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Care in Chronic Obstructive Lung Disease (CAROL): a randomised trial in general practice

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Short title / running head

The CAROL Cluster Randomised Trial

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Take home message

Disease management using a care bundle increases guideline adherence in general practice care for COPD

Abstract

Background

Disease management of chronic obstructive pulmonary disease (COPD) is complex and shortcomings in general practice care for COPD are common. A care bundle is a disease management aid reminding and steering specific elements of care.

Objectives

To test whether a COPD care bundle delivered to general practitioners (GPs) and practice assistants (PAs) increases the implementation of key elements of COPD care.

Methods

Cluster-randomised clinical trial, 1:1 randomisation of GPs, one-year follow-up. The intervention introduced a COPD care bundle and aimed at enhancing collaboration between GPs and PAs. The control group continued usual care. The primary outcome measure was the composite score from nine key elements of COPD care measured at patient level.

Results

We enrolled thirty-five GPs and 216 patients with a median age of 69 years, 59% female, 69% GOLD group A or B. After one year, the between-group difference in change of the primary outcome measure was +2.2 (95% CI +1.5 to +2.9) in favour of the intervention group. The intervention was associated with significantly higher implementation rates in 7 out of 9 key elements of care.

Conclusion

Disease management using a COPD care bundle increased the implementation of key elements of COPD care in general practice.

Introduction

Chronic obstructive pulmonary disease (COPD) is of high and increasing prevalence and contributes importantly to worldwide years of life lost.[1, 2] COPD, however, is a preventable disease and modifiable risk factors and many effective interventions that reduce symptoms and improve prognosis have been identified. Guidelines amalgamate the existing evidence into practically applicable treatment recommendations.[3, 4] Nonetheless, we continue to observe shortcomings in COPD care delivered in general practice.[5–10] This is of special concern because the majority of COPD patients are treated in general practice and are in early disease stages when preventive interventions have the most potential to improve outcomes.[11–14]

Evidence-based care for COPD is complex because it is stage- and symptom-dependent and comprises multimodal interventions: Disease-assessment requires spirometry and collection of several variables (e.g. symptom severity and exacerbation history) to determine stage and treatment. Therapeutic measures with robust evidence-base (subsequently referred to as “key elements of COPD care”) comprise smoking cessation[15], influenza vaccination[16], appropriate pharmacologic therapy (also ensuring correct inhalation technique)[3, 17–21], pulmonary rehabilitation[22], sustaining physical activity[23], self-management education[24–26] and proactive, integrated disease management [27].

While some key elements of COPD care are straightforward to deliver such as influenza vaccination, others require time, knowledge, skills and inter-professional collaboration and coordination. The plethora of key elements and the individual implications of each one of them add up to a bundle of interventions that is complex to coordinate and deliver. This is critical, especially in general practice, where doctors

struggle with putting into practice the broad and continuously expanding field of general medicine and complex interventions are at risk of being left behind.

Organisational changes and structured disease management aids can facilitate implementation of complex care pathways. For COPD, such approaches have already been successfully tested in hospital medicine. So called “COPD care bundles” have been used as reminder lists summarising key elements of care to be implemented on the individual patient-level before hospital discharge. In hospital-based COPD care, care bundles succeeded in not only raising implementation rates of key elements of care but also in reducing readmission rates.[28] In primary care, COPD disease management trials are scarce. One trial aimed to increase implementation of best-practice guidelines by having home visits from specifically trained nurses who developed individualised care plans with COPD patients and which resulted in improved quality of care.[29] A trial implementing a COPD management guideline, monthly nurse and three-monthly GP visits, a patient-specific care plan and enhancing collaboration between healthcare providers resulted in reduced hospital admissions, less hospital days and increased implementation of some key-elements of care.[30] Previous trials’ intensive and multimodal interventions, however, render attribution of the identified effects to individual intervention components difficult.

The aim of this trial was to test, whether an intervention focussing on general practice teams including implementation of a COPD care bundle along with specific coaching to support organisational and behavioural changes would result in an increased implementation rate of key elements of COPD care.

