The impact of case finding on the recruitment yield for COPD research in primary care: an observational study

Markun, Stefan; Rosemann, Thomas; Dalla-Lana, Kaba; Steurer-Stey, Claudia

Abstract: BACKGROUND: Recruiting patients for research in primary care is difficult with diseases that tend to remain underdiagnosed, such as chronic obstructive pulmonary disease (COPD). Researchers may consider introducing case finding into patient recruitment, but the impact on recruitment yield is largely unknown. OBJECTIVES: To assess the impact of case finding on recruitment yield and population characteristics in primary care-based COPD research. METHODS: For a cluster randomized controlled trial of COPD in primary care, an opportunistic case finding strategy was introduced into patient recruitment, in addition to recruiting patients with previously diagnosed COPD. The recruitment process and performance of the primary care physicians (PCPs) were analysed. The numbers and characteristics of patients identified by case finding were compared with those of patients with previously diagnosed COPD. RESULTS: Thirty-five PCPs approached 398 patients and successfully recruited 216 patients during 1 year. The mean number of patients recruited was 6.3 (range 0-16) per PCP. Case finding contributed 71 patients (32.9%) with significantly milder disease, with FEV1 % predicted +16.7 (95% CI: +11.3 to +22.0), a COPD Assessment Test difference of -4 points (95% CI: -2 to -6; p < 0.001), and fewer exacerbations resulting in a higher rate of GOLD class A (85.9 vs. 45.5%; p < 0.001). The smoking rate was significantly higher among patients with newly diagnosed COPD (70.4 vs. 48.6%; p = 0.002). CONCLUSION: Case finding increased the number of patients recruited by 50%. The COPD patients identified by case finding differed importantly from those with previously diagnosed COPD. Researchers should be aware of COPD underdiagnosis and the potential impact of case finding during patient recruitment.

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The impact of case finding on the recruitment yield for COPD research in primary care: an observational study

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Short title / running head
Case finding uncovers important COPD subpopulation

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Keywords
Chronic obstructive pulmonary disease, trial recruitment, case finding,
underdiagnosis, primary care
Abstract

Background
Recruiting patients for research in primary care is difficult in diseases that tend to remain underdiagnosed like chronic obstructive lung disease (COPD). Researchers may consider introducing case finding in patient recruitment but the impact on recruitment yield is largely unknown.

Objectives
To assess the impact of case finding on recruitment yield and population characteristics in primary care based COPD research.

Methods
For a cluster RCT on COPD in primary care, an opportunistic case finding strategy was introduced in patient recruitment in addition to recruiting patients with previously diagnosed COPD. Recruitment process and performance of primary care physicians (PCPs) was analysed. Numbers and characteristics of patients identified by case finding were compared with those of patients with previously diagnosed COPD.

Results
Thirty-five PCPs approached 398 and successfully recruited 216 patients during one year. The mean number of patients recruited was 6.3 (range 0 to 16) patients per PCP. Case finding contributed 71 (32.9%) patients with significantly milder disease with FEV1 % +16.7 (95%CI: +11.3 to +22.0), CAT difference -4 points (95%CI: -2 to -6, p=<0.001), and less exacerbations resulting in a higher rate of GOLD class A (86.6% vs. 53.3%, p=<0.001). Smoking rate was significantly higher in patients with newly diagnosed COPD (70.4% vs. 48.6%; p=0.002).
Conclusion

Case finding increased the number of recruited patients by 50%. The COPD patients identified by case finding differed importantly from those with previously diagnosed COPD. Researchers should be aware of COPD underdiagnosis and the potential impact of case finding during patient recruitment.
Introduction

Research in primary care is complicated by a number of well recognized factors. Prevalence of individual disease for example is low and even the most common chronic conditions account only for a small minority of the reasons for encounter[1]. Consecutively, compared to specialized settings, only small proportions of patients are eligible for studies on specific diseases. Therefore, researchers need to allow for comparably long recruitment periods or need to bring together large numbers of primary care physicians (PCPs) volunteering in study participation to achieve sufficient patient recruitment. Unfortunately, trials in primary care most often fail to achieve intended recruitment goals or need to be prolonged substantially [2]. Moreover, PCPs themselves are difficult to motivate for study participation. Time constraints, low interest in research in general and increasing regulatory and administrative requirements are often mentioned important barriers for PCPs in this context [3-11].

