

Accuracy and cost-effectiveness of different screening strategies for identifying undiagnosed COPD among primary care patients (≥ 40 years) in China

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BMJ Open Accuracy and cost-effectiveness of different screening strategies for identifying undiagnosed COPD among primary care patients (≥ 40 years) in China: a cross-sectional screening test accuracy study: findings from the Breathe Well group

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ABSTRACT

Objectives To examine the accuracy and cost-effectiveness of various chronic obstructive pulmonary disease (COPD) screening tests and combinations within a Chinese primary care population.

Design Screening test accuracy study.

Setting Urban and rural community health centres in four municipalities of China: Beijing (north), Chengdu (southwest), Guangzhou (south) and Shenyang (northeast).

Participants Community residents aged 40 years and above who attended community health centres for any reason were invited to participate. 2445 participants (mean age 59.8 (SD 9.6) years, 39.1% (n=956) male) completed the study (February–December 2019), 68.9% (n=1684) were never-smokers and 3.6% (n=88) had an existing COPD diagnosis. 13.7% (n=333) of participants had spirometry-confirmed airflow obstruction.

Interventions Participants completed six index tests (screening questionnaires (COPD Diagnostic Questionnaire, COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE), Chinese Symptom-Based Questionnaire (C-SBQ), COPD-SQ), microspirometry (COPD-6), peak flow (model of peak flow meters used in the study (USPE)) and the reference test (ndd Easy On-PC)).

Primary and secondary outcomes Cases were defined as those with forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) below the lower limit of normal (LLN-GLI) on the reference test. Performance of individual screening tests and their combinations was evaluated, with cost-effectiveness analyses providing cost per additional true case detected.

Results Airflow measurement devices (sensitivities 64.9% (95% CI 59.5% to 70.0%) and 67.3% (95% CI 61.9% to

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Defining airflow obstruction according to the lower limit of normal increased the likelihood that identified cases were true chronic obstructive pulmonary disease.
- ⇒ Recruiting participants from both urban and rural community hospitals maximised the generalisability of our findings to primary care patients.
- ⇒ This study did not explore optimal cut-points for index tests, thus, further work is required.
- ⇒ While the study was conducted in four geographically disparate municipalities, our findings may not be generalisable to all adults ≥ 40 years old in China.

72.3%), specificities 89.7% (95% CI 88.4% to 91.0%) and 82.6% (95% CI 80.9% to 84.2%) for microspirometry and peak flow, respectively) generally performed better than questionnaires, the most accurate of which was C-SBQ (sensitivity 63.1% (95% CI 57.6% to 68.3%) specificity 74.2% (95% CI 72.3% to 76.1%)). The combination of C-SBQ and microspirometry used in parallel maximised sensitivity (81.4%) (95% CI 76.8% to 85.4%) and had specificity of 68.0% (95% CI 66.0% to 70.0%), with an incremental cost-effectiveness ratio of £64.20 (CNY385) per additional case detected compared with peak flow.

Conclusions Simple screening tests to identify undiagnosed COPD within the primary care setting in China is possible, and a combination of C-SBQ and microspirometry is the most sensitive and cost-effective. Further work is required to explore optimal cut-points and effectiveness of programme implementation.

Trial registration number ISRCTN13357135.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common long-term condition characterised by persistent respiratory symptoms and airflow limitation.¹ Nearly one-third of the 3.2 million annual global deaths from COPD are from China^{2,3} where COPD ranks among the top three leading causes of death with associated direct medical costs of 118% of local average annual income.⁴ COPD develops slowly, resulting in delays in symptom recognition and high rates of underdiagnosis. Ninety per cent of the estimated 100 million people with COPD in China are undiagnosed; slightly higher than the 60%–80% underdiagnosis rate worldwide.^{5–9} Symptom reporting and recognition are lower in China, with 60% of diagnosed patients not reporting symptoms such as cough, expectoration and wheeze.¹⁰

While COPD screening programmes are not currently endorsed in the USA and UK,^{11–13} considering the high proportion and heavy burden of undiagnosed disease,⁴ early identification is being prioritised in China. National policies recommend screening for undiagnosed COPD¹⁴, but do not specify which screening tests to use. Furthermore, though spirometry is required for clinical diagnosis,¹ it is not widely available in primary care settings in China. Therefore, screening could reduce the numbers needing spirometry referral.

Globally, various COPD screening tools have been developed, including questionnaires and airflow measurement devices.^{15–17} However, accuracy studies were mainly conducted in Western countries and have not been validated in a Chinese population where the distribution and underlying causes of undiagnosed COPD may differ. Furthermore, the majority of Chinese studies have used

secondary or tertiary care COPD populations rather than people from community settings.^{18,19} Finally, the cost-effectiveness of different screening tests have not been previously estimated in China; a crucial consideration given the high prevalence of COPD in this middle-income country.

We examined the accuracy and cost-effectiveness of various screening tests and combinations within a Chinese primary care population.

METHODS

Study design and participants

We conducted a cross-sectional, multicentre study to evaluate the accuracy and cost-effectiveness of various COPD screening tests and test combinations in primary care in China. Full details of participant recruitment and study assessments are described in the published protocol.²⁰

Participants were recruited from one urban and one rural community health centre (CHC) in each of four municipalities: Beijing (North China), Chengdu (south-west China), Guangzhou (south China) and Shenyang (northeast China) (figure 1). Between February and December 2019, community-dwelling residents aged 40 years and above who attended CHCs for any reason were invited to participate, either directly by the attending clinician, or through poster or social media (WeChat) advertisements. Participants who were unable to give informed consent, had contraindications for spirometry or unable to perform the test for other reasons were excluded.

