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Effects of PACK training on the management of asthma and chronic obstructive pulmonary disease by primary care clinicians during 2 years of implementation in Florianópolis, Brazil: extended follow-up after a pragmatic cluster randomised controlled trial with a stepped-wedge design

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ABSTRACT

Background Training primary care doctors and nurses to use Practical Approach to Care Kit (PACK) improved management of asthma and chronic obstructive pulmonary disease (COPD) in a previous randomised trial. The present study examined the training effects including a second year of follow-up with expanded coverage of repeated training sessions.

Methods Using a stepped-wedge cluster randomised trial design, 48 clinics were randomly allocated either to sequence A: (1) no intervention, (2) no intervention, (3) intervention or sequence B: (1) no intervention, (2) intervention, (3) intervention, during three 12-month periods. Primary outcomes were change in treatment and spirometry ordering. Effects of any exposure to the training, and of exposure to the first and second years of training, were estimated with mixed effect logistic regression models.

Results Any exposure to training was associated with increased changes in treatment (OR adjusted for calendar time (OR) 1.29, 95% CI 1.02 to 1.64) and more spirometry ordering (OR 1.55, (95% CI 1.22 to 1.97)) in asthma patients, and with more spirometry ordering (OR 1.50 (95% CI 1.15 to 1.96)) in patients with COPD. Change in asthma treatment was more likely during the first and second year of exposure to training compared with no exposure (ORs 1.43 (95% CI 1.09 to 1.87); 1.91 (95% CI 1.21 to 3.02)), respectively. Spirometry was more likely during the first and second year of exposure in asthma patients (ORs 1.76 (95% CI 1.34 to 2.30); 2.05 (95% CI 1.32 to 3.19)) and in patients with COPD (ORs 1.57 (95% CI 1.18 to 2.10)); 1.71 (95% CI 1.08 to 2.70)).

Conclusion Extended follow-up suggested that PACK training continued to be effective in improving chronic respiratory care and that effective intervention delivery was sustainable for 2 years.

Trial registration number NCT02786030.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Practical Approach to Care Kit (PACK) training was shown to improve investigation and treatment of asthma and chronic obstructive pulmonary disease in a randomised trial in Florianópolis, Brazil.

WHAT THIS STUDY ADDS

⇒ PACK Brazil trial clinics were followed for an additional year during which the initial control clinics also received the training intervention. Sustained and improved effects were found for up to 2 years of intervention.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The sustainability and replicability of PACK's effects suggest that it is suitable for upscaling in Brazil and could potentially be beneficial for other long-term conditions and in other middle-income countries.

INTRODUCTION

Brazil has experienced increased life expectancy and decreasing mortality over the past

30 years, with 6.8 years increased life expectancy and 5.7 years increased healthy life expectancy between 1990 and 2016.[1] This is partly due to the expansion of Brazil's Unified Health System (Sistema Único de Saúde).[2 3] The burden of chronic respiratory disease has decreased, largely due to reductions in smoking. Between 1990 and 2016, years of life lost due to chronic obstructive pulmonary disease (COPD) decreased by an estimated 44% and years lived with disability due to asthma decreased by 25%.[1] However, analysis of Brazilian data from the Global Burden of Disease 2019 study showed that tobacco use and air pollution were still leading risk factors for mortality, through their effects on chronic respiratory and cardiovascular disease (CVD) and neoplasms.[4] For many people with asthma or COPD, these conditions are not diagnosed or appropriately treated.[5 6] Local initiatives to increase access to asthma treatment in Brazil have led to reductions in hospital admissions, confirming the potential for wider implementation.[7–10] Increased life expectancy has led to increased prevalence of multimorbidity, with chronic respiratory disease often coexisting with other chronic conditions such as CVD and CVD risk factors, and poor mental health.[1] These comorbid conditions are also often not identified or are suboptimally treated—a casualty of clinical inertia that is a pervasive problem in chronic disease management worldwide.[11]

A promising approach to addressing these problems is to strengthen the clinical skills and decision-making of health professionals working in Brazil's public sector primary care facilities. This is a strategy of the Practical Approach to Care Kit (PACK). PACK comprises a point of care clinical decision support tool or guide, containing algorithmic diagnostic and treatment recommendations for management of important health conditions commonly managed in primary care.[12] A second component of PACK is clinic-based educational outreach training in the use of the PACK guide during all consultations.[13] The implementation approach of the PACK programme is to embed the use of the guide into everyday clinical practice and provide a standard of care for clinicians, health managers and policy-makers. The PACK clinical decision guides are localised to match the policy, burden of disease and resources of different countries and settings[14] through a mentored development process. PACK programmes also include health system strengthening strategies, such as clarifying and strengthening health professionals' roles and scope of practice and clarifying referral pathways. PACK for adults was initially developed, evaluated and implemented at large scale in South Africa, and versions have been developed for other countries including Nigeria, Ethiopia, Malawi, Botswana and Indonesia.[15–17]

