Case finding for chronic obstructive pulmonary disease in primary care: a pilot randomised controlled trial

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an increasingly important cause of morbidity and mortality worldwide. It is responsible for considerable healthcare use, accounting for at least 1.4 million GP consultations and 1 million inpatient days in the UK, costing the NHS over £800 million per year. However, COPD remains substantially undiagnosed. Reasons include poor attendance at primary care by individuals with chronic respiratory symptoms, low index of suspicion by primary care practitioners, and probable underuse of spirometry in primary care. Unrecognised COPD contributes to avoidable emergency admissions and hospitalisations, spurring a national drive to identify these ‘missing millions’. Early identification of undiagnosed disease has become an integral part of the National Clinical Outcomes Strategy for COPD and Asthma in England. There have been a number of single-arm studies examining a variety of approaches to case finding or screening for COPD in primary care, such as questionnaires and hand-held spirometers. However, there are no published comparative studies. The most effective method of case finding thus remains unknown.

A pilot randomised controlled trial (RCT) was conducted, comparing two approaches to case finding for COPD, to help inform the operational design of a large RCT and to help local primary care service providers and commissioners decide whether to invest in case finding in the local population.

METHOD

Study design

The study was a pilot RCT comparing two methods of case finding for COPD in two general practices in the West Midlands, UK.

Population/setting

Sandwell is a metropolitan borough in the West Midlands and is the 12th most economically deprived local authority area in the UK, with an ethnically diverse population. It also has a high prevalence of COPD (1.73% in 2008/2009), associated mortality (direct age-standardised rate 36.7 per 100,000 population), and a smoking prevalence of 25%.

Recruitment of general practices

Modelling data were used to identify general practices with an estimated number of 100 or more patients with undiagnosed COPD. Those with a nurse holding accredited spirometry training were selected. Two out of eight eligible practices agreed to participate (list sizes 12,750 and 5,630).

Eligible patients

Ever-smokers aged 35–79 years with no history of COPD or asthma were identified and randomised, using a computerised algorithm, to either a ‘targeted’ or ‘opportunistic’ intervention arm.
### Intervention and comparator

A simple respiratory screening questionnaire (available from the author) was adapted from the Medical Research Council (MRC) respiratory questionnaire, as, at the time of the study, other screening questionnaires had not been widely validated. It included questions about demographic information (age, sex and ethnic group), symptoms of COPD (chronic cough, dyspnoea, sputum, wheeze and their duration), smoking history, and occupational exposures.

Patients allocated to the ‘targeted’ arm were sent an invitation letter, respiratory questionnaire, consent form, and a prepaid return envelope in the post by the research team. In the ‘opportunistic’ arm, electronic prompts were added to medical records to provide the same questionnaire pack when patients next presented to their GP or practice nurse. These prompts were kept active over 3–6 months between 21 May 2010 and 31 January 2011. Patients in both intervention arms who did not return their questionnaire were sent up to two further reminders by post.

Patients reporting at least one chronic respiratory symptom (such as cough, phlegm, MRC grade 2 dyspnoea or above, or wheeze) lasting for at least 3 months were invited for spirometry at their surgery.

### Spirometry assessment

Spirometry was performed by a practice nurse using Microloop and Micro GP spirometers with Spida 5 software and according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. Airflow obstruction was defined as pre-bronchodilator forced expiratory volume in 1 second of $<80\%$ ($FEV_1 < 80\%$) and forced expiratory volume/forced vital capacity ratio of less than 0.7 ($FEV_1/FVC < 0.7$), in accordance with the previous National Institute for Health and Clinical Excellence (NICE) guidelines. The first five spiromgrams in each practice were quality checked by a respiratory scientist at the University of Birmingham, according to ATS/ERS criteria.

### Outcomes

The primary outcome was the difference in proportion of patients identified with COPD in the ‘targeted’ and the ‘opportunistic’ arms. Patients were defined as having COPD if they had both the required respiratory symptoms and pre-bronchodilator airflow obstruction. Patients meeting the criteria for COPD were referred to their GP or specialist respiratory nurse for further management.

### Sample size calculation

To detect a 5% difference in the proportion of patients identified with COPD, 474 eligible patients would be needed in each arm of the study to achieve a power of 80% at a 5% confidence level.

### Statistical analysis

Differences in proportions and 95%
Confidence intervals (CIs) were calculated using a two-proportion z test with Stata (version 10). The number needed to screen (NNS) to identify one patient with COPD was also calculated.

Sensitivity analyses were undertaken to extrapolate the data to a 12-month period, assuming that identification of cases in the ‘opportunistic’ arm would remain at the same rate as that observed. The case-finding yield and NNS for each intervention arm were also modelled for varying spirometry attendance rates.