Strategies supporting recruitment of patients and/or physicians for research projects in primary care have been developed and assembled [12]. Still, data on effectiveness of these strategies is limited and recruiting remains an unpredictable but critical stage in primary care based research [13, 14]. To facilitate patient recruitment, electronic medical records can be used and such strategies will become increasingly feasible with their ongoing implementation also in primary care. Such records, however, logically can only identify patients with previously diagnosed diseases. Therefore, such a sampling method may be unreliable in diseases that tend to be underdiagnosed in the healthcare setting harbouring the research project. Chronic obstructive pulmonary disease (COPD) is of unquestioned epidemiologic importance given its high and increasing prevalence, socioeconomic
burden and loss in quality of life in affected patients [15, 16]. Despite the fact that the majority of patients with COPD are treated in primary care, clinical research concentrates on secondary or tertiary care for COPD leaving the majority of the affected population underrepresented in trials [17-19]. Moreover, commonly used selection criteria for COPD trials admit only a minority of the affected population and representativeness for the “real life” COPD patients has been further questioned [20]. Research in primary care is needed to answer the question of external validity of trials conducted on COPD in specialized settings. However, COPD is known to be widely underdiagnosed in primary care, bringing up a further obstacle to COPD research in this important healthcare setting[21, 22]. To address the issue of COPD underdiagnosis several case finding strategies have been proposed and opportunistic strategies (focusing on the at-risk population during a routine practice visit) are thought to be efficient [23].

In this study we describe the recruitment process of a cluster randomized trial on COPD in primary care where a case finding strategy has been implemented. The aim of the study was to assess recruiting performance, the contribution of case finding on the total number of recruited patients and also to compare characteristics of the sub-populations with COPD identified by case finding versus previously diagnosed COPD.

Methods

Study design, setting, registration and ethics statement

This observational study was produced with data collected during the recruitment process and with baseline data from the Improving Care in Chronic Obstructive Lung Disease (CAROL) Study. It is a cluster-randomized multi centred
trial conducted in primary care practices located in the two largest cities of the Canton of Zurich Switzerland. The trial has been registered at ClinicalTrials.gov (NCT01921556) and the trial’s study protocol has been published [24]. In brief, the trial’s intervention aimed at improving chronic care for COPD patients in primary care. The intervention was based on the Chronic Care Model and consists in a multifaceted training for PCPs and their practice assistants in COPD care [25]. 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.

**Recruitment of primary care physicians**

According to the trial’s power-calculation our goal was to recruit at least 30 PCPs (each recruiting eight to ten patients). About 1300 PCPs practicing in the trial’s locations were sent a formal letter from our institute and the cantonal Department of Health in July 2013. Additionally, the study was presented at peer group meetings of regional PCPs’ networks. All PCPs were given a brief description of the study including study aim and eligibility criteria and a prominent description of requirements and benefits of study participation (incentives were 50 Swiss Francs per recruited patient and 200 Swiss Francs compensation for those randomized to the intervention group involving participation at the teaching sessions). Interested PCPs and their practice assistants were invited at kick-off meetings where complete background information and study aims were presented. After the kick-off meetings, we enrolled 35 PCPs and their practice assistants, who all completed a training in how to conduct and interpret a spirometry according to international standards[26].
Case finding strategy and implementation of patient recruitment

We chose our case finding strategy to be the opportunistic approach of consecutive patients in routine practice visits aged at least 45 years, who were smokers or ex-smokers with at least 10 pack-years (PY). With this feasible strategy we expected to newly detect COPD in at least 20% of the approached individuals[27]. In addition to the criteria from case finding, inclusion criteria for participating in the CAROL study were: available informed consent and diagnosis or confirmation airflow obstruction (FEV1/FVC < 0.7) in spirometry. Exclusion criteria were: visiting the practice for emergency purposes only, insufficient German language skills, asthma or hay fever or a co-occurring disease with an estimated life expectancy of less than six months. The case finding strategy and the following recruitment process were instructed and exemplified in a teaching session after the spirometry training. PCPs entered the patient recruitment period after completion of the training.

