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Relation of changes in PEF and FEV1 in exercise challenge in children

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Abstract

Decrease in forced expiratory volume in one second (FEV_1) of 10% or 15% in exercise challenge test is considered diagnostic for asthma, but a decrease of 15% in peak expiratory flow (PEF) is recommended as an alternative. Our aim was to assess the accuracy of different PEF cut-off points in comparison to FEV_1.

We retrospectively studied 326 free running exercise challenge tests with spirometry in children 6–16 years old. FEV_1 and PEF were measured before and 2, 5, 10 and 15 min after exercise. Receiver operating characteristics (ROC) analysis, sensitivity, specificity, positive and negative predictive values (PPV and NPV) and $\varkappa$-coefficient were used to analyse how decrease in PEF predicts decrease of 10% or 15% in FEV_1.

In the ROC analysis, areas under the curve were 0.851 ($p < 0.001$) and 0.921 ($p < 0.001$) for PEF decrease to predict a 10% and 15% decrease in FEV_1, respectively. The agreement between changes in PEF and FEV_1 varied from slight to substantial ($\varkappa$ values of 0.199–0.680) depending on the cut-points. Lower cut-off for decrease in PEF had higher sensitivity and NPV, while higher cut-off values had better specificity and PPV. Decrease of 20% and 25% in PEF seemed to be the best cut-offs for detecting 10% and 15% decrease in FEV_1, respectively. Still, a fifth of the positive findings based on PEF were false.

Change in PEF is not a precise predictor of change in FEV_1 in exercise test. The currently recommended cut-point of 15% decrease in PEF seems to be too low and leads to high false positive rate.

KEYWORDS
asthma, bronchoconstriction, spirometry

1 | INTRODUCTION

Asthma is the most common chronic disease in children and worldwide it ranks among the top 20 conditions for disability-adjusted life years (Vos et al., 2012). Asthma is characterized by a multitude of symptoms including wheeze, chest tightness, breathlessness and cough together with variable expiratory airflow limitation. The severity of the symptoms and airflow obstruction vary over time, and they are often triggered by physical exercise (Global Initiative for Asthma, 2022). In children and adolescents, detecting exercise induced bronchoconstriction (EIB) with spirometry after an exercise challenge test is one of the many tests used in asthma diagnostics.

Home peak expiratory flow (PEF) monitoring is often used as an alternative tool to diagnose asthma and PEF-monitoring has a long history in clinical trials on asthma. Currently, spirometry and change in forced expiratory volume in 1 second (FEV_1) is considered as the gold standard over PEF to detect variable airways obstruction. Some data already indicates PEF not to be the optimal in specific situations like in assessing bronchodilator response (Thiadens et al., 1999). PEF also seems to have poor reliability as a single measure in assessing lung function (Llewellin et al., 2002), but it could prove more useful in detecting variation over time when recorded multiple times daily, in the context of home peak flow monitoring (Ratageri, 2001) or exercise challenge test. Although FEV_1 is recommended over PEF, the relation between change in PEF and change in FEV_1 concerning EIB is not fully clear. In fact, different cut-points to diagnose EIB are proposed in current guidelines including decrease of 10%, 12% or 15% in FEV1 (Global Initiative for Asthma, 2022; Scottish Intercollegiate Guidelines Network, British Thoracic Society, 2019) or a decrease of 15% in PEF (Global Initiative for Asthma, 2022). Peak flow metres have the advantage of being robust and cheap, and this may be an important factor favoring the use of PEF in asthma diagnostics for example, in countries where spirometry is not widely available in primary care.

Our aim was to assess the relation between change in PEF and change in FEV_1 during exercise challenge and to evaluate the accuracy of different PEF cut off points to diagnose EIB in comparison to FEV_1. Our hypothesis was that PEF would not be very accurate in representing changes in lung function assessed by FEV1. The currently recommended cut off value for diagnosing asthma with PEF in exercise challenge test is 15% (Global Initiative for Asthma, 2022). Analysing the sensitivity, specificity, PPV and negative predictive values (NPV) could be of great clinical significance if the currently used cut off value is suboptimal.

