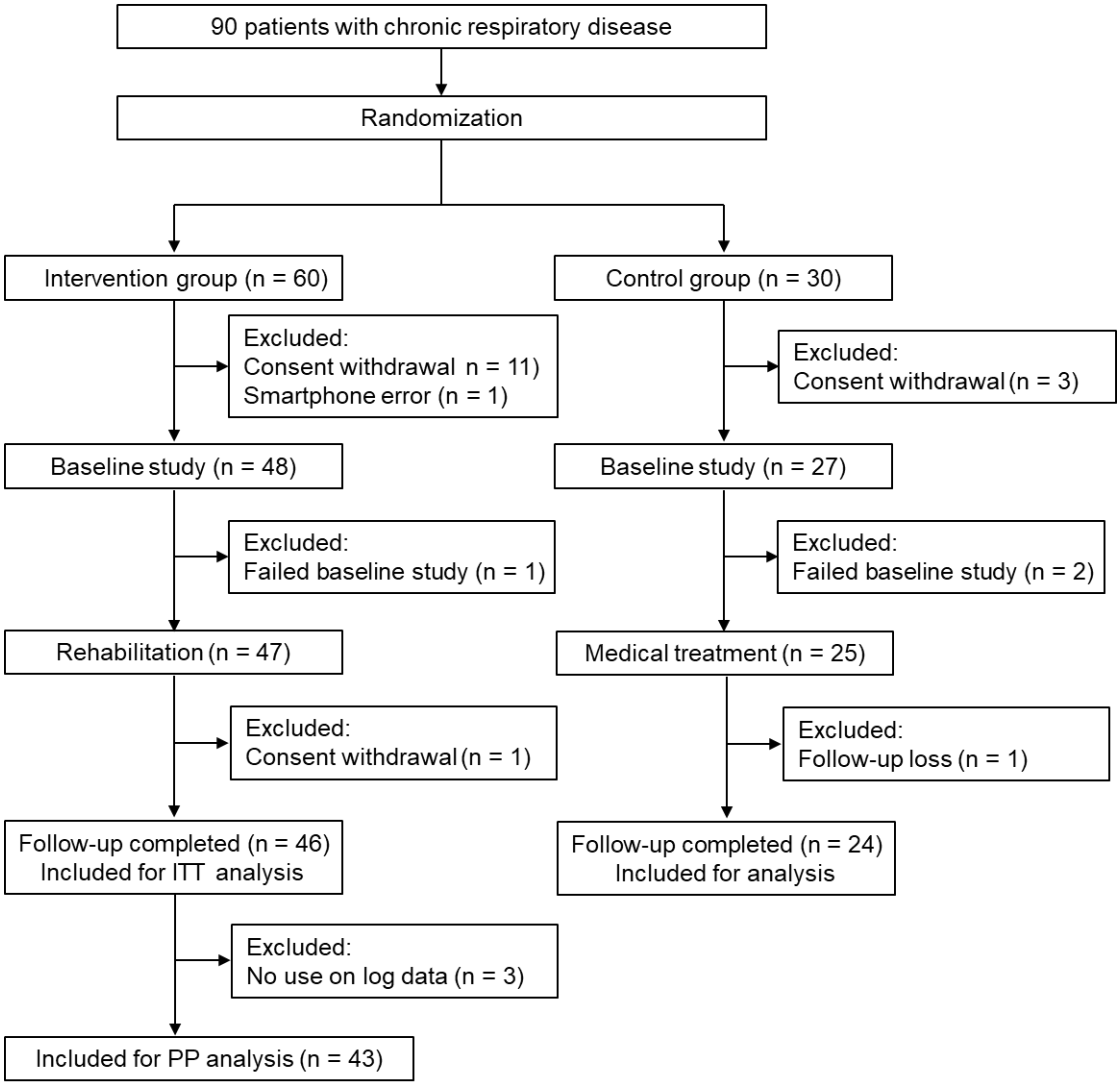
Study process and baseline characteristics

A total of 90 participants were recruited and allocated per the intervention and control group (60 and 30, respectively). Among 75 participants eligible for baseline study, 72 completed baseline study. Among the intervention group, 47 started rehabilitation and 46 completed follow-ups (included in the intention to treat analysis). Thereafter, 3 were identified having no application-use history on log data,

and 43 were included in the per protocol analysis. Among the control group, 25 started follow-up and 24 completed follow-ups. In total, 77.8% participants completed follow-ups (Figure 11). No participants reported musculoskeletal injury or disease exacerbation related to rehabilitation program during the study period.

Table 10 shows the baseline characteristics of the study participants. Their median age was 65.0 (IQR 61.0–72.0) years and 48 (68.6%) were men. Forty-four (62.9%) participants had smoking history. Approximately three quarters of participants (53, 75.7%) had obstructive lung disease.

Figure 11. Study flowchart.



ITT, intention to treat; PP, per protocol.

Table 10. Baseline characteristics of participants.

	Total (n = 70)	Intervention (n = 46)	Control (n = 24)	*P* value
Age (years)	65.5 [61.0–72.0]	64.0 [60.0–68.0]	67.5 [62.5–74.5]	0.143
Male sex	48 (68.6)	35 (76.1)	13 (54.2)	0.063
Body weight (kg)	61.0 [54.0–71.4]	61.0 [54.0–71.8]	59.0 [53.0–70.2]	0.397
Height (cm)	167.0 [160.0–172.0]	168.1 [161.0–172.0]	164.5 [157.0–168.0]	0.036
BMI (kg/m^2)	23.0 [20.0–25.4]	23.0 [19.8–25.3]	22.9 [20.8–25.6]	0.892
Ever-smoker	44 (62.9)	32 (69.6)	12 (50.0)	0.110
Respiratory disease				0.289
Obstructive	53 (75.7)	34 (73.9)	19 (79.2)	
Bronchiectasis	14 (20.0)	11 (23.9)	3 (12.5)	
Restrictive	3 (4.3)	1 (2.2)	2 (8.3)	
Comorbidities				
Diabetes mellitus	9 (12.9)	5 (10.9)	4 (16.7)	0.481
Hypertension	20 (28.6)	13 (28.3)	7 (29.2)	0.937
Dyslipidemia	18 (25.7)	11 (23.9)	7 (29.2)	0.636
Malignancy	6 (8.6)	2 (4.3)	4 (16.7)	0.171
Lung resection	3 (4.3)	1 (2.2)	2 (8.3)	0.269

Data are presented as median [interquartile range] or count (%), unless otherwise indicated.

BMI, body mass index.

Clinical parameters of participants

In the per protocol analysis, the baseline CAT score of the intervention group was higher than that of the control group (median 16.0 vs 11.0, $P = 0.076$), although not statistically significant. At follow-up, it was significantly lower in the intervention group compared to the control group (median 7.0 vs 10.0, $P = 0.039$). Furthermore, the International Physical Activity Questionnaire (IPAQ) (median 1488.0 vs 1164.0, $P = 0.037$) and mMRC dyspnea scale (median 1.0 vs 2.0, $P = 0.010$) of the

intervention group significantly improved compared with those of the control group (Table 11). At 12 weeks after the end of rehabilitation, CAT score of the intervention group was not significantly different from that of the end of rehabilitation (median 7.0 vs 8.0, $P = 0.771$, Figure 12). In the intention to treat analysis, statistically significant difference was noted in mMRC dyspnea, but not in CAT score and IPAQ (Table 12).

Comparing clinical outcomes of the intervention group between the baseline and follow-up, CAT score, IPAQ, mMRC dyspnea scale, EQ-5D-5L index, and HINT-8 index significantly improved compared with those of the control group (Table 13, 14).

Table 11. Comparison of clinical outcomes of participants between the intervention and control group (per protocol analysis).

	Total (n = 67)	Intervention (n = 43)	Control (n = 24)	*P* value
Baseline				
*VO_2max (ml/kg/min, n = 65)	15.3 [11.5–18.3]	15.7 [12.7–19.2]	13.4 [9.0–16.1]	0.064
CAT score	14.0 [8.0–19.0]	16.0 [9.5–20.0]	11.0 [7.5–17.0]	0.076
IPAQ (n = 65)	693.0 [23.1–1535.3]	792.0 [26.0–1737.8]	445.5 [11.6–1188.0]	0.230
mMRC dyspnea scale	1.0 [1.0–2.0]	1.0 [1.0–2.0]	2.0 [1.0–2.0]	0.532
EQ-5D-5L index	0.816 [0.752–0.862]	0.816 [0.743–0.861]	0.822 [0.777–1.000]	0.412
HINT-8 index	0.804 [0.750–0.862]	0.792 [0.735–0.859]	0.811 [0.784–0.863]	0.162
FEV1 (%predicted)	51.0 [42.5–65.8]	57.0 [44.3–66.8]	49.0 [38.5–56.0]	0.110
FVC (%predicted)	73.0 [66.3–87.5]	75.0 [66.3–87.5]	72.0 [64.0–86.0]	0.388
DL_{CO} (%predicted)	58.0 [45.0–67.0]	61.0 [53.5–67.0]	50.0 [45.0–65.0]	0.295
Hand grip strength (kg)	32.0 [25.7–39.2]	33.7 [28.0–41.0]	27.9 [21.5–37.1]	0.121
Limb muscle mass (kg)				
Upper limb	4.8 [3.5–5.7]	5.0 [3.9–6.0]	4.3 [3.3–5.5]	0.058
Lower limb	15.0 [12.4–16.8]	15.6 [13.1–17.0]	14.5 [10.8–15.6]	0.049
Follow-up				

*VO_2max (ml/kg/min, n = 65)	12.9 [11.0–16.1]	14.0 [10.6–18.4]	12.7 [11.3–13.7]	0.244
CAT score	8.0 [5.0–16.8]	7.0 [4.0–15.0]	10.0 [6.5–18.5]	0.039
IPAQ (n = 62)	1386.0 [876.0–2772.0]	1488.0 [1250.3–3027.8]	1164.0 [618.8–2205.0]	0.037
mMRC dyspnea scale	1.0 [1.0–2.0]	1.0 [1.0–1.8]	2.0 [1.0–2.0]	0.010
EQ-5D-5L index	0.862 [0.786–1.000]	0.871 [0.814–1.000]	0.829 [0.768–1.000]	0.225
HINT-8 index	0.821 [0.751–0.876]	0.828 [0.767–0.891]	0.795 [0.728–0.848]	0.088
FEV1 (%predicted)	50.0 [40.5–67.8]	58.0 [43.5–69.0]	45.0 [37.5–54.5]	0.060
FVC (%predicted)	73.0 [67.3–87.5]	77.0 [69.3–87.5]	71.5 [63.0–86.0]	0.221
DL_{CO} (%predicted, n = 66)	61.0 [49.0–71.0]	62.0 [51.0–71.8]	57.0 [48.0–64.8]	0.203
Hand grip strength (kg)	32.7 [22.7–39.5]	33.3 [27.7–41.7]	24.0 [20.6–37.0]	0.075
Limb muscle mass (kg)				
Upper limb	4.6 [3.6–5.9]	4.8 [3.8–6.1]	4.3 [3.5–5.5]	0.172
Lower limb	15.0 [12.2–16.8]	15.4 [13.0–16.9]	14.4 [10.8–16.0]	0.078

Data are presented as median [interquartile range].

*VO_2max was measured using a cardiopulmonary exercise test.

VO_2max, maximal oxygen consumption; CAT, chronic obstructive lung disease assessment test; mMRC, mMRC Modified Medical Research Council; IPAQ, International Physical Activity Questionnaire; EQ-5D-5L, Euro-QoL 5-Dimension 5-Level; HINT-8, Health-related Quality of Life Instrument with 8 Items; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide.

Table 12 Comparison of clinical outcomes of participants between the intervention and control group (intention to treat analysis).

