

Table 6: GRADE table: Can airway obstruction measured by spirometry (FEV₁/FVC ratio) help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity		0.51 to 0.69		Baseline Prevalence	20%		50%			
Specificity		0.28 to 0.76			Typically seen in primary care		Typically seen in specialist care			
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	4 studies ^{1,2,3,4} 1451 patients	diagnostic accuracy study	serious ^a	not serious	serious ^b	not serious ^c	none	102 to 138	255 to 345	⊕⊕○○ LOW
False negatives								62 to 98	155 to 245	
True negatives	4 studies ^{1,2,3,4} 1451 patients	diagnostic accuracy study	serious ^a	not serious	serious ^b	not serious ^c	none	224 to 608	140 to 380	⊕⊕○○ LOW
False positives								192 to 576	120 to 360	

Explanations

- a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
- b. Pooled data could not be obtained and is represented as a range. Probably due to a threshold effect – accuracy values represent best balance between sensitivity and specificity at a cut-off around FEV₁/FVC ratio of 77%. Specificity and absolute TN and FP effects per 1000 patients tested are highly variable.
- c. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.
- Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Nekoe H., Graulich E., Schleich F., Guissard F., Paulus V., Henket M., et al. (2020) Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 6:(2):00169–02020
2. Hunter CJ., Brightling CE., Woltmann G., Wardlaw AJ., Pavord ID. (2002) A Comparison of the Validity of Different Diagnostic Tests in Adults With Asthma. Chest 121:(4):1051–1057
3. Bougard N, Nekoe H, Schleich F, Guissard F, Paulus V, Donneau AF, Louis R. Assessment of diagnostic accuracy of lung function indices and FeNO for a positive methacholine challenge. Biochem Pharmacol. 2020 Sep;179:113981.
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Table 7: GRADE table: Can Peak Expiratory Flow Variability testing help diagnose asthma in patients with episodic/chronic suggestive symptoms ?

Sensitivity	0.05 to 0.93	Baseline Prevalence		20%	50%
Specificity	0.75 to 1.00			Typically seen in primary care	Typically seen in specialist care

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	6 studies ^{1,2,3,4,5,6} 1372 patients	diagnostic accuracy study	serious ^a	not serious ^{b,c}	serious ^d	not serious ^e	none	10 to 186	25 to 465	⊕⊕○○ LOW
False negatives								14 to 190	35 to 475	
True negatives	6 studies ^{1,2,3,4,5,6} 1372 patients	diagnostic accuracy study	serious ^a	not serious ^{b,c}	serious ^d	not serious ^e	none	600 to 800	375 to 500	⊕⊕○○ LOW
False positives								0 to 200	0 to 125	

Explanations

- a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
- b. Confidence not limited due to indirectness although 1 study included patients aged >7, 1 study included patients aged 13-23
- c. Confidence not limited due to indirectness although 1 study selected patients with symptoms of cough only and 1 study 46% of patients on ICS whilst being tested
- d. Pooled data could not be obtained and is represented as a range. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable.
- e. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.
- Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

- Goldstein, . Comparisons of Peak Diurnal Expiratory Flow Variation, Postbronchodilator FEV1 Responses, and Methacholine Inhalation Challenges in the Evaluation of Suspected Asthma. Chest ; 2001.
- Ulrik, . Recognition of Asthma in Adolescents and Young Adults: Which Objective Measure is Best?. Journal of Asthma; 2005.

3. Thiadens, . Value of measuring diurnal peak flow variability in the recognition of asthma: a study in general practice. ERJ; 1998.
4. Nair, . Use of peak flow variability and methacholine responsiveness in predicting changes from pre-test diagnosis of asthma. ERJ; 1999.
5. Otter, . Testing bronchial hyper-responsiveness: provocation or peak expiratory flow variability?. British Journal of General Practice,; 1997.
6. Hunter CJ, Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID.. A comparison of the validity of different diagnostic tests in adults with asthma. Chest; 2002.

