Performance of alternative COPD case-finding tools: a systematic review and meta-analysis

ELENA SCHNIEDERS, ELYESA ÜNAL, VOLKER WINKLER, PETER DAMBACH, VALÉRIE R. LOUIS, OLAF HORSTICK, FLORIAN NEUHANN*, ANDREAS DECKERT*

Data Supplement

Table E1: Terms for literature search

Category	Terms	Terms for search (spelling variations)	Mesh Term for search
COPD	COPD	COPD	COPD
	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease	COPD
	Chronic obstructive airway disease	Chronic obstructive airway disease Chronic obstructive airways disease	COPD
	COAD	COAD	COPD
	Chronic obstructive lung disease	Chronic obstructive lung disease	COPD
	Chronic airflow obstruction	Chronic airflow obstruction	COPD
	Chronic lung disease	Chronic lung disease	..
	Chronic obstructive bronchial disease	Chronic obstructive bronchial disease	..
	Airway obstruction	Airway obstruction Airways obstruction	..
	Chronic bronchitis	Chronic bronchitis	Chronic bronchitis
	Pulmonary emphysema	Pulmonary emphysema Pulmonary emphysemas	Pulmonary emphysema
	Focal emphysema	Focal emphysema	Pulmonary emphysema
	Panacinar emphysema	Panacinar emphysema	Pulmonary emphysema
	Panlobular emphysema	Panlobular emphysema	Pulmonary emphysema
	Centriacinar emphysema	Centriacinar emphysema	Pulmonary emphysema
	Centrilobular emphysema	Centrilobular emphysema	Pulmonary emphysema
	Asthma-COPD overlap syndrome	Asthma-COPD overlap syndrome Asthma COPD overlap syndrome Asthma- Chronic obstructive disease overlap syndrome Asthma Chronic obstructive disease overlap syndrome	Asthma- COPD overlap syndrome
Diagnosis	Diagnosis	Diagnosis Diagnostic	Diagnosis
	Screening	Screening Screenings	..
	Case finding	Case finding Case-finding	..
	Questionnaire	Questionnaire Questionnaires	Available, but was not used
	Undiagnosed	Undiagnosed	..
	Identification	Identify Identification	..
	Detection	Detection	..
	Test	Test Tests	..
	Peak Flow	Peak Flow Peak Expiratory Flow PEF	..
Primary Care	Primary Care	Primary Care	Primary Health Care
	Primary Health Care	Primary Health Care Primary Healthcare	Primary Health Care

	General Practice	General Practice Family Practice	General Practice

Example: PubMed: (COPD[Mesh] OR Chronic bronchitis[Mesh] OR Pulmonary emphysema[Mesh] OR Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome[Mesh] OR “COPD” OR “chronic obstructive pulmonary disease” OR “chronic obstructive airway disease” OR “chronic obstructive airways disease” OR “COAD” OR “chronic obstructive lung disease” OR “chronic airflow obstruction” OR “chronic lung disease” OR “chronic obstructive bronchial disease” OR “airway obstruction” OR “airways obstruction” OR “chronic bronchitis” OR “Pulmonary emphysema” OR “Pulmonary emphysemas” OR “Focal emphysema” OR “Panacinar emphysema” OR “Panlobular emphysema” OR “Centriacinar emphysema” OR “Centrilobular emphysema” OR “Asthma-COPD overlap syndrome” OR “Asthma COPD overlap syndrome” OR “Asthma-chronic obstructive pulmonary disease overlap syndrome” OR “Asthma chronic obstructive pulmonary disease overlap syndrome”) AND (Diagnosis[Mesh] OR “diagnosis” OR “diagnostic” OR “screening” OR “screenings” OR “case finding” OR “case-finding” OR “questionnaire” OR “undiagnosed” OR “identify” OR “identification” OR “detection” OR “test” OR “tests” OR “Peak Expiratory Flow” OR “Peak Flow” OR “PEF”) AND (Primary Health Care[Mesh] OR “primary care” OR “primary health care” OR “primary healthcare” OR General Practice[Mesh] OR “general practice” OR “family practice”)