Methods

Study design, setting, registration and ethics statement

We conducted a parallel group cluster randomised trial with general practices working in the Swiss canton of Zurich. The local ethics committee approved the study (ethics committee of the Canton of Zurich, reference number KEK-ZH 2013-0189), informed consent was retrieved from all participating subjects and the study was conducted according to tenets of the Declaration of Helsinki and good clinical practice guidelines. The trial has been registered at ClinicalTrials.gov (NCT01921556) and the trial's study protocol is published.[31]

Participants

Recruitment of general practitioners (GPs) started in 2013 by mass mailings and visits at GP-network meetings. We enrolled 35 GPs after a nine months GP recruitment period. We trained GPs and their practice assistants in standardised spirometry to enhance accuracy of diagnostic testing for COPD. Patient recruitment started in December 2013. A detailed report of this trial's recruitment period has been published.[12]

Eligibility criteria for GPs were a) primary care physician in the canton of Zurich and b) board certification in general medicine or internal medicine. General practitioners approached consecutive patients aged at least 45 years, with at least 10 pack-years (PY) smoking history and proposed to perform spirometry. If airflow obstruction (FEV1/FVC < 0.7) was confirmed, GPs gained informed consent if available and performed formal study inclusion. Exclusion criteria for patients were: emergency consultations, insufficient German language skills to complete study

questionnaires, asthma or hay fever or estimated life expectancy of less than six months.

Data collection

Data was collected using self-administered questionnaires (see supplementary material) at patient recruitment (T0) and 12 months after the intervention (T1). General practitioners completed a questionnaire about their own demographic characteristics and working environment. We pilot-tested the patient questionnaire with six COPD patients from the targeted group and made according adjustments to improve comprehensibility. The questionnaire asked for sociodemographic data, smoking status, 12-months retrospective view on delivered key elements of care (see below) and symptoms including the COPD assessment test (CAT). GPs filled in a questionnaire that asked for anthropometric patient data including current spirometry results, 12-months retrospective COPD exacerbations and COPD driven health service utilisation as well as prescribed pulmonary drugs. Table 1 shows the measured key elements of care including the levels of measurements and the applicable patient subgroups.

1

Table 1: List of measured key elements of COPD care including subgroup applicability, outcome component and measurement level				
	Key elements of COPD care	Applicable patient subgroup	Component of Outcome	Measurement level
1	Smoking cessation advice	smokers only	Primary	Patient
2	Smoking cessation intervention	smokers only	Primary	Patient
3	Influenza vaccination	all patients	Primary	Patient
4	Inhalation technique[1)]	all patients	Primary	Patient
5	Appropriate pharmacological treatment	all patients	Primary	GP
6	Assessment of physical activity	all patients	Primary	Patient
7	Advice for physical activity	all patients	Primary	Patient
8	Patient education	all patients	Primary	Patient
9	Assessment of exacerbation frequency	all patients	Primary	GP
10	Integration of other healthcare providers	GOLD C and D patients	Secondary	Patient
11	Referral to pulmonary rehabilitation	GOLD C and D patients	Secondary	Patient
12	Action plan for exacerbation management	GOLD C and D patients	Secondary	Patient
Table 1: Key elements of care including applicable patients and measurement level [1)] Performing: explanation and demonstration and assessment of patient's inhaler technique				

2

Intervention

We delivered the intervention after the patient recruitment period in a half-day workshop with GPs and their practice assistants. The intervention aimed at implementing the COPD care bundle and induce organisational and behavioural changes in the general practice teams: First, we refreshed knowledge about Swiss COPD guidelines[4] and distributed a pocket guide. Then, GPs and practice assistants were to discuss and tailor their individual pathways of COPD care. Case vignettes and role-plays were used to actively involve GPs and practice assistants with tasks and responsibilities. We proposed to use the COPD care bundle as a checklist to remind and tick-off the individual key elements of COPD care in individual patients. We expected the care bundle's design as a checklist to increase internal motivation for behavior change.[32, 33] We delivered no intervention to the "usual care" control group.

After 6 months, we delivered a three-hour refresher workshop to the practice teams again using case vignettes and role-plays after conducting a survey among practice teams to inform us about their specific needs for support.

Outcomes

Primary outcome

Between-group difference in the change of implemented key elements of COPD care after one year (see Table 1; composite score being the sum of all implemented key elements ranging from 0 to 9 in smokers and 0 to 7 in non-smokers).

Secondary outcomes

1. Between-group difference in proportions of GOLD C or D patients who received referral to pulmonary rehabilitation, a written action plan for exacerbation management or coordinated care.
2. Between-group difference in symptom severity measured with the CAT instrument.

Sample size

Based on available data from Switzerland[5, 8], we assumed a mean number of 4 (SD 2.3) implemented key elements of COPD care. We assumed a 1.5 points increase to be a relevant improvement and used this difference to calculate the sample size: Given a power of 90% and a significance level alpha of 5%, as well as an intra-cluster correlation coefficient of 0.04, we targeted at recruiting 30 GPs each recruiting eight patients, resulting in 240 patients. To allow for drop-out we set a recruitment target of 35 GPs.