Eligible participants provided informed consent at the start of the assessment visit, prior to height and weight measurement and completion of all index and reference

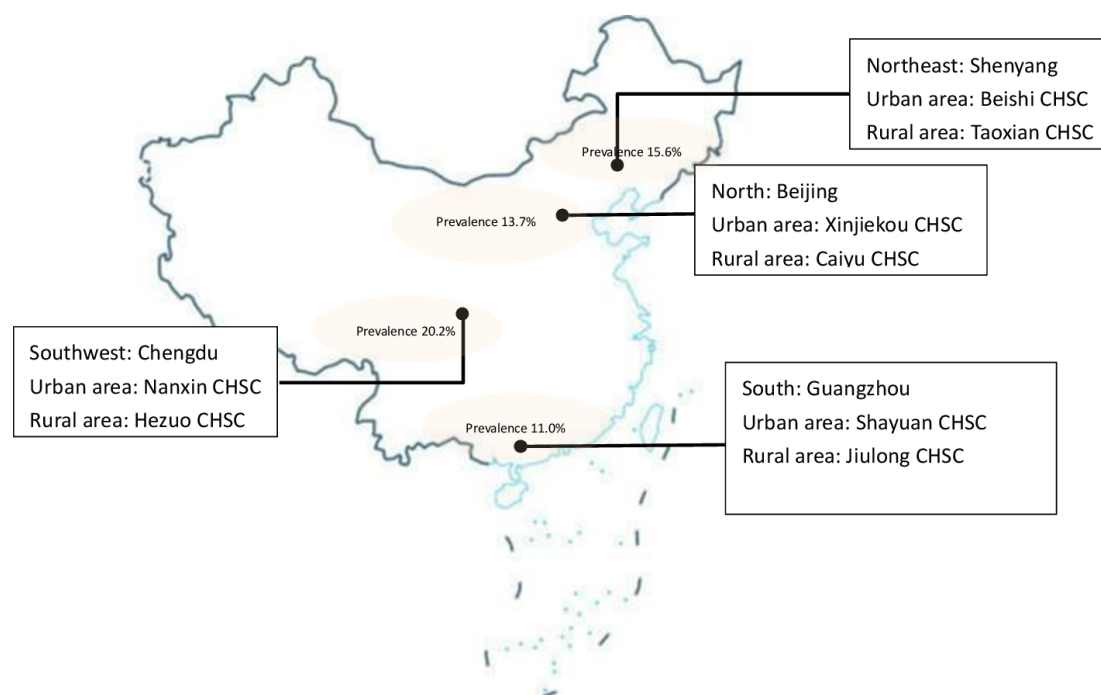


Figure 1 Map of breathe Well-China research sites. CHSC, Community Health Service Center.

tests. Participants also completed a study questionnaire concerning demographics, smoking status, exposures, medical diagnoses, respiratory symptoms²¹ and quality of life.²² Data were entered into a secure online Research Electronic Data Capture database.^{23 24}

Participants with airflow obstruction on the reference test were offered health education, smoking cessation advice, influenza vaccination and inhalers if relevant, or referred to tertiary hospitals for further treatment including pharmacotherapy or pulmonary rehabilitation.

Study assessment

Index tests

The six index tests included four screening questionnaires: COPD Diagnostic Questionnaire (CDQ, cut-point ≥ 20),^{16 25} COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE) (cut-point ≥ 2),²⁶ COPD Screening Questionnaire (COPD-SQ, cut-point ≥ 16)¹⁹ and the Chinese Symptom-Based Questionnaire (C-SBQ, cut-point ≥ 17)¹⁸ and two airflow measurement devices: microspirometry (Vitalograph COPD-6, cut-point for positive test forced expiratory volume in one second (FEV₁)/FEV₆ < 0.78),^{27 28} peak flow (model of peak flow meters used in the study (USPE), cut-point < 350 L/min men, < 250 L/min women).²⁶ Questionnaires were selected to maximise symptom capture and minimise item duplication, while allowing comparison of the most relevant questionnaires (online supplemental appendix 1). Previously defined cut-points were used to identify participants at risk of COPD.

Trained researchers provided instructions before participants performed three prebronchodilator manoeuvres with each airflow measurement device. The order of administering peak flow or microspirometry alternated by participant, and the best forced expiratory volume in one second (FEV₁) and FEV₆ measure for each device were used for analyses, irrespective of which attempt they came from.

Participants completed the four screening questionnaires immediately after administration of a bronchodilator (400 ug, Salbutamol). Questionnaires were intended to be self-completed, although researchers were available to assist if needed.

Reference test

The reference test was quality diagnostic spirometry (ndd Easy On-PC), performed 20–60 min after bronchodilation. Spirometry was administered by a second researcher not involved in the index tests and blind to their results. Participants performed a minimum of 3 blows, and a maximum of 6, until repeatability within 100 ml or 5%.²⁹ Flow volume curves were classified according to the American thoracic Society/European Respiratory Society (ERS)²⁹ criteria. Tests with at least three curves meeting these criteria, were 'good'. 'Acceptable' tests contained at least one curve which concurred with the criteria, allowing accurate assessment of forced expiratory volume

in one second (FEV₁). If accurate assessment was not possible the curves were classified as 'unacceptable', and the test was excluded from analysis. All traces were over-read for quality by one of three independent respiratory experts and graded according to standard criteria,²⁹ without knowledge of the index test results.