Table 8a: GRADE table: Can FeNO (25 ppb) help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.53 (95% CI: 0.33 to 0.72)		Baseline Prevalence	20%		50%				
Specificity	0.72 (95% CI: 0.61 to 0.81)			Typically seen in primary care		Typically seen in specialist care				
Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	6 studies ^{1,2,3,4,5,6} 1535 patients	diagnostic accuracy study	not serious ^a	not serious	serious ^b	not serious ^c	none	106 (66 to 144)	265 (165 to 360)	⊕⊕⊕○ MODERATE
False negatives								94 (56 to 134)	235 (140 to 335)	
True negatives	6 studies ^{1,2,3,4,5,6} 1535 patients	diagnostic accuracy study	not serious ^a	not serious	serious ^b	not serious ^c	none	576 (488 to 648)	360 (305 to 405)	⊕⊕⊕○ MODERATE
False positives								224 (152 to 312)	140 (95 to 195)	

Explanations

a. Following the Quadas2 assessment of risk of bias, despite patient selection was not totally homogenous in the included studies, the study design, index test, reference standard and flow and timing were similar in all the included studies.

b. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable across different studies using same cut-off (25 ppb).

c. Imprecision of data is mainly due to heterogeneity

Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Arora R, Thornblade CE, Dauby PA, Flanagan JW, Bush AC, Hagan LL. Exhaled nitric oxide levels in military recruits with new onset asthma. *Allergy Asthma Proc.* 2006 Nov-Dec;27(6):493-8. doi: 10.2500/aap.2006.27.2904. PMID: 17176784.
2. Nekoe H, Graulich E, Schleich F, et al. Are type-2 biomarkers of any help in asthma diagnosis? *ERJ Open Res* 2020; 6: 00169-2020
3. Heffler E, Guida G, Marsico P, Bergia R, Bommarito L, Ferrero N, Nebiolo F, De Stefani A, Usai A, Bucca C, Rolla G. Exhaled nitric oxide as a diagnostic test for asthma in rhinitic patients with asthmatic symptoms. *Respir Med.* 2006 Nov;100(11):1981-7. doi: 10.1016/j.rmed.2006.02.019. Epub 2006 Apr 3. PMID: 16584881.
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5. Malinovschi A, Backer V, Harving H, Porsbjerg C. The value of exhaled nitric oxide to identify asthma in smoking patients with asthma-like symptoms. *Respir Med.* 2012 Jun;106(6):794-801. doi: 10.1016/j.rmed.2012.02.009. Epub 2012 Mar 8. PMID: 22405608.
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Table 8b: GRADE table: Can FeNO (40 ppb) help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.61 (95% CI: 0.37 to 0.81)		Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care					
Specificity	0.82 (95% CI: 0.75 to 0.87)									
Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	6 studies ^{1,2,3,4,5,6} 1638 patients	diagnostic accuracy study	not serious ^a	not serious	serious ^b	not serious ^c	none	122 (74 to 162)	305 (185 to 405)	⊕⊕⊕○ MODERATE
False negatives								78 (38 to 126)	195 (95 to 315)	
True negatives	6 studies ^{1,2,3,4,5,6} 1638 patients	diagnostic accuracy study	not serious ^a	not serious	serious ^b	not serious ^c	none	656 (600 to 696)	410 (375 to 435)	⊕⊕⊕○ MODERATE
False positives								144 (104 to 200)	90 (65 to 125)	

Explanations

a. Following the Quadas2 assessment of risk of bias, despite patient selection was not totally homogenous in the included studies, the study design, index test, reference standard and flow and timing were similar in all the included studies.

b. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable across different studies using same cut-off (25 ppb).

c. Imprecision of data is mainly due to heterogeneity

Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Arora R, Thornblade CE, Dauby PA, Flanagan JW, Bush AC, Hagan LL. Exhaled nitric oxide levels in military recruits with new onset asthma. Allergy Asthma Proc. 2006 Nov-Dec;27(6):493-8. doi: 10.2500/aap.2006.27.2904. PMID: 17176784.
2. Heffler E, Guida G, Marsico P, Bergia R, Bommarito L, Ferrero N, Nebiolo F, De Stefani A, Usai A, Bucca C, Rolla G. Exhaled nitric oxide as a diagnostic test for asthma in rhinitic patients with asthmatic symptoms. Respir Med. 2006 Nov;100(11):1981-7. doi: 10.1016/j.rmed.2006.02.019. Epub 2006 Apr 3. PMID: 16584881.

