Case-finding and improving patient outcomes for chronic obstructive pulmonary disease in primary care: the BLISS research programme including cluster RCT

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Scientific summary

BLISS research programme

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Scientific summary

Background

At least half of people with chronic obstructive pulmonary disease are undiagnosed, but the best approach for identifying them is not established. Furthermore, screening is not recommended because it is not yet known if it leads to clinical benefits.

There is increasing recognition that chronic obstructive pulmonary disease is heterogeneous, and, although a number of prognostic models have been developed, most prognostic models include people with more severe disease within secondary care. It is not known which combination of phenotypic characteristics best predict prognosis in the larger primary care chronic obstructive pulmonary disease population, particularly in relation to respiratory hospitalisations.

Effective treatment for those with mild chronic obstructive pulmonary disease is limited. Physical activity promotion is a potential intervention, but its acceptability to primary care chronic obstructive pulmonary disease patients is unknown.

A substantial proportion of chronic obstructive pulmonary disease patients are of working age. Although there is some evidence that they have poorer employment history and work productivity, the main factors that are associated with these outcomes have not to our knowledge been previously studied.

The aim of this programme was to address the above uncertainties.

Objectives

Work package 1

- Ascertain the clinical effectiveness and cost-effectiveness of targeted case-finding (opportunistic or active) compared with routine care.
- Develop a Markov model to compare the cost-effectiveness of systematic case-finding with current practice.
- Explore the views of patients and primary care staff on chronic obstructive pulmonary disease case-finding.
- Describe the clinical management of screen-detected chronic obstructive pulmonary disease patients in primary care.
- Assess the long-term effectiveness of chronic obstructive pulmonary disease case-finding on respiratory hospitalisations and mortality.
- Compare outcomes among screen-detected chronic obstructive pulmonary disease patients who were adequately managed by their general practitioner with those among patients who were not.

Work package 2

- Recruit a primary care cohort of 2000 new and existing chronic obstructive pulmonary disease patients.
- Test the validity of existing chronic obstructive pulmonary disease prognostic models in a primary care chronic obstructive pulmonary disease population.
- Develop a prognostic model (BLISS index) to predict respiratory hospitalisations suitable for a primary care population.
- Explore the barriers to and facilitators of physical activity participation among people with chronic obstructive pulmonary disease.

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Work package 3

- Examine factors associated with occupational performance [employment, absenteeism and presenteeism (working while unwell)] among chronic obstructive pulmonary disease patients of working age.
- Examine how disease progression is associated with occupational performance.
- Assess the feasibility of offering occupational health assessment with recommendations to people with chronic obstructive pulmonary disease.

Methods

Work package 1: TargetCOPD cluster randomised controlled trial

Fifty-four general practices were randomly assigned to either targeted case-finding or routine care. Eligible patients were people who had smoked, were aged 40–79 years and did not have a previous chronic obstructive pulmonary disease diagnosis. Those in the targeted arm were further randomly assigned to receive a symptom screening questionnaire either at any general practitioner visit (opportunistic) or by post (active). Respondents reporting relevant respiratory symptoms were invited for diagnostic post-bronchodilator spirometry.

Primary outcomes were percentage of the eligible population diagnosed with chronic obstructive pulmonary disease within 1 year (yield) and cost per new chronic obstructive pulmonary disease diagnosis using trial data.

At 4–5 years' follow-up, data on mortality and hospitalisations were obtained from NHS Digital for all eligible patients, and case-found chronic obstructive pulmonary disease patients were invited to complete a health questionnaire to report on their health-related quality of life as well as treatments received for chronic obstructive pulmonary disease. For case-found patients, we also obtained data from electronic health records on whether or not they had been added to the practice's Quality and Outcomes Framework chronic obstructive pulmonary disease register within 12 months and whether or not they had been prescribed a range of chronic obstructive pulmonary disease treatments.

Cox proportional hazards models adjusted for potential confounding factors were used to model the time to clinical outcomes (i.e. death, first respiratory hospital admission) in the intervention and routine arms. Time to event was censored at death (for admission) or study end date if no event occurred.

For case-found patients, we used logistic and Poisson regression to compare mortality, hospitalisation and health-related quality of life among those who were and those who were not added to the chronic obstructive pulmonary disease register, adjusting for baseline values and relevant confounders.