Airflow obstruction was defined as post-bronchodilator forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC) ratio below the lower limit of normal (LLN) using the Global Lung Initiative (GLI) equations.

Sample size

The Alonzo method³⁰ for paired test accuracy studies was used to calculate the sample size. Assuming independence of tests and prevalence of 12%, we required 1622 participants to detect a difference in sensitivity of 10% (95% vs 85%)^{16 26 31 32} for the comparison of CAPTURE and peak flow for example) with 90% power. With lower test sensitivity (90% vs 80%) 2279 participants are needed to detect this difference with 90% power.

Statistical analysis

The diagnostic performance of each index test was investigated by presenting 2×2 tables and calculating the sensitivity, specificity, positive predictive value and negative predictive value with 95% CIs. Comparative test accuracy was assessed by calculating the difference in sensitivity and specificity, presenting 95% CIs and using McNemar's test.

The primary analysis compared the sensitivity and specificity between the CAPTURE screening questionnaire and the peak flow meter. The comparison was specified a priori as CAPTURE was rigorously developed, accounted for exposures other than smoking and was intended for use in conjunction with peak flow. Secondary analyses evaluated the comparative performance of all other individual index tests, as well as plausible combination test strategies. Test strategies were formed using two predetermined combinations for appropriate pairs of individual index tests (questionnaires and lung function tests); first, to maximise sensitivity, where a participant with a positive result for either index test would be positive for the strategy (parallel testing strategy) and second, to maximise specificity, where a participant would need a positive result on both index tests to be positive for the strategy (serial testing strategy).

All analyses were conducted in Stata V.15.

Economic analysis

We conducted a cost-effectiveness analysis to calculate the cost per additional case detected for all tests and combination strategies. The strategies were ordered by the number of true cases detected, from least to greatest and the principle of dominance was applied to eliminate redundant strategies (where they were more costly and less effective). Each test was then compared with the next best alternative. For the purpose of this paper, the individual index tests and the combination strategy with the highest sensitivity were compared.

The unit costs and quantity of any equipment, medication and consumables required, staff time (and salary costs) to deliver each individual test and use of facilities were determined to calculate the healthcare costs of delivering each screening test/strategy. Each individual test was timed at a sample of assessment clinics to estimate an overall mean time and range for each test. Equipment costs were depreciated (at 3.5% a year) over the estimated lifespan of the equipment (ranging from 1 to 6 years). Cost per patient visit was calculated assuming the equipment would be used for 12000 patients per clinic per year. It was also assumed that positive cases would be confirmed with quality diagnostic spirometry (assuming 4000 patients/year). Costs were calculated in UK£ for a price year of 2019, and converted to Chinese Yuan (¥) using Purchasing Power Parities³³ with a conversion rate of 6.0 (online supplemental appendix 2).

The paper follows the Standards for Reporting Diagnostic accuracy studies (STARD) guidance³⁴ for reporting studies of diagnostic accuracy.

RESULTS

Sample

We invited 6198 eligible people to the study. A total of 2560 (41.3%) consented, of whom 25 withdrew and 90 were excluded from analysis (86 because of incorrect inhaler technique, four had unusable spirometry data). A total of 2445 participants with complete data on all index and reference test were included in the final analysis (figure 2). Approximately two-thirds (68.0%) were recruited through their attending clinician, 24.5% via advertisements and 7.5% through word of mouth.

The mean age of participants was 59.8 (SD 9.6), 39.1% (n=956) were male, two-thirds (n=1684, 68.9%) were never smokers and over half lived in an urban area (1338,

54.7%). 46.7% had no diagnosed conditions (n=1142); the most common diagnosed condition was hypertension (n=842, 34.4%), 3.6% (n=88) had an existing COPD diagnosis and 8.4% (n=205) had an existing chronic bronchitis/emphysema diagnosis (table 1). 99.8% of participants had an acceptable usable spirometry (with 63.3% (n=1547) defined as good). 13.6% (n=333) of participants had spirometry-confirmed airflow obstruction using the LLN criteria, of whom 175 (52.5%) had moderate to severe obstruction, that is, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II or above.¹ Those with airflow obstruction were older (63.5 vs 69.2 years) and more likely to be male (59.8% vs 35.8%), have a positive smoking history (55.5% vs 27.3%) and childhood respiratory infections (14.7% vs 7.8%) compared with those without airflow obstruction. Respiratory symptoms of wheeze, productive cough or breathlessness (Modified British Medical Research Council (mMRC) ≥ 2) were reported by 52.9% of those with airflow obstruction (66.3% of those who were GOLD stage II or above), and 25.1% of those without. Among participants with no previously reported COPD diagnosis, the prevalence of obstruction was 9.9% (n=218), of whom 89 (40.8%) were GOLD stage II or above. Using the forced expiratory volume in one second (FEV₁)/forced vital capacity (FVC)<0.7 criteria,¹ 17.4% (n=425) of all participants had airflow obstruction.