The patient recruitment period started in December 2013 (after PCPs had completed spirometry training) and ended in January 2014. To support recruitment in practices we followed recommended principles of minimal administrative complexity and disruption, giving feedback (monthly email to PCPCs with benchmarking recruitment performance and three weekly outreach calls to practice assistants) and placing reminders on desks in practices [12]. Furthermore we supported PCPs in the interpretation of specific spirometry results if needed.

Measures and data collection

PCPs completed a questionnaire about themselves at their own enrolment in the study. The questionnaire comprised socio-demographic questions, questions
about medical specialization, full or part-time working, practice organization and the estimated number of patient contacts each day.

For each recruited patient, the following set of data was collected by the PCP:
timing of COPD diagnosis (identified by case finding or previously), spirometry results, dyspnoea according to modified British Medical Research Council Dyspnoea Scale (mMRC) [28], comorbidities, smoking status, COPD medication and health service utilization because of COPD.

The patient questionnaire was self-administered and piloted with six COPD patients in order to improve comprehensibility. The following set of data was collected: sociodemographic information, smoking habits and attitudes, COPD management recommendations and therapies received from the PCP during the last year (i.e. process indicators, primary endpoint of the CAROL trial), current COPD symptoms, exacerbations during previous year, actions taken if exacerbations occurred including health service utilization and the COPD assessment test (CAT) [29]. PCPs and the patients received pre-stamped envelopes for sending the completed questionnaires directly to the study centre. PCPs and patients had no access to each other’s answers.

Outcomes

Outcomes for this study were: 1) PCP recruiting performance, 2) the contribution of case finding to the total number of patients recruited, 3) characteristics of recruited patients and differences between the COPD patients identified by case finding and those with previously diagnosed COPD.

Statistical analysis

We report counts and proportions for categorical data as well as means and standard deviations (SD) or medians and interquartile ranges (IQR) as appropriate.
We compared groups applying bivariate statistics using T-test or Wilcoxon rank sum test for continuous data and Chi-squared test or Fisher’s exact test for nominal data and report p-values or 95% confidence intervals (95% CI) when appropriate. The minimum clinically important difference in the COPD assessment test (CAT) has been defined as two points [30]. Missing values were inquired at the respondents and completed accordingly if available.

Results

Primary care physicians’ characteristics and recruiting performance

Thirty-five PCPs from 21 different practices entered the patient recruiting period. Recruitment of these PCPs took nine months. PCPs’ median age was 49.7 (IQR 42.8 to 58.3) years and 26 (74.3%) were male. 31 (88.6%) were working in group-practices together with one to five colleagues (not necessarily participating in the study). Twenty-three (65.7%) were specialized in general medicine, 13 (37.1%) in internal medicine. Twenty-three (65.7%) of the PCPs reported to work full time, 60% was the lowest part-time assignment. On average, the PCPs estimated to see 24.6 (SD: 5.9) patients on a typical working day.

During the one-year patient recruiting period, each PCP approached on average 11.4 (SD: 8.6) patients, with considerable variability between the individual PCPs ranging from 0 to 31 patients. From a total of 398 eligible patients, 51 (12.8%) declined study participation or spirometry testing. From 147 consenting patients with previously diagnosed COPD, two were excluded because obstruction was not confirmed in spirometry. From 200 consenting patients who were identified by the case finding criteria, 71 (35.5%) had obstruction in spirometry. Therefore, from all
398 approached patients, PCPs recruited 216 (54.3%). The flowchart of the recruitment process is shown in Figure 1.

Each PCP recruited 6.3 patients (SD: 4.5, range 0 to 16) on average. The maximum of recruited patients per month was reached in the 4th month after study begin, followed by a rapid decline with stabilization after 9 months. Recruiting performance over time is shown in Figure 2.