**Economic analysis**

A simple cost-effectiveness analysis was undertaken using costs for the 2010/2011 financial year. For the main analysis, capital (equipment) costs were based on purchase prices and RCT over a 5-year period using a 3.5% discount rate. The costs associated with the study (Table 1) were summated and divided by the number of patients diagnosed with COPD, to calculate the cost per case identified in each intervention arm. The difference in costs was divided by the difference in the number of patients diagnosed with COPD over a 12-month period in each intervention arm, to calculate the incremental cost-effectiveness ratio (ICER). The analysis was also modelled to calculate the cost per patient diagnosed with a spirometry attendance of 90%.

**Regulatory approval**

The National Research Ethics Service advised that ethical approval would not be required as this was considered a service evaluation. Case finding for COPD was already being undertaken in primary care in England through a variety of approaches and the aim of this study was to evaluate the effectiveness of two such approaches. Furthermore, the two arms of the study were considered to be in equipoise with respect to potential benefits and harms.

**RESULTS**

**Characteristics of eligible patients**

A total of 1634 patients fulfilling the inclusion criteria were identified. Of these, 815 were randomised to the ‘targeted’ arm and 819 to the ‘opportunistic’ arm (Figure 1). Approximately two-thirds were male (Table 2) and 90% were in the two most socioeconomically-deprived quintiles. Patients in both arms were similar in terms of age, sex, and socioeconomic status.

**Response to respiratory questionnaires**

A total of 1071 respiratory screening questionnaires were distributed; 813 (99.8%) patients in the ‘targeted’ arm were sent questionnaires by post; 258 (31.5%) eligible patients in the ‘opportunistic’ arm attended their general practice during the

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**Table 2. Sociodemographic characteristics of patients initially selected**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Targeted</th>
<th>Opportunistic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n (%)</td>
<td>815 (49.9)</td>
<td>819 (50.1)</td>
<td>1634 (100)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>511 (62.7)</td>
<td>526 (64.2)</td>
<td>1037 (63.5)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>50.9 (11.2)</td>
<td>51.1 (11.7)</td>
<td>51.0 (11.5)</td>
</tr>
<tr>
<td>Mean IMD (SD)</td>
<td>43.7 (14.2)</td>
<td>42.1 (14.3)</td>
<td>42.9 (14.3)</td>
</tr>
<tr>
<td>IMD quintile, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1*</td>
<td>601 (73.7)</td>
<td>560 (68.4)</td>
<td>1161 (71.1)</td>
</tr>
<tr>
<td>2</td>
<td>144 (17.7)</td>
<td>175 (21.4)</td>
<td>319 (19.52)</td>
</tr>
<tr>
<td>3</td>
<td>63 (7.7)</td>
<td>76 (9.3)</td>
<td>139 (8.51)</td>
</tr>
<tr>
<td>4</td>
<td>4 (0.5)</td>
<td>7 (0.9)</td>
<td>11 (0.67)</td>
</tr>
<tr>
<td>5*</td>
<td>3 (0.4)</td>
<td>1 (0.1)</td>
<td>4 (0.24)</td>
</tr>
</tbody>
</table>

IMD = Index of Multiple Deprivation (a measure of socioeconomic deprivation). SD = standard deviation. *Most deprived; *Least deprived.

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**Figure 1. Patient flow through the study (percentages are given as a proportion of the previous level).** Or did not receive questionnaire in practice.
Overall, 323 questionnaires were returned, 188 (58.2%) with no reminders, 58 (18.0%) with one reminder, and 77 (23.8%) with two reminders. The overall response was higher in the ‘opportunistic’ than in the ‘targeted’ arm (43% versus 26%, respectively; Figure 1).

Characteristics of responding patients

The characteristics of patients who returned their questionnaire and consented to participate are listed in Table 3. Those in the ‘opportunistic’ arm were more likely to be male (67.6% in the ‘opportunistic’ arm versus 60.8% in the ‘targeted’ arm), and tended to be older and less deprived than responders from the ‘targeted’ arm.

Two hundred and forty-seven responders (72.4%) reported at least one respiratory symptom, of which dyspnoea was the most common (64.4%; Table 3). The proportion of patients with respiratory symptoms was slightly higher in the ‘targeted’ arm (74.1% versus 69.2% in the ‘opportunistic’ arm), although rates of dyspnoea were similar in both groups.

Spirometry assessment

Two hundred and forty-seven patients were subsequently offered spirometry, of whom 98 (39.7%) attended (Table 3), with higher attendance among the ‘targeted’ arm. Of these, 16 (16.3%) had pre-bronchodilator airway obstruction, which was irreversible in 13 (13.3%).

