Population-based case-finding to identify subjects with undiagnosed asthma or COPD

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ABSTRACT

Background: ∼5–10% of adults may have undiagnosed airflow obstruction. The objective of this study was to develop a population-based case-finding strategy to assess the prevalence of undiagnosed airflow obstruction (asthma or COPD) amongst adults with respiratory symptoms in Canada.

Methods: Adults without a previous history of asthma, COPD or lung disease were recruited using random digit-dialling and asked if they had symptoms of dyspnoea, cough, sputum or wheeze within the past 6 months. Those who answered affirmatively completed the Asthma Screening Questionnaire (ASQ), COPD-Diagnostic Questionnaire (COPD-DQ) and COPD Assessment Test (CAT). Those with an ASQ score of ⩾6 or a COPD-DQ score of ⩾20 underwent pre- and post-bronchodilator spirometry to diagnose asthma or COPD.

Results: 12 117 individuals were contacted at home and assessed for study eligibility. Of the 1260 eligible individuals, 910 (72%) enrolled and underwent spirometry. Ultimately, 184 subjects (20% of those enrolled) had obstructive lung disease (73 asthma and 111 COPD). Individuals found to have undiagnosed asthma or COPD had more severe respiratory symptoms and impaired quality of life compared with those without airflow obstruction. The ASQ, COPD-DQ, and CAT had ROC areas for predicting undiagnosed asthma or COPD of 0.49, 0.64 and 0.56, respectively. Four descriptive variables (age, BMI, sex and pack-years smoked) produced better receiver operating characteristic (ROC) values than the questionnaires (ROC area=0.68).

Conclusion: 20% of randomly selected individuals who report respiratory symptoms in Canada have undiagnosed airflow obstruction due to asthma or COPD. Questionnaires could exclude subjects at low risk but lack the ability to accurately find subjects with undiagnosed disease.

Introduction

Within the North American population, 8% of adults have been diagnosed with asthma and 6% have been diagnosed with COPD [1–3]. Collectively, these diseases cost North Americans in excess of US$90 billion in direct and indirect costs every year [4, 5]. However, physician-diagnosed asthma and COPD represent only a fraction of individuals living with these diseases. Population-based studies suggest that the prevalence of undiagnosed obstructive lung disease (OLD) may be double that of diagnosed disease [6].

A clinical diagnosis of asthma or COPD requires that a patient exhibit respiratory symptoms and have evidence of physiological airflow limitation on spirometry. For asthma there should be evidence of variable airflow obstruction or airway hyperresponsiveness, whereas a diagnosis of COPD requires evidence of persistent post-bronchodilator airflow obstruction [7, 8]. Spirometry is the most important test used to establish a diagnosis; however, studies have demonstrated that spirometry is often not integrated into clinical practice in North American communities [9, 10]. This under-utilisation of spirometry leads to under-diagnosis of individuals living with the disease. Under-diagnosis of asthma and COPD can also occur if individuals living with undiagnosed asthma or COPD fail to seek medical attention for their respiratory symptoms, or if they have limited access to medical care [11–13].

The US Preventive Services Task Force (USPSTF) published a systematic review assessing published evidence on the benefits and risks of screening for COPD among asymptomatic adults [14]. The task force recommended "against screening for COPD in asymptomatic adults" [15]. However, the USPSTF noted that this recommendation applies only to asymptomatic adults. Critical to the assessment is the USPSTF's conclusion that current medical treatments for COPD reduce symptoms and respiratory exacerbations. Thus, even though the USPSTF recommended against screening asymptomatic adults, its report pointed out that this recommendation is not applicable to "at-risk persons who present to clinicians with symptoms." The USPSTF Recommendation Statement also "encourages clinicians […] to pursue active case-finding for COPD in patients with risk factors, such as exposure to cigarette smoke" or respiratory symptoms [15].

Case-finding studies to identify undiagnosed asthma in the community are relatively sparse relative to studies for COPD. Nevertheless, undiagnosed asthma remains a prevalent and important public health problem. A Danish study of 1149 subjects who reported respiratory symptoms found 493 (43%) with definite asthma; of these 249 (51%) were undiagnosed [16]. Studies have also shown impaired quality of life and higher healthcare utilisation in adult individuals with undiagnosed asthma compared to those without asthma [17].

Current task force recommendations require consideration of the differences between screening, (i.e. testing large numbers of apparently healthy people to detect unrecognised disease at an earlier stage) and case-finding (i.e. evaluating subgroups of people at increased risk of having a disease to make a diagnosis earlier than would occur by waiting for them to present with symptoms or signs). A case-finding approach as is used in this study specifically targets those who have symptoms they have not reported, perhaps because they have not been asked.