**Contribution of case finding to total number of patients recruited**

Among the 216 recruited patients, 145 (67.1%) had a previously diagnosed COPD and the median duration of illness was five (IQR 2 to 8) years. From 200 patients who underwent spirometry without having a previous COPD diagnosis (case finding population), 71 had COPD. This corresponded to a 35.6% specificity of case finding in individuals without previously diagnosed COPD. These 71 individuals identified by case finding contributed 32.9% of the study population and case finding therefore increased the overall recruitment yield by 49.0%.

**Patient characteristics and subpopulation differences**

Overall, included patients were 68.1 (SD 9.7) years old on average and 59.5% male. Clinically most important differences between the subpopulation identified by case finding and those with previous COPD diagnosis appeared in the severity of airflow limitation reflected by FEV1 that resulted +16.7 (95%CI: +11.3 to +22.0) percentage points higher in the subpopulation identified by case finding. Also the between-group difference in the CAT summary score was clinically importantly different indicating milder symptoms and impairment in the subpopulation identified by case finding: between-group difference in medians of -4 (95%CI: -2 to -6) points. Moreover, a lower proportion of patients having ≥2 exacerbations or at least 1 exacerbation with hospitalisation in the previous 12 months was noted in this
subpopulation (5.6% versus 23.4%, p=0.001). In terms of the updated GOLD guidelines [26] this translated to a significantly higher rate of GOLD classification A (86.6% versus 53.3%, p=<0.001) in the subpopulation with case finding COPD diagnosis. Furthermore, the proportion of active smokers was higher in the subpopulation of case finding-identified COPD (70.4% compared to 48.6%, p=<0.002). Chronic comorbidities were more common in the subpopulation with previous COPD diagnosis (mean number of chronic comorbidities 1.2 vs. 0.8, p=0.01). More detailed comparative patient characteristics are given in Table 1.
Discussion

Main findings
Case finding substantially supported recruitment by contributing one out of three patients to the total study population.
The population identified by case finding differed importantly from the population with previously diagnosed COPD and notably influenced important characteristics of the total population recruited.

Interpretation of findings in relation to previously published work
In population based studies, patients with undiagnosed COPD have been found to outnumber the patients with diagnosed COPD and also to have higher current smoking rates and have less severe limitation of airflow. Furthermore, an important variation between international healthcare systems was found with the proportion of undiagnosed versus diagnosed individuals ranging from 50% to 98%[21]. In primary care the proportions of undiagnosed COPD patients are similarly variable and undiagnosed individuals have consistently been shown to be less symptomatic [22, 27, 31-34]. Results from our study are in line with previous epidemiological research as we identified a relevant proportion of patients with undiagnosed COPD in primary care in significantly earlier stages of the disease. Concerning case finding, we identified an undiagnosed case of COPD in every third patient falling under the predefined case finding criteria. This detection rate was above our expectations, however, our case finding criteria might have had higher specificity because of older age and additional minimum number of PYs than the criteria for opportunistic case finding recently described with a detection rate around 20% [23].
The clinical importance of case finding and early detection of COPD consists in creating opportunities for early preventive interventions especially if modifiable risk factors can be targeted. In this context, smoking cessation is the intervention with highest beneficial impact on disease progression and specific recommendations to increase smoking cessation rates in COPD patients exist.[26, 35] In primary care, where most COPD patients are in early disease stages, the potential of preventive measures is highest. Here, in addition to clinical aspects, we describe important methodological implications to case finding in COPD research: Knowing about the difficulties to implement patient recruitment in primary care, researchers are naturally tempted to make use of electronic medical record searches to identify eligible cases. Such approaches are already followed and thought to produce representative patient samples [36, 37]. Without knowledge about COPD underdiagnosis in the studied population, however, such strategies are at risk to produce biased samples since they might miss large proportion of the population intended to represent. In our setting, an approach relying only on previously identified cases, would have most likely recruited a different population. Especially concerning is that the differences appeared in the most important prognostic variables namely airflow limitation and smoking status. Underdiagnosis of COPD can therefore be an important source of sampling bias by systematically occurring in milder diseased individuals. Since diagnostic performance for COPD is known to be setting-specific, recruitment methods drawing only from previously identified cases of COPD are likely to produce heterogeneous patient samples in different health care settings. Consecutively, populations are difficult to compare across studies and moreover still not represent the majority of the diseased population even if performed in primary care.
Strengths and limitations of the study

To our knowledge, this is the first report emphasizing the implications of case finding for recruitment of COPD patients in primary care based research. This article describes the advantages of case finding for research purposes and contributes to research methodology in primary care and COPD. Furthermore, this is the first comprehensive report giving detailed insights into the recruitment strategy and recruitment outcomes of a primary care based cluster randomized study on COPD, thus supporting researchers embarking on similar research projects.