2 | METHODS

2.1 | Study design

We retrospectively collected all free running exercise challenge tests with spirometry conducted at Tampere university hospital between 1 January 2012 and 31 December 2017. To find the right sample size our main analysis was 'what are the sensitivity and specificity of PEF decrease ≥15% to find EIB defined as FEV1 decrease ≥15%'. We estimated that sensitivity and specificity would be 0.85 and 0.65, respectively. We knew from our previous project that about 20% of the exercise tests are positive (i.e., FEV1 decreases at least 15%). Using precision margin of 0.1 and α error of 5%, the required sample size is 245 tests. We found from our data sources 326 tests during the study period fulfilling the needed sample size. Medical history, including any allergies, was gathered from patient records. The study was approved by the local ethics committee (R15022) and the study is reported according to STARD guideline (STARD, 2015).

2.2 | Spirometry measurements and exercise challenge

Spirometry was performed according to international recommendations (Graham et al., 2019). The running was conducted outside, next to Tampere University Hospital. Mean values for air humidity, temperature and relative humidity of outdoor air during the tests were 5 g/m^3, 4°C and 77%, respectively. Spirometry was performed inside a laboratory in the hospital. Experienced nurses monitored heart rate and the intensity of exercise. The exercise level was considered sufficient if heart rate (measured with FT4; Polar Ltd) was >85% of calculated maximal value (205−age/2) and the duration of exercise was over 6 min. We collected FEV_1, PEF and FVC from all spirometries. Spirometry was measured first before the exercise challenge and 2, 5, 10 and 15 min after the exercise challenge. Then children under and over 10 years of age were given 300 and 400 µg of salbutamol, respectively. Spirometry was repeated 15 min after salbutamol inhalation. The reliability of the data was ensured by going through every measurement individually. Two trained physicians from the Department of Clinical Physiology and Nuclear Medicine, who were blinded to the properties of outdoor air, visually assessed technical reliability and the patients' blowing technique and evaluated reproducibility of the parameters according to international guidelines (Graham et al., 2019). We excluded data that was clearly faulty and a result of human or technical error. Outliers were not excluded if the surprising measurement did not stem from an error. Missing data was excluded.

2.3 | Statistics

The software IBM SPSS Statistics for Windows, version 27 (IBM Corp.), was used for the data analysis. Additionally, some calculations were performed using Microsoft Excel for Microsoft 365 MSO (version 2110 Build 16.0.14527.20234). Receiver operating characteristics (ROC), sensitivity [(true positive/(true positive + false negative)) × 100], specificity [(true negative/(false positive + true negative)) × 100], positive predictive values (PPV) [(true positive/(true positive + false positive)) × 100], NPV [(true negative/(false negative + true negative)) × 100] and $\varkappa$ coefficient were used to compare decrease in PEF and decrease in FEV_1 as outcome measures. As the result of exercise challenge test in clinical practice (EIB or not) is independent of at which time point a certain decrease in PEF or FEV_1 is reached we conducted the analyses independent of time point; did a certain decrease in PEF (10%, 15%, 20%, 25% and 30%) *at any time point after the challenge* predict presence of decrease in FEV_1 (10% or 15%) *at any time point after the challenge*. To check if the relation between change in PEF and change in FEV1 is similar in different age groups and between sexes, we conducted the analyses separately in younger (age under 11 years) and older (age at least 11 years) children and separately in boys and girls.

TABLE 1 Patient characteristics in 326 subjects with technically reliable spirometry results in exercise challenge test.