The proportion with pre-bronchodilator airflow obstruction out of those originally identified was higher in the ‘targeted’ (10/815 or 1.2% [95% CI = 0.47% to 1.99%]; NNS = 82) than the ‘opportunistic’ arm (6/819 or 0.7% [95% CI = 0.15% to 1.32%]; NNS = 137). This difference was not statistically significant (0.5%, 95% CI = –0.5% to 1.5%).

Overall, most (87.5%) of the airflow obstruction identified was mild and only 12.5% was moderate (these two patients were both from the ‘opportunistic’ arm).

Sensitivity analyses

The ‘opportunistic’ arm ran for 3 months in one practice and 6 months in the other. Extrapolating to a 12-month period would increase the numbers identified in the ‘opportunistic’ arm to 16 patients (1.95% [95% CI = 1.00% to 2.90%]; NNS = 51). This would translate into a higher case-finding yield than in the ‘targeted’ arm (difference = 0.73% [95% CI = –0.49% to 1.94%]), although again this is not statistically significant.

There was some uncertainty about how many patients with respiratory symptoms were actually invited for spirometry. The
case-finding yield and NNS were therefore further modelled for varying spirometry attendance rates (Figure 2). In the best case scenario with a 90% spirometry attendance, the case-finding yield could be improved to 2.6% (NNS = 39) and 4.5% (NNS = 23) for the ‘targeted’ and ‘opportunistic’ arms, respectively.

**Cost-effectiveness analysis**

When extrapolated to 12 months, and including the cost of a spirometer and nebuliser, the ‘opportunistic’ approach was more cost effective than the ‘targeted’ approach (£265.19 versus £461.34, respectively per COPD diagnosis; Table 4). The ‘opportunistic’ approach dominated the ‘targeted’ approach, since it was both cheaper overall and estimated to pick up more cases over a 12-month period. The same was true when excluding the costs of a spirometer and nebuliser (£242.20 versus £285.39 for the ‘opportunistic’ and ‘targeted’ arms, respectively) and when modelling for a 90% spirometry attendance. The difference in costs was largely driven by the difference in the proportion of patients undergoing spirometry who were diagnosed with COPD.

**DISCUSSION**

**Summary**

In this pilot study, there was no statistically significant difference in the case-finding yield between an opportunistic and a targeted postal approach to case finding for COPD over the study period of 3–6 months, although a greater proportion of cases was identified with the targeted approach. However, extrapolation of the results over the course of 1 year suggests that an opportunistic approach may be more efficient. Overall, most (87.5%) of the airflow obstruction identified was mild (FEV1 50–80% of predicted).

The study findings suggest that the opportunistic approach was also more cost effective than the targeted approach, although with little material difference.

**Table 4. Cost effectiveness of case finding extrapolated to 12 months**

<table>
<thead>
<tr>
<th>Items</th>
<th>Based on numbers observed</th>
<th>Based on 90% spirometry attendance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Including cost of spirometer and nebuliser, £</td>
<td>Excluding cost of spirometer and nebuliser, £</td>
</tr>
<tr>
<td>Questionnaire pack</td>
<td>305.91</td>
<td>12.57</td>
</tr>
<tr>
<td>Administration</td>
<td>2445.00</td>
<td>2457.00</td>
</tr>
<tr>
<td>Reminders</td>
<td>488.62</td>
<td>327.69</td>
</tr>
<tr>
<td>Spirometry</td>
<td>1006.08</td>
<td>1077.94</td>
</tr>
<tr>
<td>Total</td>
<td>4613.40</td>
<td>4242.99</td>
</tr>
<tr>
<td>Number diagnosed</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Cost per diagnosis</td>
<td>461.34</td>
<td>265.19</td>
</tr>
</tbody>
</table>

ICER = incremental cost-effectiveness ratio. O = opportunistic. T = targeted. ‘Opportunistic’ arm dominates over ‘targeted’ arm (that is: it is both cheaper and more effective).
in costs this reflects the greater yield after spirometry. The cost effectiveness could be further improved by increasing spirometry attendance. In the best case scenario, improving spirometry attendance to 90% would cost £151.74 per diagnosis of COPD through the opportunistic approach, when excluding the cost of a nebuliser and spirometer.

Limitations of the study
As a small pilot study in two general practices, the findings should be interpreted with some caution and may not be generalisable to other primary care populations and settings. Nevertheless, there are several important results that may impact on future research and services.