Table E2: Conduct of quality assessment with the QUADAS Tool

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions(yes/no/unclear)	Was a consecutive or random sample of patients enrolled? ➔ All studies included a consecutive or random sample: Yes	Were the index test results interpreted without knowledge of the results of the reference standard? - Yes: If Index tests with a pre-specified threshold were interpreted and conducted before the reference standard or interpreted blindly - No: If Index test had no pre-specified threshold, because the optimal threshold was then found knowing the result of the reference standard - Unclear: If order or blinding was not specified	Is the reference standard likely to correctly classify the target condition? ➔ Given the strict eligibility criteria for spirometry, all included studies used the gold standard as a reference: Yes	Was there an appropriate interval between index test(s) and reference standard? - Yes: If interval was under 24 hours - No: If interval was over 24 hours - Unclear: If Index test and reference test were not conducted at the same appointment but it was unclear how large the time interval was
	Was a case-control design avoided? - Yes: If a case-control design was avoided - No: If the study used a case-control design	If a threshold was used, was it pre-specified? - Yes: If threshold was pre-specified - No: If threshold was not pre-specified - Unclear: If multiple tests were evaluated and some	Were the reference standard results interpreted without knowledge of the results of the index test? - Yes: If the interpretation was blinded to the Index Test with a prespecified threshold or if the Index test had no pre-specified threshold, as the interpretation of	Did all patients receive a reference standard? ➔ Given the eligibility criteria for the systematic review, all patients received the gold standard

	Did the study avoid inappropriate exclusions? ➔ All studies avoided inappropriate exclusions: Yes	of them did not have a pre-specified cut-off	the Index Test was therefore depended on the result of the reference test and the reference test therefore had to be interpreted first - No: If it was specified that the reference standard was interpreted knowing the result of the Index test - Unclear: If order or blinding of tests was unclear	Did all patients receive the same reference standard? - Yes: If all patients received a post-bronchodilator spirometry - No: If only patients with pre-bronchodilator obstruction received post-bronchodilator spirometry (still accepted as the gold standard)
				Were all patients included in the analysis? - Yes: If it was stated that all patients were included - No: If enrolled patients were excluded for any reason - Unclear: If it was not specified if a participant was excluded
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias? - High: If one question was answered with No - Low: If all questions were answered with Yes	Could the conduct or interpretation of the index test have introduced bias? - High: If one question was answered with No - Low: If all questions were answered with Yes - Unclear: If one question was answered with Unclear	Could the reference standard, its conduct, or its interpretation have introduced bias? - High: If one question was answered with No - Low: If all questions were answered with Yes - Unclear: If one question was answered with Unclear	Could the reference standard, its conduct, or its interpretation have introduced bias? - High: If one question was answered with No - Low: If all questions were answered with Yes - Unclear: If one question was answered with Unclear
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

	➔ Applicability given for all studies, as there are no special patients selection rules stated in our review question: Yes	➔ Applicability given for all studies, as only Index tests were included in the systematic review that are specific tests for COPD and no further restrictions were given: Yes	➔ Applicability given for all studies, as the strict eligibility criteria for the gold standard confirm applicability