	Total (n = 70)	Intervention (n = 46)	Control (n = 24)	*P* value
Baseline				

*VO_2max (ml/kg/min, n = 68)	15.0 [11.5–18.0]	15.5 [12.6–18.7]	13.4 [9.0–16.1]	0.090
CAT score	14.5 [8.0–19.0]	16.5 [9.0–20.0]	11.0 [7.5–17.0]	0.074
IPAQ (n = 68)	693.0 [23.1–1498.5]	742.5 [23.1–1605.0]	445.5 [11.6–1188.0]	0.282
mMRC dyspnea scale	1.0 [1.0–2.0]	1.0 [1.0–2.0]	2.0 [1.0–2.0]	0.631
EQ-5D-5L index	0.816 [0.750–0.862]	0.811 [0.740–0.858]	0.822 [0.777–1.000]	0.362
HINT-8 index	0.805 [0.750–0.860]	0.796 [0.733–0.859]	0.811 [0.784–0.863]	0.173
FEV1 (%predicted)	51.0 [41.0–66.0]	56.0 [44.0–67.0]	49.0 [38.5–56.0]	0.156
FVC (%predicted)	73.0 [65.0–86.0]	75.0 [65.0–86.0]	72.0 [64.0–86.0]	0.473
DL_{CO} (%predicted)	56.5 [45.0–67.0]	57.5 [44.0–67.0]	50.0 [45.0–65.0]	0.512
Hand grip strength (kg)	32.9 [25.7–39.8]	34.0 [28.1–41.3]	27.9 [21.5–37.1]	0.082
Limb muscle mass (kg)				
Upper limb	4.9 [3.5–5.7]	5.0 [4.0–6.0]	4.3 [3.3–5.5]	0.051
Lower limb	15.0 [12.4–16.6]	15.6 [13.1–17.0]	14.5 [10.8–15.6]	0.047
Follow-up				
*VO_2max (ml/kg/min, n = 68)	12.8 [11.0–16.1]	13.4 [10.5–17.8]	12.7 [11.3–13.7]	0.376
CAT score	8.0 [5.0–17.0]	7.5 [4.0–16.0]	10.0 [6.5–18.5]	0.086
IPAQ (n = 65)	1386.0 [859.1–2772.0]	1477.5 [1137.5–3012.0]	1164.0 [618.8–2205.0]	0.068
mMRC dyspnea scale	1.0 [1.0–2.0]	1.0 [1.0–2.0]	2.0 [1.0–2.0]	0.021
EQ-5D-5L index	0.862 [0.783–1.000]	0.871 [0.787–1.000]	0.829 [0.768–1.000]	0.387
HINT-8 index	0.819 [0.751–0.876]	0.825 [0.763–0.882]	0.795 [0.728–0.848]	0.136
FEV1 (%predicted)	50.0 [40.0–68.0]	58.0 [42.0–69.0]	45.0 [37.5–54.5]	0.096
FVC (%predicted)	73.0 [67.0–86.0]	75.5 [69.0–86.0]	71.5 [63.0–86.0]	0.232
DL_{CO} (%predicted, n = 69)	60.0 [48.8–71.0]	62.0 [51.0–71.0]	57.0 [48.0–64.8]	0.353
Hand grip strength (kg)	32.7 [23.3–40.2]	33.3 [27.8–41.8]	24.0 [20.6–37.0]	0.049
Limb muscle mass (kg)				
Upper limb	4.7 [3.7–5.9]	4.9 [3.8–6.0]	4.3 [3.5–5.5]	0.136

Lower limb	14.9 [12.4–16.6]	15.4 [13.5–16.9]	14.4 [10.8–16.0]	0.074

Data are presented as median [interquartile range].

*VO_2max was measured using a cardiopulmonary exercise test.

VO_2max, maximal oxygen consumption; CAT, chronic obstructive lung disease assessment test; mMRC, mMRC Modified Medical Research Council; IPAQ, International Physical Activity Questionnaire; EQ-5D-5L, Euro-QoL 5-Dimension 5-Level; HINT-8, Health-related Quality of Life Instrument with 8 Items; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide.

Table 13. Comparison of clinical outcomes of participants between the baseline and follow-up (per protocol analysis).

	Baseline	Follow-up	*P* value
Intervention (n =43)			
*VO_2max (ml/kg/min)	15.7 [12.7–19.2]	14.0 [10.6–18.4]	0.045
CAT score	16.0 [9.5–20.0]	7.0 [4.0–15.0]	< 0.001
IPAQ (n = 41)	792.0 [23.1–1649.3]	1488.0 [1250.3–3027.8]	< 0.001
mMRC dyspnea scale	1.0 [1.0–2.0]	1.0 [1.0–1.8]	0.006
EQ-5D-5L index	0.816 [0.743–0.861]	0.871 [0.814–1.000]	< 0.001
HINT-8 index	0.792 [0.735–0.859]	0.828 [0.767–0.891]	< 0.001
FEV1 (%predicted)	57.0 [44.3–66.8]	58.0 [43.5–69.0]	0.266
FVC (%predicted)	75.0 [66.3–87.5]	77.0 [69.3–87.5]	0.040
DL_{CO} (%predicted)	61.0 [53.5–67.0]	62.0 [51.0–71.8]	0.083
Hand grip strength (kg)	33.7 [28.0–41.0]	33.3 [27.7–41.7]	0.735
Limb muscle mass (kg)			
Upper limb	5.0 [3.9–6.0]	4.8 [3.8–6.1]	0.472
Lower limb	15.6 [13.1–17.0]	15.4 [13.0–16.9]	0.557
Control (n = 24)			
*VO_2max (ml/kg/min, n = 22)	13.4 [9.0–16.1]	12.7 [11.3–13.7]	0.446
CAT score	11.0 [7.5–17.0]	10.0 [6.5–18.5]	0.782
IPAQ (n = 21)	198.0 [11.6–1237.5]	1164.0 [618.8–2205.0]	0.005
mMRC dyspnea scale	2.0 [1.0–2.0]	2.0 [1.0–2.0]	0.739

EQ-5D-5L index	0.822 [0.777–1.000]	0.829 [0.768–1.000]	0.257
HINT-8 index	0.811 [0.784–0.863]	0.795 [0.728–0.848]	0.085
FEV1 (%predicted)	49.0 [38.5–56.0]	45.0 [37.5–54.5]	0.464
FVC (%predicted)	72.0 [64.0–86.0]	71.5 [63.0–86.0]	0.779
DL_{CO} (%predicted, n = 23)	50.0 [45.0–65.0]	57.0 [48.0–64.8]	0.167
Hand grip strength (kg)	27.9 [21.5–37.1]	24.0 [20.6–37.0]	0.290
Limb muscle mass (kg)			
Upper limb	4.3 [3.3–5.5]	4.3 [3.5–5.5]	0.117
Lower limb	14.5 [10.8–15.6]	14.4 [10.8–16.0]	0.670

Data are presented as median [interquartile range].

*VO_2max was measured using a cardiopulmonary exercise test.

VO_2max, maximal oxygen consumption; CAT, chronic obstructive lung disease assessment test; mMRC, mMRC Modified Medical Research Council; IPAQ, International Physical Activity Questionnaire; EQ-5D-5L, Euro-QoL 5-Dimension 5-Level; HINT-8, Health-related Quality of Life Instrument with 8 Items; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide.

Table 14 Comparison of clinical outcomes of participants between the baseline and follow-up (intention to treat analysis)

	Baseline	Follow-up	*P* value
Intervention (n =46)			
*VO_2max (ml/kg/min)	15.5 [12.6–18.7]	13.4 [10.5–17.8]	0.031
CAT score	16.5 [9.0–20.0]	7.5 [4.0–16.0]	< 0.001
IPAQ (n = 44)	742.5 [23.1–1605.0]	1477.5 [1137.5–3012.0]	< 0.001
mMRC dyspnea scale	1.0 [1.0–2.0]	1.0 [1.0–2.0]	0.004
EQ-5D-5L index	0.811 [0.740–0.858]	0.871 [0.787–1.000]	< 0.001
HINT-8 index	0.796 [0.733–0.859]	0.825 [0.763–0.882]	< 0.001
FEV1 (%predicted)	56.0 [44.0–67.0]	58.0 [42.0–69.0]	0.299
FVC (%predicted)	75.0 [65.0–86.0]	75.5 [69.0–86.0]	0.019
DL_{CO} (%predicted)	57.5 [44.0–67.0]	62.0 [51.0–71.0]	0.064
Hand grip strength (kg)	34.0 [28.1–41.3]	33.3 [27.8–41.8]	0.076
Limb muscle mass (kg)			

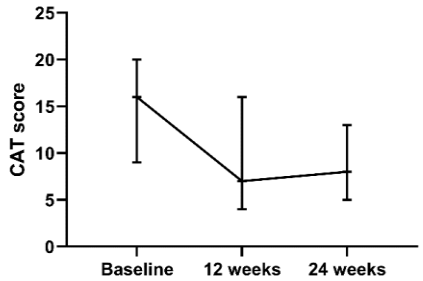
Upper limb	5.0 [4.0–6.0]	4.9 [3.8–6.0]	0.532
Lower limb	15.6 [13.1–17.0]	15.4 [13.5–16.9]	0.404
Control (n = 24)			
*VO_2max (ml/kg/min, n = 22)	13.4 [9.0–16.1]	12.7 [11.3–13.7]	0.446
CAT score	11.0 [7.5–17.0]	10.0 [6.5–18.5]	0.782
IPAQ (n = 21)	198.0 [11.6–1237.5]	1164.0 [618.8–2205.0]	0.005
mMRC dyspnea scale	2.0 [1.0–2.0]	2.0 [1.0–2.0]	0.739
EQ-5D-5L index	0.822 [0.777–1.000]	0.829 [0.768–1.000]	0.257
HINT-8 index	0.811 [0.784–0.863]	0.795 [0.728–0.848]	0.085
FEV1 (%predicted)	49.0 [38.5–56.0]	45.0 [37.5–54.5]	0.464
FVC (%predicted)	72.0 [64.0–86.0]	71.5 [63.0–86.0]	0.779
DL_{CO} (%predicted, n = 23)	50.0 [45.0–65.0]	57.0 [48.0–64.8]	0.167
Hand grip strength (kg)	27.9 [21.5–37.1]	24.0 [20.6–37.0]	0.290
Limb muscle mass (kg)			
Upper limb	4.3 [3.3–5.5]	4.3 [3.5–5.5]	0.117
Lower limb	14.5 [10.8–15.6]	14.4 [10.8–16.0]	0.670

Data are presented as median [interquartile range].

*VO_2max was measured using a cardiopulmonary exercise test.

VO_2max, maximal oxygen consumption; CAT, chronic obstructive lung disease assessment test; mMRC, mMRC Modified Medical Research Council; IPAQ, International Physical Activity Questionnaire; EQ-5D-5L, Euro-QoL 5-Dimension 5-Level; HINT-8, Health-related Quality of Life Instrument with 8 Items; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide.

Figure 12. Change in COPD assessment test score of the intervention group.



Comparison of clinical parameters among subgroup participants

When defining physically active participants as IPAQ > 1000 at baseline, 19 was considered as physically active participants among the intervention group. At follow-up, their VO_2max (median 14.3 vs 12.7 ml/kg/min, $P = 0.0498$) and IPAQ (median 2779.0 vs 1164.0, $P = 0.009$) were significantly higher than those of the control group. Furthermore, their CAT score (median 5.0 vs 10.0, $P = 0.005$) and mMRC dyspnea scale (1.0 vs 2.0, $P = 0.034$) were significantly lower than those of the control group. When comparing their clinical parameters between baseline and follow-up, significant improvements were observed in CAT score, EQ-5D-5L index, and HINT-8 index (Table 15, 16, Figure 13).

When defining good compliance as completion > 50% of assigned exercise program, 17 was considered as compliant participants among the intervention group. At baseline, their VO_2max and CAT score were significantly higher than those of the control group. At follow-up, their CAT score did not differ significantly from that of the control group. Furthermore, their IPAQ was significantly higher than that of the control group at follow-up. When comparing their clinical parameters between baseline and follow-up, significant improvements were observed in CAT score, EQ-5D-5L index, and HINT-8 index (Table 17, 18).