Data from the trial and our cohort study (work package 2) as well as from the published literature were used to develop a Markov decision-analytic model to compare the cost-effectiveness of a 3-yearly case-finding programme aimed at people who have smoked aged > 50 years with current practice, taking a health service perspective.

We interviewed patients who had been invited for screening and primary care staff in targeted case-finding practices to explore their views on screening.

Work package 2: Birmingham primary care chronic obstructive pulmonary disease cohort

Patients aged ≥ 40 years with previously diagnosed chronic obstructive pulmonary disease from 71 practices, as well as those reporting chronic respiratory symptoms as part of the TargetCOPD trial, were invited to join the cohort study. Participants underwent detailed baseline assessment, were followed up with 6-monthly questionnaires and underwent a final assessment at $\approx$3 years.

Using data from those with chronic obstructive pulmonary disease in the cohort, linked to mortality data obtained from NHS Digital, we sought to validate the ADO (age, dyspnoea, airflow obstruction) prognostic score. This was shown to be the most discriminatory among current indices in predicting mortality in a recent review. Discrimination was calculated using the *c*-statistic. Calibration was assessed by comparing predicted with actual probability of mortality.

To develop a new index to predict respiratory admissions, we considered 23 candidate variables identified from the literature and by a clinician stakeholder group. Self-reported and clinical data from cohort patients were linked to hospitalisation data obtained through NHS Digital. The primary outcome was the record of at least one respiratory admission within 2 years of cohort entry. The model was developed using backward elimination ($p < 0.157$ for retention). Fractional polynomials were considered and multiple imputation using chained equations was used for missing data. Discrimination and calibration were assessed. Bootstrapping was used for internal validation and the optimum-adjusted performance statistics were estimated.

A purposive sample of 26 cohort patients with a range of chronic obstructive pulmonary disease severity participated in one of four focus groups to explore perceived barriers to and facilitators of physical activity engagement, using the social cognitive theory framework. Thematic analysis identified key concepts related to the patients' self-efficacy beliefs.

Work package 3: occupational performance and outcomes in chronic obstructive pulmonary disease

Using baseline data of cohort participants who were of working age, we compared the sociodemographic, clinical and occupational characteristics of people who were in paid employment with those of people who were not. Among those in paid employment, we examined characteristics associated with absenteeism (self-report over previous 12 months) and presenteeism (Stanford Presenteeism Scale).

Longitudinal multivariable regression analyses, adjusting for clinical, sociodemographic, occupational and labour market factors among participants in paid employment, were conducted to examine the effects of disease progression [forced expiratory volume in 1 second decline, respiratory hospitalisations (exacerbations), increase in Medical Research Council dyspnoea score, worsening Chronic Obstructive Pulmonary Disease Assessment Test score] on employment, absenteeism and presenteeism.

Cohort participants who were in paid employment at baseline were invited for a tailored occupational health assessment to explore and identify workplace factors that might contribute to their work performance and to recommend appropriate modifications. Participants' self-management practices were also assessed. Recommendations were sent to the participant and, with their permission, to their general practitioner and employer. We examined acceptability and feasibility of the intervention.

Results

Work package 1

Effects of case-finding on yield

A total of 74,818 patients took part. Very few new cases of chronic obstructive pulmonary disease were diagnosed in routine practice. The yield from targeted case-finding was significantly higher (adjusted odds ratio 7.45, 95% confidence interval 4.80 to 11.55) and active case-finding was more clinically effective (adjusted odds ratio 2.34, 95% confidence interval 2.06 to 2.66) and more cost-effective than the opportunistic-only approach (£333 vs. £376 per case detected, respectively).

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Decision-analytic model of cost-effectiveness of case-finding

Our model predicted that the incremental cost-effectiveness ratio of a systematic 3-year case-finding programme compared with routine care was £16,596 per additional quality-adjusted life-year gained if assumptions hold, giving this a high probability of being cost-effective using the UK willingness-to-pay threshold of £20,000 per quality-adjusted life-year.