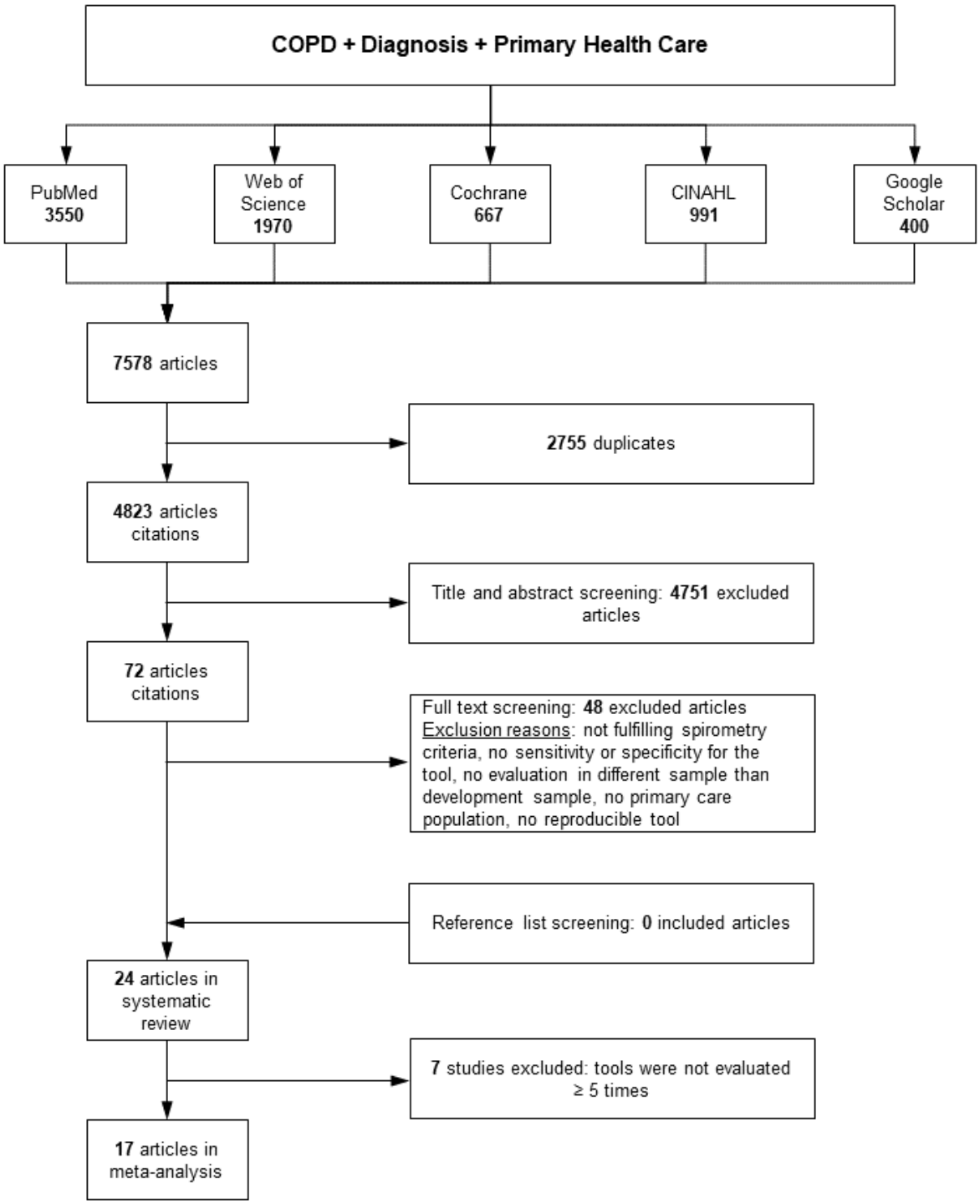


Figure E1: Flow chart of literature search results

***Table E3: Quality assessment of all 24 included studies**; table was constructed with the QUADAS tool, retrosp. validation= retrospective validation in initial study cohort through split-sample validation, *= study is included in meta-analysis*