Table 15. Comparison of clinical outcomes of participants between the intervention (initially active, IPAQ > 1000) and control group. – subgroup analysis

	Total (n = 43)	Intervention (n = 19)	Control (n = 24)	*P* value
Baseline				
*VO_2max (ml/kg/min, n = 41)	14.8 [11.2–17.9]	15.6 [13.4–18.1]	13.4 [9.0–16.1]	0.108
CAT score	12.0 [7.3–18.0]	17.0 [7.5–19.0]	11.0 [7.5–17.0]	0.203
IPAQ (n = 41)	1386.0 [198.0–2079.0]	1836.0 [1485.0–3297.0]	445.5 [11.6–1188.0]	< 0.001

mMRC dyspnea scale	2.0 [1.0–2.0]	1.0 [1.0–2.8]	2.0 [1.0–2.0]	0.916
EQ-5D-5L index	0.816 [0.763–0.862]	0.804 [0.723–0.859]	0.822 [0.777–1.000]	0.461
HINT-8 index	0.807 [0.774–0.862]	0.806 [0.757–0.856]	0.811 [0.784–0.863]	0.385
FEV1 (%predicted)	48.0 [41.3–58.0]	48.0 [44.3–62.8]	49.0 [38.5–56.0]	0.557
FVC (%predicted)	73.0 [63.0–89.0]	75.0 [63.0–90.5]	72.0 [64.0–86.0]	0.470
DL_{CO} (%predicted)	58.0 [45.5–67.5]	62.0 [55.3–68.3]	50.0 [45.0–65.0]	0.152
Hand grip strength (kg)	34.1 [25.8–40.8]	37.1 [31.3–44.7]	27.9 [21.5–37.1]	0.014
Limb muscle mass (kg)				
Upper limb	5.1 [3.5–5.8]	5.7 [4.7–6.1]	4.3 [3.3–5.5]	0.004
Lower limb	14.9 [12.0–16.9]	16.4 [13.2–17.9]	14.5 [10.8–15.6]	0.020
Follow-up				
*VO_2max (ml/kg/min, n = 41)	12.9 [11.7–15.2]	14.3 [12.0–19.1]	12.7 [11.3–13.7]	0.0498
CAT score	7.0 [5.0–16.8]	5.0 [3.3–10.0]	10.0 [6.5–18.5]	0.005
IPAQ (n = 39)	1386.0 [825.4–2965.5]	2799.0 [1386.0–3324.0]	1164.0 [618.8–2205.0]	0.009
mMRC dyspnea scale	1.0 [1.0–2.0]	1.0 [1.0–1.0]	2.0 [1.0–2.0]	0.034
EQ-5D-5L index	0.862 [0.783–1.000]	0.871 [0.837–1.000]	0.829 [0.768–1.000]	0.114
HINT-8 index	0.821 [0.744–0.876]	0.843 [0.805–0.906]	0.795 [0.728–0.848]	0.030
FEV1 (%predicted)	48.0 [39.3–57.5]	49.0 [42.3–62.5]	45.0 [37.5–54.5]	0.316
FVC (%predicted)	72.0 [65.3–88.0]	72.0 [66.3–88.8]	71.5 [63.0–86.0]	0.501
DL_{CO} (%predicted, n = 42)	60.0 [50.0–68.0]	63.0 [53.3–71.0]	57.0 [48.0–64.8]	0.136
Hand grip strength (kg)	32.7 [22.8–39.5]	34.2 [31.8–42.9]	24.0 [20.6–37.0]	0.018
Limb muscle mass (kg)				
Upper limb	5.0 [3.7–6.0]	5.9 [4.2–6.6]	4.3 [3.5–5.5]	0.014
Lower limb	15.4 [12.1–16.9]	16.5 [13.7–17.5]	14.4 [10.8–16.0]	0.018

Data are presented as median [interquartile range].

*VO_2max was measured using a cardiopulmonary exercise test.

VO_2max, maximal oxygen consumption; CAT, chronic obstructive lung disease assessment test;

mMRC, mMRC Modified Medical Research Council; IPAQ, International Physical Activity

Questionnaire; EQ-5D-5L, Euro-QoL 5-Dimension 5-Level; HINT-8, Health-related Quality of Life Instrument with 8 Items; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide.

Table 16 Comparison of clinical outcomes of participants (the intervention group, initially active, IPAQ > 1000) between the baseline and follow-up.

	Baseline	Follow-up	*P* value
Intervention (n =19)			
*VO_2max (ml/kg/min)	15.6 [13.4–18.1]	14.3 [12.0–19.1]	0.421
CAT score	17.0 [7.5–19.0]	5.0 [3.3–10.0]	< 0.001
IPAQ (n = 18)	1809.0 [1485.0–3180.0]	2799.0 [1386.0–3324.0]	0.523
mMRC dyspnea scale	1.0 [1.0–2.8]	1.0 [1.0–1.0]	0.011
EQ-5D-5L index	0.804 [0.723–0.859]	0.871 [0.837–1.000]	< 0.001
HINT-8 index	0.806 [0.757–0.856]	0.843 [0.805–0.906]	0.001
FEV1 (%predicted)	48.0 [44.3–62.8]	49.0 [42.3–62.5]	0.887
FVC (%predicted)	75.0 [63.0–90.5]	72.0 [66.3–88.8]	0.614
DL_{CO} (%predicted)	62.0 [55.3–68.3]	63.0 [53.3–71.0]	0.420
Hand grip strength (kg)	37.1 [31.3–44.6]	34.2 [31.7–42.9]	0.227
Limb muscle mass (kg)			
Upper limb	5.7 [4.7–6.1]	5.9 [4.2–6.6]	0.840
Lower limb	16.4 [13.2–17.9]	16.5 [13.7–17.5]	0.695

Data are presented as median [interquartile range].

*VO_2max was measured using a cardiopulmonary exercise test.

VO_2max, maximal oxygen consumption; CAT, chronic obstructive lung disease assessment test; mMRC, mMRC Modified Medical Research Council; IPAQ, International Physical Activity Questionnaire; EQ-5D-5L, Euro-QoL 5-Dimension 5-Level; HINT-8, Health-related Quality of Life Instrument with 8 Items; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide.

Table 17. Comparison of clinical outcomes of participants between the intervention (compliance > 50%) and control group. – subgroup analysis

	Total (n = 41)	Intervention (n = 17)	Control (n = 24)	*P* value
Baseline				
*VO_2max (ml/kg/min, n = 39)	15.4 [10.5–20.0]	17.9 [13.7–23.5]	13.4 [9.0–16.1]	0.024
CAT score	14.0 [9.0–18.3]	17.0 [11.8–20.8]	11.0 [7.5–17.0]	0.023
IPAQ (n = 39)	792.0 [24.8–1611.0]	792.0 [302.8–2258.3]	445.5 [11.6–1188.0]	0.161
mMRC dyspnea scale	2.0 [1.0–2.0]	2.0 [1.0–2.3]	2.0 [1.0–2.0]	0.966
EQ-5D-5L index	0.816 [0.746–0.862]	0.792 [0.732–0.821]	0.822 [0.777–1.000]	0.188
HINT-8 index	0.806 [0.751–0.862]	0.792 [0.732–0.836]	0.811 [0.784–0.863]	0.153
FEV1 (%predicted)	50.0 [41.5–60.8]	53.0 [44.0–68.0]	49.0 [38.5–56.0]	0.272
FVC (%predicted)	73.0 [62.5–88.3]	78.0 [62.5–88.3]	72.0 [64.0–86.0]	0.443
DL_{CO} (%predicted)	58.0 [45.0–67.3]	62.0 [52.8–67.5]	50.0 [45.0–65.0]	0.327
Hand grip strength (kg)	31.8 [25.1–39.3]	34.1 [29.8–42.0]	27.9 [21.5–37.1]	0.098
Limb muscle mass (kg)				
Upper limb	4.7 [3.5–5.5]	5.0 [4.3–5.5]	4.3 [3.3–5.5]	0.204
Lower limb	14.5 [12.4–15.9]	14.9 [13.6–16.4]	14.5 [10.8–15.6]	0.199
Follow-up				
*VO_2max (ml/kg/min, n = 39)	12.9 [11.4–16.2]	16.2 [12.0–21.6]	12.7 [11.3–13.7]	0.040
CAT score	10.0 [5.0–17.3]	10.0 [3.0–16.3]	10.0 [6.5–18.5]	0.272
IPAQ (n = 37)	1386.0 [859.1–2772.0]	2359.5 [1270.5–3163.5]	1164.0 [618.8–2205.0]	0.025
mMRC dyspnea scale	1.0 [1.0–2.0]	1.0 [1.0–2.0]	2.0 [1.0–2.0]	0.145
EQ-5D-5L index	0.829 [0.772–1.000]	0.846 [0.772–0.871]	0.829 [0.768–1.000]	0.779
HINT-8 index	0.804 [0.746–0.856]	0.822 [0.782–0.861]	0.795 [0.728–0.848]	0.272
FEV1 (%predicted)	48.0 [39.8–67.5]	58.0 [45.8–70.0]	45.0 [37.5–54.5]	0.118

FVC (%predicted)	73.0 [64.8–88.5]	79.0 [69.0–90.5]	71.5 [63.0–86.0]	0.302
DL_{CO} (%predicted, n = 40)	61.0 [48.5–70.5]	67.0 [57.8–71.3]	57.0 [48.0–64.8]	0.106
Hand grip strength (kg)	31.4 [22.5–38.5]	35.1 [29.3–42.4]	24.0 [20.6–37.0]	0.053
Limb muscle mass (kg)				
Upper limb	4.6 [3.6–5.6]	4.6 [4.1–5.6]	4.3 [3.5–5.5]	0.354
Lower limb	14.5 [12.3–16.0]	14.5 [13.5–16.4]	14.4 [10.8–16.0]	0.264

Data are presented as median [interquartile range].

*VO_2max was measured using a cardiopulmonary exercise test.

VO_2max, maximal oxygen consumption; CAT, chronic obstructive lung disease assessment test; mMRC, mMRC Modified Medical Research Council; IPAQ, International Physical Activity Questionnaire; EQ-5D-5L, Euro-QoL 5-Dimension 5-Level; HINT-8, Health-related Quality of Life Instrument with 8 Items; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide.

Table 18 Comparison of clinical outcomes of participants (the intervention group, compliance > 50%, between the baseline and follow-up.

	Baseline	Follow-up	*P* value
Intervention (n =17)			
*VO_2max (ml/kg/min)	17.9 [13.7–23.5]	14.5 [13.5–16.4]	0.071
CAT score	17.0 [11.8–20.8]	10.0 [3.0–16.3]	0.004
IPAQ (n = 16)	792.0 [209.6–1908.0]	2359.5 [1270.5–3163.5]	0.013
mMRC dyspnea scale	2.0 [1.0–2.3]	1.0 [1.0–2.0]	0.083
EQ-5D-5L index	0.792 [0.732–0.821]	0.846 [0.772–0.871]	0.009
HINT-8 index	0.792 [0.732–0.836]	0.822 [0.782–0.861]	0.034
FEV1 (%predicted)	53.0 [44.0–68.0]	58.0 [45.8–70.0]	0.346
FVC (%predicted)	78.0 [62.5–88.3]	79.0 [69.0–90.5]	0.079
DL_{CO} (%predicted)	62.0 [52.8–67.5]	67.0 [57.8–71.3]	0.038
Hand grip strength (kg)	34.1 [29.8–42.0]	35.1 [29.3–42.4]	0.813
Limb muscle mass (kg)			
Upper limb	5.0 [4.3–5.5]	4.6 [4.1–5.6]	0.313
Lower limb	14.9 [13.6–16.4]	14.5 [13.5–16.4]	0.517

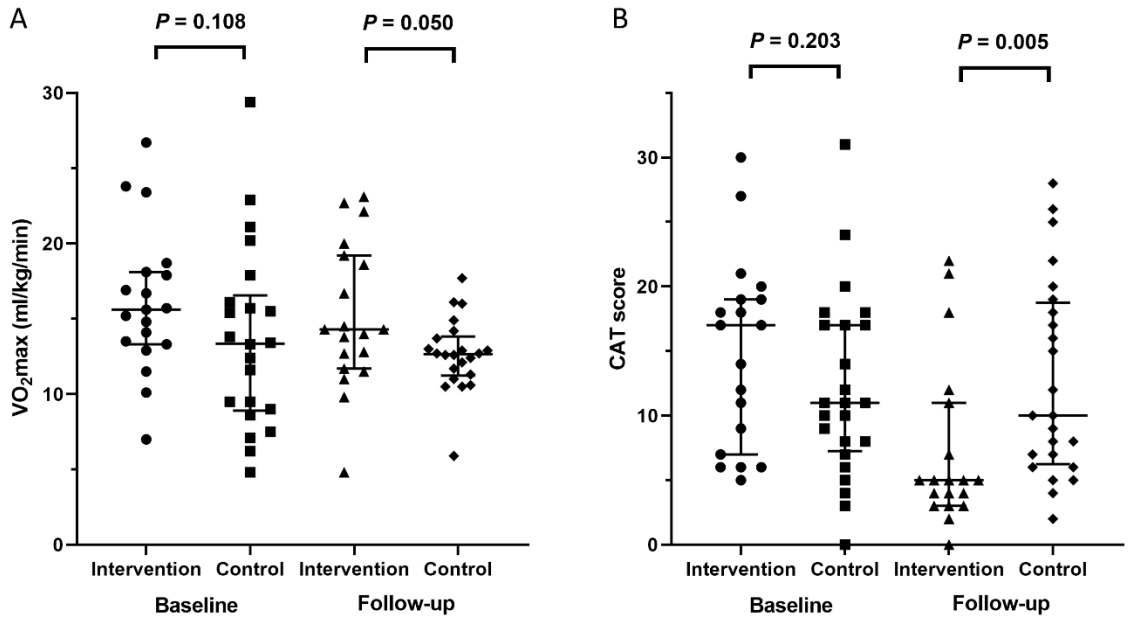
Data are presented as median [interquartile range].

