Effect of PEP flute self-care versus usual care in early covid-19: non-drug, open label, randomised controlled trial in a Danish community setting

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ABSTRACT OBJECTIVE

To determine whether positive expiratory pressure (PEP) by PEP flute self-care is effective in reducing respiratory symptoms among community dwelling adults with SARS-CoV-2 infection and early stage covid-19.

DESIGN

Non-drug, open label, randomised controlled trial.

SETTING

Capital Region and Region Zealand in Denmark from 6 October 2020 to 26 February 2021.

PARTICIPANTS

Community dwelling adults, able to perform self-care, with a new SARS-CoV-2 infection (verified by reverse transcription polymerase chain reaction tests) and symptoms of covid-19.

INTERVENTION

Participants were randomised to use PEP flute self-care in addition to usual care or have usual care only. Randomisation was based on permuted random blocks in a 1:1 ratio, stratified for sex and age (<60 or ≥60 years). The PEP self-care group was instructed to use a PEP flute three times per day during the 30 day intervention.

MAIN OUTCOME MEASURES

Primary outcome was a change in symptom severity from baseline to day 30, as assessed by the self-reported COPD (chronic obstructive pulmonary disease) assessment test (CAT), which was adjusted

for baseline values and stratification factors.

Participants completed the CAT test questionnaire every day online. Secondary outcomes were self-reported urgent care visits due to covid-19, number of covid-19 related symptoms, and change in self-rated health, all within 30-days' follow-up.

RESULTS

378 participants were assigned to the PEP flute self-care intervention (n=190) or usual care only (n=188). In the PEP self-care group, the median number of days with PEP flute use was 21 days (interquartile range 13-25). For the intention-to-treat population, a group difference was observed in changes from baseline in CAT scores of -1.2 points (95% confidence interval -2.1 to -0.2; P=0.017) in favour of the PEP flute self-care group. At day 30, the PEP flute self-care group also reported less chest tightness, less dyspnoea, more vigour, and higher level of daily activities, but these differences were small, and no consistent effects were seen on the secondary outcomes. No serious adverse events were reported.

CONCLUSIONS

In community dwelling adults with early covid-19, PEP flute self-care had a significant, yet marginal and uncertain clinical effect on respiratory symptom severity, as measured by CAT scores.

TRIAL REGISTRATION

ClinicalTrials.gov NCT04530435.

Introduction

Covid-19 leads to morbidity and mortality worldwide. Healthcare systems face disruption,^{1,2} and this societal susceptibility makes prevention of severe covid-19 pivotal. However, the window to intervene is short—from symptom onset to intensive care unit admission.^{3,4} The disease trajectory is difficult to predict³ and measures to remedy early stage disease are lacking.

A cornerstone in hospital treatment is the use of continuous positive airway pressure to avoid critical stage covid-19.^{5,6} As self-care, positive expiratory pressure (PEP) is used for chronic obstructive pulmonary disease (COPD),⁷ and PEP can prevent pneumonia among patients with leukaemia, presumably by preventing manifest lung infiltrates via alveoli inflation and the loosening of secretions.⁸ PEP can increase functional residual capacity and improve airway clearance. Increased gas exchange and decreased atelectasis are reported after PEP use.⁹ Analogously, PEP could have beneficial effects in covid-19.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Current evidence on covid-19 treatment is based on pharmacological studies conducted in patients in hospital, and little is known on how to alter the course of early stage disease

Home based interventions to help individuals with covid-19 overcome the course of disease with fewer symptoms could be advantageous from an economic and disease prevention perspective

WHAT THIS STUDY ADDS

Use of positive expiratory pressure (PEP), by PEP flute self-care, appears to have significant but marginal and uncertain effects on respiratory symptom severity. Individuals with PEP flute self-care reported less chest tightness and dyspnoea than those with usual care, as well as more energy and higher scores on daily activities, but these effects were small and of uncertain clinical importance. Treatment options are needed for early covid-19 in community settings, and more research is needed to establish efficacy of non-drug interventions for airway clearance.

Measures that are based at home have a high impact on society at low cost. We hypothesised that regular use of a readily available PEP device could relieve respiratory symptoms, measured by the COPD assessment test (CAT) in community dwelling individuals with early covid-19 compared with usual care.¹⁰ We also explored the effects of PEP self-care on self-reported urgent care visits for covid-19 (including admission to hospital, acute care check-up appointments, and designated covid-19 clinics), self-rated health, and various symptoms.