A systematic review was conducted by the USPSTF to assess the tools used for the identification of undiagnosed COPD [14, 15]. The review determined that the COPD-Diagnostic Questionnaire (COPD-DQ) is the most extensively studied questionnaire (five studies, n=3048). The questionnaire score ranges from 0 to 38. At a threshold score of 20, sensitivity and specificity values are 63.0% and 70.1%, respectively [18, 19]. Case-finding methodologies for undiagnosed asthma are sparse. The Asthma Screening Questionnaire (ASQ) is a six-item questionnaire that contains questions pertaining to cough, wheeze, shortness of breath and chest tightness provoked by activities such as laughing, physical activity or talking on the phone [18]. The ASQ score range is 0–20. The sensitivity and specificity of the ASQ at various threshold values has not been studied [20].

The objectives of this study were to develop a population-based case-finding strategy to identify randomly selected community-dwelling individuals with undiagnosed airflow obstruction in order to assess the prevalence of undiagnosed asthma or COPD amongst adults with respiratory symptoms in Canada. Secondary objectives were to assess the ability of the available case-finding questionnaires to accurately identify subjects with undiagnosed disease, and to determine whether a new composite questionnaire could improve predictability. Our study explicitly excluded subjects with a previous history of asthma, COPD or other lung diseases, as the intent was to discover new cases of previously undiagnosed asthma or COPD.

Methods

Participant recruitment

Adults ⩾18 years of age were recruited in a two-step process from 19 June 2017 to 16 May 2019, using random digit-dialling of land lines and cell phones located within a 90-min radius of the 10 most populous metropolitan areas in Canada. This technique has been previously used to recruit a random sample from the Canadian urban and rural population [21]. A sample initial contact telephone script follows:

> "Hello, my name is Amanda and I'm calling from The Ottawa Hospital. We are conducting a research study and you would help us greatly by answering one question only; this will take less than 15 seconds of your time. We are looking to call back individuals who have experienced breathing problems within the past 6 months. Symptoms of potential breathing problems include shortness of breath, wheezing, increased mucus or sputum, or prolonged cough. Is there anyone in your home who is 18 years of age or older and has experienced one or more of these symptoms in the past 6 months?"

Those households who responded affirmatively received a call back from the local study coordinator; the individual within the household who was identified as having respiratory symptoms was verbally consented and screened for study entry over the telephone. Subjects were excluded from participating if they: 1) had a previous physician diagnosis of asthma, COPD, cystic fibrosis, bronchiectasis, pulmonary fibrosis or lung cancer; 2) had a history of use of an inhaled respiratory medication other than as-needed salbutamol or inhaled nasal medications; 3) had contraindications for spirometry, including a history of myocardial infarction, stroke, aortic/cerebral aneurysm, eye surgery or detached retina within the previous 3 months; 4) were unable to provide or refused to provide informed consent; 5) were in the third trimester of pregnancy; or 6) were <18 years of age. All subjects determined to be eligible completed the ASQ *via* telephone. Those who were ⩾60 years old, as well as subjects who were <60 years old who scored <6 points on the ASQ, were also administered the COPD-DQ. Those who scored ⩾20 points on the COPD-DQ or ⩾6 points on the ASQ were invited to visit the study site for spirometry.

Study procedure

Once they arrived at the study site, subjects signed written informed consent and then all subjects underwent pre- and post-bronchodilator spirometry administered by certified study personnel to confirm the presence of OLD. Asthma was diagnosed in subjects whose forced expiratory volume in 1 s (FEV_1) improved by ⩾12% and ⩾200 mL following bronchodilator administration with 400 µg of salbutamol [7]. COPD was diagnosed in subjects whose post-bronchodilator FEV_1/forced vital capacity (FVC) ratio remained below the lower 95% confidence limit of normal (the lower 95% confidence limit for a healthy normal, adjusted for sex, age and height) [8]. Subjects who met spirometry criteria for both conditions were considered to have COPD with some bronchodilator reversibility and were classified as COPD for the purposes of the present analysis.

The COPD Assessment Test (CAT) was administered to all participants to measure respiratory symptoms. The CAT is a validated questionnaire composed of eight questions about the severity of respiratory symptoms and generates a summed total score ranging from 0 (no impact on daily activities) to 40 (very high impact on daily activities) [22]. A CAT threshold total score of >10 points has been associated with symptomatic COPD [23]. We used The St George's Respiratory Questionnaire (SGRQ) to assess quality of life specific to respiratory diseases.

Statistical analysis

Descriptive measures for subjects classified with or without OLD were summarised using arithmetic means and standard deviations, where applicable. Receiver operating characteristic (ROC) curves for the disease outcomes of asthma, COPD and OLD were computed for each of the ASQ, COPD-DQ and CAT questionnaires using published scoring formulas for these instruments. Areas under their ROC curves (AUC) were also computed using non-parametric procedures. Sensitivity and specificity values for the questionnaires were calculated using recommended diagnostic threshold scores reported in the literature, as cited earlier.