*VO_2max was measured using a cardiopulmonary exercise test.

VO_2max, maximal oxygen consumption; CAT, chronic obstructive lung disease assessment test; mMRC, mMRC Modified Medical Research Council; IPAQ, International Physical Activity Questionnaire; EQ-5D-5L, Euro-QoL 5-Dimension 5-Level; HINT-8, Health-related Quality of Life Instrument with 8 Items; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DL_{CO}, diffusing capacity for carbon monoxide.

Figure 13. Comparison of primary outcomes of participants between the intervention (initially active, IPAQ > 1000) and control group.

Data are shown for: (A) maximal oxygen consumption (VO_2max) and (B) chronic obstructive pulmonary disease assessment test (CAT) score.



Ease-of-use of the application

Among the intervention group, approximately 80% of participants answered that they thought the application was easy to use (i.e., “very easy” = 53.5% and “easy” = 27.9%), and 60% answered that it

was helpful to improve dyspnea symptom (i.e., “vert helpful” = 27.9% and “helpful” = 34.9%). Moreover, 79.1% of the participants answered that they wanted to use the application if it were available commercially, and the most attractive point of it was that it suggested exercise program suitable to their condition (44.1%, Table 19).

Table 19. Application service evaluation questionnaire.

Question	N = 43
How easy and convenient was the application service provided to you?	
Very easy	23 (53.5%)
Easy	12 (27.9%)
So so	5 (11.6%)
Difficult	2 (4.7%)
Very difficult	1 (2.3%)
How helpful was the application service to improv your dyspnea symptom?	
Very helpful	12 (27.9%)
Helpful	15 (34.9%)
So so	11 (25.6%)
Not helpful	1 (2.3%)
Not helpful at all	4 (9.3%)
Do you want to use the application service if it is commercialized?	
Yes	34 (79.1%)
No	9 (20.9%)
If yes, why do you want to use it?	
I can exercise with the app, although I do not visit hospital.	0 (0%)
I can get a reward if I exercise.	0 (0%)
I can check how much I exercise.	14 (41.2%)
The app suggests exercise suitable to my condition.	15 (44.1%)
I think that the app is easier and more convenient than other apps.	5 (14.7%)
To use the app is more convenient than to visit hospital.	0 (0%)
What was the most attractive point of the application service?	
It is good to have a partner to exercise with.	1 (2.3%)
It is good to get a reward after I exercise.	1 (2.3%)
It is good to be able to check how much I have exercised.	16 (37.2%)

It is good that the application suggest exercise suitable to my condition.	18 (41.9%)
It is good that the app is easier to use and understand than other apps.	7 (16.3%)

Data are presented as count (%).

DISCUSSION

Chapter 1

Principal Results and Implications

We reviewed and described the clinical outcomes of smartphone application-based pulmonary rehabilitation in patients with COPD. Participants and interventions were heterogenous in their characteristics; however, participants with smartphone application-based pulmonary rehabilitation showed favorable outcomes in exercise capacity, symptom score, quality of life, and hospitalization, compared to participants with conventional pulmonary rehabilitation. In the meta-analysis, the 6MWD, mMRC dyspnea scale, SGRQ, and exacerbations were not inferior in the smartphone application-based pulmonary rehabilitation group compared with the control group, and the CAT score was superior to that in the control group. Considering difficulties in practicing center-based conventional pulmonary rehabilitation, smartphone application-based pulmonary rehabilitation may be a useful treatment option when conventional pulmonary rehabilitation is not feasible.

Smartphone application-based pulmonary rehabilitation

Pulmonary rehabilitation has been traditionally delivered in an outpatient, inpatients, or community setting, comprising ≥ two sessions per week and at least four weeks [56]. In 2015, the American Thoracic Society/European Respiratory Society policy statement requested researches to adopt alternative formats for pulmonary rehabilitation and to demonstrate at least comparable clinical outcomes to those of traditional pulmonary rehabilitation programs, as well as evaluation of cost-effectiveness and safety [57]. Since then, clinical trials have reported data on the clinical outcomes and safety of pulmonary rehabilitation program models, including home-based rehabilitation, telerehabilitation, Web-based rehabilitation, community rehabilitation, primary care rehabilitation, rehabilitation requiring minimal resources, and combined heart failure/pulmonary rehabilitation

models [19]. A smartphone application-based pulmonary rehabilitation can be regarded as a type of telehealth interventions [30] which provide healthcare at a distance through the telecommunications or virtual technology [58]. It may improve accessibility of pulmonary rehabilitation for patients with chronic respiratory diseases through providing healthcare access and service for patients who are geographically or socially isolated, engaged with full-time work, or hard to transport due to their disease or comorbidities [30].

Further development of application

Various types of applications were used in the studies. Some authors used newly developed applications and others used myCOPD or social messenger WeChat [21, 23, 25]. Some applications, such as myCOPD, provided self-management programs for COPD, including education and symptom management [21, 25]; however, other applications provided only exercise programs [22, 24]. Although this study focused on clinical improvements in participants with pulmonary rehabilitation, it should also be considered that overall self-management programs have affected clinical outcomes. However, pulmonary rehabilitation is defined as a comprehensive intervention which includes exercise training, education, and behavioral change [6]. Recently, Holland et al. suggested that desirable components of pulmonary rehabilitation should include education, self-management training, smoking cessation, and action plan for exacerbation, as well as a home exercise program [19]. Therefore, applications which provided both exercise and self-management programs should be included in smartphone application-based pulmonary rehabilitation.

Considering challenges in center-based pulmonary rehabilitation and the shortage of healthcare resources, home-based pulmonary rehabilitation has been studied as an alternative to center-based pulmonary rehabilitation [59-64]. However, compliance to pulmonary rehabilitation is an important issue in home-based pulmonary rehabilitation, and lack of motivation was an important reason for poor compliance [65]. In case of home-based pulmonary rehabilitation without supervision, patients with good compliance showed significant improvement in CAT score, BODE index, and FEV_1 compared

with patients with poor compliance [66]. Similarly, Crooks et al. described that there was an estimated −0.22 (95% CI −0.74–0.31) decrease in the CAT score for every 7-day increase in application use, adjusted for baseline CAT score, COPD severity and site [21]. However, North et al. reported that as time passed, the number of application users decreased in smartphone application-based pulmonary rehabilitation [25]. Therefore, patients are required to steadily run the application and perform pulmonary rehabilitation to achieve clinical improvement. Various methods were used in studies to enhance compliance, such as text messages with activity proposals, telephone contacts, incentives, and communication with other participants [22, 23, 26, 28, 29]. Additionally, activity level (step counts) was monitored using pedometer and fed back to participants [22, 26, 28, 29]. In real-world practice, health care intervention and action plans should be considered in case of poor compliance, because they might reflect patients' deconditioning or acute exacerbation [19, 23, 65].

Further development of rehabilitation program

In clinical practice, exercise level in pulmonary rehabilitation should be individualized according to a patient's exercise capacity [5, 6]. Therefore, in smartphone application-based pulmonary rehabilitation, maintaining appropriate exercise level is a matter of concern. Some applications provided adjustable exercise regimens according to the change of participants' exercise capacity [22, 24, 28, 29]. Kwon et al. designed exercise level adjusted according to the maximum walking speed in 6-minute walk test and the degree of breathing difficulty after exercise [24]. Vorrink et al. designed physical activity goals set according to average steps per day [28]. To maintain appropriate exercise level, applications should provide adjustable and individualized exercise program based on patient's exercise capacity and activity level data collected using wearable devices or smartphone-mounted sensors.

Considering the study designs included in this review, it is important to develop strategies to improve compliance to rehabilitation and design individualized exercise programs to achieve significant improvements in clinical outcomes in future studies. Moreover, most studies had rather small sample sizes to demonstrate the efficacy of pulmonary rehabilitation programs [24-26]. In addition, most studies

did not provide data regarding application usage, which could have been used in the subgroup analysis related to compliance [21, 25]. Therefore, further studies with larger sample sizes and application usage are needed.

Furthermore, nutrition support is an important part of pulmonary rehabilitation [5, 19]. In this review, some of the included applications provided disease education; however, a nutrition support program was not provided [21, 23, 25-27, 36]. Nutrition support may be helpful in maintaining an adequate BMI and increasing muscle mass in patients with COPD [5, 19]. Exercise training accompanied by nutrition support might improve respiratory sarcopenia and enhance clinical benefits [12]; thus, further studies are needed in this area.

Clinical outcomes and prognosis

Exercise capacity and physical activity can predict prognosis in patients with COPD. Exercise capacity is inversely correlated with mortality in patients with COPD [67]. Physical activity is also inversely correlated with exacerbation and mortality in patients with COPD [68]. Some previous studies reported physical activity as daily step counts, and these variables had too wide range of distribution to be synthesized in the meta-analysis [21, 27]. Moreover, the 6MWD did not show a significant difference in the meta-analysis, while Wang et al. reported improvements in the ISWT and limb muscle mass in the intervention group [29]. Thus, further studies are required to ascertain whether smartphone application-based pulmonary rehabilitation can improve exercise capacity and physical activity in patients with COPD.

In some studies, we noticed that smartphone application-based pulmonary rehabilitation improved quality of life, including the SGRQ, clinical COPD questionnaire, and chronic respiratory disease questionnaire results [21-23, 25, 26, 28]. Among them, the CAT score showed a significant improvement in the intervention group through the meta-analysis [20, 21, 23-25, 27]. The CAT score was correlated with the severity of airflow limitation and disease exacerbation in patients with COPD [69, 70]. Taken together, smartphone application-based pulmonary rehabilitation programs might improve clinical outcomes,

such as acute exacerbation and mortality. Unfortunately, in the meta-analysis, there was no statistically significant difference between groups in acute exacerbations because the study periods (i.e., 3–6 months) might have been too short to observe acute exacerbations [21, 25, 26]. Therefore, further studies with long-term follow-up are required to evaluate the effect of smartphone application-based pulmonary rehabilitation on acute exacerbations and mortality.

Limitations

First, discrepancies in the baseline status of participants were one of the main obstacles in synthesizing clinical outcomes. North et al. evaluated participants after hospitalization with an acute exacerbation [25]. Vorrink et al. and Wang et al. evaluated physical activity in participants with COPD after pulmonary rehabilitation [28, 29]. Despite this heterogeneity, participants with smartphone application-based pulmonary rehabilitation showed consistently favorable results in clinical parameters. Second, discrepancies in the clinical parameters were also an obstacle in synthesizing clinical outcomes. Among various parameters for exercise capacity, a meta-analysis could be performed on 6MWD as it is used in most studies [20, 22, 24, 26, 28] and is a well-established surrogate marker in patients with COPD [10, 71]. Questionnaires about quality of life, including the SGRQ, EuroQol 5-dimension 5-level, clinical COPD questionnaire, chronic respiratory disease questionnaire, also showed generally favorable results in patients undergoing smartphone application-based pulmonary rehabilitation [21-23, 25, 26, 28]. Although clinical outcomes did not show statistically significant improvement in participants with smartphone application-based pulmonary rehabilitation and decisive evidence was hard to be derived, this study showed that clinical outcomes generally favored smartphone application-based pulmonary rehabilitation. Considering the difficulties with center-based pulmonary rehabilitation in real-world practice, smartphone application-based pulmonary rehabilitation could be a reasonable alternative to conventional pulmonary rehabilitation.