Stakeholder views on case-finding

Both patients and primary care staff generally considered screening to be valuable. Patients highlighted the presence of symptoms and convenience of the screening process as factors promoting screening attendance. Better support from secondary care, an increase in specialist chronic obstructive pulmonary disease nurses and better community respiratory service provision would support primary care staff in undertaking case-finding. Patient barriers to screening attendance included psychological and practical factors, such as time, availability and perceived lack of general practitioner time. Primary care staff had concerns around lack of resource for increasing workload and potential harm from overdiagnosis.

Management of case-found patients

A year after case-finding, approximately one-fifth of case-found patients but > 90% of routinely diagnosed patients had been added to a chronic obstructive pulmonary disease register. Patients who had been added to a chronic obstructive pulmonary disease register were significantly more likely to receive appropriate chronic obstructive pulmonary disease-related care (more than five items of clinical assessment and/or management) than those who had not been added to a register. However, even among those on the register, fewer than one-quarter of eligible patients had ever been referred to pulmonary rehabilitation and a significant proportion of smokers had not received smoking cessation support.

Effectiveness of case-finding on clinical outcomes

Over a mean follow-up of 4.3 years, 4.8% (1557/32,743) of patients in the case-finding arm and 4.5% (1899/41,950) in the routine arm had a respiratory hospitalisation (adjusted hazard ratio 1.04, 95% confidence interval 0.73 to 1.47). The corresponding hazard ratio for mortality was 1.15 (95% confidence interval 0.82 to 1.61), suggesting that, overall, there was no significant difference in risk of hospitalisation and mortality between case-found and routine care arms and there was no noteworthy difference in outcomes between those in the two case-finding intervention arms. Among the case-found patients, when comparing those who were and those who were not on the chronic obstructive pulmonary disease register, there was no statistically significant difference in clinical outcomes or in EuroQol-5 Dimensions scores, although the Chronic Obstructive Pulmonary Disease Assessment Test score was higher in those on the chronic obstructive pulmonary disease register (mean difference 2.317, 95% confidence interval 0.481 to 4.153), indicating greater impact of chronic obstructive pulmonary disease on their health-related quality of life.

Work package 2

Birmingham chronic obstructive pulmonary disease cohort

Data on 2250 patients (97.8%) were available over 3 years. Six-monthly questionnaires were completed by approximately two-thirds of patients. Over the period of follow-up (minimum 1.8 years, maximum 3.8 years), 382 patients (17%) had at least one respiratory hospital admission and 124 patients died.

Validation of age, dyspnoea, airflow obstruction prognostic score

Valid data were available for 1701 chronic obstructive pulmonary disease patients with airflow obstruction (309 case-found patients). Age, dyspnoea, airflow obstruction prognostic scores discriminated 3-year mortality accurately (*c*-statistic 0.73, 95% confidence interval 0.67 to 0.79), with similar discriminatory ability for 2- and 1-year mortality (*c*-statistic 0.72, 95% confidence interval 0.67 to 0.77 and 0.73 and 95% confidence interval 0.66 to 0.80, respectively). However, there was some overprediction, which was more pronounced at 1- and 2-year mortality time points (calibration

slopes 0.96, 0.80 and 0.79 for 3- 2- and 1-year mortality, respectively) and in those with higher baseline age, dyspnoea, airflow obstruction prognostic scores.

Development of the Birmingham Lung Improvement StudieS prognostic index

Among 1564 previously diagnosed and 330 case-found patients, 253 (13%) had a respiratory admission within 2 years (367 had a respiratory admission over median follow-up of 3 years). Out of 23 candidate variables, six were retained in the final developed model: age, Chronic Obstructive Pulmonary Disease Assessment Test score, respiratory admissions in the previous 12 months, body mass index, diabetes and forced expiratory volume in 1 second percentage predicted. After adjustment for optimism, the primary model performed well in discriminating between those with and without 2-year respiratory admissions (*c*-statistic 0.75, 95% confidence interval 0.72 to 0.79).

Barriers to and facilitators of physical activity engagement

Several barriers to and facilitators of engagement with physical activity, closely related to self-efficacy beliefs and symptom severity, were identified. Barriers were health related, psychological, attitudinal and motivational. Self-regulation (e.g. keeping a routine), self-efficacy (sense of achievement), enjoyment and social aspects of physical activity motivated participation.