Characteristics	Value
Age (year)	11.0 (2.6)
Gender	
Female	140 (42.9)
Male	186 (57.1)
Height (cm)	151.5 (89.8)
Weight (kg)	43.1 (15.5)
Clinical diagnosis of asthma	183 (56.1)
Allergic sensitization to pollen or animal allergens	
Not tested or data not available	140 (42.9)
Positive	126 (38.7)
Negative	60 (18.4)
FVC (% predicted)	100.4 (12.5)
FVC *z*-score	−0.22 (4.0)
FEV_1 (% predicted)	94.2 (12.3)
FEV_1 *z*-score	−0.82 (3.7)
FEV_1/FVC (% predicted)	93.7 (8.3)
FEV_1/FVC *z*-score	−0.99 (1.5)
Max heart rate during exercise (bpm)	195.2 (9.0)
Duration of exercise (min)	7.8 (0.7)
Proportions of children fulfilling different criteria for EIB	
≥10% decrease in FEV_1	140 (42.9)
≥15% decrease in FEV_1	76 (23.3)
≥10% decrease in PEF	216 (66.3)
≥15% decrease in PEF	161 (49.4)
≥20% decrease in PEF	102 (31.3)
≥25% decrease in PEF	66 (20.2)
≥30% decrease in PEF	48 (14.7)

Note: The results are presented as mean (SD) for continuous variables or as *n* (%) for categorical variables.

Abbreviations: EIB, exercise induced bronchoconstriction; FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow.

3 | RESULTS

Out of the 366 children who had an exercise challenge test conducted during the study period, 326 produced technically reliable spirometry data and were included in the primary analyses. On average, the children were 11 years old (Table 1). There were more males than females and they had on average normal lung function before exercise. Almost half of the children had a decrease in FEV_1 of at least 10%, but only less than a quarter had a decrease in FEV_1 of at least 15%. Depending on the chosen cut-off value, a significant decrease in PEF was measured in 14.7%–66.3% of the children.

Figure 1 shows the relation between percentage change of FEV_1 and percentage change of PEF. There was a strong positive linear correlation between changes in FEV_1 and PEF. The relative change in PEF is on average slightly less than the relative change in FEV_1, and the slope is 0.94 instead of 1.0. The difference between the rates of decline was statistically significant ($p < 0.01$).

Figure 2 shows the percentage of children that experienced a certain PEF decrease according to presence or absence of EIB based on either a 10% or a 15% decrease in FEV_1. In both cases, decreases over each cut-off level of PEF were more prevalent in those with EIB. However, decreases in PEF over each cut-off level were observed also in those children who did not experience EIB based on change in FEV_1. On the other hand, not all children with EIB had any significant reductions in PEF.

3.1 | Changes in PEF and FEV_1 and interpretation of exercise challenge test

In clinical practice, exercise challenge test is considered positive if a certain decrease in lung function is achieved at any time point after the challenge. Figure 3a,b presents ROC-curves of PEF change compared against EIB defined as a 10% or a 15% decrease in FEV_1, respectively. PEF change seemed to represent EIB slightly better when defined with a 15% decrease in FEV_1 compared to a cut-off value of 10% decrease in FEV_1.

Table 2 presents the sensitivity, specificity, PPV, NPV and Cohen's κ coefficient for different cut-points of PEF decrease in predicting a 10% or a 15% decrease in FEV_1 after the exercise challenge. A lower cut-off value for decrease in PEF was associated with higher sensitivity and NPV in predicting EIB, while a higher cut-off value for decrease in PEF was associated with better specificity and PPV in predicting EIB. Twenty percent seemed to be the best cut-off value in decrease of PEF for detecting a 10% decrease in FEV_1, and 25% decrease in PEF seemed to be the best to predict a 15% decrease in FEV_1. Still, in both cases, about a fifth of the tests interpreted positive based on PEF change were false positives.

To check if the relation between change in PEF and change in FEV_1 is similar in different age groups and between sexes, we conducted the analyses separately in younger (age under 11 years) and older (age at least 11 years) children and separately in boys and girls. We found no significant difference between these groups in the relation between PEF change and FEV_1 change.