Performance of individual tests and screening strategies

Among the screening questionnaires, the C-SBQ had the highest sensitivity in detecting airflow obstruction at 63.1% (95% CI 57.6% to 68.3%), CAPTURE the lowest sensitivity (51.7% (95% CI 46.1% to 57.1%)), with CDQ (55.0% (95% CI 49.4% to 60.4%)) similar to COPD-SQ (55.3% (95% CI 49.7% to 60.7%)). The CDQ had the

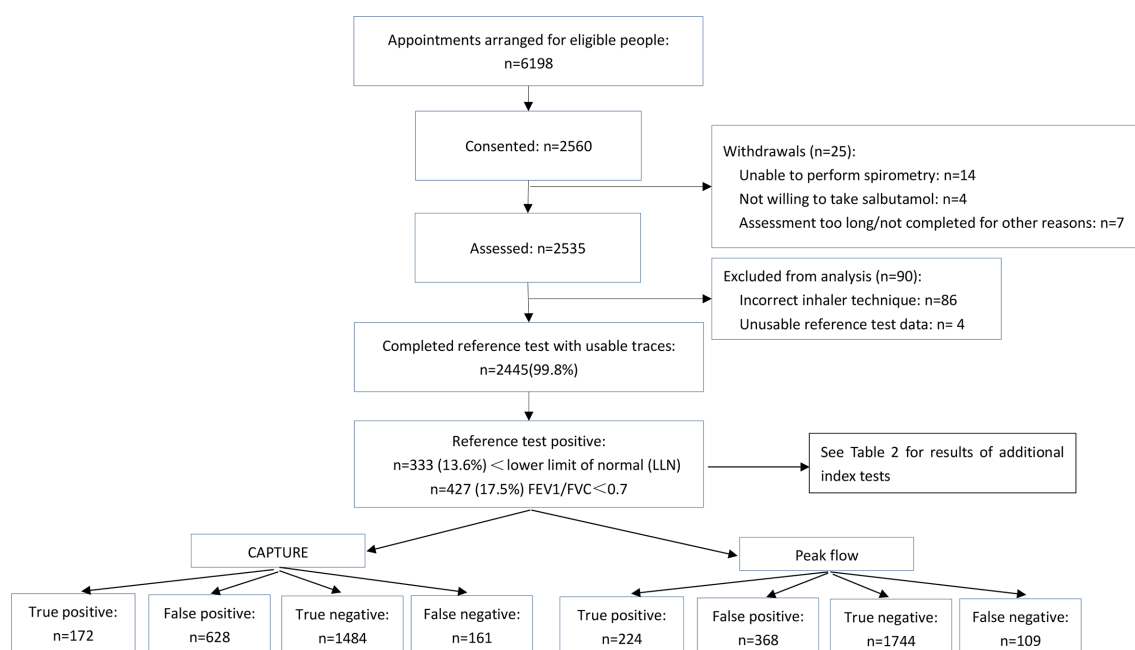


Figure 2 Study flow chart.

Table 1 Characteristics of study participants

Characteristic	Total sample (n=2445)	Reference test positive (n=333)	Reference test negative (n=2112)
Male sex, n (%)	956 (39.1%)	199 (59.8%)	757 (35.8%)
Age in years; mean (SD)	59.8 (9.6)	63.5 (8.9)	59.2 (9.6)
BMI; mean (SD)	24.9 (3.5)	24.3 (3.4)	25.0 (3.4)
Education, n (%)			
High school or below	1879 (76.9)	277 (83.2%)	1602 (75.9%)
Above high school	566 (23.1)	56 (16.8%)	510 (24.1%)
Employment status, n (%)			
Employed	674 (27.6%)	54 (16.2%)	620 (29.4%)
Unemployed	665 (27.2%)	98 (29.4%)	567 (26.9%)
Retired	1106 (45.2%)	181 (54.4%)	925 (43.8%)
Living in urban areas; n (%)	1338 (54.7%)	174 (52.3%)	1164 (55.1%)
Smoking status, n (%)			
Current smoker	472 (19.3%)	113 (33.9%)	359 (17.0%)
Ex-smoker	289 (11.8%)	72 (21.6%)	217 (10.3%)
Never smoker	1684 (68.9%)	148 (44.5%)	1536 (72.7%)
Male	--	27 (18.2%)	--
Female	--	121 (81.8%)	--
Pack years; mean (SD)	9.0 (17.8)	18.0 (21.0)	7.6 (16.8)
Health in general, n (%)			
Very good-good	1255 (51.3%)	127 (38.1%)	1128 (53.4%)
Fair-very bad	1190 (48.7%)	206 (61.9%)	984 (46.6%)
Diagnosed conditions, n (%)			
COPD	88 (3.6%)	64 (19.2%)	24 (1.1%)
Chronic bronchitis/emphysema	205 (8.4%)	93 (27.9%)	112 (5.3%)
Asthma	105 (4.3%)	48 (14.4%)	57 (2.7%)
Tuberculosis	41 (1.7%)	12 (3.6%)	29 (1.4%)
Hypertension	842 (34.4%)	119 (35.7%)	723 (34.2%)
Diabetes mellitus	330 (13.5%)	43 (12.9%)	287 (13.6%)
Heart disease	274 (11.2%)	43 (12.9%)	231 (10.9%)
Other	269 (11.0%)	31 (9.3%)	238 (11.3%)
None of the above	1142 (46.7%)	106 (31.8%)	1036 (49.1%)
Symptoms, n (%)			
At least occasional wheeze	322 (13.2)	110 (33.0)	212 (10.0)
Productive cough	457 (18.7)	117 (35.1)	340 (16.1)
mMRC, n (%)			
Grade 0–1	2222 (90.9%)	257 (77.2%)	1965 (93.0%)
Grade 2–4	223 (9.1%)	76 (22.8%)	147 (7.0%)
CAT, mean (SD)	6.1 (5.4%)	8.9 (6.9%)	5.6 (4.9%)
Bronchitis, pneumonia or severe whooping cough in childhood	169 (6.9%)	38 (11.4%)	131 (6.2%)
Tuberculosis in childhood	45 (1.8%)	11 (3.3%)	34 (1.6%)
Exposure to pollutants*, n (%)			
Current/past exposure	2256 (92.3%)	307 (92.2%)	1949 (92.3%)
Never	189 (7.7%)	26 (7.8%)	163 (7.7%)