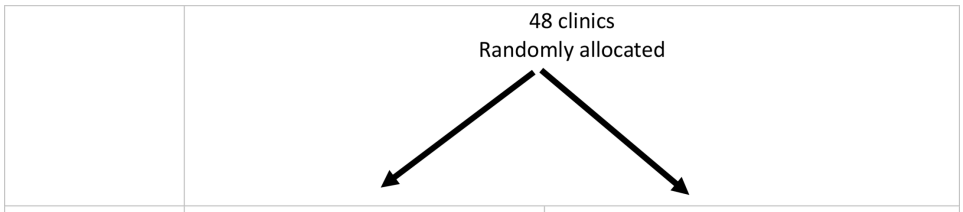
Implementation of PACK for adults, PACK Adulto, in Brazil began in 2016 in municipal primary care facilities in the city of Florianópolis, following localisation of the programme by municipal health leads mentored by PACK's developers, the University of Cape Town's Knowledge Translation Unit (KTU).[18] Conditions covered by the comprehensive PACK Adulto guide include over 40 commonly presenting symptoms and 24 chronic conditions. The PACK training curriculum in Florianópolis included modules on general health check-up, respiratory symptoms, dengue fever, genital ulcers and syphilis, back pain, abdominal pain, asthma, COPD, cardiovascular risk, diabetes, hypertension, HIV, tuberculosis, antenatal care, depression and alcohol misuse. Of these conditions, asthma and COPD were of particular interest to the investigators because local family physicians considered them to be frequently underdiagnosed and undertreated in Florianópolis and because several of the investigators had experience of strengthening primary respiratory care in low-resource settings. The effectiveness of PACK training on management of asthma and COPD care in that city was evaluated in a pragmatic parallel arm cluster randomised control trial from July 2016 to March 2018.[19 20] It was found to increase investigation of asthma and COPD and had beneficial effects on asthma treatment, although effects on COPD treatment were small and not statistically significant.

A limitation of most trials of complex health system interventions is that they usually only continue for relatively short periods such as a year, although interventions and their effects may not be sustained for longer periods especially when they are implemented at larger scale.[21–24] A systematic review of studies of sustainability of evidence-based interventions in healthcare found that in only 23% of them could sustained effects be found 2 years after initial implementation.[21 24] Extended follow-up after such trials is, therefore, needed, to show whether delivery of the interventions can feasibly be continued, and whether their effects on outcomes change over time. The present study aimed to answer the outstanding question of whether the PACK programme and its effects could be extended and sustained during a second year of implementation and expansion. It incorporates data collected during the initial trial and continues follow-up of individuals during a second year, during which the initial control clinics also received training. The objectives were (1) to estimate the effects on outcomes of any exposure to training (regardless of duration) compared with no training and (2) to estimate dose effects on outcomes of exposure to 1 and to 2 years of training, compared with no training,

METHODS

Study design

The study had a stepped-wedge cluster randomised control trial design, with two steps after baseline, incorporating and following on from a parallel arm cluster randomised trial[19 20] (figures 1 and 2). It entailed extended follow-up of clinics and patients that participated in the original randomised trial, including an additional year of follow-up during which clinics in both arms received the intervention that had been provided only to one of the arms during the original trial. This extended



Period	Sequence A 24 clinics	Sequence B 24 clinics
T0 (baseline)	**No intervention** 2812 participants with asthma 1379 participants with COPD	**No intervention** 2563 participants with asthma 1590 participants with COPD
T1	**No intervention** 2768 participants with asthma - including 2305 (82%) followed up from baseline 1307 participants with COPD - including 1157 (84%) followed up from baseline	**Intervention delivered** 2642 participants with asthma - including 2103 (82%) followed up from baseline 1565 participants with COPD - including 1353 (85%) followed up from baseline
T2	**Intervention delivered** 2648 participants with asthma - including 2071 (74%) followed up from year 0 1252 participants with COPD - including 1043 (76%) followed up from baseline	**Intervention delivered** 2648 participants with asthma - including 1865 (73%) followed up from baseline 1217 participants with COPD - including 1217 (77%) followed up from baseline

Figure 1 Study design and participants. T0, T1 and T2 are 12-month periods during which outcomes are measured. The effect of the intervention is estimated by comparing outcomes measured during the 'wedge' of periods during which clinics received the intervention (T2 in sequence A; T1 and T2 in sequence B) with periods during which clinics did not receive the intervention (T0 and T1 in sequence A; T0 in sequence B). COPD, chronic obstructive pulmonary disease.

follow-up was planned after completion of the original trial and was not included in the original trial's registered protocol (https://clinicaltrials.gov/ NCT02786030).

Each cluster was 1 of 48 municipal clinics in Florianópolis, Brazil. Before any training began, the 48 clinics were randomly allocated to intervention and control arms in a 1:1 ratio within 6 strata, using nQuery Advisor. The strata were defined by numbers of doctor–nurse teams in each clinic, and by their geographical location in higher or lower income residential areas of the municipality. With the present stepped-wedge design, the original random allocation entailed that 24 clinics were randomly allocated to sequence A: (1) no intervention, (2) no intervention, (3) intervention during periods T0, T1 and T2, respectively, and that 24 clinics were allocated to sequence B: (1) no intervention, (2) intervention and (3) intervention (figures 1 and 2). That is, sequence A clinics received training during T2 only; sequence B clinics received training during T1 and T2. T0, T1 and T2 are defined as follows.