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Dickens 2020* [20]	☺	☺	☺	☹	☺	☺	☺
Lopez Varela 2019 [33]	☺	☺	?	☺	☺	☺	☺
Fujita 2019 [34]	☺	☺	☺	☹	☺	☺	☺
Ronaldson 2018* [26]	☺	☺	☺	☹	☺	☺	☺
Demirci 2017 [36]	☺	☺	?	☹	☺	☺	☺
Hidalgo 2017* [40]	☺	☹	☺	?	☺	☺	☺
Spyratos 2017* [24]	☺	☺	☺	☹	☺	☺	☺
Weiss 2017 [27]	☺	☺	☺	☹	☺	☺	☺
Kim 2016* [21]	☺	☹	☺	?	☺	☺	☺
Labor 2016* [29]	☺	☹	☺	☹	☺	☺	☺
Lopez Varela 2016 [28]	☺	☹	☺	☹	☺	☺	☺
Llordes 2016* [43]	☺	?	?	☹	☺	☺	☺
Sogbetun 2016* [23]	☺	☺	?	☹	☺	☺	☺
Sogbetun (retrosp. validation) 2016 [42]	☺	☹	☺	☹	☺	☺	☺
Represas-Represas 2016* [38]	☺	☹	☺	☹	☺	☺	☺
Stanley 2014* [25]	☺	☺	☺	☹	☺	☺	☺
van den Bemt 2014* [30]	☺	☺	☺	☹	☺	☺	☺
Cui 2012 [31]	☹	☺	☺	?	☺	☺	☺
Miravitlles 2012* [41]	☹	☹	☺	☹	☺	☺	☺
Thorn 2012* [35]	☺	☹	☺	?	☺	☺	☺
Frith 2011* [39]	☺	?	☺	☹	☺	☺	☺
Sichletidis 2011* [22]	☺	☺	?	☹	☺	☺	☺
Kotz 2008* [32]	☺	☺	☺	☹	☺	☺	☺
Price 2006* [37]	☺	☹	☺	?	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

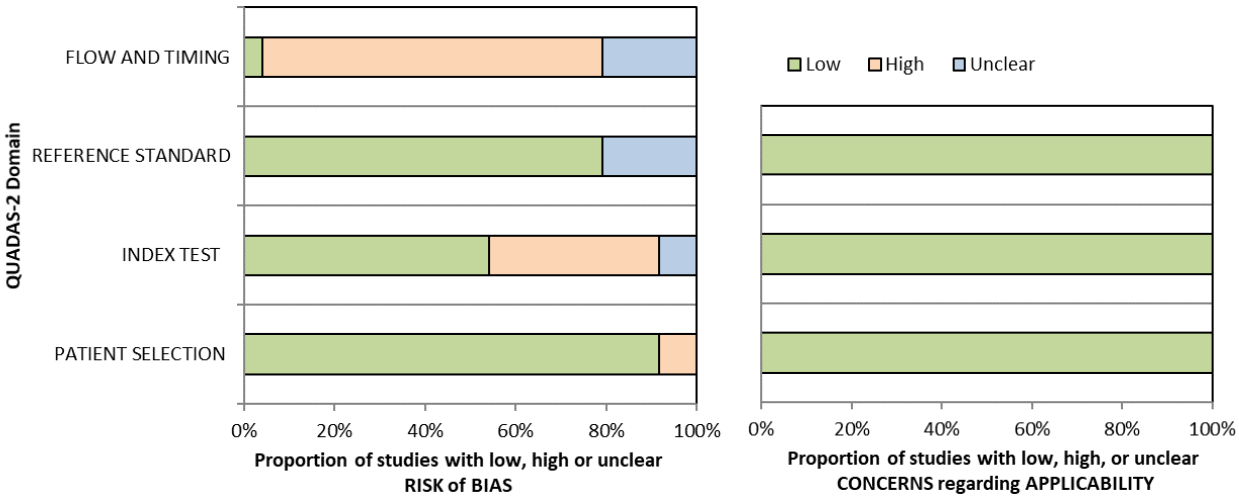
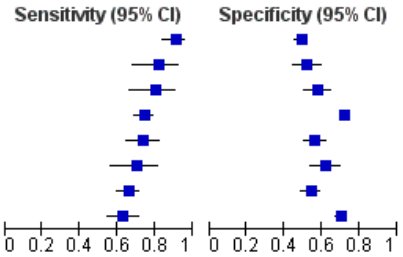