Work package 3

Factors associated with occupational outcomes

Among 608 cohort participants of working age, 248 (40.8%) were in paid employment. Older age (odds ratio 0.28, 95% confidence interval 0.12 to 0.65), lower educational level (odds ratio 0.43, 95% confidence interval 0.19 to 0.97), poorer BODE (body mass index, airflow obstruction, dyspnoea, and exercise) prognostic score (odds ratio 0.10, 95% confidence interval 0.03 to 0.33) and history of high occupational exposure to vapours, gases, dusts or fumes (odds ratio 0.32, 95% confidence interval 0.12 to 0.85) were associated with a lower probability of being employed. Of those in paid employment, higher levels of dyspnoea were associated with both absenteeism and presenteeism (p-trend < 0.01). Additionally, occupational vapours, gases, dusts or fumes exposure was associated with presenteeism (p-trend < 0.01).

Follow-up data were available for 174 of those in paid employment at baseline. Over a mean follow-up of 25.8 months, 144 (82.8%) participants remained employed. The point estimate suggested an inverse association between increasing respiratory hospital admissions and probability of remaining in work (odds ratio 0.32, 95% confidence interval 0.09 to 1.14; $p = 0.08$), although wide confidence intervals suggest that further research is needed.

Prospective absenteeism data were available for 113 participants (mean follow-up of 19.5 months). Worsening breathlessness (incidence rate ratio 3.06, 95% confidence interval 1.29 to 7.26; $p = 0.01$) and increasing respiratory hospital admissions (incidence rate ratio 2.01, 95% confidence interval 1.09 to 3.69; $p = 0.03$) were associated with increased sickness absence. Follow-up presenteeism data were available for 163 participants (86.2%), where 43 (26.4%) had worsening presenteeism. This was significantly associated with worsening Chronic Obstructive Pulmonary Disease Assessment Test score (odds ratio 5.74, 95% confidence interval 1.18 to 27.83; $p = 0.03$) and there was some evidence of association with worsening dyspnoea.

Occupational health feasibility study

Only 35 (11.3%) of the eligible patients agreed to take part in the occupational health study. Of these, 80.0% received at least one occupational health recommendation and all received self-management recommendations. However, only 37.3% of recommendations were reported as implementable. The very low uptake rates for the intervention and low implementation of recommendations suggests that, in its current format, the intervention is not feasible.

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Conclusions

Despite screening resulting in higher yield of undiagnosed cases of chronic obstructive pulmonary disease and promising results from our health economic model, we did not find evidence of clinical benefit at 4 years' trial follow-up. The poor clinical management of chronic obstructive pulmonary disease generally, and low addition of case-found patients to the practice chronic obstructive pulmonary disease register, may explain the findings. The benefit of current treatments in case-found patients remains unknown.

For a screening programme to be implemented and have high uptake, it is important to raise patient awareness of chronic obstructive pulmonary disease risk factors and symptoms and provide training and additional resources for primary care. In particular, it is important to ensure that management pathways for diagnosed chronic obstructive pulmonary disease patients are optimised before further cases are identified.

We have developed a new index, using data from people with chronic obstructive pulmonary disease in a UK primary care setting, that has good discrimination performance in predicting respiratory hospitalisations. This needs external validation and examination of its impact on care and outcomes. We confirmed that the age, dyspnoea, airflow obstruction score is discriminatory for predicting mortality in a primary care population.

Among people with chronic obstructive pulmonary disease who are of working age, having greater breathlessness, a greater number of respiratory admissions and greater occupational exposure to vapours, gases, dusts or fumes are associated with poorer work productivity. Although our occupational health intervention was not feasible, modifiable workplace adaptations and self-management actions were identified for almost all participants, suggesting possible benefit from such assessments in a different context.

Recommendations for further research

- Development and evaluation of interventions to improve management of chronic obstructive pulmonary disease in primary care, including pathways to manage case-found chronic obstructive pulmonary disease.
- Evaluation of existing interventions in case-found chronic obstructive pulmonary disease.
- External validation of the BLISS index in new data.
- Evaluation of impact of using the BLISS index to guide patient management.
- Development and evaluation of interventions to reduce dyspnoea and vapours, gases, dusts or fumes exposure on occupational outcomes in people with chronic obstructive pulmonary disease.

Trial registration

This trial is registered as ISRCTN14930255.

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