Multivariate stepwise logistic regression was used to find the combination of questions in the ASQ and CAT questionnaires that best predicted an outcome of OLD. The COPD-DQ questionnaire was not used in this analysis because this questionnaire was only administered to a subset of 499 subjects. Four descriptive variables, age, body mass index (BMI), sex and pack-years smoked, were included in the pool of candidate variables. One question from the ASQ was removed from the candidate pool because it was judged to lack clinical face validity: subjects who reported coughing when laughing were found to be less

likely to have OLD, and this question was thus removed. The stepwise procedure used entry and removal thresholds for p-values of 0.01 and 0.05, respectively. No variable was forced into the regression model. The set of questions selected by the stepwise logistic regression is referred to here as the eight-item questionnaire. In the first stage, stepwise regression selected the predictor variables from the candidate pool. The second stage involved taking the best predictor variables from the first stage and re-estimating the regression function for the set of selected predictors. Predicted logistic scores and estimated probabilities of disease for the eight-item questionnaire were computed. A ROC curve was generated for the eight-item regression model, as well as sensitivity and specificity values for a selection of cut-points for the predicted probability of OLD.

Each of the eight CAT questions is a 0–5 rating scale for severity of a COPD symptom. Although the rating scales are implicitly ordinal (progressing from none to very severe), we discovered that the scales have non-monotonic associations with the disease outcome variable. To account for this tendency, a logistic regression function was computed for each symptom by regressing disease outcomes on a subject's rating responses. The predicted logistic score for each subject was then taken as the subject's response measure for the question. The supplementary material (section S.3) provides additional technical detail and illustrations of this re-scoring procedure.

The OLD outcome consists of two clinically distinct component outcomes: asthma or COPD. To investigate the ability of the eight-item questionnaire to predict these component outcomes, multinomial stepwise logistic regression was used to estimate separate predictive functions for the two component outcomes. The predicted probabilities from these separate functions, when added together, give an estimate of the probability of OLD. ROC curves and AUC values for these separate predictive functions are reported.

A cross-validation of the eight-item model was conducted in which random draws of 80% of the study sample were selected to estimate the model and then the estimated model was used to predict outcomes of the remaining 20% of subjects who were withheld. The predictive check was repeated with 1000 random draws. The average predictive performance as measured by sensitivity and specificity was then assessed. All logistic regression models were also tested for goodness of fit using a Hosmer–Lemeshow test.

Statistical analysis was performed using STATA 15 statistical software (StataCorp, College Station, TX, USA). The study was approved by The Ottawa Health Science Network Research Ethics Board as well as the Ethics Boards of the other nine participating study hospitals.

Results

Figure 1 depicts the results of the case-finding strategy. 12 117 individuals were contacted using random digit-dialling and were screened for entry into the study. 10 411 were excluded. The most common reasons for exclusion were pre-existing physician-diagnosed COPD or asthma (n=3936). Of the 1706 remaining participants, 446 (26%) subjects were excluded because they did not score ⩾6 points on the ASQ or ⩾20 points on the COPD-DQ. Ultimately, 1260 individuals were eligible to undergo spirometry; however, 350 did not attend for spirometry or were unable to complete adequate spirometry. The remaining 910 individuals (72% of those eligible) successfully completed pre- and post-bronchodilator spirometry and were evaluated for a diagnosis of asthma or COPD. Of 910 participants, all but two individuals fully completed the ASQ and CAT questionnaires. According to study protocol, only 499 completed the COPD-DQ questionnaire. Of 910 symptomatic participants, 184 (20%) subjects had spirometry consistent with a diagnosis of OLD, comprised of 73 (8.0%) cases of asthma and 111 (12.2%) cases of COPD. The COPD cases included 24 who met spirometry criteria for both COPD and asthma.

Table 1 presents the mean summary statistics for the 910 study subjects divided into two groups: those with OLD (n=184) and those without spirometric evidence of OLD (n=726). The group with OLD had a history of heavier smoking; mean total pack years of 31.4 *versus* 19.8 (p<0.001). The mean FEV_1 predicted was 75.1% in the OLD group compared with 95.8% in the group without OLD (p<0.001), and the mean pre-bronchodilator FEV_1/FVC ratio was significantly different between groups (0.63 *versus* 0.77; p<0.001). Subjects with OLD had poorer health-related quality of life compared with those without OLD; the mean ±SD SGRQ total score was 40.5±18.5 in the group with OLD *versus* 37.0±17.3 in those without OLD (p<0.001).

The mean COPD-DQ score in the group with OLD was 23.4 *versus* 20.8 in the group without OLD (p<0.001). The mean CAT score in the group with OLD was 18.2 *versus* 16.7 in the group without OLD (p<0.001). The mean ASQ score did not differ between groups.