Randomisation

The level of randomisation was the individual GP and allocation ratio was 1:1. We performed randomisation of GPs six months after initiation of patient recruitment to minimise the effect of the openly labelled treatment group allocation on recruitment performance. To balance groups for the considerable variation in recruiting performance, we ranked GPs according to their number of recruited patients and assigned random group allocation with block size of two. A researcher not involved in this study produced the random sequence using the statistic program STATA. This randomisation method was applied to minimise risk of imbalanced allocation counts

due to differences in recruiting performance. Furthermore, it balanced GPs for the possible confounding effect originating from the motivation to contribute to the trial, which we assumed to be associated with recruiting performance. The group allocations we communicated to GPs with the instruction not to pass this information to their patients. Patients, however, were aware that their GP would either continue usual care or start an experimental, potentially more comprehensive COPD care.

Statistical methods

We report counts and proportions for categorical data as well as means and standard deviations (SD) or medians and interquartile ranges (IQR) as appropriate. For bivariate group comparisons, we used a Welch-test or a Wilcoxon rank sum test for continuous data and a Chi-squared for categorical data and report p-values. The primary outcome was calculated with a linear regression model. The primary outcome measure at T1 was the dependent variable and, as independent variables, the group allocation as well as following adjustment variables to minimise confounding: count of implemented processes at T0, patient age, sex, education years, COPD stage and study follow-up time (days). We report the estimated between-group difference and the according 95% confidence intervals (95% CI). In a separate analysis we assess for a cluster-effect by adding the cluster variable (individual GPs) to the abovementioned regression model under a random effects assumption. We made no adjustments for a potential contamination effect originating from GPs in different study arms but located within the same group practice (therefore accepting a risk of underestimating the between group-difference in the trial results). To assess for selective dropout we analysed for between-group differences in counts and reasons for dropout. To assess the robustness of our

results we carried out sensitivity analyses simulating missing data under several assumptions (multiple imputation method, last observation carried forward and imputing the average score of the control group). Statistical analysis we performed using R version 3.2.0. (https://www.R-project.org/).

Results

Study population

Of the 35 GPs entering patient recruitment, 33 started recruiting and two withdrew before randomisation, therefore 33 GPs were randomized (16 intervention group and 17 control group). Eighteen GPs (contributing 111 patients) from intervention and control group were co-located in group practices. During the one-year recruitment period, GPs recruited 216 patients (90% of recruitment goal) starting in December 2013. Recruitment stopped when the number of newly recruited patients per month was <5. The study intervention was delivered in January 2015 and follow-up measures were conducted in January 2016. Patients median age was 69 years, 59% were female, 69% GOLD group A or B. Per chance, the intervention group had less severe obstruction FEV1% (median= 70% v.s. 65%, p=0.035) and a lower CAT summary score (median = 9 v.s. 12, p=0.033). Table 2 and Table 3 give detailed patient and GP characteristics including study-group comparisons.

At T1, 161 patients completed follow-up (drop-out rate 25%) and the study ended as set out in the protocol. Figure 1 depicts patient and cluster recruitment and retention over the trial periods. When testing dropout counts, a significant between-group difference appeared (intervention group n=32, control group n=23, p=0.049). Active withdrawal of patients was the most common reason for discontinuation, there was however, no significant between-group difference in reasons for discontinuation (p=0.165).

Table 2: Characteristics of total study patient population (n=216) and comparison by group assignment

Category	Intervention group		Control group		p value
	mean, median or n	(SD), iqr or %	mean, median or n	(SD), iqr or %	
Total n	101	100%	115	100%	
Age (years)	68	63 to 75	67	60 to 73	0.260
Male	60	59.4%	68	59.1%	0.967
BMI	25.9	(5.99)	25.6	(4.63)	0.753
GOLD group A[1)]	68	67.3%	59	51.3%	0.101
GOLD group B	9	8.9%	13	11.3%	
GOLD group C	16	15.8%	25	21.7%	
GOLD group D	8	7.9%	18	15.7%	
FEV1 %	70	55 to 86	65	51 to 76	0.035
≥1 exacerbations in past 12 months	27	26.7%	46	40.0%	0.089
new COPD diagnosis at recruitment	37	36.6%	34	29.6%	0.270
composite score of implemented key elements of care[2)]	4.1	(2.0)	4.6	(1.7)	0.035
CAT summary score	9	6 to 15	12	8 to 16	0.033
mMRC category 0	27	27.3%	25	22.7%	0.904
mMRC category 1	42	42.4%	48	43.6%	
mMRC category 2	23	23.2%	28	25.5%	
mMRC category 3	7	7.1%	9	8.2%	
mMRC category 4	0	0%	4	3.6%	
active smokers	56	55.4%	64	55.7%	0.976
Pack-Years	44	30 to 59	45	35 to 60	0.277
Diabetes	14	14.0%	14	12.6%	0.767
Hypertension	50	51.0%	63	55.3%	0.537
Coronary heart disease	16	16.3%	22	19.6%	0.533
Congestive heart failure	12	12.0%	9	8.0%	0.335
Depression	19	19.8%	23	20.5%	0.894
Follow-up days	410	398 to 428	440.5	410 to 481	<0.001