Methods

Study design and participants

The PEP-CoV trial was an investigator initiated, open label, randomised controlled trial in a community setting, approved by the Health Research Ethics Committee (H-20035929) and Danish Data Protection Agency (Capital Region P-2020-879). The trial was prospectively registered on 28 August 2020 (ClinicalTrials.gov NCT04530435). The protocol is available online (supplementary material).

Eligible individuals were community dwelling adults who underwent reverse transcription polymerase chain reaction (RT-PCR) testing at health service test sites and who were verified for having a SARS-CoV-2 infection for the first time. Departments of Clinical Microbiology in the Capital Region and Region Zealand (about 2.7 million inhabitants) consecutively provided test result data (supplementary material). Study invitations were sent to eligible participants via the secure platform Digital Post, used by 93% of the Danish population (<https://lifeindenmark.borger.dk/apps-and-digital-services/Digital-Post>). Responders were screened for eligibility (eligibility criteria: manifest symptoms of covid-19, having a smartphone, able to perform self-care) by telephone. Throughout the trial, all communication with eligible and actual participants was handled by secure email or telephone.

Randomisation, procedures, and trial intervention

After electronic informed consent, participants replied to a telephone administered questionnaire about present covid-19 symptoms,^{11 12} symptom severity, educational background, health literacy (in the "Understanding" and "Engagement" sections of the Health Literacy Questionnaire),¹³ and self-rated health (that is, habitual health before onset of covid-19). Subsequently, participants were randomised to usual care only or PEP self-care in addition to usual care using the REDCap (Research Electronic Data Capture) application.¹⁴ The allocation was equal (1:1), based on permuted random blocks of varied sizes and stratified for sex and age (<60 or ≥60 years).

Usual care is defined elsewhere,¹⁰ as official health service advice of self-quarantine, sufficient intake of liquid especially in case of high body temperature, and use of over-the-counter drugs to relieve symptoms. Participants allocated to PEP received (by express post) a PEP kit with resistors (yellow, size 2.5 mm; blue, 3.0 mm; green, 3.5 mm; Intersurgical, Berkshire,

UK). Participants were instructed to use PEP at least three times per day for 30 days, or at least while still they had respiratory symptoms. Video guides included instructions for resistor choice and daily hygienic maintenance (web videos 1 and 2).

Use of PEP flutes is considered safe,¹⁵ and the only contraindication would be for individuals with an undrained pneumothorax.⁹ If participants use the PEP flutes as instructed, they can supposedly reach a lung pressure of 10 cm H₂O, whereas coughing generates 80-120 cm H₂O lung pressure.¹⁶ In self-quarantine conditions, aerosol generation posed no problem. If uncomfortable, participants were advised to stop the PEP session and encouraged to contact the trial's designated hotline.

Participants were informed of official covid-19 self-care recommendations and advised to contact the healthcare services, if needed, in the same way as they would otherwise do without trial enrolment (supplementary material). All participants received text messages on days 1-30, to prompt reporting symptoms to REDCap questionnaires, without access to previous scores. Participants completed the CAT test questionnaire every day online. As adherence assessment, the PEP group reported the resistor (colour) and daily number of PEP sessions. To avoid attrition, participants in both groups were contacted halfway through the study.

Outcomes

The primary outcome was change in self-reported total CAT score from baseline to day 30. This score is validated to evaluate COPD symptoms,¹⁷ and consists of eight items; cough, phlegm, chest tightness, dyspnoea, activities of daily living at home, feeling safe at home despite symptoms (modified for this trial from feeling safe at leaving home despite symptoms), sleep quality, and vigour. Various translations of the CAT questionnaire are available online.¹⁸ Each item is scored between 0 and 5 points, with a total CAT score ranging from 0 to 40 (higher scores indicate more severe symptoms). A CAT score of 5 is considered to be the upper limit of normal in healthy non-smokers.¹⁹ A respiratory symptoms subscore including scores for cough, phlegm, chest tightness, and dyspnoea ranged from 0 to 20 points.