Outcomes were recorded during three 12-month periods: T0: before any training began (1 May 2015 to 30 April 2016); T1: after training began in sequence B clinics (1 July 2016–30 June 2017); and T2: after training began in sequence A clinics and continued in sequence B clinics (1 April 2018–31 March 2019) (figures 1 and 2). There was a 2-month transition period between T0 and T1 during which PACK guides were distributed to clinics without training, and a 9-month transition period between T1 and T2 because of disruptions to municipal services caused by three strikes of municipal workers.

Regarding dose of exposure to training, during T0 no clinics were exposed to the training. During T1, sequence B clinics were exposed to a first year of training and

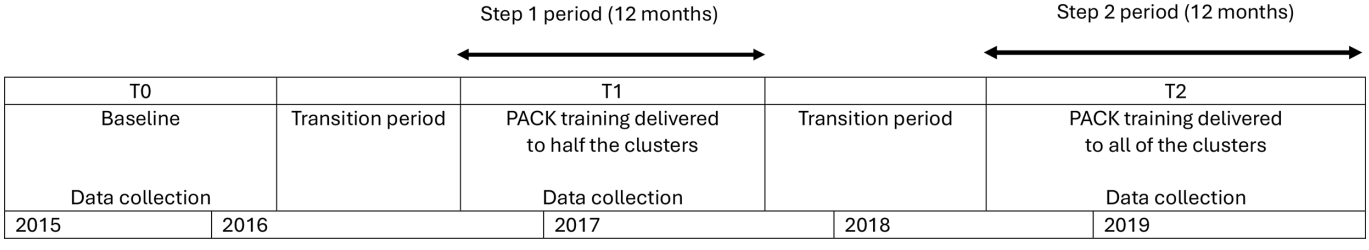


Figure 2 Timeline of the trial. PACK, Practical Approach to Care Kit.

sequence A clinics were not exposed to training. During T2, sequence B clinics were exposed to a second year of training and sequence A clinics were exposed to a first year of training.

The study had an open cohort design, including any eligible individuals who attended a participating clinic during any of the three periods. A secondary statistical analysis was restricted to the closed cohort of individuals who attended during all three periods.

The nature of the intervention targeted at doctors and nurses meant that healthcare professionals could not be blinded. However, patients were unaware of whether their clinic had received the intervention.

Patient and public involvement

Patients and public were not involved in carrying out this study. However, Brazilian health professionals and health professional organisations were consulted in developing the PACK guide.

Study population

Eligible individuals were all patients aged 18 years and over, who attended a participating clinic during the T0, T1 and T2 periods, with a diagnosis of asthma or COPD ever recorded since 1 January 2010. They were identified using a consolidated municipal database of electronic medical records in which diagnoses were coded using International Classification of Disease (ICD-10) diagnostic codes (codes 40–47). All eligible individuals were included in the study, using medical records to measure their outcomes.

Delivery of PACK in sequence A and sequence B clinics

Both sequence A and sequence B clinics were provided with the PACK guide at the end of the T0 in May 2016, and it remained available thereafter. This study evaluated the effects of the PACK programme, which consisted of training supported by mentorship and health system strengthening. The effects of the guide unsupported by training could not be directly estimated because there was no period during which one arm had the guide and the other arm did not. The intervention and control conditions have been described in greater detail elsewhere.[19 20]

The PACK guide is an integrated, comprehensive clinical decision support tool for use during primary healthcare consultations with adult patients.[12] A global version provides an evidence-aligned and WHO guidance-aligned clinical approach to common symptoms, including cough, difficulty breathing, wheeze and chest pain, and chronic conditions, including asthma, COPD, CVD and risk, and depression. The chronic respiratory diseases section covers investigation, diagnosis and acute and chronic treatment of asthma and COPD, and use of inhalers, spacers and peak flow metres. It also contains the screening for and management of common co-morbidities including CVD and depression. The Florianópolis version, PACK Brasil Adulto—versão Florianópolis, was adapted to fit local needs, resources, and local and national guidelines and protocols, and translated into Brazilian Portuguese. It was first published in 2016 and updated annually during the study period.[18]

PACK training comprised educational outreach for primary care doctors and nurses on how to use the PACK guide based on clinical case scenarios covering a range of conditions common in primary care, including respiratory diseases.[13] During T1, initial training was delivered in sequence B facilities over 12 sessions, followed by monthly maintenance training sessions. During T2, training sessions were delivered in both sequence A and sequence B facilities throughout the year. Training was led by pairs of facility trainers who were primary care clinicians and worked in the same facility or nearby. Facility trainers were trained and supported by local master trainers who received initial training and ongoing mentorship and support from the KTU team. Training was delivered to all primary care doctors and nurses delivering adult patient-facing care in each clinic, all of whose clinical responsibilities included caring for patients with asthma and COPD. After initial training, ongoing support included facility trainers visiting each clinic monthly, and the trainers continuing discussions with facility trainers using email and a WhatsApp group. Newly appointed doctors and nurses received additional training sessions delivered by local trainers. This intervention, comprising group training sessions, ongoing mentorship, support and health system strengthening, continued in the same way in sequence B clinics during T2. In T1, 160 sequence B staff were trained, and in T2, 320 sequence B and sequence A staff were trained.