[1)] GOLD groups are classified according to the 2017 report[3]

[2)] This T0 score comprises both patients with and without previously diagnosed COPD and is therefore not to be understood as a measure for usual care in general practice COPD care

102

Table 3: Characteristics of GPs randomised in the study (n=33) and comparison by group assignment

Variable	Intervention group		Control group		p value
	mean, median or n	(SD), iqr or %	mean, median or n	(SD), iqr or %	
total n	16	100%	17	100%	
age (years)	50	44 to 59	47	42 to 56	0.407
Sex (male)	13	81.2%	11	70.6%	0.438
single practice	2	12.5%	2	11.8%	1.000
group practice	14	87.5%	15	88.2%	1.000
electronic medical record	13	81.2%	13	76.5%	1.000
paper based medical record	3	18.8%	4	23.5%	1.000
practice assistants workforce-equivalents in full time jobs	2.3	1.9 to 3.4	2.7	1.8 to 4.0	0.773
estimated number of patients seen per day	25	20 to 30	25	20 to 30	0.581
patients approached	11	4 to 19	10	8 to 17	0.914
patients recruited	6	2 to 10	6	5 to 10	0.638

103

Primary outcome

After one year, the mean composite score of implemented key elements changed from 4.1 to 5.1 (+1.0) in the intervention group and changed from 4.6 to 3.5 (-1.1) in the control group. A linear regression model adjusting for baseline characteristics (Table 4) revealed a between-group difference of +2.2 (95% CI +1.5 to +2.9) implemented key elements in favour of the intervention group. Significantly increased implementation was found in 7 out of 9 individual key elements (Figure 2). We detected no significant cluster effect originating from individual GPs.

Table 4: Coefficients of the primary outcome's linear regression model

	Estimate	Std. Error	95% confidence interval
intervention group (ref=control group)	2.2	0.64	1.5 to 2.9
primary outcome at T0	0.4	0.38	0.2 to 0.6
Age	0.0	0.11	-0.1 to 0
sex (ref=female)	0.2	0.02	-0.5 to 0.9
10 to 12 years education years (ref=<12)	-0.5	0.36	-1.2 to 0.3
>=13 years education years (ref=<12)	0.2	0.38	-0.7 to 1.1
number of exacerbations in one year	0.0	0.46	-0.2 to 0.2
fev1 %	0.0	0.09	0 to 0
CAT summary score at T1	0.0	0.00	0 to 0.1
Follow-up time (days)	0.0	0.01	0 to 0

Secondary outcomes

In GOLD C and D patients (n=67; 31%), no significant between-group difference appeared in the outcomes: integration of other healthcare providers, referral to pulmonary rehabilitation, or delivery of exacerbation action plans (Figure 2).

After one year, the mean CAT summary score decreased from 10.7 to 9.5 (-1.2) in the intervention group and increased from 12.8 to 13.9 (+1.1) in the control group. Linear regression model adjusting for baseline disparities showed an estimated difference in change of -1,1 (95% CI = -3.3 to +1.1, p=0.32) in the intervention group.

Additional analyses

Regarding intervention effects on individual key elements of COPD care, we identified different patterns. Implementation of certain key elements primarily increased in the intervention group (i.e. smoking cessation intervention, inhalation technique, patient education), while in other key elements between-group differences were primarily due to an attrition in the control group (i.e. smoking cessation advice, physical activity assessment and advice). Figure 3 illustrates net differences of implementation rates between T0 and T1 per studied group.

The intervention effect on the primary outcome was stable and remained relevant in all sensitivity analyses: Multiple imputation method (imputed datasets n=5): between-group difference of +1.6 (95% CI +0.8 to +2.4); last observation carried forward method: +2.3 (95% CI +1.5 to +3.1), imputation of control group average: +2.0 (95% CI +1.3 to +2.8).