Secondary outcomes were self-reported urgent care visits during the study (see supplementary material, including the statistical analysis plan). Other outcomes were the number of covid-19 related symptoms at day 30 and any change in self-rated health up to day 30. At 30 day follow-up, individuals in the PEP group was asked the open question "How do you describe the PEP flute effect?" Outcomes of drug treatment and clinical progression including mortality²⁰ for the entire study population awaits access to register data from the Danish health authorities and will be reported later.

Statistical analysis

Using 80% power at a 0.05 level, 141 participants in each group were needed to show an a priori expected

mean group difference of at least two points in the change in CAT score, equivalent to the clinically meaningful effect established in COPD.¹⁹ Anticipating attrition, we aimed to include 400 participants.

We did the primary analysis using the intention-to-treat population (all randomised participants). Continuous outcomes were analysed by use of repeated measures mixed linear models, which included participants as random effects, and included group, day, and the corresponding interaction as fixed effects factors, adjusted for baseline values and the stratification factors. Missing outcome data were handled by the mixed linear models.²¹

Dichotomous outcomes were analysed by logistic regression with the same fixed effects and adjustments; however, models included data only from baseline and day 30. Missing outcome data were imputed semi-automatically to generate five datasets according to data as observed, and four different worst or best scenarios. We did sensitivity analyses for the continuous outcomes by repeating the primary analyses on the per protocol population (supplementary material). Further, the primary analysis was repeated, adjusting for age as a continuous variable rather than the cutoff threshold at 60 years. We also analysed individual CAT items using the primary analysis (repeated measures linear mixed models). All analyses were performed by use of the statistical software SAS version 9.4 (SAS Institute, Cary, NC, USA).

Patient and public involvement

Neither the public nor patients were involved in the trial design, analyses, or reporting because the study was urgently designed responding to a pandemic crisis.

Results

Trial recruitment began on 6 October 2020. Enrolment stopped on 26 February 2021 before reaching the target sample size, owing to slow recruitment (as a result of the successful infection control measures in Denmark). Of 8386 community dwelling adults with a positive PCR test result, 635 responded; 378 responders were included in the study and were allocated to receive either PEP (as an add-on to usual care; n=190) or usual care only (n=188), defining the intention-to-treat population that was included in all primary analyses (fig 1).

Characteristics between the two groups were similar (table 1). Most participants were women (n=274; 72.5%) and younger than 60 years (n=324; 85.7%; range 19-80 years), and self-rated their health as good to excellent before covid-19 (n=362; 95.8%). Information of ethnic origin was unavailable. Median illness duration at inclusion was four days (interquartile range 3-7) with an average number of 11 symptoms (standard deviation 3.4) related to covid-19 within the past week. Cough was the predominant respiratory symptom (table 1).

In the PEP group, 177 (93.2%) received the PEP kit within three days from inclusion (mean 1.6 days; range 0-10). Participants underwent a median of 2.5

(interquartile range 1.5-2.9) PEP sessions per day and reported using the PEP flute for a median of 21 days (interquartile range 13-25; supplementary material). In the self-reports, the highest number of PEP flute sessions registered for one day was three (n=103), four (n=34), five (n=21), six (n=8), and seven or more (n=3). PEP use (as expressed by the mean number of sessions per day) decreased in correlation to the decrease in average CAT score throughout the 30 day trajectory (supplementary material). Overall, the most frequently used resistor was green (44%; n=1926) followed by yellow (30%; n=1289) and blue (26%; n=1150). At follow-up, 56 participants (29.5%) reported PEP use to provoke coughing of phlegm, which was rarely known to be present. Uncertain or no effect of PEP self-care was reported by 51 (26.8%) participants (with few respiratory symptoms).

We saw a significant group difference in the changes from baseline to day 30 in the CAT score (-1.2 points (95% confidence interval -2.1 to -0.2); P=0.017), in favour of the PEP group (table 2). Figure 2 shows the trajectories of the mean CAT scores per day from baseline. We saw no significant group differences in mean changes from baseline in the CAT respiratory symptoms subscore (table 2).

