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Letter to the editor - Comment on following paper in Pediatrics International:

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Addressing selection bias in diagnostic accuracy studies

Running title (max 40 characters):

Selection bias in diagnostic accuracy

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Main text

544 of 500 words, max 5 refs

Exercise-challenge testing is the reference standard method to diagnose exercise-induced bronchoconstriction (EIB). The method requires advanced technical equipment, is time consuming and involves active cooperation. For these reasons, researchers try to use other tests to diagnose EIB. Fractional exhaled nitric oxide (FeNO) has been proposed as an alternative method of diagnosing EIB, but it is not clear how accurate this test is.

We read with great interest the study by Kim et al.(1), which investigated the diagnostic accuracy of FeNO in predicting EIB in children with asthma. The study was performed using clinical routine data from asthmatic children aged 6-16 years. 60 out of 242 (25%) performed both FeNO and exercise-challenge tests. They found that FeNO was positively associated with a fall in FEV1 after exercise and FeNO had the ability to detect a fall in FEV1 of at least 10% with an area under the curve (AUC) of 0.77. The optimal FeNO cut-off was 20 ppb with a sensitivity of 82% and specificity of 61%. The authors conclude that FeNO may be a clinically useful diagnostic tool for diagnosing EIB in children.

The study was based on retrospectively collected routine care data where only a fraction of children seen in the outpatient clinics was included: namely, those that performed both FeNO and exercise-challenge test. Usually clinical testing such as FeNO and exercise-challenge testing are performed by indication for example due to asthma severity or symptom patterns. Therefore, the study population (children who performed the tests) was probably not equal to the target population (children with asthma). This kind of selection bias, also called referral bias, has been associated with falsely raised sensitivity of the test in question (2-4). We believe that this selection bias is important to account for when judging whether FeNO can be used to diagnose EIB.

Evidence from other studies show that FeNO is linearly associated with a fall in FEV1 after exercise, but the strength of the association and whether it is possible to set a cut-off for diagnosing EIB in children is not clear. A study including an unselected sample of 121 children aged 6-15 years with mild to moderate asthma found that the optimal FeNO cut-off point depended on whether the children were currently on inhaled corticosteroids (cut-off=12 ppb) or not (cut-off=21 ppb)(5). Another study in an unselected sample of 224 children at high risk of asthma found FeNO to be

associated with a fall in FEV1 but no cut-off point could be found to predict EIB (6). This evidence shows that characteristics of the study sample influences the ability of FeNO to accurately diagnose EIB.

We commend Kim et al. for their valuable contribution to the evidence on the predictive properties of FeNO to predict EIB in children. It seems that FeNO is related to EIB and may be used for diagnosing EIB, but we need more studies in unselected asthmatic children to judge generalizability of the existing findings and to identify the optimal FeNO cut-off level for predicting EIB in children. We believe it is important to consider the effect of bias in diagnostic accuracy studies. Tools such as the QUADAS-2(7) could be used as a checklist before conducting a study to ascertain the risk of bias and thereby increase the quality of future studies.

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Disclosure

The authors have no financial disclosures to declare.

Author contribution

The manuscript was written and revised by both authors.

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