***Figure E2: Quality assessment of all 24 included studies**; figure was constructed with the QUADAS tool*

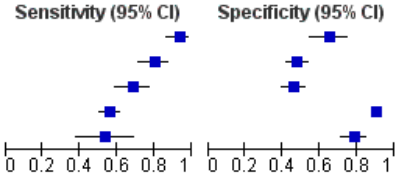
CDQ with threshold in (≥XX)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sichletidis 2011 (17)	101	493	10	474	0.91 [0.84, 0.96]	0.49 [0.46, 0.52]
Ronaldson 2018 (n.a.)	37	82	8	89	0.82 [0.68, 0.92]	0.52 [0.44, 0.60]
Price 2006 (19.5)	37	85	9	115	0.80 [0.66, 0.91]	0.57 [0.50, 0.64]
Spyratos 2017 (17)	260	807	91	2076	0.74 [0.69, 0.79]	0.72 [0.70, 0.74]
Llordes 2016 (17)	79	132	28	168	0.74 [0.64, 0.82]	0.56 [0.50, 0.62]
Frith 2011 (19.5)	40	56	17	91	0.70 [0.57, 0.82]	0.62 [0.54, 0.70]
Kotz 2008 (19.5)	183	183	95	215	0.66 [0.60, 0.71]	0.54 [0.49, 0.59]
Stanley 2014 (19.5)	87	274	51	642	0.63 [0.54, 0.71]	0.70 [0.67, 0.73]



COPD-PS with threshold in (≥X)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Miravitlles 2012 (4)	74	33	5	61	0.94 [0.86, 0.98]	0.65 [0.54, 0.74]
Llordes 2016 (4)	86	157	21	143	0.80 [0.72, 0.87]	0.48 [0.42, 0.53]
Sogbetun 2016 (5)	70	140	32	120	0.69 [0.59, 0.77]	0.46 [0.40, 0.52]
Spyratos 2017 (5)	197	288	154	2595	0.56 [0.51, 0.61]	0.90 [0.89, 0.91]
Ronaldson 2018 (n.a.)	24	37	21	134	0.53 [0.38, 0.68]	0.78 [0.71, 0.84]



Micro spirometers with FEV1/FEV6 threshold in (≤0.XX)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hidalgo Sierra 2017 (0.69)	82	2	0	71	1.00 [0.96, 1.00]	0.97 [0.90, 1.00]
van den Bemt 2014 (0.72)	41	9	3	51	0.93 [0.81, 0.99]	0.85 [0.73, 0.93]
Llordes 2016 (0.78)	94	83	13	217	0.88 [0.80, 0.93]	0.72 [0.67, 0.77]
Miravitlles 2012 (0.75)	67	14	12	80	0.85 [0.75, 0.92]	0.85 [0.76, 0.92]
Represas-Represas 2016 (0.78)	95	72	19	176	0.83 [0.75, 0.90]	0.71 [0.65, 0.77]
Dickens 2020 (0.77)	279	31	58	176	0.83 [0.78, 0.87]	0.85 [0.79, 0.90]
Frith 2011 (0.74)	46	43	11	104	0.81 [0.68, 0.90]	0.71 [0.63, 0.78]
Thorn 2012 (0.73)	61	45	16	183	0.79 [0.68, 0.88]	0.80 [0.74, 0.85]
Kim 2016 (0.77)	33	33	12	112	0.73 [0.58, 0.85]	0.77 [0.70, 0.84]
Labor 2016 (0.78)	31	20	12	164	0.72 [0.56, 0.85]	0.89 [0.84, 0.93]

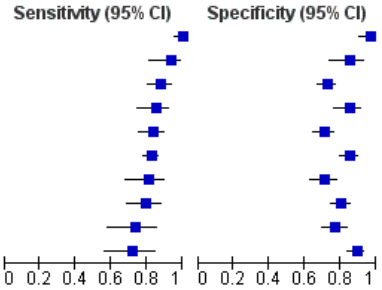


Figure E3: Descriptive analysis: coupled forest plot of sensitivity and specificity with 95% confidence intervals of studies included in meta-analysis with corresponding threshold of tool; *sorted by sensitivity, CDQ= COPD Diagnostic Questionnaire, COPD-PS= COPD Population Screener, n.a.= not available*