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6. Nekoe H, Graulich E, Schleich F, et al. Are type-2 biomarkers of any help in asthma diagnosis? *ERJ Open Res* 2020; 6: 00169-2020

Table 8c: GRADE table: Can FeNO (50 ppb) help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.19 to 0.56	Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care
Specificity	0.77 to 0.95			

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	3 studies 858 patients	diagnostic accuracy study	not serious ^a	not serious	not serious ^b	serious ^c	none	38 to 112	95 to 278	⊕⊕⊕○ MODERATE
False negatives								88 to 162	222 to 405	
True negatives	3 studies 858 patients	diagnostic accuracy study	not serious ^a	not serious	not serious ^b	serious ^c	none	616 to 760	384 to 475	⊕⊕⊕○ MODERATE
False positives								40 to 184	25 to 116	

Explanations

a. Following the Quadas2 assessment of risk of bias, despite the interpretation of the index test could have introduced some bias in 2/3 studies, the study design, reference standard and flow and timing were similar in all the included studies.

b. Pooled data could not be obtained and is represented as a range. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable.

c. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.

Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Heffler E, Guida G, Marsico P, Bergia R, Bommarito L, Ferrero N, Nebiolo F, De Stefani A, Usai A, Bucca C, Rolla G. Exhaled nitric oxide as a diagnostic test for asthma in rhinitic patients with asthmatic symptoms. *Respir Med*. 2006 Nov;100(11):1981-7. doi: 10.1016/j.rmed.2006.02.019. Epub 2006 Apr 3. PMID: 16584881.
2. Malinovschi A, Backer V, Harving H, Porsbjerg C. The value of exhaled nitric oxide to identify asthma in smoking patients with asthma-like symptoms. *Respir Med*. 2012 Jun;106(6):794-801. doi: 10.1016/j.rmed.2012.02.009. Epub 2012 Mar 8. PMID: 22405608.

3. Nekoe H, Graulich E, Schleich F, et al. Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 2020; 6: 00169-2020

Table 9: GRADE table: Can measuring blood eosinophil count help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.15 to 0.59	Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care
Specificity	0.39 to 1.00			

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	5 studies ^{1,2,3,4,5} 1286 patients	diagnostic accuracy study	serious ^a	not serious	serious ^b	not serious ^c	none	30 to 118	75 to 295	⊕⊕○○ LOW
False negatives								82 to 170	205 to 425	
True negatives	5 studies ^{1,2,3,4,5} 1286 patients	diagnostic accuracy study	serious ^a	not serious	serious ^b	not serious ^c	none	312 to 800	195 to 500	⊕⊕○○ LOW
False positives								0 to 488	0 to 305	

Explanations

a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.

b. Pooled data could not be obtained and is represented as a range. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable. Probably due to a threshold effect – accuracy values represent best balance between sensitivity and specificity typically at a cut-off between 4 and 6%.

c. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.

Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Popović-Grle S., Mehulić M., Pavčić F., Babić I., Beg-Zec Z. (2002) Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. Coll Antropol 26 Suppl:119–27
2. Yurdakul AS., Dursun B., Canbakan S., Çakaloğlu A., Çapan N. (2005) The Assessment of Validity of Different Asthma Diagnostic Tools in Adults. J Asthma 42:(10):843–846
- Hunter CJ., Brightling CE., Woltmann G., Wardlaw AJ., Pavord ID. (2002) A Comparison of the Validity of Different Diagnostic Tests in Adults With Asthma. Chest 121:(4):1051–1057

3. Tilemann L., Gindner L., Meyer F., Szecsenyi J., Schneider A. (2011) Differences in local and systemic inflammatory markers in patients with obstructive airways disease. *Prim Care Respir J* 20:(4):407–413
4. Nekoe H., Graulich E., Schleich F., Guissard F., Paulus V., Henket M., et al. (2020) Are type-2 biomarkers of any help in asthma diagnosis? *ERJ Open Res* 6:(2):00169–02020