Table 2 shows the sensitivity, specificity and AUC for the ASQ, COPD-DQ and CAT questionnaires when the questionnaires were used to identify the disease for which they were each designed, asthma or COPD
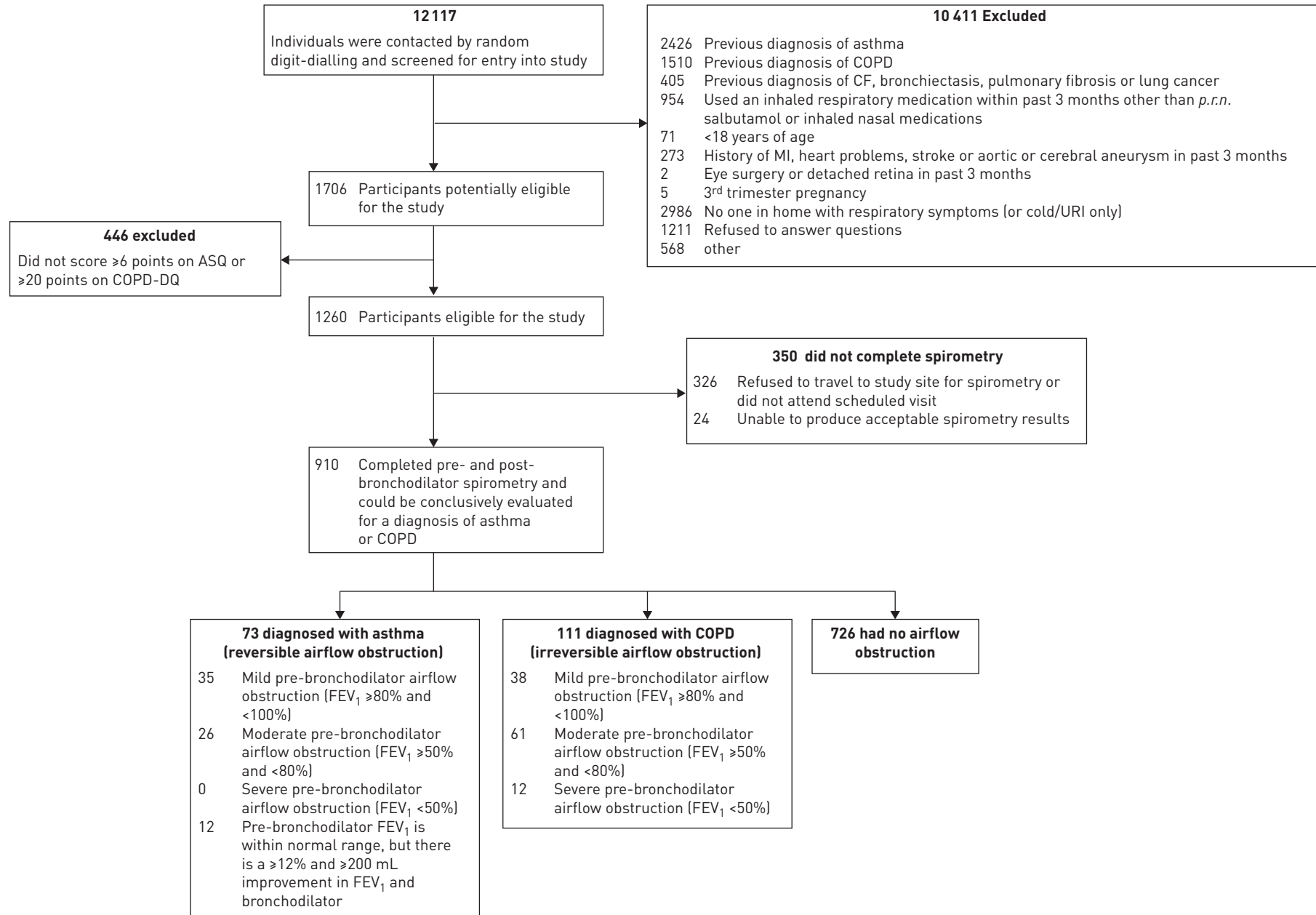
12 117

Individuals were contacted by random digit-dialling and screened for entry into study

10 411 Excluded

2426 Previous diagnosis of asthma
1510 Previous diagnosis of COPD
405 Previous diagnosis of CF, bronchiectasis, pulmonary fibrosis or lung cancer
954 Used an inhaled respiratory medication within past 3 months other than *p.r.n.* salbutamol or inhaled nasal medications
71 <18 years of age
273 History of MI, heart problems, stroke or aortic or cerebral aneurysm in past 3 months
2 Eye surgery or detached retina in past 3 months
5 3rd trimester pregnancy
2986 No one in home with respiratory symptoms (or cold/URI only)
1211 Refused to answer questions
568 other