The average number of covid-19 related symptoms at day 30 decreased to around 5, with no significant group difference. More participants in the PEP group reported urgent care visits than in the usual care group. However, this group difference was not significant (table 2 and supplementary material). Changes from baseline in self-rated health showed a small but significant group difference (0.2 points (95% confidence interval 0.01 to 0.4); P=0.041; table 2). At day 30, the predominant respiratory symptom was shortness of breath, with half of participants still reporting this symptom within the past week. Among general symptoms, fatigue was most frequently reported at baseline and follow-up (table 1 and table 2).

The sensitivity analyses confirmed the primary analyses, except for the change from baseline in self-rated health (supplementary material). In the individual CAT items, four items showed significant small group differences at day 30 (chest tightness -0.24 points (95% confidence interval -0.40 to -0.09); P=0.002), dyspnoea -0.28 points (-0.46 to -0.09); P=0.004), activities of daily living -0.40 points (-0.60 to -0.21); P<0.001), and vigour -0.42 points (-0.62 to -0.22); P<0.001; fig 3). In total, 20 participants reported adverse events related to PEP use but no serious adverse events (table 3).

Three participants in the PEP self-care group stopped using the PEP flute (one from headache, two from discomfort by PEP induced coughing). The remaining participants who reported adverse events were recommended to alter their PEP use (eg, reduce the number of respirations in each session in the case of dizziness, to prevent hyperventilation); otherwise their adverse events resolved naturally. In the usual care group, one participant who felt discomfort by self-reporting symptoms avoided replying to the daily CAT questionnaire.

Fig 1 | Trial flow. RT-PCR=reverse transcription polymerase chain reaction; PEP=positive expiratory pressure; CPAP=continuous positive airway pressure; *Data provided by the Departments of Clinical Microbiology at the Copenhagen University Hospitals Rigshospitalet, Herlev, and Hvidovre, covering the entire Capital Region; and at the Zealand University Hospital Slagelse covering the Region Zealand. †According to the study protocol, these three participants are in the per protocol population

Discussion

Principal findings

In this randomised, non-drug intervention study for individuals with early covid-19, PEP flute self-care showed a significant effect on self-reported severity of respiratory symptoms, compared to usual care. However,

the estimated treatment difference in the CAT score in our study was smaller than the two points minimal clinical important difference used in people with COPD¹⁹ and does not represent a robust demonstration of effectiveness.

Our fully remote trial with PEP kit delivery by mail makes PEP a cheap, easily accessible, and feasible

Table 1 | Baseline characteristics of intention-to-treat study population using PEP flute self-care versus usual care for early covid-19. Data are number (%) of participants unless stated otherwise

Characteristic	PEP flute self-care (n=190)	Usual care (n=188)
Personal characteristics		
Age (years; mean (standard deviation))	46.7 (13.0)	47.0 (13.3)
Age ≥60 years	27 (14.2)	27 (14.4)
Female sex	138 (72.6)	136 (72.3)
Body mass index (mean (standard deviation))	26.1 (5.2)	25.5 (4.9)
CAT score (mean (standard deviation); higher scores indicate more severe symptoms)		
Total score (range 0-40)	13.1 (7.0)	12.5 (6.8)
Respiratory symptoms subscore (range 0-20)	5.9 (3.7)	5.7 (3.7)
No of covid-19 related symptoms within past week	11.0 (3.4)	11.1 (3.3)
Respiratory symptoms within past week		
Cough	161 (84.7)	161 (85.6)
Runny or stuffy nose	136 (71.6)	139 (73.9)
Sneezing	132 (69.5)	123 (65.4)
Sore throat	105 (55.3)	108 (57.5)
Shortness of breath	96 (50.5)	108 (57.5)
Chest pain	73 (38.4)	83 (44.2)
Other symptoms within past week		
Feeling of illness	177 (93.2)	176 (93.6)
Fatigue	168 (88.4)	172 (91.5)
Headache	160 (84.2)	157 (83.5)
Fever or fever sensation	159 (83.7)	152 (80.9)
Muscle or joint pain	142 (74.7)	142 (75.5)
Chills	124 (65.3)	103 (45.2)
Lack of appetite	90 (47.4)	92 (48.9)
Lost or altered sense of taste	88 (46.3)	86 (45.7)
Lost or altered sense of smell	83 (43.7)	75 (39.9)*
Nausea or loathing for food	53 (27.9)	65 (34.6)
Diarrhoea	51 (26.8)	57 (30.3)
Reddened or itchy eyes	44 (23.2)	34 (18.1)
Abdominal pain	39 (20.5)	46 (24.5)
Vomiting	11 (5.8)	7 (3.7)
Pain at micturition	5 (2.6)	2 (1.1)
Days from onset of symptoms to trial inclusion (median (interquartile range))	4 (3-6)	4 (3-7)
Self-rated health before covid-19		
Score (1-5; mean (standard deviation))†	2.0 (0.9)	1.9 (0.8)
Excellent	55 (28.9)	65 (34.6)
Very good	85 (44.7)	77 (41.0)
Good	42 (22.1)	38 (20.2)
Fair	6 (6.2)	8 (4.2)
Poor	2 (1.1)	0 (0.0)
Health professional education		
Health literacy	70 (36.8)	81 (43.1)
Understanding‡	17.2 (2.3)	17.3 (2.4)
Engagement‡	17.0 (2.8)	17.0 (2.8)
Smoking habits including e-cigarettes		
Everyday smoker	6 (3.2)	10 (5.3)
Weekly/social occasions smoker	5 (2.6)	10 (5.3)
Quit smoking/never smoked	179 (94.2)	168 (89.4)
Alcohol intake		
Units of alcohol per week in average	2.9 (3.7)	3.0 (4.3)