Chapter 2

In this study, we evaluated a smartphone application-based rehabilitation program for patients with chronic respiratory diseases. We found that the smartphone application-based rehabilitation program improved the clinical outcomes of participants, including exercise capacity and quality of life. Furthermore, older adult patients with chronic diseases can easily perform the rehabilitation program. Thus, smartphone application-based rehabilitation may be a useful treatment option for older adult patients with chronic diseases.

Exercise capacity and physical activity are important prognostic indicators for patients with chronic respiratory disease. For example, exercise capacity has been found to be an important predictor of mortality in patients with COPD [67]. In addition, low levels of physical activity were found to be correlated with high risks for disease exacerbation and mortality in patients with COPD [68]. This study demonstrated that exercise capacity can improve via an application-based rehabilitation program in elderly patients with chronic disease. Unfortunately, physical activity levels, such daily step counts, were not measured in this study. This would be simple to implement since it could be measured using a smartphone-mounted pedometer. Thus, further development of the application is required to obtain this data.

We found that the application-based rehabilitation program was associated with significantly improved quality of life for all groups of participants. In particular, patients with chronic respiratory disease reported significant improvements in CAT score, a predictor of the severity of airflow limitation and acute exacerbation in patients with COPD [69, 70]. By improving exercise capacity and quality of life through rehabilitation programs, clinical outcomes such as disease exacerbation may be improved. We noted that no patient experienced acute disease exacerbation during the study period. Therefore, further studies are needed to evaluate the effect of rehabilitation on acute exacerbation or mortality using long-term follow-up assessments performed after the end of rehabilitation.

As previously described, compliance to rehabilitation program is an important issue in home-based rehabilitation [65]. A previous study reported an estimated −0.22 (95% CI, −0.74–0.31) decrease in the

CAT score in every 7-day increase in application use for pulmonary rehabilitation [21]. However, another study reported that as time passed, the number of smartphone application users undergoing pulmonary rehabilitation decreased [25]. Therefore, to steadily use the application and perform rehabilitation program, initial professional assessment and goal setting are important [24]. Enabling self-monitoring and self-evaluation, such as feedback using wearable device and adjustable exercise program, is also important in real-world practice [24]. Moreover, patients' preferences should be considered in designing eHealth platforms to enhance user engagement [72].

In this study, participants showed low levels of compliance; however, in the subgroup analysis, significant improvement in VO_2max was noted in compliant participants with chronic pulmonary disease. In a previous study of home-based pulmonary rehabilitation without supervision, participants with good compliance showed significant improvement in clinical indices compared with non-compliant participants [66]. Because the lack of motivation was an important factor for poor compliance in home-based rehabilitation [65], attending physicians should emphasize the need for patients to steadily use the application and perform rehabilitation program to achieve significant clinical improvement. The first step of pulmonary rehabilitation involves fostering awareness among patients that engaging in appropriate exercise can contribute to the improvement of their symptom. In this regard, the application guided rehabilitation would be helpful. Moreover, some methods, such as regular text messages or telephone contacts from health care, can be applied to enhance motivation [22]. Repeated exposure to exercises that promote the use of the application may motivate individuals to exercise more.

In this study, the vitality dimension quantified by HINT-8 was reported as having improved significantly for participants. The rehabilitation program required walking outdoors for 30 min daily, and this may have encouraged the participants to engage in outdoor activities. Previous studies have demonstrated that exercise is associated with improved vitality in patients with chronic diseases [73, 74]. Older adult patients with chronic diseases may be sedentary and prefer to remain indoors, and therefore a significant improvement in vitality may be realized via daily walks outdoors. Taken

together, our data suggest that increased physical and outdoor activity may be an important factor improving participant quality of life in this study.

Interestingly, the memory and depression dimensions of HINT-8 improved in participants. There is considerable scientific evidence that exercise can improve the performance of memory systems, even in elderly individuals [75, 76]. For example, one study showed that aerobic exercise increased the volume of gray and white matter in the prefrontal cortices of elderly individuals [77]. Exercise has also been shown to increase blood volume, perfusion, and volume of the hippocampus in elderly individuals [78, 79]. In addition to structural changes in the brain, previous studies have also demonstrated that exercise can improve cognitive performance and functional connectivity in the brain [80, 81]. Thus, physical activity is thought to improve cognitive function, improve memory, induce antidepressant effects, and confer a sense of wellbeing [82]. Further studies are required to ascertain the associations between physical exercise and mental health in patients with chronic respiratory disease.

This study has notable strengths. Despite most participants being elderly, the application-guided rehabilitation treatment showed that they can achieve a significant improvement in exercise capacity and quality of life, particularly with respect to their mental health. Over 80% of participants perceived that the application was easy to use and became familiar with it within a remarkably short period of time. Furthermore, we did not observe disease exacerbation or musculoskeletal accidents during the study period. Previous studies also reported that adverse event rates were acceptable during home-based pulmonary rehabilitation [30, 83]. These results therefore highlight the fact that smartphone application-based rehabilitation can be successfully performed even in older adult patients with chronic diseases.

This study has some implications for further research. Although we observed significant improvement in some clinical parameters of the participants, further studies with additional participants and a randomized controlled study design are required to ascertain the efficacy of smartphone application-based rehabilitation programs. Although we noted that no patient experienced acute disease exacerbation during the study period (12 weeks), further studies are needed to evaluate the effect of

rehabilitation on acute exacerbation or mortality using long-term follow-up assessments performed after the end of rehabilitation.

This study has some limitations. Physical activity levels, such daily step counts, were not measured in this study owing to the limitation of application. Thus, further development of the application is required to obtain this data through a smartphone-mounted pedometer. Moreover, this study failed to demonstrate improvement in hand grip strength and limb muscle mass. Although the rehabilitation program provided anaerobic exercise with incremental intensity, nutritional support—such as protein supplementation—was not provided. Nutritional support to maintain adequate body mass index and muscle mass is an important component of rehabilitation in chronic disease [5, 39]. Further studies with proper nutritional support are expected to improve muscle mass and strength in patients with chronic diseases.

Chapter 3

In this study, we investigated the clinical efficacy of a smartphone application-based pulmonary rehabilitation program for patients with chronic respiratory diseases. We found that this smartphone application-based rehabilitation program improved the clinical parameters of participants, including quality of life, daily physical activity, and dyspnea symptom. Furthermore, participants who were physically active or compliant to exercise program, showed significant improvement in clinical parameters. Thus, smartphone application-based pulmonary rehabilitation may be a useful treatment option for older adult patients with chronic respiratory diseases.

We found that the application-based pulmonary rehabilitation was associated with significant improvement in CAT score, which predicts the severity of airflow obstruction and disease exacerbation in patients with COPD [69, 70]. CAT is also correlated with lung function, 6MWD, and exertional desaturation in patients with idiopathic pulmonary fibrosis or connective tissue disease-associated interstitial lung disease [84, 85]. Additionally, CAT also correlated with disease severity, lung function, and 6MWD in patients with bronchiectasis, which therefore is a valid tool in bronchiectasis

[86]. Although we included patients with a wide spectrum of chronic respiratory disease, the improvement of CAT score can predict clinical improvements in their diseases. Furthermore, CAT score of the intervention group remained stationary in 12 weeks after the end of rehabilitation. This finding also highlights clinical efficacy of application-based pulmonary rehabilitation.

Daily physical activity is important for patients with chronic respiratory disease. For example, low levels of physical activity were correlated with high risks of acute exacerbation and mortality in patients with COPD [68]. However, patients with COPD have a significantly reduced daily physical activity compared to healthy controls, although the severity of COPD was not strongly correlated with level of daily physical activity [87]. Thus, even patients with severe COPD could remain physically active and have lower risks of exacerbation and mortality. In this study, physical activity could improve through an application-based pulmonary rehabilitation in older adult patients with chronic respiratory disease. Furthermore, in the subgroup analysis, initially physically active participants showed marked improvements in clinical parameters, which reinforces the importance of physical activity. Further studies with longer follow-up would reveal lower exacerbation and mortality owing to application-based pulmonary rehabilitation.

As previously reported, compliance to rehabilitation program remains an unsolved problem in home-based pulmonary rehabilitation [65]. For application-based pulmonary rehabilitation, approximately −0.22 (95% CI, −0.74–0.31) decrease in the CAT score was estimated per 7-day increase in application use [21]. However, the number of application users decreased as study preceding (85% in the first week and 40% in the last week), but active users kept their days of application usage per week (4.9 days per week) [25]. A previous study reported that the lack of motivation was the most common reason for non-adherence in home-based pulmonary rehabilitation, and non-adherence patients with COPD experienced more exacerbation and less 6MWD [65]. In this study, 39.5% (17 of 43) participants showed good compliance as completion > 50% of assigned exercise program and they showed significant improvements in CAT score and IPAQ. Thus, physicians should emphasize patients to steadily perform pulmonary rehabilitation program with their application. The first stage of pulmonary rehabilitation includes patients' education that engaging in appropriate exercise program

can improve their symptom. Additionally, regular telephone contacts or text messages from health care providers can encourage patients' motivation [22]. Repeated exposure to exercises program would promote the application usage and motivate patients to exercise more.

This study has notable strengths. Despite most participants being older adults, they could achieve significant improvements in clinical parameters through the application-guided pulmonary rehabilitation program. Moreover, CAT score of the intervention group remained stationary even in 12 weeks after the end of rehabilitation. Over 80% of participants thought that the application was easy to use and wanted to use it if commercially available. Furthermore, we did not observe any musculoskeletal injury or disease exacerbation during the study period. Previous systematic review studies also described acceptable adverse event rates during home-based pulmonary rehabilitation [30]. These points support our hypothesis that smartphone application-based pulmonary rehabilitation can be performed successfully even in older adult patients with chronic respiratory diseases.

This study also has some limitations. First, although we observed significant improvement in physical activity, such as IPAQ, of participants, their VO_2max at follow-up was lower than that at baseline. During the study period, many participants underwent follow-up study during the summer season, hot atmosphere of which prohibited them to perform their maximal exercise capacity during the cardiopulmonary exercise tests. Moreover, some participants who experienced fatigue and malaise after the cardiopulmonary test during baseline study, gave up the test prior to reaching their maximal exercise capacity during follow-up study. Further studies should design more detailed exercise test protocol to overcome these challenges. Second, this study failed to show statistically significant difference in EQ-5D-5L index and HINT-8 index, although these were higher among the intervention group compared with the control group. Further studies with more participants may successfully improve qualities of life in patients with chronic respiratory diseases. Third, this study failed to show improvement in hand grip strength and limb muscle mass in the intervention group, although we provided muscle exercise program and nutritional supplement. Further studies should provide individualized exercise program and nutritional support to improve physical parameters in patients with chronic respiratory diseases.

Summary

In this study, we investigated the clinical feasibility and efficacy of smartphone application-based pulmonary rehabilitation in patients with chronic respiratory disease, in the aspects of exercise capacity, symptom score, and quality of life. At first, in the systematic review and meta-analysis, most studies have evaluated exercise capacity using 6MWD, because it is easy to be conducted in limited resources and correlated with VO_2max in patients with COPD [10, 71, 88]. However, we failed to denote the statistically significant difference in 6MWD in meta-analysis. Furthermore, although both 6MWD and ISWT are significantly correlated with VO_2max, ISWT has a stronger correlation with VO_2max than 6MWD [89]. Therefore, in the clinical trials, we conducted cardiopulmonary exercise test to determine VO_2max, which is a gold standard measurement for exercise capacity [40]. We believe that our work would be a cornerstone study for smartphone application-based pulmonary rehabilitation to measure VO_2max. In the subsequent single-arm interventional study, we noted significant improvement in VO_2max after rehabilitation. Unfortunately, we failed to denote significant difference in VO_2max in the randomized controlled trial and VO_2max even decreased after rehabilitation. As we have discussed earlier, we believe that the results were unsatisfactory owing to some environmental and human factors. Thus, we suggest that test room environment and field manuals for cardiopulmonary exercise test should be improved in the subsequent clinical trial.