Table 10: GRADE table: Can measuring total serum IgE be used to diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.33 to 0.51	Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care
Specificity	0.72 to 0.85			

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	4 studies ^{1,2,3,4} 1176 patients	diagnostic accuracy study	serious ^a	not serious	serious ^b	not serious ^c	none	66 to 102	164 to 255	⊕⊕○○ LOW
False negatives								98 to 134	245 to 336	
True negatives	4 studies ^{1,2,3,4} 1176 patients	diagnostic accuracy study	serious ^a	not serious	not serious	not serious ^c	none	576 to 680	360 to 425	⊕⊕⊕○ MODERATE
False positives								120 to 224	75 to 140	

Explanations

a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.

b. Pooled data could not be obtained and is represented as a range. Sensitivity, specificity and absolute effects per 1000 patients tested are highly variable. Probably due to a threshold effect – accuracy values represent best balance between sensitivity and specificity typically at a cut-off between 90-132 U/mL

c. Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.

Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Popović-Grle S., Mehulić M., Pavčić F., Babić I., Beg-Zec Z. (2002) Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. Coll Antropol 26 Suppl:119–27
2. Yurdakul AS., Dursun B., Canbakan S., Çakaloğlu A., Çapan N. (2005) The Assessment of Validity of Different Asthma Diagnostic Tools in Adults. J Asthma 42:(10):843–846

3. Tilemann L., Gindner L., Meyer F., Szecsenyi J., Schneider A. (2011) Differences in local and systemic inflammatory markers in patients with obstructive airways disease. Prim Care Respir J 20:(4):407–413
4. Nekoe H., Graulich E., Schleich F., Guissard F., Paulus V., Henket M., et al. (2020) Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 6:(2):00169–02020

Table 11: GRADE table: Can combining FeNO, blood eosinophils and IgE help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.46 (95% CI: 0.37 to 0.52)	Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care
Specificity	0.74 (95% CI: 0.64 to 0.69)			

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	1 studies ¹ 702 patients	diagnostic accuracy study	serious ^a	not serious	not serious	not serious	none	92 (74 to 104)	230 (185 to 260)	⊕⊕⊕○ MODERATE
False negatives								108 (96 to 126)	270 (240 to 315)	
True negatives	6 studies ^{1,2,3,4,5,6} 1638 patients	diagnostic accuracy study	serious ^a	not serious	not serious	not serious	none	592 (512 to 552)	370 (320 to 345)	⊕⊕⊕○ MODERATE
False positives								208 (248 to 288)	130 (155 to 180)	

Explanations

- a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
 Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

1. Nekoe H., Graulich E., Schleich F., Guissard F., Paulus V., Henket M., et al. (2020) Are type-2 biomarkers of any help in asthma diagnosis? ERJ Open Res 6:(2):00169–02020

Table 12: GRADE table: Can Bronchial Challenge Testing help diagnose asthma in patients with episodic/chronic symptoms suggestive of asthma?

Sensitivity	0.63 to 1.00				
Specificity	0.07 to 0.95				

Prevalences	20%	50%	
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Outcome	N _e of studies (N _e of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 100 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives (patients with Asthma)	3 studies 891 patients	cohort & case-control type studies	serious ^{1,2,3,a,b}	not serious ^c	not serious ^d	not serious	none	13 to 20	32 to 50	⊕⊕⊕○ Moderate
False negatives (patients incorrectly classified as not having Asthma)								0 to 7	0 to 18	
True negatives (patients without Asthma)	3 studies 891 patients	cohort & case-control type studies	serious ^{a,b}	not serious ^c	serious ^{d,e}	not serious ^e	none	6 to 76	4 to 48	⊕⊕○○ Low
False positives (patients incorrectly classified as having Asthma)								4 to 74	2 to 46	

Explanations

- a. 2 prospective case control studies, 1 retrospective database study
b. Louis et al retrospective - a total of 1610 patients were screened to select 194 who had both BDR and Methacholine
c. Ulrik et al study conducted in general population and not secondary care
d. 1 study used 8mg/ml and 16mg/ml methacholine cut-off, 2 studies used 16mg/ml cut-off for methacholine/histamine challenge
e. Specificity highly variable from 0.07-95