Primary outcomes

The two primary outcomes were indicators of clinical actions that have been shown to be associated with better health outcomes in people with asthma and COPD[8–10 25 26] and are recommended in the PACK guide.

1. Change in medication: For individuals with asthma, a change in medication was classified as (a) a first prescription of an inhaled corticosteroid (ICS) or ICS+long-acting beta$_2$ agonist (LABA) combination (LABA+ICS) or (b) a change in prescription, stepping up from short-acting beta$_2$ agonist (SABA) to ICS, or from ICS to LABA+ICS combination, or stepping down from LABA+ICS to ICS, or from ICS to SABA. For individuals with COPD, a change in medication was classified as (a) a first prescription of SABA, ICS or ICS+LABA or (b) a change in prescription, stepping up from SABA to LABA or from LABA to ICS+LABA, or stepping down from LABA+ICS to LABA, or from LABA to SABA.
2. Request for spirometry: Primary outcomes were assessed separately in individuals with asthma and in individuals with COPD, during T0 year, T1 and T2 of follow-up.

These primary outcomes differed from the primary outcome of the original trial, which was a composite score combining the medication and spirometry outcomes. In

the original trial, the intervention had statistically significant effects on the composite scores and on each component outcome. For the present study, we chose to use the separate outcomes so as to distinguish effects on investigation and treatment.

Secondary outcomes

Secondary outcomes were indicators of clinicians' awareness and management of comorbid cardiovascular conditions and depression, which are also emphasised in the PACK guide and training.

1. CVD diagnosis: first CVD diagnosis ever recorded (defined by ICD-10 I00–I99).
2. CVD risk assessment: cholesterol, glycated haemoglobin (HbA1c) or glucose tests, any blood pressure recorded or ECG requested.
3. Antidepressant medication initiation: first prescription of any tricyclic or related antidepressant, selective serotonin reuptake inhibitors or monoamine oxide inhibitors.

Secondary outcomes were assessed in individuals with either asthma or COPD or both, pooled together, during T0, T1 and T2 of follow-up.

Data collection and management

Study data, including ICD-10 diagnostic codes, medication prescribed and tests requested, were routinely recorded by healthcare professionals into electronic medical records as usual practice. These data were linked at city, clinic and patient levels, and actively managed by a designated member of the primary healthcare department (MPdA). Data from all contacts with a clinic were summarised for each participant during each year so that if an outcome was recorded at least once during the year then it was coded as positive for that person-year.

Sample size and power

The sample size was predetermined by the total number of municipal clinics in the city, and the total numbers of eligible patients attending them. Before the original trial, we expected to recruit 2900 individuals with asthma and 1400 with COPD each year in the original trial, which would have provided 90% power, with 5% significance, to detect a 26% increase in a composite asthma score and a 33% increase in composite COPD score.[19 20] For the present study, we did not perform a prospective sample size calculation because the sample size was predetermined by the number of clusters and eligible patients, and because the original trial showed that the sample size was sufficient to detect statistically significant difference in outcomes. We performed sample size and power calculations for the present study retrospectively, using the Stata user written command 'steppedwedge', which accounts for the number of steps after baseline, and for the cluster randomisation design.[27] In the present study, we recruited at least 5375 individuals with asthma and 2760 with COPD every year. With the stepped-wedge design, assuming equal size clusters, and with two steps after baseline, this sample size provided 90% power to detect a 4% difference in the asthma treatment outcome (18% vs 14.0%) and a 5% difference in in the COPD treatment outcome (13% vs 8%), with respective intraclinic correlation of outcomes of 0.01 and 0.005, and with 5% significance. The latter intraclinic correlation coefficients were estimated with one way analysis of variance of the T2 outcome data reported in this study.

Statistical analysis

Data were analysed at person-year level with an intention-to-treat analysis. CIs for proportions of individuals with each outcome were adjusted for cluster sampling of individuals within clinics, using Huber-White robust adjustment. Statistical analyses aimed (1) to estimate the independent effects on outcomes of any exposure to training (regardless of duration, corresponding to study objective (1) and (2) to estimate dose effects of the first and second year of exposure to training compared with no exposure (corresponding to study objective (2) while adjusting for calendar time and randomisation strata in all models. For each participant, there were up to three data records, depending on whether they had attended a clinic during years T0, T1 or T3. Effects were estimated with mixed-effect logistic regression models, with random cluster effects and random effects for individuals, modelled as random intercepts. This analysis model controls for both clustering of individuals within clinics and for repeated assessments of individuals and clinics over time.

In the logistic regression model used to estimate effects of any exposure to training the effect of training was estimated by comparing outcomes measured during periods when clusters were exposed to training (T2 in sequence A clinics; T1 and T2 in sequence B clinics) with periods when clinics were not exposed to training (T0 and T1 in sequence A clinics; T0 in sequence B clinics). The model also included, as covariates, randomisation strata, and time periods (T1 vs T0 and T2 vs T0) to adjust for confounding by time. This is the usual statistical model for stepped wedge trials.[28] In the logistic regression model used to estimate dose effects of training, effects were measured by comparing outcomes measured during periods when clinics had 1 year of exposure to training (T2 in sequence A clinics; T1 in sequence B clinics) or had 2 years of exposure to training (T2 in sequence B clinics), with periods when clinics were not exposed to training. This model also included time periods and randomisation strata as covariates. Algebraic definitions of the regression equations are provided in online supplemental appendix.