First, less than one-third of patients responded to the respiratory questionnaire, despite two reminders, and the response was lower in the ‘targeted’ arm. Encouraging patients in the ‘opportunistic’ arm to complete their questionnaire before leaving the practice may have improved the response. The option of combining ‘opportunistic’ and ‘targeted’ approaches may also be worthwhile. Response rates may vary by ethnicity and socioeconomic deprivation, and so a definitive RCT should include practices with diverse population characteristics.

Secondly, responders reported a high rate of respiratory symptoms indicative of COPD. It is not clear whether this reflected the general population targeted, or whether people with symptoms were more likely to respond. The latter explanation would be beneficial if a similar approach were adopted in primary care, since it would improve the efficiency of the intervention. The efficiency of case finding could also be improved by risk stratifying patients and targeting those at highest risk.

Thirdly, over a 3–6 month period, over 30% of the target population consulted their GP and were given questionnaires, which is promising for opportunistic approaches and likely to be higher over the course of a year.

Fourthly, only a small proportion of patients reporting symptoms underwent spirometry. This was secondary to both non-attendance, which is commonly faced in primary care serving socioeconomically deprived populations, and limited service capacity. The extent to which each factor contributed to the poor spirometry attendance was not measured. It is important that spirometry service capacity is sufficiently available before introducing case finding, and that follow-up is implemented for non-attendees.

Filthily, the criteria used to define airway obstruction must be carefully chosen and may impact on the proportion of false-positive diagnoses of mild to moderate COPD, especially in small older people. The diagnostic criteria used in this study (pre-bronchodilator FEV1/FVC<0.7 and FEV1<80% of predicted) have been superseded in the UK by guidelines published in 2010 by NICE, which require only an FEV1/FVC<0.7. The present study would probably underestimate the number of cases of COPD that would be identified through the two case-finding approaches if the newer diagnostic thresholds were used.

Comparison with existing literature
A variety of approaches have been used to identify new cases of COPD; however, these vary in the setting, target groups, screening tools, and diagnostic criteria. Many studies have defined COPD without taking account of respiratory symptoms, even though this is not recommended, and most studies have been relatively small in size and scope.

To the authors knowledge, only one published abstract reports a comparison of two case-finding approaches, comparing an opportunistic method with a letter and follow-up phone call among patients aged >35 years in a single general practice in the UK. This study indicated that the opportunistic approach was likely to be more efficient, even over a short screening period.

A variety of symptom-based questionnaires have been used to screen for COPD in primary care. Their case-finding yields have ranged from 2.7% to 18.6%, and are generally higher than the yield detected in the current study. However, the yield is dependent on many factors, including the denominator used (for example, eligible patients versus those who responded or received the intervention) and the diagnostic definition of COPD.

The rate of response to the respiratory questionnaire in the present study was quite low, at an average of 26% for the postal questionnaire and 43% for the opportunistic questionnaire. This may reflect the high levels of socioeconomic deprivation and low levels of health literacy in the borough. Rates of response to research studies vary but have tended to decrease over time. For example, a series of postal respiratory questionnaires in two general practices in the UK showed diminishing response rates (from 71.2% to 46% after two reminders) over a period of 10 years.
opportunistic case finding was included in both the 2004 and 2010 NICE guidelines on COPD. This concluded that opportunistic case finding in primary care is a relatively cost-effective strategy. The key determinants of its cost effectiveness are the prevalence of undiagnosed COPD and the smoking quit rate. However, this analysis included many assumptions and needs to be tested empirically in an adequately powered trial.

**Implications for practice and research**

Most of the patients identified with COPD had mild disease. This has important implications for primary care, since the therapeutic options for early-stage disease are limited. However, patients with mild disease are likely to gain more quality-adjusted life-years from smoking-cessation therapy than patients with more severe disease, and may get symptomatic relief from short-acting bronchodilators.

Case finding for COPD in this pilot study using either a targeted or an opportunistic approach only identified a relatively small number of patients with COPD. Although the estimated case-finding yield over 1 year was higher for the opportunistic approach, the difference was not statistically significant and as yet there is no firm evidence for which approach might be more cost effective.

A larger-scale RCT is needed to evaluate the effectiveness and cost effectiveness of different approaches to case finding in primary care, taking the lessons learned from this pilot study into consideration. Further work is also needed to investigate better methods of engaging high-risk populations in socioeconomically deprived areas to be aware of their respiratory health and to improve the efficiency of case finding. There is also a need to evaluate the impact of case finding on individual patients and to audit the management of those patients who are newly identified with COPD in this way. Until there is good evidence of clinical and cost effectiveness, case finding for COPD should not yet be routinely implemented in primary care.
REFERENCES