1706 Participants potentially eligible for the study

446 excluded

Did not score ≥6 points on ASQ or ≥20 points on COPD-DQ

1260 Participants eligible for the study

350 did not complete spirometry

326 Refused to travel to study site for spirometry or did not attend scheduled visit
24 Unable to produce acceptable spirometry results

910 Completed pre- and post-bronchodilator spirometry and could be conclusively evaluated for a diagnosis of asthma or COPD

73 diagnosed with asthma (reversible airflow obstruction)

35 Mild pre-bronchodilator airflow obstruction (FEV_1 ≥80% and <100%)
26 Moderate pre-bronchodilator airflow obstruction (FEV_1 ≥50% and <80%)
0 Severe pre-bronchodilator airflow obstruction (FEV_1 <50%)
12 Pre-bronchodilator FEV_1 is within normal range, but there is a ≥12% and ≥200 mL improvement in FEV_1 and bronchodilator

111 diagnosed with COPD (irreversible airflow obstruction)

38 Mild pre-bronchodilator airflow obstruction (FEV_1 ≥80% and <100%)
61 Moderate pre-bronchodilator airflow obstruction (FEV_1 ≥50% and <80%)
12 Severe pre-bronchodilator airflow obstruction (FEV_1 <50%)

726 had no airflow obstruction

FIGURE 1 Results of the case-finding strategy. CF: cystic fibrosis; MI: myocardial infarction; URI: upper respiratory infection; ASQ: Asthma Survey Questionnaire; COPD-DQ: COPD-Diagnostic Questionnaire; FEV_1: forced expiratory volume in 1 s.

TABLE 1 Characteristics of participants with or without obstructive lung disease (OLD)

	OLD	No OLD	p-value
Subjects n	184	726	
Characteristics			
Age years	61.3±14.3	57.1±15.2	<0.001
Male sex	62.3%	48.0%	<0.001
BMI	29.2±6.9	30.6±6.8	<0.001
Pre-bronchodilator spirometry			
FEV_1 L	2.26±0.77	2.87±0.81	<0.001
FEV_1 % pred	75.1±15.6	95.8±15.3	<0.001
FEV_1/FVC ratio	0.63±0.09	0.77±0.06	<0.001
Post-bronchodilator spirometry			
FEV_1 L	2.51±0.83	2.94±0.83	<0.001
FEV_1 % pred	82.8±17.7	98.0±16.2	<0.001
FEV_1/FVC ratio	0.66±0.11	0.79±0.06	<0.001
Change in FEV_1 post-bronchodilator	11.6±10.1%	2.9±4.1%	<0.001
SGRQ total score	40.5±18.5	37.0±17.3	<0.001
Diagnostic questionnaires			
ASQ score	8.5±3.6	8.7±3.6	0.130
COPD-DQ score[#]	23.4±5.2	20.8±5.3	<0.001
Symptom assessment			
CAT total score	18.2±6.9	16.7±7.0	<0.001
Smoking status %			
Lifetime nonsmokers	24.5%	43.4%	<0.001
Previous smokers	40.8%	37.2%	
Current smokers	34.8%	19.4%	
Smoking history			
Total pack-years in previous and current smokers	31.4±24.3	19.8±18.5	<0.001

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; SGRQ: St George's Respiratory Questionnaire; ASQ: Asthma Screening Questionnaire; COPD-DQ: COPD-Diagnostic Questionnaire; CAT: COPD Assessment Test. [#]: 499 subjects completed this questionnaire (116 with OLD and 383 without OLD).

accordingly, as well as when the questionnaires were used to identify the composite outcome of undiagnosed OLD. The AUCs for identification of undiagnosed OLD were 0.49, 0.64 and 0.56 for the ASQ, COPD-DQ and CAT, respectively. These performance measures for the three questionnaires rely only on their individual questions and do not incorporate any descriptive variables, such as age, BMI, sex or pack-years smoked. When the four descriptive variables (age, BMI, sex and pack-years smoked) were considered alone as predictors, they produced a combined AUC of 0.68 (table 3). The ASQ and four descriptive variables, when considered together, had an AUC of 0.69 for identifying subjects with

TABLE 2 Sensitivity, specificity and areas under the receiver operating characteristic (ROC) curve (AUC) values for the study questionnaire scores using designated thresholds

Questionnaire	Disease	Subjects n	Range[#]	Threshold ⩾	Sensitivity[¶] %	Specificity[¶] %	AUC[+]
ASQ	Asthma	908	0–20	6	93	16	0.53
	OLD	908	0–20	6	83	14	0.49
COPD-DQ	COPD	499	0–38	20	89	34	0.71
	OLD	499	0–38	20	84	34	0.64
CAT	COPD	909	0–40	10	92	15	0.58
	OLD	909	0–40	10	90	16	0.56

Values are shown for both the target disease of the questionnaire as well as for the composite outcome of obstructive lung disease (OLD). ASQ: Asthma Screening Questionnaire; COPD-DQ: COPD-Diagnostic Questionnaire; CAT: COPD Assessment Test. [#]: minimum and maximum possible scores for the questionnaire. [¶]: derived from 2×2 contingency tables for the designated thresholds. The values are not adjusted for demographic variables (age, sex, body mass index) or pack-years smoked. [+]: from non-parametric estimates of ROCs for questionnaire scores.