The statistical significance of differences in effects between 1 and 2 years exposure was tested by repeating the analyses with 1 year of exposure as reference category. The statistical significance of linear trends over 0, 1 and 2 years of exposure was tested by repeating the analyses with duration of exposure modelled as a continuous variable instead of two binary variables.

Ancillary analyses were as follows. Analyses were repeated with further adjustment for mean values of the respective outcome variable recorded in each clinic during T0. These clinic level baselines were used to enable inclusion of new individuals who did not attend during the T0. We carried out subgroup analyses to compare effects of exposure time and calendar time in two subgroups of individuals: those who either attended study clinics during all three study periods (the closed cohort), or who attended during fewer than three study periods. Individuals in the closed cohort subgroup were considered more likely to have continuing illness and engagement with primary care, and changes in this group over time were expected to be more likely. Individuals who visited less often showed new, intermittent or transient use of primary care. For the subgroup analyses, subgroup–exposure interaction covariates were added to the regression models.

We used a 5% significance level. Data were analysed with Stata V.16.

Research governance

We adhered to ethical guidance on cluster randomised trials and use of medical records for research.[29] Identification of eligible individuals and outcome measurement used pseudonymised electronic medical records, without individuals' names or contact details. It was not feasible to obtain individuals' consent to be randomised to intervention or control arms because randomisation and delivery of the intervention were at clinic level. Individuals were not asked for consent for their electronic medical records to be used for this research because it was not feasible. The research had a clear public benefit. We obtained approval for the study from the lead doctors and nurses managing the programme. Use of the data for research did not influence decisions about individuals' care, and only health department data managers had access to personal identifiers.

RESULTS

Figure 1 shows the number of individuals in each arm during each of the three calendar time periods of the study. There were altogether 7072 individuals with asthma and 3585 with COPD (including 1266 with both) in the open cohort of individuals who attended a participating clinic at any time. Of these, 3585 with asthma and 2101 with COPD were in the closed cohort who attended every year. Of 5375 individuals with asthma at baseline, 82% were followed up during T1 and 73% were followed up during T2. Of 2969 individuals with COPD at baseline, 76% were followed up during T1 and 76% were followed up during T2. Follow-up rates were similar in both arms. Only 5.7% of individuals attended both sequence B and sequence A clinics at different times, with the same probability of switching in either direction. Table 1 shows baseline characteristics of individuals, which were well balanced between the two arms.

Figure 3 shows the proportions of individuals for whom positive outcomes were recorded during baseline, T1 and T2 of follow-up in each arm (numerical results are in online supplemental table 1). Apparent effects of training are clearest in figure 2A,C and D, in which outcomes increased during T1 in sequence B while undergoing the initial training, then increased during T2 in sequence A while it received initial training. Effects are less obvious for other outcomes. Initiation or change in asthma treatment increased from baseline to T1 in sequence A, with smaller increases in both arms from T1 to T2 (figure 2A). Initiation or change in COPD treatment decreased in both arms in both periods, except for a small increase from baseline to T1 in sequence A (figure 2B). Spirometry requests for both conditions increased from baseline to T1 in individuals with asthma (figure 2C) and from T1 to T2 in individuals with COPD (figure 2D). New CVD diagnoses and CVD risk tests decreased overall, except that, from T1 to T2, CVD diagnoses increased in Sequence A, and CVD tests increased in sequence B (figure 2E,F). Similarly, new antidepressant prescriptions decreased overall, except from T1 to T2 in sequence A when they increased (figure 2G).

Estimated effects on the outcomes of any exposure to the training intervention are shown in table 2. In individuals with asthma any exposure to training was associated with more initiation or change of treatment (adjusted OR 1.29, 95% CI 1.02 to 1.64) and more spirometry ordering (OR 1.55 (95% CI 1.22 to 1.97)). In individuals with COPD any exposure to training was associated with more spirometry ordering (OR 1.50 (95% CI 1.15 to 1.96)). In individuals with either asthma or COPD, or both, any exposure to training was associated with less testing for cardiovascular risk factors (OR 0.86 (95% CI 0.76 to 0.98)).

Estimated dose effects on the outcomes of duration of exposure to training are shown in table 3. Individuals with asthma were more likely to start or change treatment during the first year (OR 1.43, 95% CI 1.09 to 1.87) and second year (OR 1.91, 95% CI 1.21 to 3.02) of clinics' exposure to training, compared with no exposure (p value for trend 0.005). The effect of 2 years of exposure was statistically significantly greater than the effect of 1 year of exposure (p=0.035). Individuals with asthma were also more likely to have spirometry during the first year (OR 1.76, 95% CI 1.34 to 2.30) and second year (OR 2.05, 95% CI 1.32 to 3.19;) of exposure to training compared with no exposure (p value for trend 0.002). Similarly, individuals with COPD were more likely to have spirometry during the first year (OR 1.57, 95% CI 1.18 to 2.10) and second year (OR 1.71, 95% CI 11.08 to 2.70) of exposure compared with no exposure (p value for trend 0.026).