PEP=positive expiratory pressure; COPD=chronic obstructive pulmonary disease; CAT=COPD assessment test.

*N=187.

†Mean based on self-rated health ranged from 1 (excellent) to 5 (poor).

‡Five item scale with a maximum of 20 points (high score indicating high health literacy).

public health intervention, even for individuals under quarantine. We aimed to conduct a pragmatic study with high implementation potential by giving directives via video supported by a telephone hotline, making a potential effective intervention an applicable solution to healthcare systems worldwide.

Comparison with other studies

Studies in similar community settings are scarce and urgently needed, as highlighted in a recent editorial.²²

Few studies have tested drug treatments in early covid-19. The PRINCIPLE study concluded against routine azithromycin use,²³ and effects of fluvoxamine on reducing clinical deterioration has been disputed.²⁴ Supplementation with zinc and ascorbic acid did not affect symptom duration.²⁵ Twice daily inhaled budesonide showed promising effect in the STOIC trial, reducing the likelihood of needing urgent medical care and shortening the recovery time.²⁶ Combining budesonide and PEP self-care, if proven effective,

Fig 2 | Trajectories of mean CAT total score in intention-to-treat study population using PEP flute self-care versus usual care for early covid-19. PEP=positive expiratory pressure; error bars=standard error; COPD=chronic obstructive pulmonary disease; CAT=COPD assessment test

could be speculated to have additive preventive effects, but this combination awaits further investigation.

In the analysis of the individual CAT items, we found no group differences in coughing, but the PEP group reported more phlegm than the usual care group early

in the 30 day trajectory (fig 3). Many participants stated that PEP provoked coughing of phlegm, suggesting an improvement in airway clearance.^{8,9} Potential plausible consequences include reduced chest tightness and dyspnoea and improved levels of vigour and activities

Table 2 | Primary and secondary outcomes at day 30 in intention-to-treat study population using PEP flute self-care versus usual care for early covid-19