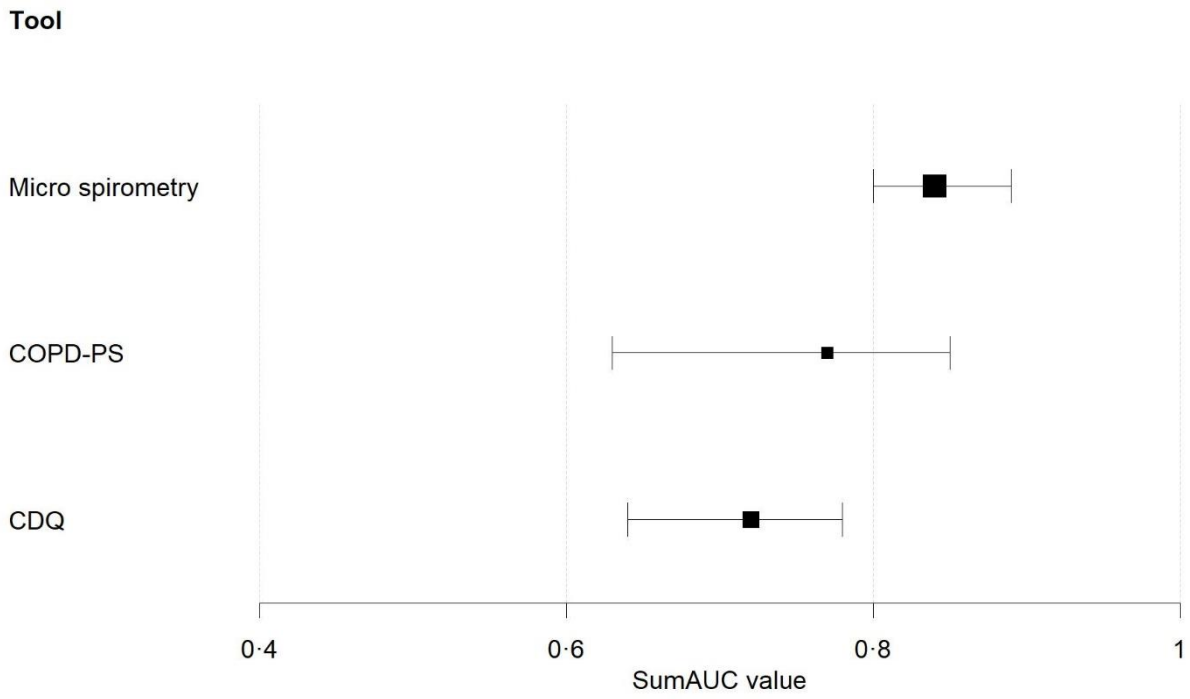


Figure E4: Meta-analysis: forest plot of summary AUC values with 95% confidence interval; *MS=micro spirometer, CDQ= COPD Diagnostic Questionnaire, COPD-PS= COPD Population Screener*

Table E4: Meta-analysis: comparison of difference in summary AUC values between tests; dAUC= difference in AUC value, MS=micro spirometer, *CDQ= COPD Diagnostic Questionnaire, COPD-PS= COPD Population Screener, ***=significant difference with p-value ≤0·001*

Comparison	dAUC [95% CI]	p-value
CDQ vs. COPD-PS	- 0·05 [-0·16, 0·1]	0·51
MS vs. COPD-PS	0·07 [-0·02, 0·22]	0·1
MS vs. CDQ	0·12 [0·06, 0·22]	0***