3.2 | Sensitivity analysis

In our primary analysis, we excluded subjects with unreliable spirometry measurements. Since the quality of measurements cannot be determined with a peak flow metre as with a spirometer, we conducted our calculations again by including also those

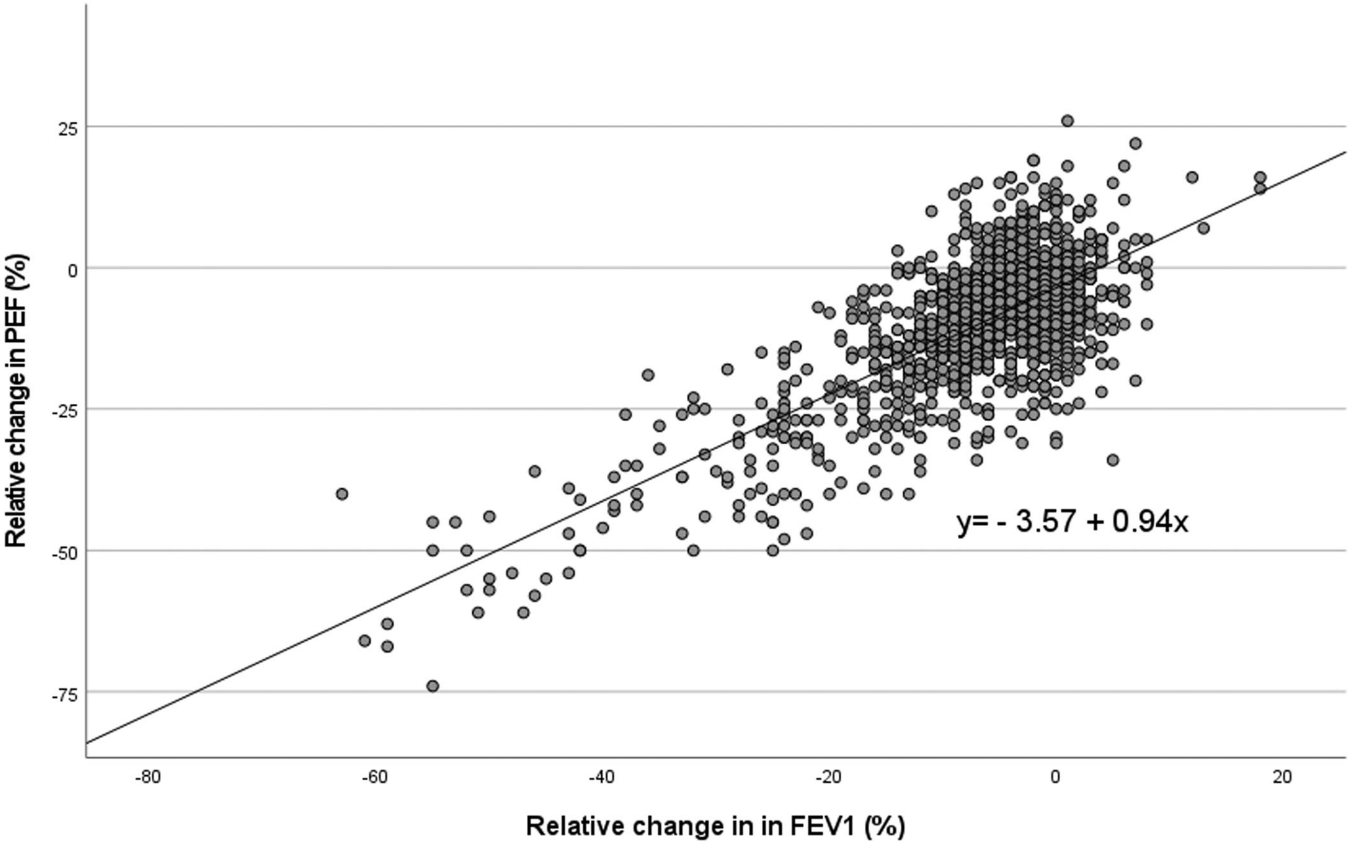

FIGURE 1 Percentage of change in PEF in relation to percentage of change in FEV_1. FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow.

measurements that were considered unreliable based on the quality criteria of spirometry. However, including unreliable measurements did not change our results in a significant way (data not presented). The difference in any given percentages were a few points at most and none of the conclusions were affected.