Continued

Table 1 Continued

Characteristic	Total sample (n=2445)	Reference test positive (n=333)	Reference test negative (n=2112)
Year(s) of exposure, mean (SD)	8.9 (6.4)	9.1 (6.6)	8.8 (6.4)
GOLD stage if <LLN, n (%)			
I (FEV ₁ ≥80% predicted)	--	158 (47.5%)	--
II (FEV ₁ 50%–79% predicted)	--	137 (41.1%)	--
III (FEV ₁ 30%–49% predicted)	--	33 (9.9%)	--
IV (FEV ₁ <30% predicted)	--	5 (1.5%)	--

*Cooking fumes, biomass smoking, gas, steams, dust.
 BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; GOLD, global initiative for chronic obstructive lung disease; LLN, lower limit of normal; mMRC, modified medical research council dyspnea scale.

highest specificity (78.6% (95% CI 76.8% to 80.4%)). CAPTURE compared with CDQ had the most obvious difference in specificity of 8.4% (–10.7% to –6.0%; $p<0.001$) ((tables 2–4)).

Both peak flow and microspirometry devices had higher sensitivity and specificity compared with all questionnaires (tables 3 and 4). Peak flow had the highest sensitivity (67.3%) and microspirometry the highest specificity (89.7%) (tables 3 and 4).

Of the combined screening strategies, C-SBQ combined with airflow measurement devices in parallel (ie, recorded as screen-positive if either test was positive) had the best performance, with sensitivities of 80.5%–81.4% and specificities of 65.5%–68%. Parallel strategies (requiring either test to be positive) optimised sensitivity and serial strategies (requiring both tests to be positive) optimised specificity. Taking CAPTURE and peak flow as an example, a parallel combination had sensitivity of 77.2% compared with 41.7% in serial combination, while the specificity significantly increased from 59.1% to 93.7% (table 2).

Overall, test performance was slightly higher when screening questionnaires were combined with microspirometry rather than peak flow. Strategies including CAPTURE performed less well compared with those based on other questionnaires. Parallel strategies including the C-SBQ had the highest sensitivities, whereas those based on the CDQ had the highest specificity (tables 2 and 3). Full comparisons of serial and parallel strategies are described in online supplemental appendix 3.

Cost-effectiveness of preferred screening tests

Analysis of the C-SBQ parallel strategies revealed that the most costly strategy was the combination of C-SBQ and microspirometry, but this also detected the most true cases (table 5). The C-SBQ alone was dominated by microspirometry (more costly, less effective). The incremental cost-effectiveness ratio for C-SBQ and microspirometry (vs peak flow) was greatest at £64.20 (CNY 385.20), but could be considered cost-effective if the threshold willingness

to pay for an additional true case detected in China is at least CNY 385.

DISCUSSION

This is the first study assessing the accuracy of individual screening tools and their combinations to identify undiagnosed COPD within Chinese community populations. We showed that the combination of a simple questionnaire and airflow measurement device could adequately identify adults requiring diagnostic spirometry. Our overall findings were consistent with a meta-analysis of studies from other countries³⁵ that airflow measurement devices were more accurate than questionnaires, and that combinations of screening tests improved ability to detect COPD in primary care. Within single test strategies, microspirometry had the best performance (sensitivity 64.9%, specificity 89.7%). For combination strategies, the C-SBQ and microspirometry used in parallel, maximised sensitivity (81.4%) with reasonable specificity (68%) and would be deemed cost-effective if the Chinese health service was willing to pay ≥CNY385 per additional case detected.

C-SBQ had the highest sensitivity of all screening questionnaires in our study, with comparable specificity. However, accuracy of the C-SBQ was worse than reported in the validation paper of the Chinese tool, with lower sensitivity (63.1% vs 82.5%) but slightly higher specificity (74.2% vs 72.9%). The observed discrepancy may be due to differences in the spectrum of clinical characteristics³⁶ (community sample rather than tertiary care population in previous study) and airflow obstruction criteria used (we used the LLN rather than the GOLD criteria).

Inclusion of the C-SBQ and the CDQ from which it was derived allowed direct comparison of the two measures, confirming that C-SBQ was more accurate for use in Chinese community populations when prioritising sensitivity (sensitivity 63.1% vs 55.0% with slightly lower specificity 74.2% vs 78.6%).