Results of ancillary sensitivity analysis supported the robustness of the primary statistical analyses. Adjustment for baseline values of the respective outcome variables did not change the estimated effects of duration of exposure to training (online supplemental table 2), compared with

Table 1 Characteristics of individuals in sequence A and sequence B during the 12-month baseline period before any training began

Characteristics	Sequence A		Sequence B	
	N	%	N	%
Individuals with asthma				
Total	2812	100	2563	100
Sex (male)	833	30	735	29
Inhaled corticosteroid ever	774	28	755	30
Short acting beta$_2$-agonist ever	729	26	697	27
Long acting beta$_2$-agonist+ICS ever	250	9	251	10
Any of the above ever prescribed	926	33	929	36
Start or change treatment*	375	13	389	15
Spirometry*	213	8	168	7
	Mean	SD	Mean	SD
Age (years)	46.8	18.3	47.5	18.0
	N	%	N	%
Individuals with COPD				
Total	1379	100	1590	100
Sex (male)	623	45	665	42
Inhaled corticosteroid ever	317	23	364	23
Short acting beta$_2$-agonist ever	289	21	326	21
Long acting beta$_2$-agonist+ICS ever	184	13	210	13
Any of the above ever prescribed	429	31	506	32
Start or change treatment*	106	8	152	10
Spirometry*	123	9	162	10
	Mean	SD	Mean	SD
Age (mean)	61.8	13.9	61.0	14.0
	N	%	N	%
Individuals with asthma or COPD				
Total	3644	100	3555	100
Sex (male)	1237	34	1172	33
Cardiovascular disease newly diagnosed	759	21	824	23
Cardiovascular risk assessed	2285	63	2320	65
Blood pressure	1874	51	1916	54
Cholesterol	1149	32	1290	36
HbA1c	428	12	448	13
Glucose	1285	36	1419	40
ECG	255	7	325	9
Antidepressant treatment started	133	4	158	4
	Mean	SD	Mean	SD
Age (years)	50.4	18.5	51.4	18.0
Clinic level mean values (used for baseline adjustment)	Mean	SD	Mean	SD
Asthma treatment	0.128	0.058	0.157	0.065
COPD treatment	0.088	0.041	0.107	0.055
Spirometry	0.074	0.053	0.094	0.053
Cardiovascular disease diagnosis	0.048	0.072	0.053	0.029
Cardiovascular risk test	0.676	0.110	0.689	0.109
Antidepressant treatment started	0.037	0.037	0.052	0.040

Continued

Table 1 Continued

Characteristics	Sequence A		Sequence B	
	N	%	N	%

*Primary outcomes.
COPD, chronic obstructive pulmonary disease; HbA1c, glycated haemoglobin; ICD-10, International Classification of Disease, 10 Revision; ICS, inhaled corticosteroid.