The main limitation of this study is the observational design. We can only assume that patients with undiagnosed COPD would truly not have found access to our total study population without the introduction of case finding. We are, however, confident that no similarly relevant proportion of patients with undiagnosed COPD would have been identified. Furthermore, the recruitment of PCPs themselves proved to be difficult and progressed slowly. We must assume that the participating PCPs represent a comparably highly motivated sample with higher interest in either COPD, research per se or both. Therefore, implementation of case finding and also its yield may perform differently in non-research environments, however, in both clinical and research settings volunteer bias occurs.

Implications for future research, policy and practice

For future research on COPD in primary care we recommend that diagnostic performance should be at least measured by implementing a case finding protocol before relying on electronic medical record searches only. This is how the risk of bias from underdiagnosis and selective recruiting can at least be assessed if researchers were still to rely on electronic medical record based recruitment. Considering the specific case finding strategy, there is little consensus on which is best. In this study
the efforts of implementing an opportunistic case finding strategy were moderate and consisted in raising the awareness for the disease among PCPs and strengthening their diagnostic skills in spirometry testing. Opportunistic case finding is already considered to be needed in every day clinical practice and we believe that also COPD research in primary care would benefit from it. This, not only by supporting notoriously difficult recruitment processes but also by increasing representativeness and comparability of selected patient samples.

Conclusions

Opportunistic case finding increased the number of recruited patients by almost 50%. The COPD patients identified by case finding differed importantly from those with previously diagnosed COPD. Researchers should be aware of the impact of case finding during recruitment, especially in healthcare settings with high rates of COPD underdiagnosis.

Acknowledgements

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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, AstraZeneca and Novartis. CSS provided consultancy or gave talks around the topic to Boehringer Ingelheim, AstraZeneca and GSK.
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Characteristics of total study population (n=216) and comparison of characteristics of the subpopulations with previously identified COPD and those identified by case finding.
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<td></td>
<td></td>
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<td>(SD), IQR or %</td>
<td>mean, median or n</td>
<td>(SD), IQR or %</td>
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<td>14.7%</td>
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<tr>
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<td></td>
<td>n and %</td>
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<td>55.6%</td>
<td>70</td>
<td>48.6%</td>
</tr>
<tr>
<td>Exacerbation at inclusion</td>
<td></td>
<td>n and %</td>
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<td>17.3%</td>
<td>30</td>
<td>22.4%</td>
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<tr>
<td>Comorbidities</td>
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<tr>
<td>diabetes</td>
<td>n and %</td>
<td></td>
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<td>13.8%</td>
<td>23</td>
<td>16.3%</td>
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<tr>
<td>hypertension</td>
<td>n and %</td>
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<td>76</td>
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<td>37</td>
<td>17.7%</td>
<td>31</td>
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<tr>
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<td>9.5%</td>
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<td>11.8%</td>
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<tr>
<td>depression</td>
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</tr>
<tr>
<td></td>
<td>41</td>
<td>19.8%</td>
<td>28</td>
<td>19.9%</td>
<td>13</td>
<td>19.7%</td>
</tr>
</tbody>
</table>

1) Welch Two Sample t-test, 2) Pearson’s Chi-squared test, 3) Fisher’s Exact Test for Count Data, 4) Wilcoxon rank sum test
Figure Legends

Figure 1  
Flowchart of the study

Figure 2  
Overall number of COPD patients (n=216) recruited per month by 35 PCPs. The light grey bars represent patients with previously diagnosed COPD, the dark-grey bars above represent patients COPD identified by case finding.