Table 2 Accuracy of index tests and strategies

Part 1	Part 2	Strategy type	TP	FP	TN	FN	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)
CAPTURE	n/a	Individual	172	628	1484	161	51.7 (46.1 to 57.1)	70.3 (68.3 to 72.2)	21.5 (18.7 to 24.5)	90.2 (88.7 to 91.6)
CDQ	n/a	Individual	183	451	1661	150	55.0 (49.4 to 60.4)	78.6 (76.8 to 80.4)	28.9 (25.4 to 32.6)	91.7 (90.4 to 92.9)
C-SBQ	n/a	Individual	210	545	1567	123	63.1 (57.6 to 68.3)	74.2 (72.3 to 76.1)	27.8 (24.6 to 31.2)	92.7 (91.4 to 93.9)
COPD-SQ	n/a	Individual	184	479	1633	149	55.3 (49.7 to 60.7)	77.3 (75.5 to 79.1)	27.8 (24.4 to 31.3)	91.6 (90.3 to 92.9)
Peak flow	n/a	Individual	224	368	1744	109	67.3 (61.9 to 72.3)	82.6 (80.9 to 84.2)	37.8 (33.9 to 41.9)	94.1 (92.9 to 95.1)
Microspirometry	n/a	Individual	216	217	1895	117	64.9 (59.5 to 70.0)	89.7 (88.4 to 91.0)	49.9 (45.1 to 54.7)	94.2 (93.1 to 95.2)
CAPTURE	Peak flow	Parallel (OR)	257	863	1249	76	77.2 (72.3 to 81.6)	59.1 (57.0 to 61.2)	22.9 (20.5 to 25.5)	94.3 (92.9 to 95.5)
CDQ	Peak flow	Parallel (OR)	259	663	1449	74	77.8 (72.9 to 82.1)	68.6 (66.6 to 70.6)	28.1 (25.2 to 31.1)	95.1 (93.9 to 96.2)
C-SBQ	Peak flow	Parallel (OR)	268	729	1383	65	80.5 (75.8 to 84.6)	65.5 (63.4 to 67.5)	26.9 (24.2 to 29.7)	95.5 (94.3 to 96.5)
COPD-SQ	Peak flow	Parallel (OR)	259	687	1425	74	77.8 (72.9 to 82.1)	67.5 (65.4 to 69.5)	27.4 (24.6 to 30.3)	95.1 (93.8 to 96.1)
CAPTURE	Microspirometry	Parallel (OR)	262	764	1348	71	78.7 (73.9 to 83.0)	63.8 (61.7 to 65.9)	25.5 (22.9 to 28.3)	95.0 (93.7 to 96.1)
CDQ	Microspirometry	Parallel (OR)	261	585	1527	72	78.4 (73.6 to 82.7)	72.3 (70.3 to 74.2)	30.9 (28 to 34.1)	95.5 (94.4 to 96.5)
C-SBQ	Microspirometry	Parallel (OR)	271	675	1437	62	81.4 (76.8 to 85.4)	68.0 (66.0 to 70.0)	28.6 (25.8 to 31.6)	95.9 (94.7 to 96.8)
COPD-SQ	Microspirometry	Parallel (OR)	262	620	1492	71	78.7 (73.9 to 83.0)	70.6 (68.7 to 72.6)	29.7 (26.7 to 32.8)	95.5 (94.3 to 96.4)
CAPTURE	Peak flow	Serial (AND)	139	133	1979	194	41.7 (36.4 to 47.2)	93.7 (92.6 to 94.7)	51.1 (45 to 57.2)	91.1 (89.8 to 92.2)
CDQ	Peak flow	Serial (AND)	148	156	1956	185	44.4 (39.0 to 50.0)	92.6 (91.4 to 93.7)	48.7 (42.9 to 54.5)	91.4 (90.1 to 92.5)
C-SBQ	Peak flow	Serial (AND)	166	184	1928	167	49.8 (44.4 to 55.4)	91.3 (90.0 to 92.5)	47.4 (42.1 to 52.8)	92 (90.8 to 93.2)
COPD-SQ	Peak flow	Serial (AND)	149	160	1952	184	44.7 (39.3 to 50.3)	92.4 (91.2 to 93.5)	48.2 (42.5 to 53.9)	91.4 (90.1 to 92.5)

Continued

Table 2 Continued

Part 1	Part 2	Strategy type	TP	FP	TN	FN	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)
CAPTURE	Microspirometry	Serial (AND)	126	81	2031	207	37.8 (32.6 to 43.3)	96.2 (95.3 to 96.9)	60.9 (53.9 to 67.6)	90.8 (89.5 to 91.9)
CDQ	Microspirometry	Serial (AND)	138	83	2029	195	41.4 (36.1 to 46.9)	96.1 (95.2 to 96.9)	62.4 (55.7 to 68.8)	91.2 (90.0 to 92.4)
C-SBQ	Microspirometry	Serial (AND)	155	87	2025	178	46.5 (41.1 to 52.1)	95.9 (94.9 to 96.7)	64.0 (57.7 to 70.1)	91.9 (90.7 to 93)
COPD-SQ	Microspirometry	Serial (AND)	138	76	2036	195	41.4 (36.1 to 46.9)	96.4 (95.5 to 97.2)	64.5 (57.7 to 70.9)	91.3 (90.0 to 92.4)

Serial = positive on BOTH tests required for screen positivity; Parallel = positive on EITHER test required for screen positivity.
CAPTURE, COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk; CDQ, COPD Diagnostic Questionnaire; COPD, chronic obstructive pulmonary disease; C-SBQ, Chinese Symptom-Based Questionnaire; FN, false negative; FP, false positive; n/a, not applicable; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

Direct comparison between our findings and those of previous studies was limited by differences in populations and pretest probabilities. COPD among never smokers is more common in China than in western countries and we included never smokers in this study to maximise the range of potential COPD risk factors represented for example, environmental exposures such as dust, biomass fumes and passive smoking, as well as active smoking. Inevitably this contributed to the lower test performance observed. Furthermore, the CAPTURE questionnaire was originally designed to detect more severe COPD. The different case definition in our study therefore precludes direct comparison with previous studies (we plan to report accuracy for detecting more severe clinically significant COPD in a future publication).