TABLE 3 Areas under the receiver operating characteristic curve (AUC) for detecting obstructive lung disease measured for: the descriptive variables alone; the individual questionnaires combined with the descriptive variables; and the composite eight-item questionnaire

	AUC
Descriptive variables[#]	0.68
Descriptive variables+ASQ	0.69
Descriptive variables+COPD-DQ	0.68
Descriptive variables+CAT	0.69
Eight-item questionnaire[¶]	0.74

ASQ: Asthma Screening Questionnaire; COPD-DQ: COPD-Diagnostic Questionnaire; CAT: COPD Assessment Test. [#]: age, sex, body mass index, pack-years smoked; [¶]: includes descriptive variables.

undiagnosed OLD. The combined COPD-DQ and descriptive variables had an AUC of 0.68 while the combined CAT and descriptive variables had AUC of 0.69 (table 3).

Two-stage stepwise logistic regression was applied to questions found in the ASQ and the CAT, and to the four descriptive variables. The stepwise procedure selected eight questions (table 4). This eight-item questionnaire demonstrated a modest improvement in identifying undiagnosed OLD compared with the individual questionnaires (table 3). The first four items of the eight-item questionnaire include demographic and smoking variables: age, BMI, sex and pack-years smoked. The remaining four items include two questions from the ASQ and two from the CAT (table 4). Responses to the items are weighted by their regression coefficients and summed. The weighted sum represents a logistic score that can be converted mathematically into a probability estimate for OLD. A cut-off of 10% for this probability gives sensitivity and specificity values of 89% and 30%, respectively (supplementary table S1). The AUC was 0.74 for the eight-item questionnaire. Supplementary table S2 displays a case demonstration calculating the estimated probability of OLD for a random subject taken from our study population.

Internal cross-validation of the eight-item questionnaire revealed mean sensitivity and specificity pairs of 87% and 29%, respectively, over 1000 repeated samples. A Hosmer–Lemeshow test showed an acceptable goodness of fit of the logistic regression model for the eight-item questionnaire (p=0.244).

The eight-item questionnaire was evaluated against asthma and COPD disease outcomes independently. The questionnaire demonstrated an AUC of 0.64 for identifying persons with undiagnosed asthma with only one item of the eight-item questionnaire having statistical significance (table 5). The questionnaire performed best at identifying undiagnosed COPD, with an AUC of 0.84, and all eight items in the

TABLE 4 The eight-item questionnaire and associated logistic regression coefficients for detecting undiagnosed obstructive lung disease

Question	Possible responses	Coefficient	p-value
Age	Number in years	0.020	0.002
Male sex	Yes/no	0.395	0.031
BMI	Number as $kg \cdot m^{-2}$	−0.044	0.003
Pack-years smoked	Number as $packs \cdot day^{-1} \cdot years\ smoked^{-1}$	0.024	0.000
Do you experience worsening of wheezing following physical activity?	Yes/no	0.604	0.001
Do you experience shortness of breath following physical activity?	Yes/no	0.526	0.044
I have no phlegm in my chest at all – my chest is completely full of phlegm[#]	0–5	0.802	0.001
I sleep soundly – I don't sleep soundly because of my chest condition[#]	0–5	1.045	0.023

BMI: body mass index. [#]: the original 0–5 responses for the phlegm and sleep questions taken from the COPD Assessment Test questionnaire are re-scored before multiplying by the corresponding regression coefficient in the risk calculation. See Section S.3 of the supplementary material for technical explanations.
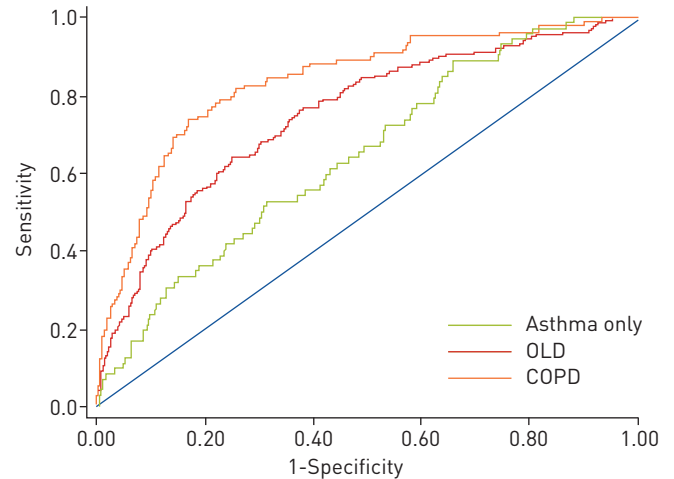
TABLE 5 The eight-item questionnaire for detecting undiagnosed asthma

