Accepted author's manuscript. Published in final edited form as: European Respiratory Journal 2020; 55(5): 2000636. Publisher DOI: 10.1183/13993003.00636-2020

A clinically significant bronchodilator response in children. How should it be measured? Reply

From the authors:

We thank F. Guezguez and H. Ben Saad for raising important questions on recommendations for assessing a bronchodilator response (BDR) in children. The authors summarise how recommended outcome measures and cut-offs for BDR in children vary between guidelines, and raise questions about our study [1].

To clarify: our study did not focus on bronchodilator reversibility testing in children or compare different outcome measures. Rather, we assessed the contribution of a detailed history and a variety of tests for diagnosing asthma in children aged 6–16 years referred to pulmonary outpatient clinics. We compared the diagnostic performance (sensitivity, specificity) of different commonly performed tests: skin-prick tests, measurement of exhaled nitric oxide fraction (F_{ENO}), spirometry, bronchodilator reversibility and bronchial provocation tests (BPT) by exercise, methacholine and mannitol against an asthma diagnosis from the paediatric pulmonologist. Thus, we used tests, outcomes and cut-offs commonly recommended and used in clinical practice. In addition, for examinations that provided a continuous (rather than a binary) output, such as forced expiratory volume in 1 s (FEV_1), BDR or F_{ENO}, we also assessed which cut-off distinguished best between those with and without asthma. We found that the combined sensitivity and specificity was highest for reported symptoms (frequent wheeze, night-time awakening due to wheeze, and wheeze triggered by pollen or pets). Among the tests, the area under the curve was highest for F_{ENO} and BPT by methacholine or exercise, and lower for spirometry, bronchodilator reversibility and skin-prick tests.

F. Guezguez and H. Ben Saad ask how we had assessed FEV_1 increase: as percentage of the initial value, as percentage of the predicted value, or as absolute increase. We calculated BDR as percentage increase of the initial FEV_1 (in mL) using the following formula: (FEV_1 post-bronchodilator − FEV_1 pre-bronchodilator)/ FEV_1 pre-bronchodilator. This is the most widely used method for calculating reversibility and recommended by most guidelines [2–4]. FEV_1 pre- and post-bronchodilator was measured in triplicate and American Thoracic Society/European Respiratory Society guidelines reproducibility criteria were applied [5]. Second, they indicated that BDR can also be calculated for forced vital capacity and peak expiratory flow. Although this is true, FEV_1 is the most widely recommended outcome, as it is less subject to cooperation and has higher reproducibility [2, 3].

Third, they wondered what evidence we used to base our cut-off levels on. The 12% cut-off is recommended in all recent guidelines, but derives from studies in adults, expert opinion, or studies that compared severe asthmatics with healthy children. Recent population-based studies have questioned this cut-off for the paediatric population [6, 7]. In our study of children seen for evaluation of possible asthma in paediatric outpatient clinics, a cut-off of 10% had the highest combined sensitivity and specificity. However, we want to stress that cut-off levels for diagnostic tests that produce an outcome on a continuous scale are artificial and an oversimplification. We lose information if we force a continuous measure into a binary one. There is a trade-off between sensitivity and specificity, and depending on the clinical question, higher or lower cut-offs can be preferable. In general, the further away a result is from the mean of the frequency distribution in healthy children, the more likely it is that it is pathological. There is no such thing as a "true" cut-off that distinguishes unequivocally between healthy and diseased. For clinical application, a cut-off is often helpful, but factors such as pre-test probability, place of the test in the diagnostic algorithm, and costs must also be considered.

In conclusion, we fully agree with F. Guezguez and H. Ben Saad that more research is needed to evaluate the usefulness of diagnostic tests for asthma in children. We also agree that cut-offs should be critically questioned and defined based on evidence from the patient population of interest (*i.e.* children suspected with asthma) and not based on studies in adults or on expert opinion.

Carmen C.M. de Jong[1], Eva S.L. Pedersen[1], R. Mozun[1], Myrofora Goutaki[1,2], Daniel Trachsel[3], Juerg Barben[4] and Claudia E. Kuehni [1,2]

[1]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland.[3]2Paediatric Respiratory Medicine, Children's University Hospital of Bern, University of Bern, Bern, Switzerland. Paediatric Respiratory Medicine,Children's University Hospital of Basel, Basel, Switzerland. [4]Paediatric Respiratory Medicine, Children's Hospital of Eastern Switzerland, St Gallen, Switzerland.

Correspondence: Claudia E. Kuehni, University of Bern, Institute of Social and Preventive Medicine, Mittelstrasse 43, CH-3012 Bern, Switzerland. E-mail: claudia.kuehni@ispm.unibe.ch

Conflict of interest: None declared.

References:

1 de Jong CCM, Pedersen ESL, Mozun R, *et al.* Diagnosis of asthma in children: the contribution of a detailed history and test results. *Eur Respir J* 2019; 54: 1901326.

2 NICE. Guideline Asthma Diagnosis and Monitoring. www.nice.org.uk/guidance/ng80/resources/asthma-diagnosis- monitoring-and-chronic-asthma-management-pdf-1837687975621 Date last updated: November 2017, December 2019.

3 National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol* 2007; 120: Suppl. 5, S94–S138.

4 Pellegrino R, Decramer M, van Schayck CP, *et al.* Quality control of spirometry: a lesson from the BRONCUS trial. *Eur Respir J* 2005; 26: 1104–1109.

5 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.

6 Murray C, Foden P, Lowe L, *et al.* Diagnosis of asthma in symptomatic children based on measures of lung function: an analysis of data from a population-based birth cohort study. *Lancet Child Adolesc Health* 2017; 1: 114–123.

7 Tse SM, Gold DR, Sordillo JE, *et al.* Diagnostic accuracy of the bronchodilator response in children. *J Allergy Clin Immunol* 2013; 132: 554–559.