To further explore the adoption of the intervention, we asked the GPs in the intervention group how they implemented the COPD care bundle in the T1 questionnaire. In 47 (69%) patients, the GPs used the care bundle as the intended checklist to complete, but in 9 (13%) as a recall list only and in 12 (18%) the care bundle was not used at all. To further explore the intervention's effects on health service utilisation, we assessed the 1-year frequency of planned and emergency COPD-driven practice visits as well as emergency department stays and hospitalisations at T1. A significant between-group difference appeared in the median number of planned practice visits: intervention group median = 3 (IQR 0 to 4) versus control group median = 1 (IQR 0 to 3; p=0.04) but not within the other modes of health service utilisation.

Discussion

This cluster-randomised trial showed that a multifaceted intervention introducing a COPD care bundle to general practice teams increased the implementation rates of key elements of care compared to usual care based on patient self-report and previous 12-months recall. The between-group difference in implemented key elements of care was composed of an almost equal net increase in the intervention group and net decrease in the control group. The intervention therefore increased implementation rates of some key elements but also prevented the otherwise occurring attrition of others. More than two thirds of the patients were in early disease stages, significant intervention effects on disease-specific quality of life (CAT score) were not observed after one year.

Care bundles are effective on relevant outcomes such as disease progression, quality of life or exacerbation rates in hospital based COPD care.[28] In our study, we detected significantly improved implementation of key elements recommended by guidelines and based on robust evidence.[15–25, 27] We were unable to detect a direct impact on quality of life. However, owing to early disease stages and the slowly progressing natural course of the disease, a longer surveillance period may be required to demonstrate effects on patient outcomes. Yet, particularly in early disease stages of COPD, interventions retain the greatest potential for effects and should therefore be cornerstone of care.[14, 34] In this context, it is noteworthy that we found the largest effects of our intervention for measures with strong evidence for improving prognosis including smoking cessation interventions, physical activity promotion, patient education and influenza vaccination.

Complexity of care is associated with variation of care and integrated standardised pathways of care are advocated to improve quality and outcomes.[35]

Integration of care brings potential benefits to COPD patients and initiatives aim at fostering integrated care approaches in disease management for COPD.[27, 36] Integrated care is, however, an umbrella term for heterogeneous components of care organisation and not an unambiguously defined one-size-fits-all model.[37] Interestingly, the recent and so far largest trial testing integrated care for COPD by Kruis et. al. found no relevant effects on patient outcomes. This does not question integrated care in general but it illustrates that little is known about the effect of the individual components aligning under the term.[38] In this study, we promoted horizontal integration: redesigning COPD workflows handled by GPs and practice assistants and implementing a care bundle as a pragmatic, flexible and collaborative disease management aid. The significant increase of planned consultations in the intervention group can be interpreted as redesign towards more proactive care culture in the targeted practices.[39]

We regard this study as a first and promising COPD care bundle implementation trial in general practice. However, subsequent research in the field is needed to better understand the potential of this approach. A direct integration of the care bundle in electronic medical records may increase its adoption by physicians, and further contribute to closing the gap in general practice health service delivery for COPD patients. Furthermore, relevant outcomes should be directly measured but longer surveillance periods should are required to enable this. The number of patients withdrawing from the study may be related to dissatisfaction with intensified healthcare delivery, possibly mediated by increasing costs and time expenditures. In Switzerland, only healthcare costs exceeding a patient-dependent minimum are reimbursed by statutory health insurance, therefore increased financial expenditures may have indeed contributed to dissatisfaction of a minority of patients. This effect may strongly vary according to financial coverage in different countries. The patient

198 experience of the intervention should be examined and the costs associated with any
199 benefits gained should be considered before conclusions about net benefits of
200 intensified disease-management can be drawn.
201

202 **Strengths and limitations of the study**

203 Some strengths and limitations must be mentioned: To our knowledge, this is
204 the first report of a COPD care bundle implementation in general practice with a
205 cluster randomised design. So far in this context the only available evidence was
206 derived from hospital care or from general practice studies with different disease
207 management interventions.[28–30] Another strength lies in the outcome assessment
208 at the patient side: patient-recalled processes of care presumably reflect the
209 successfully delivered elements of care better than the non-recalled ones. On the
210 other hand, this implies the limitation that the trial presumably underestimates the
211 actually delivered elements of care. This potential recall bias, however, does not
212 invalidate the between group difference we detected. The trial's open label design is
213 clearly a limitation to the study. In the control group, GPs might have felt discouraged
214 knowing about their allocation to the usual care group, biasing the between group
215 difference in favour to the intervention group. Also, there is a risk for contamination
216 bias because half of the patients were treated in group practices where GPs from
217 both study arms were collocated. Contamination, however, would have biased our
218 results towards zero and therefore rather strengthens our positive findings. The
219 significantly higher drop-out rate in the intervention group is another important
220 concern: even if reasons for drop-out were similar it is still possible that a subgroup of
221 patients felt uncomfortable with intensified healthcare provided in the intervention
222 group leading to undesirable self-deprivation from medical care. Lastly, despite