4 | DISCUSSION

In this retrospective study, we found that compared to FEV_1, PEF is a suboptimal metric for diagnosing EIN. The currently recommended cut-off value of 15% decrease in PEF is not optimal because over half of the positive tests are false positives if compared to a decrease of 15% in FEV_1. Even with the cut-off value of decrease in PEF being 25%, which we determined to be the best, over a fifth of the positives are false. Using a cut-off value that high also leads to a diminished sensitivity.

To our best knowledge, there are no previous studies on the sensitivity, specificity, PPV, NPV and $\varkappa$-value of using PEF instead of FEV_1 in detecting EIB in children. Although AUC in ROC analysis was fairly large, the clinical interpretation of exercise test (positive or negative) differed significantly if the judgement was based on changes in PEF or FEV_1. Even with the best cut-off values in PEF decrease about a fifth of the positive tests were consider false positives. Gianni et al. have studied these variables in a similar setting in adults and their findings are quite different from ours. When EIB was defined as a 15% decrease in FEV_1, the sensitivity and specificity of a 15% decrease in PEF were 18% and 95%, respectively, to detect EIB (Giannini et al., 1997) (90.8% and 62.4% in our study). It is unclear where these differences could stem from but the population being different could be one possibility. Another explaining factor could be that their study had a relatively small population size of 50 patients for exercise challenge and of those patients 50% experienced EIB whereas in our study EIB was only found among 23.3% of the population.

We found two studies assessing the correlation between changes in FEV_1 and PEF in children with EIB, but these papers did not calculate the same variables as we did (Akar et al., 2015; Gharagozlou et al., 2007). Both studies found changes in FEV_1 and PEF to have a ‘strong’ or a ‘positive’ correlation, but a correlation cannot be used to assess their value in clinical decision making based on fixed cut-offs. Gharagozlou's study found that in asthmatic patients, there can be significant changes in FEV_1 while PEF changes remain insignificant. Assessments based on changes in PEF can sometimes lead to overestimating or underestimating airway obstruction if compared to changes in FEV_1. In some studies, the cut-off for decrease in FEV_1 to detect EIB has been 20% (La Force et al., 2022), and that would obviously reflect also on the PEF cut-off values.

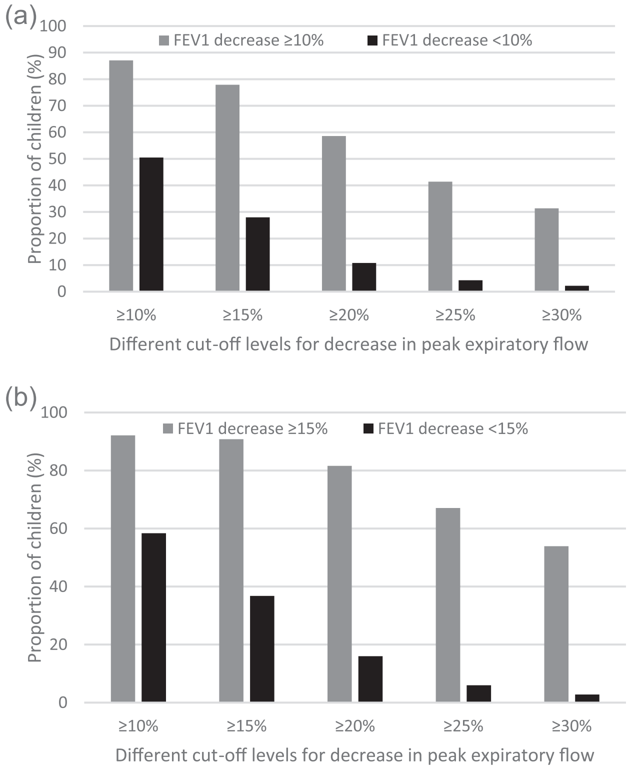

FIGURE 2 Percentage of children that experienced a certain PEF decrease according to presence or absence of exercise induced bronchoconstriction based on either a 10% (a) or a 15% (b) decrease in FEV_1. FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow.