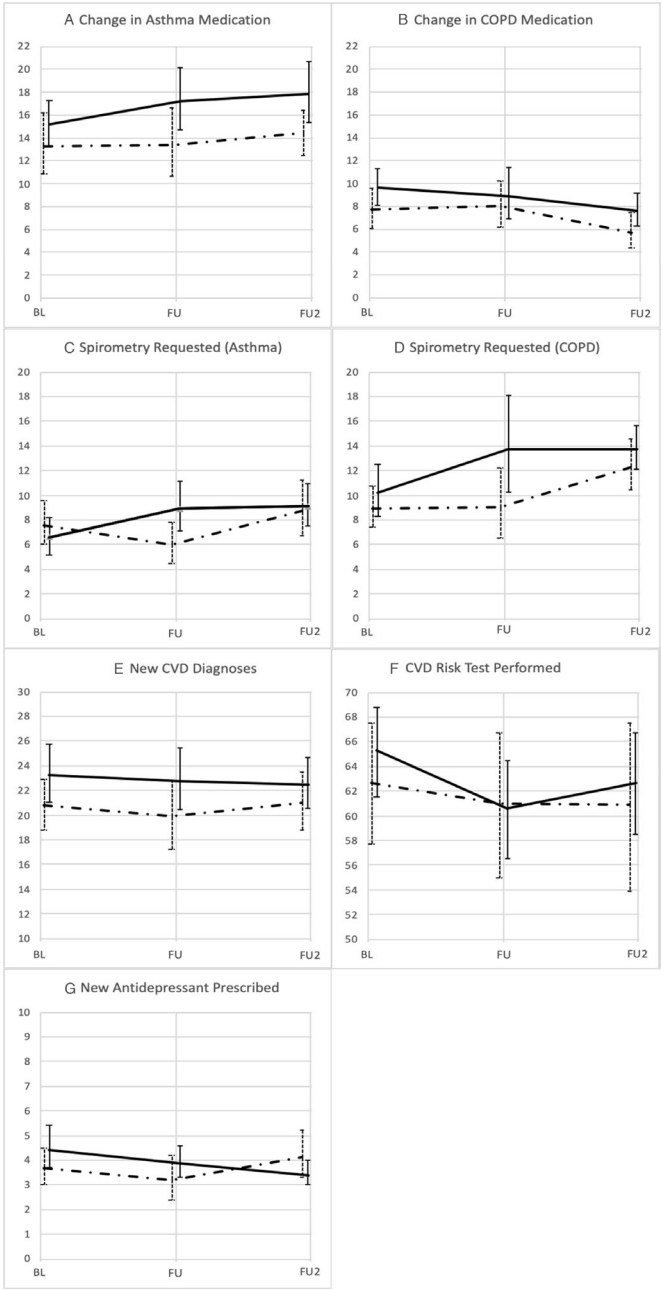


Figure 3 Percentage (95% CI) of individuals with outcomes recorded in sequence A and sequence B clinics during baseline and follow-up periods. Sequence A and sequence B clinics during baseline and follow-up periods; sequence A: dashed line, sequence B: solid line. BL, baseline; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FU, year 1 follow-up T1; FU2, year 2 follow-up T2.

table 3). In the subgroup analyses (online supplemental table 3), there was a significant effect of exposure to training on COPD treatment only in the closed cohort of individuals present for all 3 years of the study, with increased ORs during the first and second year of exposure (OR 1.36 (95% CI 0.97 to 1.90); 2.37 (95% CI 1.36 to 4.11); p value for trend 0.003; p value for interaction 0.01).

DISCUSSION

This study is an advance on many trials of complex educational interventions in healthcare, in which interventions and their effects are often not continued after the trials' end and may not be sustainable.[21–24] The results of this study indicate that the delivery and effects of a complex educational intervention like PACK could be sustained beyond the end of the original trial. First, the estimated effects on spirometry and treatment when effects on clinics that received the scaled up intervention were combined with effects on the original intervention clinics, were at least as large as the effects on the same outcomes reported in the original trial.[20] Second, the effects increased with increasing duration of exposure to the intervention, as shown by the statistically significant trends, and the significantly greater effect on asthma treatment with two than with 1 year of exposure. Third, it was feasible to deliver the intervention for an additional year and to extend it to cover the whole city. However, as discussed below, the step-wedge design and the primary outcomes of this follow-up study differed from the original trial's prespecified parallel arm design and composite primary outcomes, and therefore, these findings should be interpreted as exploratory and with caution.

Since completion of the present study, PACK Brasil Adulto has continued to be delivered in Florianópolis beyond the end of 2023, that is, for more than 6 years. Reviews of research on the sustainability of evidence-based educational interventions in healthcare have found that effects are more likely to be sustained if there is (a) engaged and supportive leadership of intervention delivery, (b) ongoing access to education and training and (c) routine monitoring of intervention delivery.[21 24] Delivery of PACK Brasil Adulto in Florianópolis has met all of these conditions, which helps to explain its success.

An original feature of PACK is that it aimed to improve medical care for a wide range of health conditions in an integrated way. This makes it particularly suited to management of individuals with multiple long-term conditions, and to increasing clinicians' awareness that patients known to have one condition may have others

Table 2 Effects of any exposure to intervention (regardless of duration), with and without adjustment for baseline values of outcome*

Outcomes	Not adjusted for baseline			Adjusted for baseline†		
	OR	95% CI	P value	OR	95% CI	P value
Individuals with asthma						
Start or change in treatment	1.26	0.99 to 1.60	0.064	1.29	1.02 to 1.64	0.033
Spirometry ordered	1.64	1.29 to 2.10	<0.001	1.55	1.22 to 1.97	<0.001
Individuals with COPD						
Start or change in treatment	1.07	0.79 to 1.44	0.671	1.05	0.80 to 1.37	0.729
Spirometry ordered	1.53	1.17 to 2.01	0.002	1.50	1.15 to 1.96	0.003
All Individuals						
New cardiovascular diagnosis	1.14	0.95 to 1.36	0.157	1.14	0.95 to 1.36	0.159
Any cardiovascular risk test	0.86	0.76 to 0.99	0.031	0.86	0.76 to 0.98	0.023
New antidepressant	1.22	0.94 to 1.58	0.127	1.18	0.92 to 1.52	0.193

*Mixed effect logistic regression models, adjusted for randomisation stratum.
†Also adjusted for mean clinic level baselines values of respective outcome variable.
COPD, chronic obstructive pulmonary disease.

that are undiagnosed or undertreated. The wide clinical scope of PACK can, however, make it difficult to demonstrate effects on any particular condition, and previous trials of interventions addressing multimorbidity have rarely found any effects.[30] This study shows that it is possible to demonstrate condition-specific effects of an intervention addressing multiple conditions, but also found that it did not change management of cardiovascular conditions and depression in people with chronic respiratory disease.