References

1. Porpodis, . Comparison of diagnostic validity of mannitol and methacholine challenges and relationship to clinical status and airway inflammation in steroid naïve asthmatic patients.. Journal of Asthma; 2017.
2. Louis, . Bronchodilation Test with Inhaled Salbutamol Versus Bronchial Methacholine Challenge to Make an Asthma Diagnosis: Do They Provide the Same Information?. JACI in Practice; 2019.
3. Ulrik, . Recognition of Asthma in Adolescents and Young Adults: Which Objective Measure is Best?. Journal of Asthma; 2005.

Table 13: GRADE table: Can sGAW measurement help diagnose asthma in adults with episodic/chronic suggestive symptoms?

Sensitivity	0.50 to 0.51	Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care
Specificity	0.71 to 0.74			

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	2 studies ^{1,2}	diagnostic accuracy study	serious ^a	serious ^b	not serious	not serious	none	100 to 102	250 to 255	⊕⊕○ ○ LOW
False negatives	921 patients							98 to 100	245 to 250	
True negatives	2 studies ^{1,2}	diagnostic accuracy study	serious ^a	serious ^b	not serious	not serious	none	568 to 592	355 to 370	⊕⊕○ ○ LOW
False positives	921 patients							208 to 232	130 to 145	

Explanations

a. Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.

b. Topalovic 2015 included patients with obstructive disease including COPD and bronchiectasis. The diagnosis of asthma was unclear and the authors focused on non-obstructive asthma

Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded





References

1. Bougard N, Nekoe H, Schleich F, Guissard F, Paulus V, Donneau AF, Louis R. Assessment of diagnostic accuracy of lung function indices and FeNO for a positive methacholine challenge. *Biochem Pharmacol.* 2020 Sep;179:113981.

2. Topalovic M, Derom E, Osadnik CR, Troosters T, Decramer M, Janssens W; Belgian Pulmonary Function Study Investigators. Airways resistance and specific conductance for the diagnosis of obstructive airways diseases. *Respir Res.* 2015 Jul 22;16(1):88.

Table 14: GRADE table: Can RV/TLC measurement help diagnose asthma in adults with episodic/chronic suggestive symptoms ?

Sensitivity	0.28 to 0.71	Baseline Prevalence	20% Typically seen in primary care	50% Typically seen in specialist care
Specificity	0.68 to 0.88			

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1.000 patients tested		Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 20%	pre-test probability of 50%	
True positives	2 studies ^{1,2}	diagnostic accuracy study	serious ^a	not serious	serious ^b	not serious ^c	none	56 to 142	140 to 355	  LOW
False negatives	770 patients							58 to 144	145 to 360	
True negatives	2 studies ^{1,2}	diagnostic accuracy study	serious ^a	not serious	serious ^b	not serious ^c	none	544 to 704	340 to 440	  LOW
False positives	770 patients							96 to 256	60 to 160	

Explanations

- Limitations in the selection of patients with suspected disease. Spectrum bias potentially leads to inflated estimation of the diagnostic performance.
 - Pooled data could not be obtained and is represented as a range. Probably due to a threshold effect – accuracy values represent best balance between sensitivity and specificity at a cut-off around RV/TLC ratio of 102 to >125%. Absolute effects per 1000 patients tested are highly variable.
 - Imprecision of data is mainly due to heterogeneity of data and representation of ranges instead of pooled data.
- Serious: The more serious the limitation are, the more likely is that the quality of evidence will be downgraded

References

- Bougard N, Nekoe H, Schleich F, Guissard F, Paulus V, Donneau AF, Louis R. Assessment of diagnostic accuracy of lung function indices and FeNO for a positive methacholine challenge. *Biochem Pharmacol*. 2020 Sep;179:113981.
- Stanbrook MB, Chapman KR, Kesten S. Gas trapping as a predictor of positive methacholine challenge in patients with normal spirometry results. *Chest*. 1995 Apr;107(4):992-5.