In the aspects of quality-of-life, we observed significant improvements in CAT score after rehabilitation in the meta-analysis and clinical trials. Moreover, we also observed significant improvements in EQ-5D-5L and HINT-8 index after rehabilitation in both single-arm study and randomized controlled study. However, we failed to note a significant difference in both index between the intervention and control arm after rehabilitation in the randomized controlled study. Because we have estimated study sample size to determine a clinically significant improvement in VO_2max, the sample size may be insufficient for quality of life measurement index. Further studies with more participants are required.

This study evaluated hand grip strength and limb muscle mass in the aspect of sarcopenia. However, we failed to note a significant improvement in these parameters during the single-arm study. In the subsequent randomized controlled trial, although we provided the intervention group with protein supplementary drinks, we could not observe improvements, either. This may be because the intensity or frequency of muscle exercise (anaerobic exercise) in the rehabilitation program was not sufficient for improving muscle strength and mass. Additionally, considering the characteristics of the application-based rehabilitation program, which is performed self-directed by individual, improvements can be more prominent in the quality of life measurements than in exercise capacity or muscle strength. Accordingly, we have observed similar tendencies in our meta-analysis. Therefore, the contents of muscle exercise of rehabilitation programs require to be reinforced in the future studies. If the application were to be commercialized as a subscription service, periodic update of exercise programs may be one of the essential factors in maintaining users in the long run.

CONCLUSION

In this study, we investigated the feasibility and clinical efficacy of smartphone application-based pulmonary rehabilitation in patients with chronic respiratory disease. First, we performed a systematic review and meta-analysis to compare the clinical outcomes of smartphone application-based pulmonary rehabilitation in patients with COPD. Afterward, we developed a smartphone application-based rehabilitation programs and performed a prospective single arm interventional study, followed by a randomized controlled trial study.

Our systematic review demonstrated that many smartphone applications have been applied for pulmonary rehabilitation in patients with COPD. In some studies, patients who participated in smartphone application-based pulmonary rehabilitation showed favorable outcomes in exercise capacity, symptom score, quality of life, and hospitalization compared with those who underwent conventional pulmonary rehabilitation. In the meta-analysis, the CAT score in the smartphone application-based pulmonary rehabilitation group was superior to that in the control group.

In the subsequent clinical trials, the smartphone application-based pulmonary rehabilitation program described here improved clinical outcomes, including exercise capacity, physical activity, quality of life, and dyspnea symptom, in patients with chronic respiratory diseases. Particularly, participants who were physically active or compliant to exercise program, showed significant improvement in clinical parameters. Furthermore, older adult patients with chronic diseases could easily and safely perform smartphone application-based pulmonary rehabilitation.

Therefore, in real-world practice, smartphone application-based pulmonary rehabilitation can be a useful treatment option older adult patients with chronic respiratory diseases when center-based conventional pulmonary rehabilitation is not feasible.

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Supplementary Material

PICOTS-SD search strategy for a smartphone application for patients with chronic pulmonary disease

1) Population

- Adult patients with chronic pulmonary (lung, respiratory) disease

- Chronic pulmonary (lung, respiratory) diseases:
  1) COPD, chronic obstructive pulmonary disease, emphysema, chronic bronchitis
  2) Asthma, bronchial asthma
  3) Bronchiectasis, cystic fibrosis
  4) ILD, interstitial lung disease, IIP, idiopathic interstitial pneumonia, IPF, idiopathic pulmonary fibrosis, NSIP, nonspecific interstitial pneumonia, RB-ILD, Respiratory bronchiolitis interstitial *lung disease, DIP,* Desquamative interstitial pneumonia, OP, organizing pneumonia, AIP, acute interstitial pneumonia, CTD-ILD, connective tissue disease-related interstitial lung disease, pneumoconiosis, hypersensitivity pneumonitis
  5) Critical care, intensive care, critical illness, critically ill, ICU

2) Intervention

- Mobile application, mobile apps, smartphone application, smartphone apps, mobile pulmonary rehabilitation

3) Comparison

- No treatment, placebo, basic supportive care, standard (conventional) medical treatment, education

4) Outcomes

- Body weight, BMI (body mass index)

- 6-minute walk (walking) test: distance, saturation

- Endurance shuttle walk (walking) test, incremental shuttle walk (walking) test

- CPET (cardiopulmonary exercise test)

- Pulmonary function test: FEV_1, FVC, DLCO
- Acute exacerbation, hospitalization, mortality
- HRQOL (health-related quality of life), QOL (quality of life)
  COPD: CAT, SGRQ, SGRQ-C, EQ-5D, CCQ, CRQ
  Asthma: ACT, AQLQ, SGRQ, EQ-5D
  Bronchiectasis: SGRQ, LCQ, CRQ
  ILD: SGRQ, SGRQ-I, K-BILD, SF-36, SOBQ
  Critical care: SGRQ, CRQ, SF-36

5) Time

- 2007–2021

6) Setting

- No limitations

7) Study design

- Randomized controlled trial, quasi-randomized trial, non-randomized trial/quasi-experimental study, controlled before-and-after study, before-and-after study

Supplementary Table

Supplementary Table 1. Inclusion and exclusion criteria of the included studies.

First author	Inclusion criteria	Exclusion criteria
Barata PI [20]	Age > 45 years, will participate, no exacerbation in the last three months, no prior rehabilitation in the last three months, former smoking history, non-smoking status, owning a mobile smartphone, able to use a smartphone, stationary bicycle at home (for the online group), owning a pulse oximeter.	Exacerbation in the last three months, other comorbidities that could interfere with their current health status, use of medication that could affect exercise response, active smoking status, musculoskeletal conditions that could impair exercise, an impaired vision that could affect the use of the mobile application, not having a stationary bicycle at home, a cognitive impairment that could affect the understanding of the exercises.
Crooks MG [21]	Aged 40–80 years with either mild–moderate COPD (forced expiratory volume in 1 s (FEV_1) >50% predicted and FEV_1/forced vital capacity ratio <70%) or COPD of any severity diagnosed within the past 12 months Current or ex-smokers with internet access and able to use a web platform in English	A COPD exacerbation within 4 weeks before enrolment housebound Another medical condition considered by the investigator to confound study outcomes
Demeyer H [22]	Physician-based diagnosis of COPD Age >40 with a smoking history of at least 10 pack-years Not actively participating in a pulmonary rehabilitation program at the moment of inclusion (or did not plan to start) Stable patients as well as patients with an acute exacerbation in the last month Patients using walking aids or those on long-term oxygen treatment	Any comorbidity limiting a normal activity patterns Another respiratory disease as a primary diagnosis Unable to understand or operate a smartphone device

Jiang Y [23]	Aged 60 years and older Confirmed diagnosis of COPD according to the diagnosis and treatment guidelines for chronic obstructive pulmonary disease, forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.7, FEV_1<80% predicted Use of WeChat for effective communication	Patients with mental disorders, cognitive disorders, and limb dysfunction; with unstable heart disease or arrhythmia requiring drug intervention; with a history of myocardial infarction or cerebral infarction in the previous year; too weak to perform the muscle strength test; with hypertension that could not be controlled with drugs; with a history of syncope after exercise
Kwon H [24]	Patients with COPD (1) Age>20 years (2) Postbronchodilator forced expiratory volume in 1 second (FEV_1) of <80% compared with the reference range (3) Ability to walk >150 m in a 6MWT (4) Android smartphone owner	Patients who were unable to follow the exercise regimen
North M [25]	A primary COPD diagnosis as defined by the NICE guidelines and using an inhaled device Age 45 years or older Current or ex-smoker for over 10 years Ability to access and use an internet enabled device.	An allergy to saccharin due to it being contained within the placebo inhalers

Park SK [26]	(a) COPD (b) Aged 45 years or old (c) Classified as either GOLD Stage 1, 2, or 3 (d) Smartphone and could text messages (e) Ability to communicate.	(a) Psychiatric disorder (b) Hospitalization and discharge within 8 weeks due to a COPD exacerbation (c) Oxygen saturation<93% in a stable state (d) Saturation levels that decreased to 85% after a six-minute walk test (6MWT) (e) Severe respiratory symptoms in a stable state (f) Pulmonary rehabilitation within 12 months (g) Other diseases that made physical activity and/or exercise difficult (h) Usage of assistive devices to walk or problems with balance.
Spielmanns M [27]	COPD patients willing and able to sign the informed consent form for use of their pseudonymized clinical data within the scope of the present interventional trial COPD patients who have completed an in-hospital pulmonary rehabilitation program for an average duration of 3 weeks Diagnosis of COPD, defined as forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) < 70% predicted, FEV1< 80% predicted after bronchodilation, with or without chronic	The patient is unable to conduct the exercise training program due to physical, cognitive, or safety reasons, as judged by the investigators, e.g., lower limb joint surgery within the preceding 3 months, unstable cardiac diseases, predominant neurological limitations, and planned surgical or other interventions disturbing the study intervention Significant psychiatric disorders, legal incapacity, or limited legal capacity. Patient participation in another clinical trial with an investigational medication within 30 days prior to study entry Patients already using the KAIA COPD app

	symptoms (cough, sputum production) corresponding to GOLD stage II–IV Completion of an inpatient pulmonary rehabilitation program Completion of the screening period and fulfillment of the randomization criteria as defined by the protocol Ability to use a smartphone and smartphone apps Willingness to wear an activity tracker during the 6-month study period Age ≥ 40 years of age Knowledge of German language to understand the study material, assessments, and contents of the COPD app	
Vorrink SNW [28]	Patients diagnosed with COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 or 3 (forced expiratory volume in 1 s (FEV1) 30–<80%, FEV_1/forced vital capacity (FVC) <70% after bronchodilatation) Age≥40 years Completion of a PR program of 3 months within the past 6 months Living independently	Comorbidity that greatly influences physical activity Usage of an assistive device for physical activity (e.g., walker or mobility scooter) Intermittent cessation of the PR program Exacerbation resulting in a hospital admission in the 6 months prior to the commencement of the study.
Wang CH [29]	Diagnosis of COPD [with a ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) less than 0.7 after bronchodilators] The grading of moderate-to-severe airflow limitation according to GOLD criteria Stable within three months prior to enrollment.	Requirement for oxygen therapy Presence of symptomatic cardiovascular diseases or severe systemic diseases or musculoskeletal conditions with exercise performance limitation

Supplementary Table 2. Clinical outcomes of the included studies.

1) Barata PI [20)]

Clinical outcomes	Intervention arm	Control arm
Primary outcome		
FVC (%)	71.0 ± 6.8 to 71.4 ± 6.6	70.8 ± 5.9 to 70.1 ± 5.9
FEV1 (%)	41.7 ± 4.6 to 42.2 ± 4.6	42.5 ± 4.6 to 43.1 ± 4.5
FEV1/FVC (%)	44.2 ± 6.5 to 44.5 ± 6.2	44.9 ± 5.7 to 45.2 ± 5.7
MIP (cmH_2O)	55.7 ± 12.1 to 59.9 ± 12.3	55.7 ± 15.8 to 62.5 ± 16.6
MEP (cmH_2O)	80.2 ± 13.6 to 83.3 ± 13.1	82.2 ± 12.3 to 86.8 ± 12.5
6MWT (m)	342.9 ± 61.9 to 387.3 ± 56.3	340.5 ± 85.0 to 371.5 ± 79.6
CAT	20.1 ± 5.3 to 13.9 ± 4.5	19.5 ± 5.1 to 14.7 ± 4.1
mMRC (mean rank)	39.4 to 19.5	45.25 to 27.75

Data are presented as the mean ± standard deviation or number (%), unless otherwise indicated.

FVC: forced vital capacity, FEV1: forced expiratory volume in the first second, MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure, 6MWT: 6-minute walking test, CAT: COPD assessment test, mMRC: modified Medical Research Council scale.