Question	Possible responses	Coefficient	p-value
Age	Number in years	0.004	0.611
Male sex	Yes/no	0.284	0.263
BMI	Number as kg·m^{-2}	−0.007	0.697
Pack-years smoked	Number as packs·day^{-1}·years smoked^{-1}	−0.002	0.751
Do you experience worsening of wheezing following physical activity?	Yes/no	0.335	0.202
Do you experience shortness of breath following physical activity?	Yes/no	0.419	0.236
I have no phlegm in my chest at all – my chest is completely full of phlegm[#]	0–5	1.042	0.003
I sleep soundly – I don't sleep soundly because of my chest condition[#]	0–5	1.014	0.122

BMI: body mass index. [#]: the original 0–5 responses for the phlegm and sleep questions taken from the COPD Assessment Test questionnaire are re-scored before multiplying by the corresponding regression coefficient in the risk calculation. See Section S.3 of the supplementary material for technical explanations.

questionnaire were statistically significant (table 6). The predictive capacity of the eight-item questionnaire is summarised in figure 2 with the AUC increasing from asthma, to OLD, to COPD.

Discussion

Our case-finding strategy used population-based random sampling to identify symptomatic community-dwelling adults living with undiagnosed OLD. Ultimately, 20% of the enrolled individuals were confirmed as having undiagnosed airflow obstruction due to asthma or COPD. Thus, an estimated one in five Canadians with respiratory symptoms but without a previous diagnosis of lung disease, were found to have undiagnosed OLD using our population-based case-finding strategy. Persons who had undiagnosed OLD had worse lung function, a heavier smoking history, more severe respiratory symptoms and poorer disease-specific quality of life, compared with those without OLD.

Other approaches to case-finding COPD, but not asthma, are currently being developed [24]. A recently published study used machine-learning methods to select and validate the variables that are most important in identifying patients with clinically significant COPD. The investigators used random forest analysis to reduce 44 identified variables down to a five-item CAPTURE (COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk) questionnaire [25]. Using the CAPTURE questionnaire together with measurement of peak expiratory flow exhibited the best sensitivity

TABLE 6 The eight-item questionnaire for detecting undiagnosed COPD

Question	Possible responses	Coefficient	p-value
Age	Number in years	0.037	0.000
Male sex	Yes/no	0.522	0.032
BMI	Number as kg·m^{-2}	−0.086	0.000
Pack-years smoked	Number as packs·day^{-1}·years smoked^{-1}	0.037	0.000
Do you experience worsening of wheezing following physical activity?	Yes/no	0.861	0.001
Do you experience shortness of breath following physical activity?	Yes/no	0.721	0.047
I have no phlegm in my chest at all – my chest is completely full of phlegm[#]	0–5	0.833	0.002
I sleep soundly – I don't sleep soundly because of my chest condition[#]	0–5	1.419	0.037

BMI: body mass index. [#]: the original 0–5 responses for the phlegm and sleep questions taken from the COPD Assessment Test questionnaire are re-scored before multiplying by the corresponding regression coefficient in the risk calculation. See Section S.3 of the supplementary material for technical explanations.

FIGURE 2 Receiver operating characteristic curves derived from the eight-item questionnaire for separate predictive equations for asthma, COPD and the combined composite outcome of obstructive lung disease (OLD). The respective area under ROC curve values are 0.74 (OLD), 0.64 (asthma) and 0.84 (COPD).

(89.7%) and specificity (78.1%) for distinguishing COPD cases from control subjects in a primary care setting. Similar pre-screening questionnaires have been developed in Latin-American countries. The PUMA pre-screening COPD questionnaire includes seven items: sex, age, pack-years smoking, dyspnoea, sputum, cough and whether previous spirometry was performed. In a validation study, the questionnaire had an AUG of 0.73 and showed moderate accuracy for identifying subjects with COPD within a primary care setting [26]. However, both the PUMA and CAPTURE questionnaires do not address case-finding for asthma.

We used pre-existing questionnaires to identify subjects with respiratory symptoms in order to maximise our chances of finding subjects with undiagnosed OLD. The COPD-DQ and ASQ questionnaires were used to exclude subjects at low risk, and ultimately 26% of potentially eligible subjects were excluded because both their ASQ and COPD-DQ scores fell below published thresholds associated with disease. However, neither of these two questionnaires, nor the CAT questionnaire, demonstrated good performance for case-finding undiagnosed OLD. Moreover, the set of four descriptive variables (age, sex, BMI and pack-years smoked) displayed a standalone ability to identify undiagnosed OLD (AUC 0.68), which was better than the existing questionnaires. Adding the individual questionnaires (the ASQ, COPD-DQ and CAT) to these four descriptive variables had little impact on the predictive value, with respective AUCs of 0.69, 0.68 and 0.69. The results suggest that most of the predictive strength for identifying OLD comes from these key demographic factors and an individual's smoking history. The screening questionnaires provide little, if any, value.