Outcome	Study group (least squares mean (SE) or No (%) of participants)*		Estimated treatment difference	
	PEP flute self-care (n=190)	Usual care (n=188)	Difference or odds ratio (95% CI)*	P value
Primary outcome¶				
Change in CAT score (0-40, higher scores indicate more severe symptoms)†	-8.3 (0.4)	-7.2 (0.4)	-1.2 (-2.1 to -0.2)	0.017
Secondary outcomes¶				
Change in self-rated health (1-5, higher scores indicate poorer health)‡‡	0.3 (0.08)	0.5 (0.08)	0.2 (0.01 to 0.4)	0.041
Change in CAT respiratory symptoms subscore (0-20 higher scores indicate more severe symptoms)†	-3.7 (0.2)	-3.4 (0.2)	0.4 (-0.1 to 0.9)	0.16
Overall No of covid-19 related symptoms within past week†	4.7 (0.9)	5.0 (0.8)	-0.3 (-3.5 to 2.9)	0.82
Urgent care visits‡¶	23 (11.9)	17 (8.8)	1.4 (0.36 to 5.36)	0.64
Respiratory symptoms within past week‡¶				
Shortness of breath	97 (51.1)	102 (54)	0.97 (0.5 to 1.88)	0.93
Cough	76 (39.9)	76 (40.6)	0.93 (0.48 to 1.8)	0.84
Runny or stuffy nose	70 (36.6)	72 (38.4)	0.95 (0.49 to 1.84)	0.87
Sneezing	62 (32.9)	64 (34.1)	0.89 (0.44 to 1.79)	0.74
Chest pain	35 (18.4)	42 (22.3)	0.83 (0.33 to 2.05)	0.69
Sore throat	28 (14.6)	34 (18)	0.76 (0.27 to 2.15)	0.62
Other symptoms within last week				
Fatigue	105 (55.3)	116 (61.6)	0.81 (0.43 to 1.51)	0.51
Lost or altered sense of smell	89 (46.8)	81 (43.3)§	1.12 (0.59 to 2.16)	0.73
Lost or altered sense of taste	82 (43)	76 (40.6)	1.11 (0.59 to 2.09)	0.75
Headache	59 (31.2)	65 (34.7)	0.84 (0.42 to 1.67)	0.63
Muscle or joint pain	38 (20)	39 (20.7)	0.96 (0.4 to 2.28)	0.93
Reddened/itchy eyes	38 (20)	35 (18.5)	1.05 (0.43 to 2.58)	0.91
Feeling of illness	29 (15.2)	39 (20.8)	0.67 (0.25 to 1.77)	0.44
Fever or fever sensation	26 (13.6)	24 (12.6)	1.05 (0.32 to 3.42)	0.94
Lack of appetite	24 (12.5)	29 (15.3)	0.77 (0.24 to 2.49)	0.67
Chills	23 (11.9)	22 (11.5)	0.91 (0.25 to 3.33)	0.89
Abdominal pain	19 (9.8)	33 (17.4)	0.49 (0.13 to 1.82)	0.32
Nausea or food loathing	16 (8.2)	24 (12.6)	0.56 (0.11 to 2.78)	0.50
Diarrhoea	16 (8.2)	17 (8.8)	0.89 (0.17 to 4.59)	0.89
Pain at micturition	10 (5.5)	9 (5)	0.89 (0.07 to 11.58)	0.93
Vomiting	7 (3.9)	5 (2.9)	1.04 (0.01 to 123.81)	0.99

PEP=positive expiratory pressure; SE=standard error; COPD=chronic obstructive pulmonary disease; CAT=COPD assessment test.

*Adjusted for baseline values and stratification factors (sex and age ≥60 years).

†Data for primary and some secondary outcomes are least squares mean (SE) and difference (95% confidence interval); data for other outcomes (from "Urgent care visits" onwards) are number (%) of participants and odds ratio (95% confidence interval).

‡Likert score ranging from 1 (excellent) to 5 (poor).

§N=187.

¶Missing data handled according to statistical analysis plan (see methods and supplementary material).

Fig 3 | Trajectories of mean CAT scores for individual symptoms in intention-to-treat study population using PEP flute self-care versus usual care for early covid-19. PEP=positive expiratory pressure; error bars=standard error; COPD=chronic obstructive pulmonary disease; CAT=COPD assessment test

of daily life. Correspondingly, patients with lower respiratory tract infection undergoing oscillatory PEP treatment peaked in sputum quantities after two to three days and showed improved oxygenation and inflammatory status, compared with mechanical percussion.²⁷ Our trial lacked oxygen saturation monitoring, and thus could not establish an association between PEP and improved oxygenation. Overall, many participants in our trial reported persistent covid-19 related symptoms at day 30 with symptom

profiles comparable to other epidemiological studies.²⁸ Long term follow-up of our study participants at day 90 and day 180 will be performed.

Limitations of this study

This study was an open label trial because a placebo PEP intervention was not possible. Our study had a risk of contamination bias; the usual care participants who were able to acquire the PEP-flute unprescribed, of which four participants actually did. Furthermore,

Table 3 | Adverse events reported by study participants using PEP flute self-care versus usual care for early covid-19. Data are number (%) of participants

Adverse event	PEP flute self-care (n=174)	Usual care (n=177)
Dizziness	6 (3.4)	0
Myalgia in the chest due to provoked coughing	5 (2.9)	0
Initially increased dyspnoea	3 (1.7)	0
Discomfort by huffing and coughing	3 (1.7)	0
Deterioration of already present headache	2 (1.1)	0
Nausea	1 (0.6)	0
Discomfort from daily self-report of symptoms	0	1 (0.6)
Total	20 (11.5)	1 (0.6)

PEP=positive expiratory pressure.