Our study was only conducted at one medical centre, and it is possible that the results could vary if we were to perform our analysis based on a sample from another centre with different exercise protocol or equipment. Additionally, not all our participants had asthma and there could be variance between the relation of PEF change and FEV_1 change in people with asthma compared to people without asthma. Sensitivity and specificity values are not dependent upon the number of positive reactions to a given test. However, PPV and NPV are changed by the prevalence of EIB. Thus, if this study had been performed at another medical centre with a different prevalence of EIB, that would affect our PPV and NPV.

The strengths of our study were a relatively large population size of 326 reliable exercise challenges and a careful screening process in which every measurement was assessed individually for technical reliability. We measured PEF with a spirometer instead of a peak flow metre and compared it against FEV_1 measured with the same spirometer. Had we used a peak flow metre to conduct the PEF measurements, there could have been differences in the results due to using a different type of device, and this may reflect to clinical settings where a portable peak flow metre is used. We have previously compared the spirometer we used to different types of peak flow metres and the results of PEF are similar (data not published). In a usual PEF-recording, the blow is short in contrast to the long blow required for spirometry. We have compared and confirmed that long and short blows give the same results on PEF on both the peak flow metre and the spirometer (data not published). If PEF is monitored in relation to exercise

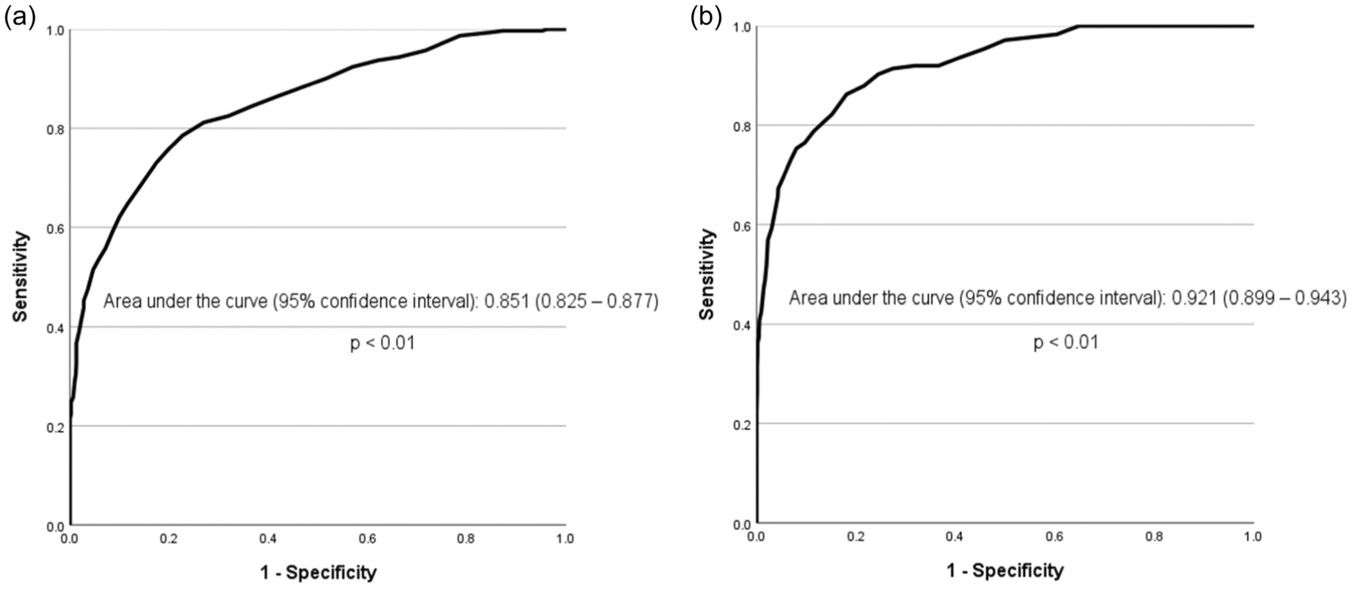

FIGURE 3 ROC analysis presenting the relationship between PEF change and a 10% decrease (a) or a 15% decrease (b) in FEV_1. FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow; ROC, receiver operating characteristics.