This study has several methodological strengths. As a pragmatic trial evaluating a city-wide intervention under real-world conditions, including municipal worker strikes and fiscal pressures, the robustness and generalisability of its findings are enhanced. The stepped-wedge design enabled identification of sustained and lagged effects. Use of electronic medical records for identification of eligible individuals and for outcome measurement avoided selection bias and provided a large sample, high statistical power to detect small effects and high follow-up

Table 3 Effects of years of exposure to training intervention

Outcomes	Duration of exposure to training intervention							
	1 year exposed to intervention compared with unexposed			2 years exposed to intervention compared with unexposed			2 years exposed vs 1 year exposed	P value for trend
	OR	95% CI	P value	OR	95% CI	P value	P value	
Individuals with asthma								
Start or change treatment	1.43	1.09 to 1.87	0.009	1.91	1.21 to 3.02	0.005	0.035	0.005
Spirometry	1.76	1.34 to 2.30	<0.001	2.05	1.32 to 3.19	0.001	0.240	0.002
Individuals with COPD								
Start or change treatment	1.11	0.84 to 1.48	0.456	1.51	0.96 to 2.39	0.072	0.061	0.089
Spirometry	1.57	1.18 to 2.10	0.002	1.71	1.08 to 2.70	0.022	0.564	0.026
All Individuals								
New cardiovascular diagnosis	1.14	0.94 to 1.39	0.174	1.16	0.84 to 1.60	0.374	0.897	0.363
Cardiovascular risk test	0.86	0.74 to 1.00	0.047	0.85	0.65 to 1.10	0.213	0.869	0.200
New antidepressant	1.20	0.92 to 1.57	0.172	0.97	0.66 to 1.43	0.869	0.101	0.836

HbA1c glycated haemoglobin.
Estimated with mixed effect logistic regression models, adjusted for calendar time and randomisation stratum.
COPD, chronic obstructive pulmonary disease.

rates, at low cost. Arms were well balanced at baseline, and adjustment for baseline values of primary outcomes made little difference to effect estimates. There was little cross-contamination of individuals changing between clinic arms.

Limitations of the study should be considered. First, the study could not evaluate the effects of exposure to the PACK guide because it was provided to both arms after the baseline period. However, there were minimal or no improvements in outcomes from baseline to T1 within sequence A, suggesting that provision of the guide alone did not change practice. Second, it was beyond the scope of the study to demonstrate sustained effects on outcomes after the end of the second year of follow-up. Third, the analysis assumed that the training provided during T1 was the same as the training provided during T2, although training sessions, which were similar in content, were delivered over shorter periods during T2 than during T1. Fourth, the primary outcomes for this study differed from the original trial's prespecified composite primary outcomes. Multiplicity of study outcomes—with two primary outcomes for each of the asthma and COPD cohorts—increased the probability that seemingly statistically significant differences could have been due to chance alone.

If we apply a Bonferroni adjustment to the significance level, reducing it to 2.5% (ie, 5%/2), that makes the effect on asthma treatment non-significant (p=0.033), but the effects on spirometry are still highly significant (p<0.001 to 0.003). Fifth, this study's stepped-wedge design was not prespecified before the original parallel arm randomised trial, but instead opportunistically took advantage of post-trial rollout of the intervention. Sixth, while the electronic medical records permitted us to include a large sample of individuals with respiratory disease, of whom a significant proportion were likely to need a change in management, they did not provide participant-level data from which to assess the accuracy of diagnoses, disease severity, need for investigation or clinical effects of changes in treatment.

The changes in primary outcomes studied were those previously shown to improve clinical respiratory outcomes at the population level.[8–10 25 26] They represented a shift from clinical inertia[11] in the management of regular attendees with these chronic diseases in the clinics under study. The likely dilution of the sample with individuals with mild or well-controlled asthma and COPD partly explains the small proportions (6%–18%) who attained the primary respiratory outcomes, and the even smaller absolute changes in these outcomes (figure 2). Furthermore, the proportions of individuals already receiving asthma and COPD treatments at baseline (table 1) were relatively high compared with similar Latin American populations,[31 32] limiting the study's ability to show the effects of increased treatment. Nevertheless, the study did show improvements in respiratory care overall which, given the large numbers of service users with asthma and COPD, would be expected to improve the respiratory health of many individuals over time.

This study confirms and extends the findings of the original trial in Florianópolis.[20] A related qualitative study of PACK trainers in Florianópolis confirmed their enthusiasm for the PACK guide and training.[33] The results of the present study also confirm the findings of our PALSA trial in which a prototype of PACK training increased provision of ICSs for asthma in South African primary care[34] and are compatible with our subsequent PALSA PLUS and STRETCH trials, which found improved respiratory diagnosis and treatment in South African primary care attendees with HIV infections.[35 36] They are an advance on our Primary Care 101 trial of a similar intervention targeting multiple chronic conditions in South Africa, which showed effects on treatment of diabetes and CVD, but not respiratory disease.[37]

CONCLUSION

This study suggests that the PACK model of educational outreach to strengthen primary care in Brazil resulted in small but significant and sustained increases in the investigation and treatment of asthma and COPD, with PACK's implementation and effects lasting up to 2 years and extended to all municipal facilities in Florianópolis. This evidence supports the implementation of PACK on a large scale in Brazil and will be of interest to other countries embarking on or considering the introduction of PACK into their primary healthcare systems. It shows, more generally, that a complex intervention covering multiple clinical conditions in a large geographically based population can have demonstrable beneficial effects on the management of specific conditions that continue for more than 1 year.

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collated the electronic medical record data. SS and MOB carried out the statistical analysis and wrote the first draft of the manuscript. All authors contributed to writing the paper and approved the final manuscript. MOB is the guarantor.

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