Of the intention-to-treat population (PEP, n=190; usual care, n=188), table shows the number of adverse events among 174 and 177 participants for the PEP self-care and usual care groups, respectively, who could be reached for 30 day follow-up via telephone.

consequential to ethical restrictions in the recruitment procedure, trial invitation was sent digitally as one information letter without knowledge of symptom status of the recipients. The high rate of eligible individuals not responding to the invitation (7751/8386) suggests that these non-responders were asymptomatic or not unwell enough to participate, or that they were too unwell to respond to the invitation. Overall, participants reported good health and high health literacy, and 40% (n=151) had a health professional education, which could limit generalisability.

Furthermore, because we lacked validated scales on covid-19 symptom severity, we used the CAT score as the primary outcome. Whether the estimated treatment difference found in our study is of clinical relevance in a covid-19 population is uncertain.²⁹ Methodological considerations for future studies are elaborated in the supplementary material.

Moreover, the trial lacked objective outcome measures. The design aimed to mirror the public health context, with an interventional risk profile not requiring the ongoing monitoring of participants. If PEP self-care can help prevent severe covid-19, its ease of use, universal applicability, low cost (<€10; £9; \$12), and lack of systemic side effects would be advantageous.

Qualitative follow-up, as planned, could give more insight into the potential for PEP self-care to empower people with covid-19 in relieving symptoms (such as chest tightness or dyspnoea) when necessary. Qualitative interviews will also give insight into the perceived feasibility of instructive video guides, particularly in relation to the optimal use of the PEP flute. The PEP group was given three different resistors to accommodate for variation in baseline respiratory capacity and changes in symptoms throughout the course of disease. Given the complexity of these self-reported data of resistor choice in relation to sex, symptom severity, body mass index, and age, interpretations of these data are not yet available and may be further validated by qualitative follow-up. Finally, the statistical analyses of secondary outcomes, urgent care visits, and symptoms could be underpowered and more research into the efficacy and safety of PEP self-care is needed.

Conclusions

In community dwelling adults with early covid-19, PEP self-care had a significant, yet marginal and uncertain clinical effect on respiratory symptom severity as measured by the CAT score. As a global response to pandemics, more research is needed into home based interventions that are safe and of low cost, and that can be easily distributed and scaled up.

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Contributors: AM conceived the study idea and MKS gathered the project team together. AM, MKS, SCL, MH, LMK, NW, and BLH contributed to the study conception and design. AM was the project manager. LMK oversaw the production of instruction videos. ASB steered the setup of data management system, supervised by MH. JDK and XCN provided the data of individuals who tested positive of SARS-CoV-2. AM and ASB handled recruitment, data collection, deliverance of intervention, and assessment of all participants. AM handled the telephone hotline and responded to requests for advice from participants, including regarding any adverse events. MH developed the allocation sequence. MH and SCL managed the data and statistical analysis. NW had the medical responsibility during conduct of the trial, and BLH was the project lead. AM drafted the first version of the manuscript. All authors read and critically revised the manuscript, and all authors approved the final manuscript and submission of the article. The article was written according to ICMJE guidelines without the use of professional writers. BLH is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: This study was approved by the health research ethics committee of the Capital Region of Denmark (H-20035929).

Data sharing: Deidentified participant data will be made available once all planned analyses have been completed and published by contacting the corresponding author (amol@ucdiakonissen.dk) for a specified purpose through a data sharing agreement, following approval of the trial lead (BLH) and with investigator support. A data dictionary will be provided.

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The authors will disseminate the study results directly to participants via secure email. The results will be also disseminated through scientific meetings and press releases. Results will be disseminated by the Parker Institute at Bispebjerg Frederiksberg Hospital. It will also be shared by study investigators through social media platforms.

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Web appendix: Supplementary material

Web video 1: Instructions for PEP flute use and choice of resistor

Web video 2: Cleaning the PEP flute