TABLE 2 Characteristics of different cut-off values in PEF decrease to predict a decrease of 10% or 15% in FEV$_1$ measured at any time point after the exercise challenge.

Decrease in PEF	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
10%					
EIB defined as A 10% decrease in FEV$_1$	87.1	48.1	56.5	82.9	0.332
EIB defined as A 15% decrease in FEV$_1$	92.1	40.4	32.4	94.3	0.199
15%					
EIB defined as A 10% decrease in FEV$_1$	77.9	71.3	67.7	80.6	0.483
EIB defined as A 15% decrease in FEV$_1$	90.8	62.4	42.9	95.6	0.384
20%					
EIB defined as A 10% decrease in FEV$_1$	60.3	88.8	80.4	74.5	0.505
EIB defined as A 15% decrease in FEV$_1$	84.9	83.4	60.8	94.8	0.600
25%					
EIB defined as A 10% decrease in FEV$_1$	44.3	95.5	87.8	70.0	0.426
EIB defined as A 15% decrease in FEV$_1$	72.9	93.7	77.3	92.2	0.680
30%					
EIB defined as A 10% decrease in FEV$_1$	34.4	97.8	91.7	67.4	0.352
EIB defined as A 15% decrease in FEV$_1$	61.2	97.1	85.4	89.9	0.649

Abbreviations: EIB, exercise induced bronchoconstriction; FEV1, forced expiratory volume in one second; NPV, negative predictive values; PEF, peak expiratory flow.

challenge with a peak flow metre instead of using a spirometer, quality control is more challenging. Often a certain repeatability in PEF values is required, but spirometry offers also the possibility of visually estimating flow volume curves for possible problems in the exhalation manoeuvre. Our results suggests that when a spirometer is used, PEF should not be used to substitute FEV$_1$ in interpreting an exercise challenge test. If an exercise test is conducted with a peak flow metre, PEF may be an even worse parameter in detecting EIB as possibilities for quality control are poorer. However, in our sensitivity analysis including also spirometries regarded technically unreliable, the relation between PEF and FEV$_1$ remained similar. This may partly be explained by the small proportion of unreliable measurements as our nurses check the quality of measurements in real-time when conducting spirometry.

PEF is often used and reasonably well studied in the context of home peak flow monitoring (Brouwer & Brand, 2008; Reddel et al., 2009). Exaggerated diurnal variation of PEF can be used to diagnose asthma (Global Initiative for Asthma, 2022). If FEV$_1$ is a better tool for detecting obstruction, home spirometry monitoring could prove to be more accurate in diagnosing asthma than home peak flow monitoring.

In conclusion, change in PEF cannot be used to substitute change in FEV$_1$ in diagnosing EIB in children. The currently recommended cut-point of 15% decrease in PEF has a reasonable sensitivity but poor specificity to predict a 10% or a 15% decrease in FEV$_1$. Thereby, over half of the positive findings of EIB according to this PEF cut-off value are false positives. The process of moving away from using PEF as a diagnostic tool is already taking place and our findings support that. If PEF is, however, used, the cut-off value for diagnosing EIB should be higher, and we suggest using a cut-off of 25% decrease in PEF.

AUTHOR CONTRIBUTIONS

All authors participated in designing this study. The data was collected by Antti Tikkakoski and Anna P. Tikkakoski. The data was analysed by Leon Csonka and Lauri Lehtimäki. Leon Csonka wrote the first draft of the manuscript and all authors participated in the revision process.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data is available from the authors for a reasonable request.

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