Online supplementary Table S3b

QUESTION

Can airway obstruction measured by spirometry help diagnose asthma in adults with episodic/chronic suggestive symptoms?	
POPULATION:	Population of adults (>18 yrs old) with diagnostic uncertainty of asthma
INDEX TEST:	FEV_1/FVC
GOLD STANDARD	1. Bronchodilation > 12% AND > 200 ml improvement 2. Airway hyperresponsiveness: PC20 < 16 mg/ml (or 8 mg/ml) of Methacholine (or Histamine) or PD mannitol < 625 mg or fall in FEV1 > 10% after exercise

ASSESSMENT

Test accuracy
How accurate is the test?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate X Varies ○ Don't know	Low sensitivity ranging from 52.6% (Stanbrook et al) to 82% (Bougard et al) to 61% (49.5-72.5) (Hunter et al) Highly variable specificity ranging from 27.9% (Stanbrook et al) to 67% for Bougard et al (with 60% (38.5-81.5) for Hunter et al). Accuracy of 61% in Hunter's paper. In Nekoee's paper a threshold of 76% was found to provide the best compromise between sensitivity (51%) and specificity (76%). The AUC was 0.67	Almost half of the patients already receiving maintenance ICS in Hunter and Bougard papers. The threshold used by Stanbrook was FEV_1/FVC <90% predicted. FEV_1/FVC threshold for Hunter: 76.6% Paper of Bougard et al: AUC 0.63 with a threshold of 77% in the derivation cohort, and AUC of 0.68 with a threshold of 79% in the validation cohort. Paper of Nekoee et al: AUC 0.67, threshold 76% The study of Hunter et al. seems unclear in regards the methods of inclusion (and treatment issues) of the population. We assessed inconsistency as a narrative way and we were able to report **inconsistency** in regards of specificity values with 60% (range 38.5 – 81.5) for

FEV_1/FVC >76.6% and 27.9% for FEV_1/FVC <90% predicted.

A better consistency is observed for sensitivity 61% (range 49.5 – 72.5) for FEV_1/FVC >76.6% and 52.6% for FEV_1/FVC <90% predicted. We did not have access to the confidence intervals of the study of Stanbrook et al, but it is likely that there is minimal or no overlap for specificity's confidence interval.

Higher specificity in the paper of Bougard but FEV_1/FVC was not an independent predictor in the multivariate analysis in that study.

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small X Moderate o Large o Varies o Don't know	Lack of accuracy but first step in the diagnostic path Variable PPV, low NPV.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large ○ Moderate ○ Small X Trivial ○ Varies ○ Don't know	None	

Certainty of the evidence of test accuracy
What is the overall certainty of the evidence of test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low **X** Low ○ Moderate ○ High ○ No included studies	Low Quality of Evidence	

Certainty of the evidence of management's effects
What is the overall certainty of the evidence of effects of the management that is guided by the test results?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low ○ Moderate ○ High ○ No included studies	First step in the diagnostic path Low quality of evidence – few data in the literature – poor accuracy	

Certainty of the evidence of test result/management
How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low X Low ○ Moderate ○ High ○ No included studies	In case of obstruction and significant reversibility, the diagnosis can be established, and treatment can be started Low quality of evidence	The TF panel made a judgement of low certainty about the likelihood that the appropriate asthma management will follow on from test results.

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention **X** Favors the intervention o Varies o Don't know	FEV_1/FVC is an index measured by spirometry, a necessary step in the path towards asthma diagnosis, in patients with symptoms suggestive of asthma but should not be used alone to make asthma diagnosis.	

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs **X** Negligible costs and savings o Moderate savings o Large savings o Varies o Don't know	FEV_1/FVC measurement by spirometry is feasible in primary care but requires a competent nurse, healthcare professional to perform accuratespirometry.	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced o Probably no impact **X** Probably increased o Increased o Varies	None Identified	

○ Don't know		

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	FEV$_1$/FVC measurement is easy and quick to perform. Not accessible at home. Completion at GP office or at the clinic.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes X Yes ○ Varies ○ Don't know	FEV$_1$/FVC requires a spirometer, feasible in primary care, quick. More feasible than Bronchial Challenge in primary care.	

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Recommendation

The TF recommends performing spirometry as part of the diagnostic work-up of adults aged ≥18 years with suspected asthma (strong recommendation for the intervention, low quality of evidence). An FEV_1/FVC <LLN or <75%, higher than the commonly utilized 70% threshold, should be considered supportive of an asthma diagnosis and should prompt further testing (see Algorithm).

A normal spirometry does not exclude asthma.

Justification

Physiological airflow obstruction and fluctuation of airway caliber, that is usually reversible, are recognized as hallmarks of asthma. Though the quality of evidence was low, the TF recommends spirometry as the first test to be conducted in the diagnostic work-up. Over-diagnosis, which occurs in approximately 30% of patients with asthma diagnosed in primary care, occurs in part because spirometry in not performed and has a substantial risk of harm due to inappropriate treatment side-effects, costs, and lack of proper diagnosis[4]. Therefore, a strong recommendation can be made despite low quality of evidence. Spirometry is readily available both in primary and secondary care, even though it might not be used sufficiently in primary care. Our research found the ratio of FEV_1/FVC cut-off providing the best combination of sensitivity and specificity is close to 75%, a threshold well above the 70% threshold generally recognized as a marker of airway obstruction. However, sensitivity at a cut-off of 75% is close to 50% and much too low to rule out asthma. Likewise, at this cut-off, specificity remains below 80% making spirometry alone insufficient to rule in asthma with confidence.