Our test accuracy study has highlighted the strengths of different screening tests, which can be used to evaluate future screening programmes. We recruited a large number of participants from urban and rural settings in four geographically diverse municipalities in China, and the proportion of never smokers in our sample (68.9%) was similar to that found in a recent nationally representative cross-sectional study in China (71.4%):³⁰ which included a younger population (age 20+). We demonstrated that lung function tests and diagnosis of COPD can be implemented by general practitioners (GPs) and nurses after a structured training course with regular quality over reading and feedback, as evidenced by 99% usable spirometry and consistently good quality spirometry in most GP sites. The fully paired study design enabled us to compare the accuracy of multiple index tests and strategies. Alternating the order of peak flow and microspirometry tests during assessments decreased the potential training effect that could have been introduced when conducting consecutive lung function tests in a research context.

We defined the reference test as airflow obstruction regardless of clinical symptoms, to reflect the methods of previous studies and also account for the differing symptom profile reported among Chinese populations, where chronic respiratory symptoms are less recognised. In our study, just over half of those with obstruction were likely to benefit from some treatment due to reported symptoms, and a further quarter of those obstructed would benefit from smoking cessation advice as they had a positive smoking history but no respiratory symptoms.

Accuracy might have differed if the GOLD criteria were used, though unlikely to substantially change the comparative performance of the tests. Defining airflow obstruction according to the LLN criteria increased the likelihood that participants testing positive on study spirometry were true COPD cases, rather than detecting comorbidities with similar clinical presentations such as cardiovascular disease.³⁷ As prebronchodilator spirometry was omitted from the study assessment to minimise participant burden and increase uptake in this large community-based study, we could not assess airflow reversibility.

Table 3 Comparative sensitivity for individual tests

Individual test	CAPTURE (95% CI, p value)	CDQ (95% CI, p value)	C-SBQ (95% CI, p value)	COPD-SQ (95% CI, p value)	Peak flow (95% CI, p value)	Microspirometry (95% CI, p value)
CAPTURE		–3.3 (–9.6 to 2.9; 0.3245)	–11.4 (–16.9 to 5.9; <0.0001)	–3.6 (–9.6 to 2.5; 0.2615)	–15.6 (–22.1 to –9.1; <0.0001)	–13.2 (–20.2 to –6.2; 0.0002)
CDQ			–8.1 (–12.6 to –3.6; 0.0003)	–0.3 (–5.3 to 4.7; 1.0000)	–12.3 (–18.7 to –6.0; 0.0001)	–9.9 (–16.7 to –3.2; 0.0037)
C-SBQ				7.8 (3.2 to 12.4; 0.0007)	–4.2 (–10.4 to 2.0; 0.1978)	–1.8 (–8.4 to 4.8; 0.6427)
COPD-SQ					–12.0 (–18.3 to –5.7; 0.0002)	–9.6 (–16.4 to –2.8; 0.0052)
Peak flow						2.4 (–4.1 to 8.9; 0.5047)
Microspirometry						

Values indicate the difference in sensitivity (with 95% CI and p values), comparing index tests in the column against index tests in the row. For example, sensitivity for CAPTURE is 3.3% lower than for CDQ (95% CI –9.6 to 2.9; 0.3245).

CAPTURE, COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk; CDQ, COPD Diagnostic Questionnaire; COPD, chronic obstructive pulmonary disease; C-SBQ, Chinese Symptom-Based Questionnaire.

Our study population included slightly more women than men (60% women). As smoking prevalence is also much lower among women, our study cannot provide an accurate estimate of COPD prevalence. However this should not impact on the estimate of screening test accuracy, which was the primary objective. It was not possible to exclude diagnosed patients with COPD from this study, as Chinese CHCs do not have COPD registers and patients are frequently unaware of their condition. However, as the aim of our study was to determine accuracy of different screening tests by comparing all tests against a reference standard, rather than to evaluate the implementation of a screening programme, inclusion of COPD patients was

justified. By including some people with known COPD, we maximised the number of test positives in the study sample.

Although China has recently introduced a national policy of COPD screening, there is no current guidance regarding the tests to use or which test characteristics (ie, sensitivity/specificity) to prioritise. Considering the estimated high prevalence of undiagnosed COPD in China, highly sensitive strategies may be preferred to maximise the number of detected cases, although this would result in large numbers being referred for diagnostic spirometry, many of whom would be false positives. However, the potential inefficiency may be offset by a recent policy to