randomisation, we found a small but statistically significant difference in disease severity variables between the study groups with the intervention group being less severely affected by COPD. We believe, however, that the influence on disease management originating from this difference would have most likely resulted in intensified treatment in the more severely ill control group – again strengthening the trial's positive finding. Ultimately, we must keep in mind that we attribute the study effects to a multifaceted and therefore "impure" intervention. Besides the care bundle or the team approach other factors delivered to the intervention group during the workshops (mainly knowledge about the key elements of COPD care) may have been important active components in the trial.

Conclusions

A disease management intervention for general practice care teams introducing a COPD care bundle increased the adherence to recommended key elements of care. Subsequent beneficial effects on relevant patient outcomes are plausible but may require years until they become apparent given the insidious disease progression and the early disease stages of COPD patients in general practice.

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Contributions

CSS, TR and KDL conceived and designed the study; SM, CSS, and KDL acquired the data; SM and CSS analysed and interpreted the data and drafted the manuscript to be revised critically by TR and KDL; SM, TR, KDL and CSS approved the final version to be published and agree to be accountable for all aspects of the study.

Competing interests

The authors SM, TR and KDL declare that no competing interests exist

CSS received fees for participation in advisory boards organised by Boehringer Ingelheim, Astra Zeneca and Novartis. CSS provided consultancy or gave talks around the topic to Boehringer Ingelheim, AstraZeneca and GSKe

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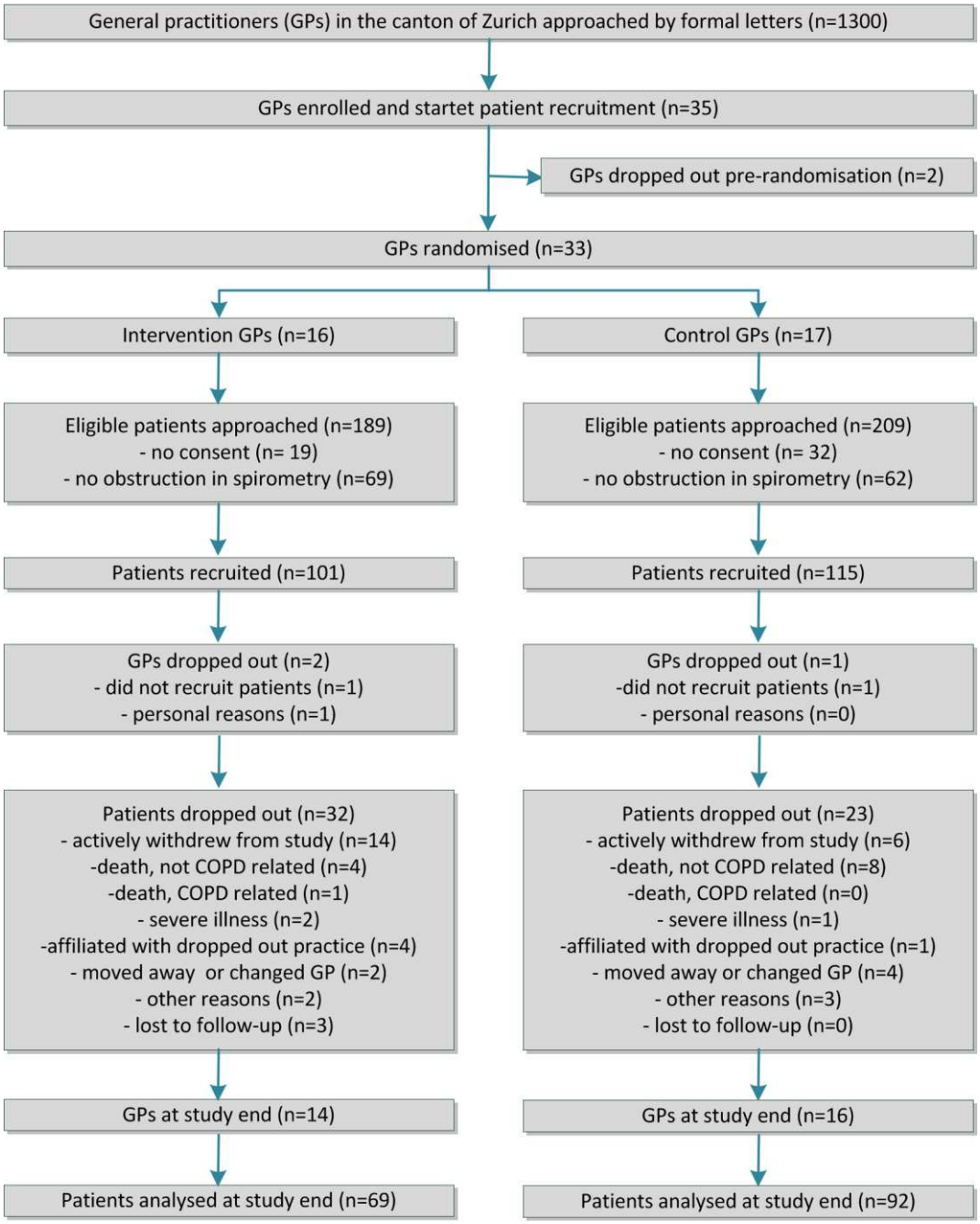
420 Figures