2) Crooks MG [21)]

Clinical outcomes	Intervention arm	Control arm
Primary outcome		
CAT	21.5 ± 8.0 to 19.2 ± 9.0	19.8 ± 5.4 to 19.8 ± 7.5
≥1 critical error	21 (72.4)	18 (58.1)
inhaler error	Difference at 3 months compared with baseline: −0.3 (0.70)	Difference at 3 months compared with baseline: 0.1 (0.71)
Average inhaler	1.1 ± 1.3	1.0 ± 1.1
errors	Difference at 3 months compared with baseline: −0.3 (1.61)	Difference at 3 months compared with baseline: −0.1 (1.20)
Secondary outcome		
PAM score	59.9 ± 15.9	69.0 ± 13.8
	Difference at 3 months compared with baseline: −0.7 (14.28)	Difference at 3 months compared with baseline: −3.5 (13.07)
SEAMS	32.8 ± 5.7	33.8 ± 4.9

	Difference at 3 months compared with baseline: 1.0 (0.00)	Difference at 3 months compared with baseline: 0.0 (−3.00)
EQ5D 5L	0.6 ± 0.3	0.7 ± 0.2
	Difference at 3 months compared with baseline: 0.1 (0.23)	Difference at 3 months compared with baseline: 0.0 (0.18)
Other outcomes		
Exacerbations	18 exacerbations, 2 ER visits, 1 hospitalization	11 exacerbations, 1 ER visit, 2 hospitalizations
Number of steps per day	4948.7 ± 1667.6 (n=5) to 5458.3 ± 2266.4 (n=4)	9060 ± 5135.1 (n=9) to 10,762 ± 7199.2 (n=9)
Adverse events	5	7

Data are presented as the mean ± standard deviation or number (%), unless otherwise indicated.

CAT: COPD assessment test, EQ5D 5L: EuroQol 5 dimensions 5-level questionnaire, VAS: visual analog scale, PAM: patient activation measurement, SEAMS: Self-Efficacy for Appropriate Medication Use Scale.

3) Demeyer H [22)]

Clinical outcomes	Intervention arm	Control arm
Primary outcome		
Number of steps per day	4305 [2841–5851] to 4767 [3080–7949]	4643 [2932–6955] to 4059 [2624–6332]
Secondary outcome		
Time in at least moderately intense physical activity (min)	14 [5–26] to 18 [6–48]	15 [5–35] to 14 [3–32]
Walking time (min)	69 ± 34	72 ± 36
	Difference at 3 months compared with baseline: 7 (95% CI 8 to 12)	Difference at 3 months compared with baseline: -10 (95% CI -14 to -6)
Movement intensity during walking (m/s^2)	1.82 ± 0.30	1.86 ± 0.36
	Difference at 3 months compared with baseline: 0.06 (95% CI 0.02 to 0.1)	Difference at 3 months compared with baseline: -0.03 (95% CI -0.06 to 0.01)

6MWD	444 ± 106 to 457 ± 108	450 ± 106 to 449 ± 118
CAT	13 [7–20] to 14 [9–19]	13 [8–18] to 13 [9–20]
CCQ mental state	1 [0–2.5] to 1 [0–2.5]	1 [0–2] to 1 [0–2]
CCQ functional state	1.5 [1–2.75] to 1.5 [1–2.75]	1.5 [0.75–2.5] to 1.75 [0.75–2.75]
CCQ symptoms	1.75 [1.25–2.5] to 1.75 [1.25–2.5]	1.75 [1.5–2.75] to 2 [1.25–2.75]
At least one exacerbation	48 (30%)	43 (27%)
Lung function variables	Lung function variables during the final visit were not different from baseline variables in either group.	
Musculoskeletal events	11	2

Data are presented as the mean ± standard deviation or median [interquartile range] or number (%), unless otherwise indicated.

CI, confidence interval; 6MWD, 6-min walk distance; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire

4) Jiang Y [23)]

Clinical outcomes	Intervention arm	Control arm
Primary outcome		
CAT	21.79 ± 6.85 to 20.85 ± 7.11	22.55 ± 6.48 to 21.70 ± 6.69
Secondary outcome		
Ex-SRES	72.25 ± 38.38 to 80.53 ± 37.72	71.48 ± 40.76 to 78.25 ± 35.40
mMRC	2.79 ± 0.66 to 2.40 ± 0.79	2.75 ± 0.70 to 2.36 ± 0.71
SGRQ-system	53.02 ± 19.90 to 43.59 ± 23.63	51.12 18.63± to 45.33 ± 22.25
SGRQ-activity	56.44 ± 23.96 to 48.74 ± 24.28	56.87 ± 22.47 to 53.46 ± 23.06
SGRQ-influence	45.83 ± 24.27 to 33.27 ± 22.86	44.92 ± 18.69 to 38.63 ± 21.88
SGRQ-total	50.24 ± 20.95 to 39.66 ± 20.92	49.57 ± 17.52 to 44.24 ± 19.90

Data are presented as the mean ± standard deviation or number (%), unless otherwise indicated.

CAT: chronic obstructive pulmonary disease assessment test, Ex-SRES: Exercise Self-Regulatory Efficacy Scale, mMRC: modified Medical Research Council scale, SGRQ: St George's Respiratory Questionnaire.

5) Kwon H [24)]

Clinical outcomes	Intervention arm	Control arm
Primary outcome		
6MWT	Fixed group	379 ± 71 to 381 ± 75
	369 ± 71 to 380 ± 77	
	Fixed-Interactive group	
	394 ± 88 to 388 ± 91	
mMRC	Fixed group	1.86 ± 0.77 to 1.73 ± 0.83
	1.75 ± 0.68 to 1.50 ± 0.63	
	Fixed-Interactive group	
	1.50 ± 0.66 to 1.46 ± 0.78	
CAT	Fixed group	15.0 ± 8.7 to 13.2 ± 8.7
	15.1 ± 7.5 to 11.9 ± 8.4	
	Fixed-Interactive group	
	15.6 ± 9.1 to 13.5 ± 9.5	

Data are presented as the mean ± standard deviation or number (%), unless otherwise indicated.

6MWT: 6 min walk test, mMRC: modified Medical Research Council scale, CAT: chronic obstructive pulmonary disease assessment test.

6) North M [25)]

Clinical outcomes	Intervention arm	Control arm
Primary outcome		
CAT	26.0 ± 8.5 to 20.7 ± 7.35	28.0 ± 5.8 to 25.1 ± 7.24
Secondary outcome		
mMRC	2.9 ± 1.3 to 2.76 ± 1.35	3.1 ± 1.1 to 2.78 ± 1.11
PAM	59.7 ± 11.4 to 64.7 ± 13.46	54.0 ± 11.2 to 56.1 ± 18.49
HAD	18.9 ± 10.6 to 15.5 ± 8.88	18.1 ± 6.1 to 18.1 ± 7.78
SGRQ	66.4 ± 16.6 to 61.9 ± 14.93	68.1 ± 13.7 to 64.1 ± 15.94
WPAI questionnaire	7.3 ± 2.0 to 6.24 ± 2.68	6.9 ± 2.3 to 6.50 ± 2.98
VSAQ	3.2 ± 2.7 to 2.94 ± 1.54	2.6 ± 1.1 to 2.95 ± 2.43
Readmission rate	0.24 ± 0.44	0.39 ± 0.50

Number of exacerbations	2.9 ± 1.6 to 1.06 ± 0.83	3.2 ± 2.0 to 1.88 ± 1.84
Number of critical errors in inhaler technique	5.1 ± 3.1 to 1.17 ± 1.70	5.0 ± 3.3 to 4.00 ± 4.97

Data are presented as the mean ± standard deviation or number (%), unless otherwise indicated.

CAT: chronic obstructive pulmonary disease assessment test, mMRC: modified Medical Research Council test for dyspnea, PAM: patient-activated measures, HAD: hospital anxiety and depression scale, SGRQ: St George's Respiratory Questionnaire, WPAI: work productivity activity impairment, VSAQ: Veterans Specific Activity Questionnaire.

7) Park SK [26)]

Clinical outcomes	Intervention arm	Control arm
Primary outcome		
self-care behavior	112.91 ± 13.34 to 122.32 ± 12.23	106.05 ± 14.79 to 106.70 ± 18.47
Secondary outcome		
6MWT distance	378.32 ± 96.96 to 433.23 ± 107.23	398.10 ± 78.67 to 437.60 ± 83.62
Exercise (min/week)	215.00 ± 225.51 to 267.73 ± 449.96	144.37 ± 129.06 to 162.50 ± 212.33
Physical activity		
Total activity count/wear time	215.64 ± 103.16 to 275.09 ± 99.79	258.85 ± 105.73 to 258.59 ± 111.47
Sedentary activity % time	0.79 ± 0.10 to 0.75 ± 0.08	0.77 ± 0.08 to 0.77 ± 0.08
LPA % time	0.18 ± 0.09 to 0.21 ± 0.08	0.20 ± 0.06 to 0.19 ± 0.06
MVPA % time	0.03 ± 0.02 to 0.05 ± 0.03	0.04 ± 0.02 to 0.04 ± 0.03
Daily step count	5223.68 ± 2899.61 to 6546.77 ± 2354.43	6756.26 ± 2978.77 to 6890.39 ± 2967.73
Symptom		
Dyspnea from UCSD-SOB	21.18 ± 16.05 to 21.45 ± 17.78	19.25 ± 13.83 to 19.70 ± 14.34
Tension-anxiety from POMS	4.86 ± 2.64 to 5.23 ± 3.19	5.75 ± 4.29 to 5.80 ± 4.61

Depression from POMS	3.55 ± 2.69 to 3.68 ± 3.29	5.20 ± 5.46 to 5.45 ± 6.89
Health-related quality of life		
PCS	43.43 ± 9.00 to 43.94 ± 8.97	46.36 ± 5.58 to 44.95 ± 5.95
MCS	51.62 ± 8.71 to 50.10 ± 8.33	52.13 ± 8.49 to 49.03 ± 11.02
Healthcare use due to exacerbation for 6 months		
ED use	1 (4.5%)	0 (0.0%)
Hospitalization	2 (9.1%)	2 (10.0%)
Outpatient clinics	3 (13.6%)	1 (5.0%)
Other outcomes		
Self-efficacy		
SEMCD	6.71 ± 1.93 to 6.89 ± 1.75	6.47 ± 1.64 to 6.69 ± 2.26
Self-efficacy for managing dyspnea	6.59 ± 2.21 to 6.73 ± 2.10	6.40 ± 2.10 to 6.85 ± 2.06
Self-efficacy for managing exacerbation	6.68 ± 1.94 to 6.95 ± 2.01	6.20 ± 2.24 to 6.75 ± 1.97
Self-efficacy for maintaining exercise	7.45 ± 1.50 to 7.77 ± 1.31	6.90 ± 2.05 to 6.75 ± 2.29
Self-efficacy for increasing physical activity	6.91 ± 2.14 to 7.91 ± 1.66	6.90 ± 1.71 to 6.75 ± 2.15
Self-efficacy for decreasing sedentary time	7.18 ± 1.76 to 7.73 ± 1.42	6.60 ± 2.09 to 7.05 ± 1.76
Perception of control	4.40 ± 0.96 to 4.75 ± 0.91	4.33 ± 1.22 to 4.68 ± 0.97
Social support	2.72 ± 0.85 to 2.73 ± 0.88	2.53 ± 0.92 to 2.79 ± 1.21

Data are presented as the mean ± standard deviation or number (%), unless otherwise indicated.

6MWT: 6 min walk test, sedentary activity % time: time spent in sedentary activity (minutes/day)/daily wear time for accelerometer, LPA: light physical activity, LPA % time: time spent in LPA (minutes/day)/daily wear time for accelerometer, MVPA: moderate to vigorous physical

activity, MVPA % time: time spent in MVPA (minutes/day)/daily wear time for accelerometer, UCSD-SOB: University of California, San Diego Shortness of Breath Questionnaire, POMS: Profile of Mood States-Short Form, PCS: physical component subscale, MCS: mental component subscale, ED: emergency department, SEMCD: Self-Efficacy for Managing Chronic Diseases 6-item scale.