Table 4 Comparative specificity for individual tests

Individual test	CAPTURE (95% CI, p value)	CDQ (95% CI, p value)	C-SBQ (95% CI, p value)	COPD-SQ (95% CI, p value)	Peak flow (95% CI, p value)	Microspirometry (95% CI, p value)
CAPTURE		–8.4 (–10.7 to –6.0; <0.0001)	–3.9 (–6.2 to –1.6; 0.0008)	–7.1 (–9.3 to –4.8; <0.0001)	–12.3 (–14.8 to –9.8; <0.0001)	–19.5 (–21.8 to –17.1; <0.0001)
CDQ			4.5 (3.0 to 5.9; <0.0001)	1.3 (–0.4 to 3.0; 0.1335)	–3.9 (–6.1 to –1.8; 0.0003)	–11.1 (–13.2 to –9.0; <0.0001)
C-SBQ				–3.1 (–4.8 to –1.5; 0.0002)	–8.4 (–10.6 to –6.2; <0.0001)	–15.5 (–17.7 to –13.3; <0.0001)
COPD-SQ					–5.3 (–7.4 to –3.1; <0.0001)	–12.4 (–14.6 to –10.3; <0.0001)
Peak flow						–7.1 (–9.1 to –5.2; <0.0001)
Microspirometry						

Values indicate the difference in specificity (with 95% CI and p values), comparing index tests in the column against index tests in the row. For example, specificity for CAPTURE is 8.4% lower than for CDQ (95% CI –10.7 to 6.0; <0.0001).

CAPTURE, COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk; CDQ, COPD Diagnostic Questionnaire; COPD, chronic obstructive pulmonary disease; C-SBQ, Chinese Symptom-Based Questionnaire.

Table 5 Per patient cost, effectiveness and cost-effectiveness of selected screening strategies

Strategy	Cost per test UK£ (CNY)	Difference in cost UK£ (CNY)	True cases detected	Difference in true cases detected	ICER UK£ (CNY) per additional true case detected
C-SBQ	2.22 (13.30)	–	0.0858	–	Dominated by microspirometry
Microspirometry	1.60 (9.60)	–0.62 (–3.70)	0.0883	0.0025	18.13 (108.78) vs no screening*
Peak flow	1.71 (10.25)	0.11 (0.64)	0.0915	0.0057	32.89 (197.36) vs microspirometry
C-SBQ and microspirometry	3.43 (20.59)	1.72 (10.35)	0.1184	0.0269	64.20 (385.20) vs peak flow

*Due to the symptom-based question being excluded from the analysis, the next option is compared with no screening. C-SBQ, Chinese Symptom-Based Questionnaire; ICER, incremental cost-effectiveness ratio.

include spirometry in routine primary care health consultations; avoiding the need to refer patients to hospital for diagnostic assessment. While the more sensitive parallel strategies may be preferential in the Chinese healthcare setting, there is a trade-off between sensitivity and specificity according to epidemiology, resources and context; hence, serial strategies may be considered optimal in other settings.

If the strategy of C-SBQ and microspirometry were used in practice and had the same accuracy as reported here, it is likely that true COPD cases who were not detected (false negatives) would have mild disease and would reattend with recurring symptoms, offering further opportunities for referral to diagnostic spirometry.

While our analyses used recommended cut-points for the index tests, it is important to explore their optimal cut-points when applied in this context, as many tests were developed with alternate purposes and/or populations in mind. Thresholds used to indicate airflow obstruction (either in the screening tests or reference test) may not be valid in the whole Chinese population as adequate reference values for lung function are currently unreliable.

Although we have determined the accuracy of different tests when used for screening Chinese community populations for undiagnosed COPD, we did not evaluate the implementation of a screening programme. A recently published model-based cost-effectiveness analysis from China which used international data on QALYs, demonstrated that use of a screening questionnaire combined with a hand-held spirometer was cost saving compared with no screening, but this did not compare different screening strategies and was not based on data from an implementation trial.³⁸ It is important to undertake a trial to compare the effectiveness and cost-effectiveness of the most efficient screening strategy identified in this study (maximising yield with acceptable false positive rate) against usual care on yield and clinical outcomes. Such a trial would need to assess uptake of screening and incorporate pathways for clinical assessment and subsequent treatment for test positive cases. In our study

sample, >75% had potential to benefit; less than half with obstruction had treatable symptoms and a further quarter with obstruction and no symptoms would benefit from smoking cessation advice. We presented cost per additional true case detected, however, no country has, to date, stated a willingness to pay threshold for this outcome. The quality-adjusted life-year (QALY) is a more common metric in health economic analyses, with established cost per QALY thresholds. Although outside the remit of our test accuracy study, future work should attempt to extrapolate cases detected to the management of patients with COPD, to assess the impact on quality of life and survival to allow the calculation of QALYs.

In conclusion, we have demonstrated that within the primary care setting in China, the most efficient screening test strategy was a combination of the C-SBQ and microspirometry where a positive test in either would result in a referral for diagnostic spirometry. Further work is required to explore optimal cut-points and there is a need for a clinical trial to evaluate whether a screening programme using this test combination is clinically and cost-effective.

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Contributors RJ and PA co-led the study design, with contributions and advice from all other authors. CC, XK and KKC contributed to decisions on outcome measures. CC and KKC advised on involving GP practices. BC, APD, AE, RJ and PA advised on lung function testing. BC and AE provided training and oversaw the quality assessment for lung function testing. APD, RJ, AJS and PA designed the testing strategy. AJS and SJ designed the analysis plan and economic evaluations respectively. ZP coordinated the data collection, with support from APD, RJ and PA. ZP conducted the statistical analysis, supported by AJS, SJ and APD. ZP and APD wrote the manuscript with input from all other authors. CC was the local PI and oversaw all activities in China. RA, JC-d-S, AF, NKG, KJ, MM, TM, SM, KS, RS, AMT and SW contributed to the development and oversight of this study. As part of the Breathe Well Global Health Research Group, all authors contributed to and approved the final version.

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