We acknowledge that the CAT is not validated as a COPD diagnostic tool and is not validated for measuring symptoms in asthmatics, nor is the COPD-DQ validated for use in diagnosing asthma. However, we used these tools in this exploratory study to determine whether we could create a new composite questionnaire that would improve prediction of undiagnosed COPD or asthma. As such, we selected questions from these assessment tools that we found were highly predictive of undiagnosed asthma or COPD, and we incorporated these questions into our eight-item questionnaire.

We used stepwise logistic regression techniques to find the combination of questions in the ASQ and CAT questionnaires that best predicted an outcome of OLD. The resulting eight-item questionnaire displayed a superior ability to predict OLD than the individual existing questionnaires. The AUC for the eight-item questionnaire for identification of OLD was still not impressive (0.74). Furthermore, only one item of the eight-item questionnaire had significant predictive ability for identifying undiagnosed asthma. These results suggest that more research is needed to build effective questionnaires for case-finding undiagnosed OLD, especially asthma, in communities. The challenge will be to find simple questions that can be posed to respondents and answered easily without requirement for lung function testing.

There are some limitations to our study. Our study identified more cases of undiagnosed COPD compared with undiagnosed asthma. This may have occurred because 24 individuals who met spirometry criteria for both conditions were considered to have COPD with some bronchodilator reversibility and were classified as COPD for the purposes of the present analysis, rather than as asthma–COPD overlap. It is possible that some of these subjects could have asthma, rather than COPD, and this might only become evident after treatment with bronchodilators and inhaled steroids fully resolves their airflow obstruction. This could ultimately result in re-classification of some subjects who met spirometry criteria for both conditions.

It is also possible that our study missed finding asthma in some subjects [19]. We did not employ bronchial challenge testing or exhaled nitric oxide fraction (F_{ENO}) testing in those who tested negative for airflow obstruction or bronchodilator reversibility (726 of 910 participants), since we wanted our case-finding strategy to be potentially translatable to community practices, and within communities bronchial challenge testing is relatively expensive and difficult to access. Therefore, some symptomatic individuals who have asthma with airway hyperresponsiveness, but without reversible airway obstruction, may have been missed. We are currently undertaking a sub-study to try to determine the prevalence of undiagnosed asthma in those subjects in our case-finding study who did not exhibit airflow obstruction or bronchodilator reversibility. Subjects who tested negative for OLD using spirometry are being enrolled and they are undergoing bronchial challenge tests, sputum induction for eosinophils, blood eosinophilia measurements and F_{ENO} measurements to attempt to discover evidence of undiagnosed asthma. This sub-study is currently ongoing. Finally, individuals with asthma or COPD who were not aware of symptoms (*e.g.* those who had significant smoking histories and potential airflow obstruction but without symptoms) were not detected using this case-finding strategy.

Another potential limitation of our study is that >12 000 phone calls had to be made, and 910 subjects tested with spirometry, in order to ultimately find 184 subjects with undiagnosed OLD. The cost of this strategy, while not a focus of the current study, was considerable. Random-digit dialling is probably not a practical or affordable way to find cases of undiagnosed asthma or COPD, although it was the right research approach to ensure selection of a representative population-based sample of subjects with respiratory symptoms for this study, in order to determine the prevalence of undiagnosed airflow obstruction in the population.

The results of our study bring up some important questions outside the scope of the current report, such as "Why are these patients undiagnosed?" and "Are there clinical benefits associated with case-finding and early diagnosis of OLD?" We are in the process of recruiting a control group of subjects with physician-diagnosed asthma or COPD to determine what patient factors and health system factors may predispose these subjects to be less likely to be diagnosed compared to subjects with physician-diagnosed disease. In addition, we are currently undertaking a clinical trial to explore whether case-finding and diagnosing previously undiagnosed OLD has value. Patients who are found to have undiagnosed asthma or COPD are being randomised to an intensive early treatment strategy based on Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines *versus* usual care. This clinical trial will allow us to determine whether detection of undiagnosed OLD, with subsequent provision of early intensive treatment, provides clinical benefit.

In summary, our study found that undiagnosed asthma and COPD can be identified in randomly selected adults from the community. Our population-based case-finding strategy found that ~20% of Canadian adults without a previous history of diagnosed lung disease, who report recent or current respiratory symptoms, have undiagnosed asthma or COPD. Existing symptom questionnaires designed for case-finding subjects were relatively unhelpful and lacked predictive ability to accurately find subjects with undiagnosed asthma or COPD in the community. More research is needed to develop better case-finding tools, especially case-finding tools for the identification of undiagnosed asthma.

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