8) Spielmanns M [27)]

Clinical outcomes	Intervention arm	Control arm
Primary outcome		
Number of steps per day	6361.4 [3401.2–8304.3] to 5016.3 [2920.3–10206.5]	5052.21 [3531.9–8999.1] to 3105.1 [606.4–4372.0]
Secondary outcome		
CAT points	16.53 ± 7.15 to 15.13 ± 8.58	16.00 ± 7.12 to 19.72 ± 6.42
STST repetitions	19.07 ± 5.77 to 22.66 ± 7.23	16.87 ± 7.07 to 19.45 ± 9.09
CRQ domains		
Dyspnoea points	4.54 ± 1.45 to 4.54 ± 1.65	4.48 ± 1.19 to 3.69 ± 1.31
Fatigue points	4.60 ± 1.22 to 4.50 ± 1.28	4.68 ± 1.31 to 3.72 ± 1.36
Emotional function points	5.40 ± 1.07 to 4.92 ± 1.27	5.14 ± 0.97 to 4.54 ± 1.40
Mastery points	5.27 ± 1.23 to 5.08 ± 1.50	4.97 ± 1.27 to 4.48 ± 1.51
Total CRQ points	4.95 ± 1.07 to 4.76 ± 1.30	4.82 ± 0.97 to 4.11 ± 1.26
Feeling thermometer degrees	61.57 ± 19 to 66.43 ± 18	61.57 ± 17 to 58.93 ± 21
HADS-A points	4.10 ± 3.33 to 4.43 ± 3.50	4.10 ± 3.50 to 5.34 ± 4.19
HADS-D points	4.23 ± 2.90 to 4.20 ± 2.95	4.23 ± 3.69 to 6.55 ± 5.08
HADS total points	8.33 ± 5.60 to 8.33 ± 5.60	8.33 ± 6.47 to 8.33 ± 6.47
Duration of sleep (hours)	7.61 ± 1.36 to 7.60 ± 1.31	7.73 ± 1.08 to 7.13 ± 1.69
Sleep efficiency (%)	91.71 ± 3.20 to 91.95 ± 2.28	90.84 ± 3.33 to 90.75 ± 2.93

Data are presented as the mean ± standard deviation or median [interquartile range] or number (%), unless otherwise indicated.

CAT: COPD Assessment Test, STST: Sit-to-Stand Test, CRQ: Chronic Respiratory Disease Questionnaire, HADS: Hospital Anxiety and Depression Scale, HADS-A: Hospital Anxiety and

Depression Scale–Anxiety Subscale, HADS-D: Hospital Anxiety and Depression Scale–Depression Subscale,

9) Vorrink SNW [28)]

Clinical outcomes	Intervention arm	Control arm
Primary outcome		
Average steps per weekday	5824 ± 3418 to 4819 ± 2883	5717 ± 2870 to 4950 ± 2634
Average METs	1.5 ± 0.05 Difference at 12 months compared with baseline: −0.055 (−0.15–0.04)	1.57 ± 0.05 Difference at 12 months compared with baseline: −0.105 (−0.22–0.01)
Secondary outcome		
6MWD	465 ± 87 to 481 ± 89	459 ± 73 to 471 ± 70
CRQ-SAS		
Dyspnea	4.83 ± 1.25 to 4.63 ± 1.49	4.81 ± 1.3 to 4.66 ± 1.21
Fatigue	4.34 ± 1.13 to 4.14 ± 1.45	4.25 ± 1.15 to 4.08 ± 1.24
Emotional function	4.95 ± 1.08 to 4.94 ± 1.28	4.78 ± 1.24 to 4.94 ± 1.17
Mastery	5.4 ± 1.12 to 5.25 ± 1.22	5.32 ± 1.12 to 5.12 ± 1.23
Body mass index	27.78 ± 4.86 to 27.95 ± 4.96	26.77 ± 5.06 to 26.62 ± 5.07

Data are presented as the mean ± standard deviation or number (%), unless otherwise indicated.

MET: metabolic equivalent of task, 6MWD: 6-min walking distance, CRQ-SAS: Self-Administered Standardized Chronic Respiratory Questionnaire.

10) Wang CH [29)]

Clinical outcomes	Intervention arm	Control arm
Primary outcome		
ISWT	261.5 ± 29.9 to 320.0 ± 30.7	251.4 ± 21.0 to 222.5 ± 28.3
Limb muscle strength		
Elbow flexion, kg	Left 11.8 ± 0.5 to 13.5 ± 0.5 Right 11.5 ± 0.6 to 14.7 ± 0.4	Left 13.3 ± 0.7 to 13.1 ± 0.5 Right 13.6 ± 0.8 to 13.2 ± 0.6

Knee extension, kg	Left 10.9 ± 0.8 to 14.7 ± 0.7 Right 10.8 ± 0.8 to 15.1 ± 0.7	Left 12.2 ± 0.9 to 12.8 ± 0.6 Right 12.0 ± 0.8 to 12.7 ± 0.6
CRP	1531.0 ± 206.4 μg/ml to 601.1 ± 144.5 μg/ml	1028.0 ± 213.1 μg/ml to 2080.0 ± 428.4 μg/ml
IL-8	3299.0 ± 839.4 pg/ml to 990.1 ± 175.6 pg/ml	at 6 months, plasma levels of IL-8 in the control group were higher than those the mobile group.
TNF-α	Did not show any difference during the period of the home exercise training program	Significantly elevated at 2, 3 and 6 months
IL-6	Unchanged in the mobile phone group	2.8 ± 0.5 pg/ml to 7.0 ± 1.0 pg/ml

Data are presented as the mean ± standard deviation or number (%), unless otherwise indicated.

국문초록

연구 배경: 호흡 재활은 만성 호흡기 질환 환자의 호흡 곤란, 삶의 질 및 운동 능력을 포함한 임상 증상을 개선하는 것으로 잘 알려져 있다. 그러나 기관 기반 호흡 재활을 수행하는데 여러 어려움이 있음이 보고되었다. 최근에는 스마트폰 애플리케이션 기반 호흡 재활이 임상에서 사용할 수 있게 되었다. 본 연구에서는 선행 문헌 고찰 및 임상 시험을 통하여 만성 호흡기 질환 환자의 스마트폰 애플리케이션 기반 호흡 재활의 임상 결과를 연구하였다.

방법: PubMed, Embase, Cochrane 및 CINAHL 데이터베이스에서 2007 년 1 월부터 2023 년 6 월 사이에 발표된 문헌을 체계적으로 검색하여 COPD 환자에서 스마트 호흡 재활과 관련된 무작위 대조 연구를 탐색하였다. 호흡 재활 프로그램은 스마트폰 애플리케이션을 기반으로 하여 운동 프로그램을 제공하였다. 운동 능력, 증상 점수, 삶의 질 및 입원을 포함한 연구 결과를 평가하였다. 메타 분석에서는 6 분 걷기 검사 거리 (6MWD), COPD 평가 테스트 (CAT) 점수, mMRC 호흡 곤란 척도, St. George's Respiratory Quality (SGRQ)의 mean difference (MD) 및 급성 악화로 인한 입원의 risk ratio (RR)을 평가하였다.

이후 연구자들은 2022 년 서울아산병원에서 단일 기관 전향적 단일 군 중재 연구를 수행하였다. 참가자들은 12 주 동안 스마트폰 애플리케이션 기반 호흡 재활을 받았고, 재활 전과 후의 임상 지표를 비교하였다. 일차 평가 변수는 심폐 운동 부하 검사에 의해 측정된 최대 산소 섭취량 (VO_2max)였다.

그 후, 연구자들은 2023 년 서울아산병원에서 만성 호흡기 질환 환자 90 명을 대상으로 단일 기관 단일 맹검 무작위 대조 연구를 수행하였다. 참가자들은 2:1 (각각 60 명과 30 명의 참가자)의 비율로 중재와 대조군에 무작위로 할당되었다. 중재군은 12 주 동안 스마트폰 애플리케이션 기반 호흡 재활을 받았고, 대조군은 통상의 외래 진료를 받았다. 일차 평가 변수는 심폐 운동 부하 검사에 의해 측정된 VO_2max 와 CAT 이었다.

결과: 1,173 개의 선별된 연구 중 10 개의 연구가 체계적 문헌 고찰에 포함되었고 9 개의 연구가 메타 분석에 포함되었다. 6 개의 연구는 다기관 연구였다. 총 1,050 명의 참가자가 있었고 대부분은 65 세 이상의 고령이었다. 포함된 연구 간에 참가자의 기초 특성, 스마트폰 애플리케이션, 중재 및 평가 변수 등에 불일치가 있었다. 메타 분석에서는 5 개의 연구에서 6MWD 를 평가했고, MD 9.52m (95% 신뢰 구간 [CI] –3.05 ~ 22.08)였다. 6 개의 연구에서 CAT 점수를 평가했고, MD –1.29 (95% CI –2.39 ~ –0.20)였다. 3 개의 연구에서 mMRC 호흡 곤란 척도를 평가했고, MD –0.08 (95% CI –0.29 ~ 0.13)였다. 2 개의 연구에서 SGRQ 를 평가했고, MD –3.62 (95% CI –9.62 ~ 2.38)였다. 3 개의

연구에서 급성 악화로 인한 입원을 평가했고, RR 0.65 (95% CI 0.27 ~ 1.53)였다. 이러한 임상 지표는 대체로 스마트폰 애플리케이션 기반 호흡 재활에서 우수하였으나, 통계적으로 유의한 차이는 CAT 점수에서만 나타났다.

후속 단일군 연구에서 총 48 명의 참가자가 모집되었고 41 명이 재활 후 방문하였다. 대상자들의 평균 연령은 67.0 세 (interquartile range, 62.0–73.0)였으며 32 명(78.0%)이 남성이었다. 임상 지표에서 VO_2max (median 13.7~15.4ml/kg/min, P = 0.049), CAT 점수 (median 14~6, P < 0.001), Euro-QoL 5-Dimension 5-Level (EQ-5D-5L) index (median 0.795~0.862, P = 0.001), Health-related Quality of Life Instrument with 8 Items (HINT-8) index (median 0.784~0.855, P < 0.001)가 크게 개선되었다. 하위 분석에서는 재활 프로그램에 순응도 높은 참가자 (n = 17, 41.5%, P = 0.012)에서 VO_2max 가 유의하게 개선되었다. 연구 기간 동안 재활 활동과 관련된 질병 악화나 근골격계 부상을 경험한 참가자는 없었다.

후속 무작위 대조군 연구에서 총 90 명의 참가자가 모집되었고, 70 명 (중재군 46 명, 대조군 24 명)이 추적 방문을 완료하였다. 중재군 43 명이 per protocol 분석에 포함되었다. 평균 연령은 65.5 세였으며 48 명(68.6%)이 남성이었다. 재활 후 CAT 점수 (median 7.0 vs. 10.0, P = 0.039)와 mMRC 호흡 곤란 척도 (median 1.0 vs. 2.0, P = 0.010)는 중재군에서 낮았고, 국제 신체 활동 설문지 점수(IPAQ) (median 1488.0 vs. 1164.0, P = 0.037)는 중재군에서 더 높았다. 하위 분석에서 신체 활동이 많거나, 재활

프로그램에 순응도가 높은 참가자에서 임상 지표 개선이 관찰되었다. 연구 기간 동안 재활 활동과 관련된 질병 악화 또는 근골격계 부상을 경험한 참가자는 없었다.

결론: 체계적 문헌 고찰에서 스마트폰 애플리케이션 기반 호흡 재활은 기존 기관 기반 호흡 재활에 비해 운동 능력, 증상 점수, 삶의 질 및 입원에서 유리한 결과를 보였다. 메타 분석에서 CAT 점수는 스마트폰 애플리케이션 기반 호흡 재활 그룹이 대조군보다 유의하게 낮았다. 이후 진행된 임상시험에서 스마트폰 애플리케이션 기반 호흡 재활 프로그램은 만성 호흡기 질환 환자의 운동 능력, 신체 활동, 삶의 질 및 호흡 곤란 증상을 포함한 임상 결과를 개선하였다. 특히 신체적으로 활동적이거나 운동 프로그램에 순응도가 높은 참가자에서 임상 지표의 유의한 개선을 보였다. 또한 만성 질환이 있는 고령의 환자들이 스마트폰 애플리케이션 기반 호흡 재활을 안전하게 수행할 수 있었다. 따라서 기존의 기관 기반 호흡 재활이 어려운 상황에서, 스마트폰 애플리케이션 기반 호흡 재활은 만성 호흡기 질환이 있는 고령의 환자에게 유용한 치료 대안이 될 수 있다.