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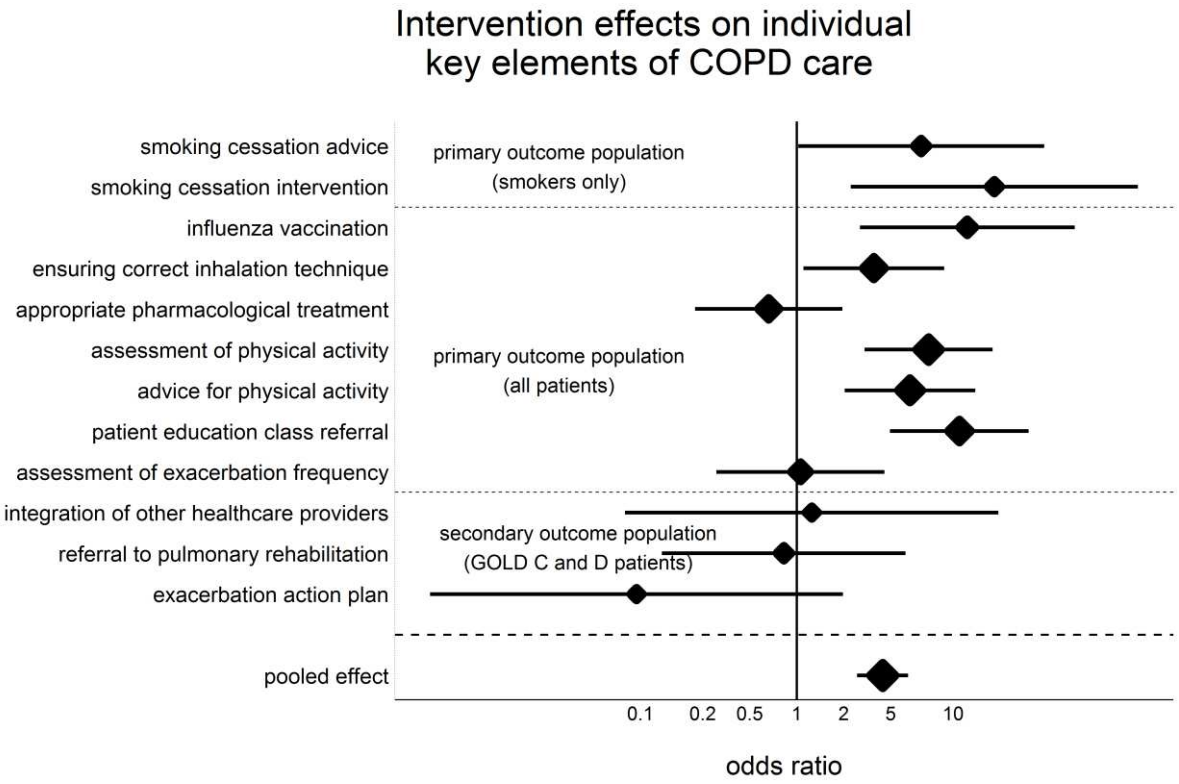
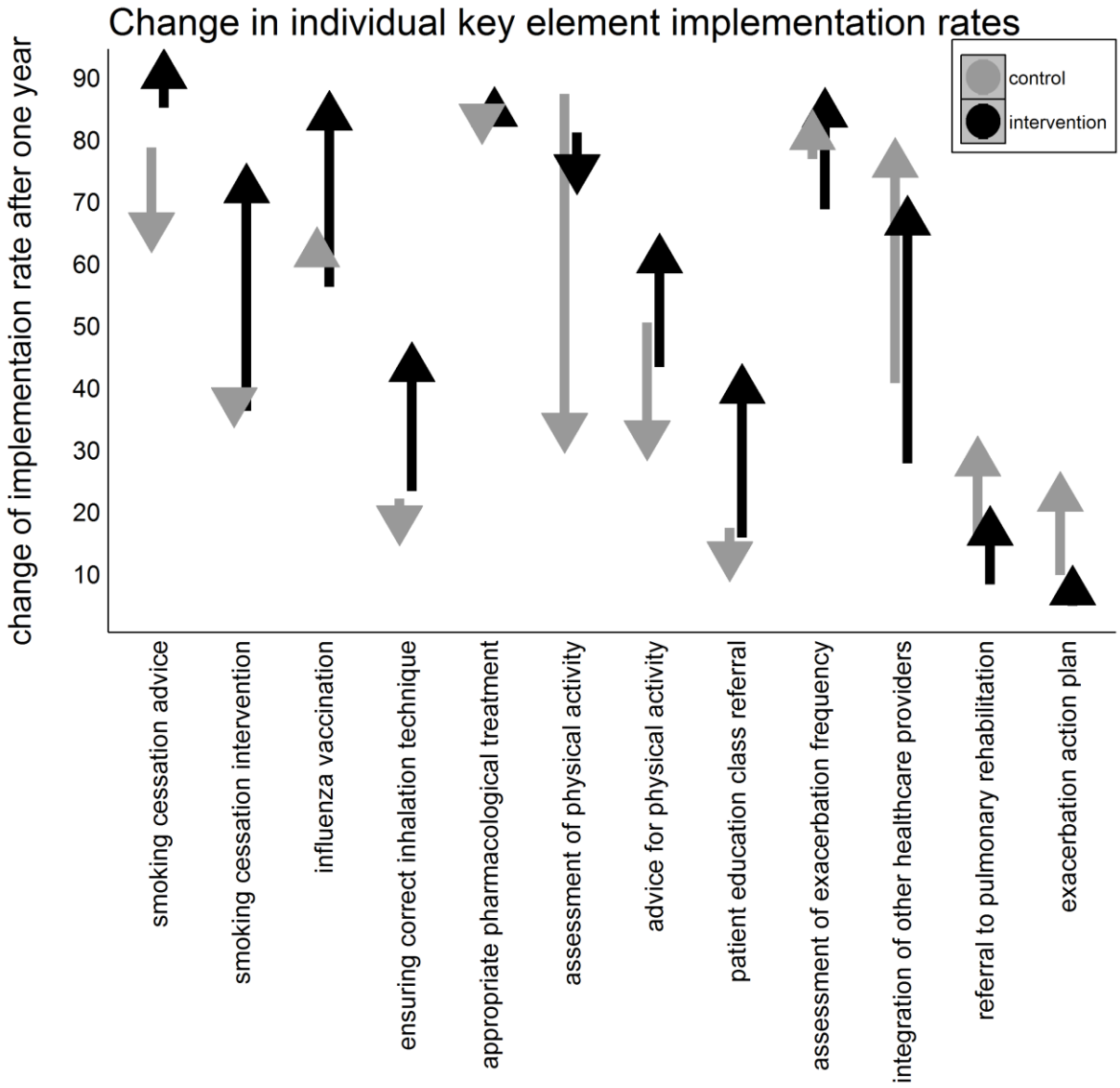

Intervention effects on individual key elements of COPD care
smoking cessation advice
smoking cessation intervention
influenza vaccination
ensuring correct inhalation technique
appropriate pharmacological treatment
assessment of physical activity
advice for physical activity
patient education class referral
assessment of exacerbation frequency
integration of other healthcare providers
referral to pulmonary rehabilitation
exacerbation action plan
pooled effect
primary outcome population (smokers only)
primary outcome population (all patients)
secondary outcome population (GOLD C and D patients)
0.1
0.2
0.5
1
2
5
10
odds ratio

423

424


Change in individual key element implementation rates
change of implementaion rate after one year
90
80
70
60
50
40
30
20
10
control
intervention
smoking cessation advice
smoking cessation intervention
influenza vaccination
ensuring correct inhalation technique
appropriate pharmacological treatment
assessment of physical activity
advice for physical activity
patient education class referral
assessment of exacerbation frequency
integration of other healthcare providers
referral to pulmonary rehabilitation
exacerbation action plan

425