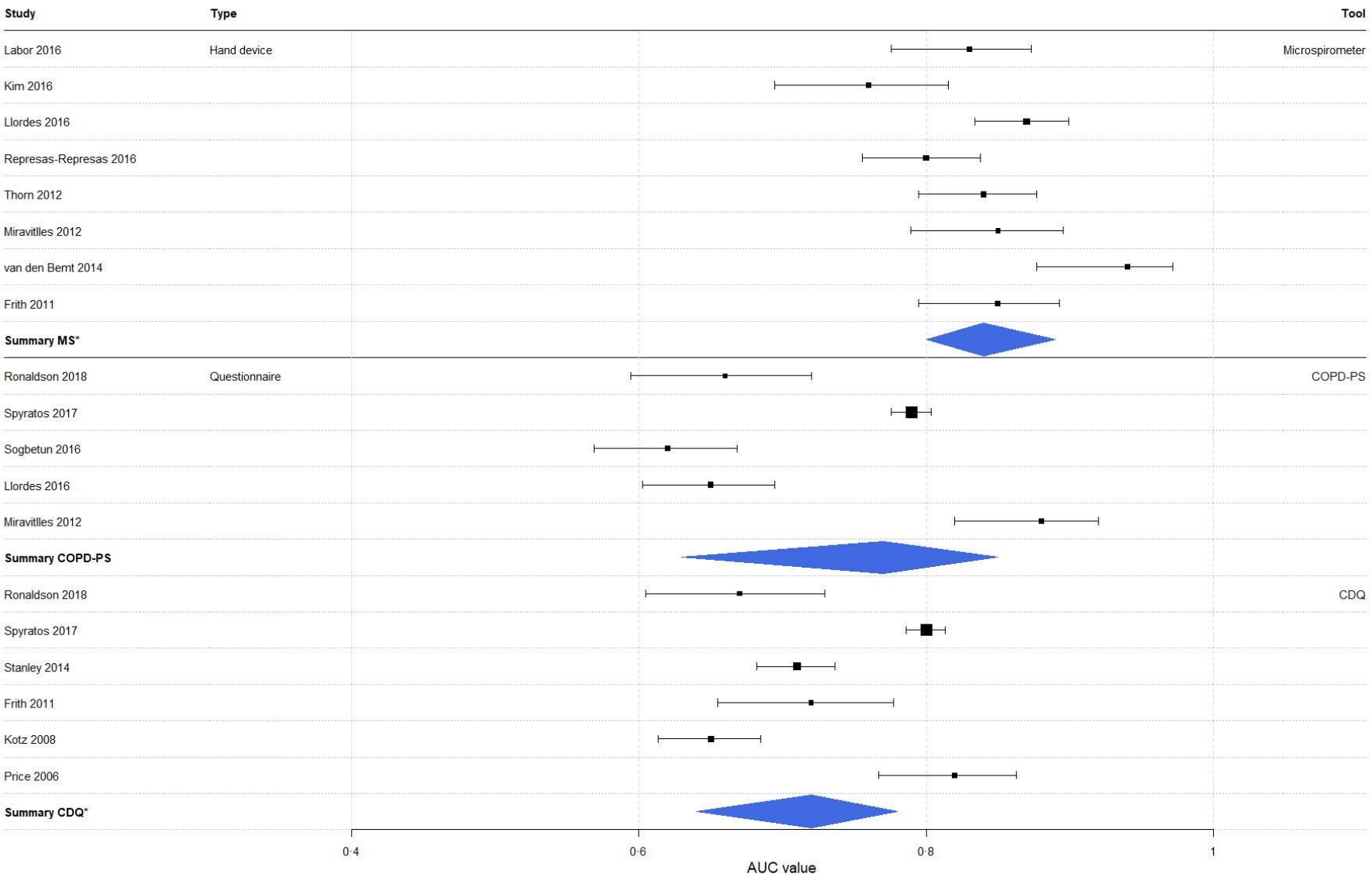


Figure E5: Forest plot with area under the curve values (AUC) and 95% confidence intervals of studies included in the meta-analysis and summary estimate of summary AUC value as a result of the bivariate meta-analysis*. *= the summary AUC value was calculated with more studies than shown, as not every study stated an AUC value; MS= micro spirometer, CDQ= COPD Diagnostic Questionnaire, COPD-PS= COPD Population Screener*