

LEON CSONKA

# Detection of Asthma-Related Bronchial Obstruction and Its Reversibility Through PEF and FEV<sub>1</sub> Measurements



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Obstruction and Its Reversibility Through  
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ACADEMIC DISSERTATION

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# ABSTRACT

Asthma is one of the most prevalent and significant chronic diseases worldwide, affecting approximately 339 million people and causing over a thousand deaths each day. Asthma diagnosis relies on characteristic symptoms and, ideally, objective lung function tests, including spirometry to detect bronchodilator response, various bronchial challenge tests to assess bronchial hyperreactivity, and the monitoring of diurnal variations in lung function. The critical parameters for asthma diagnostics are peak expiratory flow (PEF) and forced expiratory volume in one second (FEV<sub>1</sub>). However, the relationship between changes in PEF and FEV<sub>1</sub> during bronchoconstriction and bronchodilation remains unclear.

This dissertation comprises four retrospective chart reviews that aimed to assess how accurately change in PEF reflects airway obstruction and relaxation, as defined by change in FEV<sub>1</sub>, in children and adults. Exercise and methacholine challenge tests, each followed by salbutamol administration, were used as models of induced airway obstruction and subsequent dilation. Additionally, we sought to evaluate the justification for the current recommendations in international asthma guidelines for using PEF in children's exercise challenge testing and to assess whether the suggested cut-off value is optimal.

Spirometry and both challenges were performed by experienced healthcare professionals and conducted according to international guidelines. The exercise challenge consisted of free running outside, with spirometry measurements taken before exercise and at 2, 5, 10, and 15 minutes post-exercise. After the challenge, the children received salbutamol, and spirometry was repeated. The methacholine challenge involved an initial baseline spirometry measurement followed by a diluent step with saline solution and another spirometry measurement. Subsequently, cumulative methacholine doses of 18, 72, 270, 810, and 2600 µg were administered at 5-minute intervals, with spirometry measurements performed concurrently. Following the challenge, salbutamol was administered, and a final spirometry measurement was recorded. Regression analysis, Pearson correlation coefficient, Bland–Altman plot, receiver operating characteristic (ROC) analysis, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and

Cohen's kappa coefficient were used to compare changes in PEF and FEV<sub>1</sub> as outcome measures.

After excluding technically unreliable measurements, 326 exercise challenges in children and 878 methacholine challenges in adults remained. Among these, 326 children provided reliable bronchodilation data, as did 869 adults from the methacholine challenge group. The correlation between the changes in PEF and FEV<sub>1</sub> ranged from moderate to strong, with correlation coefficients between 0.67 and 0.79. Despite the ROC analyses demonstrating excellent or good areas under the curve, the individuals identified as positive by each parameter only partially overlapped. According to Cohen's kappa coefficient, the agreement between changes in PEF and FEV<sub>1</sub> ranged from slight to substantial, with values between 0.199 and 0.680.

The currently recommended cut-off value of a 15% decrease in PEF for children in the exercise challenge was not optimal for detecting a 15% reduction in FEV<sub>1</sub>, as over half of the positive tests were false. Even with a cut-off value of 25%, which showed the best agreement according to the kappa value, over a fifth of the positives were still false. This higher cut-off value also resulted in significantly diminished sensitivity (73%) but better specificity (94%) and NPV (92%). In the methacholine challenge in adults, the specificity of PEF decrease was generally higher than sensitivity, and NPV was higher than PPV in detecting a 15% reduction in FEV<sub>1</sub>. Using the cut-off value of a 15% decrease in PEF, which achieved the highest kappa coefficient, PPV for detecting a 15% reduction in FEV<sub>1</sub> was low at 59%, while NPV was markedly higher at 94%. The corresponding sensitivity and specificity were 66% and 92%, respectively.

In the bronchodilation test in children, the specificity of PEF increase was generally higher than the sensitivity, and NPV was higher than PPV. According to the kappa coefficient, a 20% improvement in PEF showed the best agreement for detecting a 12% and 0.2 L increase in FEV<sub>1</sub>, yielding low sensitivity (61%) and PPV (70%) but relatively higher specificity (88%) and NPV (83%). In the bronchodilation test in adults, we found that PEF increase had better specificity and PPV than sensitivity and NPV across all cut-off values studied. A 10% improvement in PEF yielded the highest kappa coefficient, with relatively low and similar values for sensitivity (75%), specificity (79%), PPV (77%), and NPV (77%) in detecting a 12% and 0.2 L increase in FEV<sub>1</sub>.

We conclude that PEF change is not a reliable parameter for detecting change in lung function, as defined by change in FEV<sub>1</sub>. The recommended PEF cut-off value for exercise challenge in children is suboptimal, resulting in a high false positive rate.

Given the unreliability of PEF change in detecting lung function variations and the availability of small handheld spirometers, home spirometry monitoring should be further investigated as a potential alternative to home PEF monitoring.

# TIIVISTELMÄ

Astma on yksi maailman yleisimmistä ja merkittävimmistä kroonisista sairauksista, ja se vaikuttaa noin 339 miljoonaan ihmiseen aiheuttaen yli tuhat kuolemaa päivittäin. Astman diagnosointi perustuu tyypillisiin oireisiin ja ihanteellisesti myös objektiivisiin keuhkofunktiomittauksiin, kuten spirometrialla tehtävään bronkodilataatiovasteen mittaukseen, erilaisiin provokaatiotesteihin keuhkoputkien yliherkkyyden arvioimiseksi sekä keuhkojen toiminnan vuorokausivaihtelun seurantaan. Astman diagnostiikan keskeiset parametrit ovat huippuvirtaus (PEF) ja sekuntikapasiteetti (FEV<sub>1</sub>). PEF- ja FEV<sub>1</sub>-muutosten välinen suhde keuhkoputkien supistumisen ja laajenemisen yhteydessä on kuitenkin yhä epäselvä.

Tämä väitöskirja koostuu neljästä retrospektiivisestä rekisteritutkimuksesta, joiden tavoitteena oli arvioida, kuinka hyvin suhteelliset PEF-muutokset kuvaavat keuhkoputkien supistumista ja laajenemista, kun nämä määritellään suhteellisten FEV<sub>1</sub>-muutosten perusteella lapsilla ja aikuisilla. Juoksurasitus- ja metakoliinialtistuskokeita, joita molempia seurasi salbutamolinnostelu, käytettiin indusoidun keuhkoputkien supistumisen ja laajenemisen malleina. Lisäksi tutkimuksessa pyrittiin arvioimaan kansainvälisten astmaohjeiden nykyisen suosituksen perustelut PEF-mittausten käytölle lasten juoksurasituskokeessa sekä selvittämään, onko suositeltu raja-arvo optimaalinen.

Spirometria ja molemmat altistuskokeet suoritettiin kokeneiden terveydenhuollon ammattilaisten toimesta kansainvälisiä suosituksia noudattaen. Rasituskoe koostui vapaasta ulkona juoksemisesta, ja spirometriamittaukset tehtiin ennen rasitusta sekä 2, 5, 10 ja 15 minuuttia rasituksen jälkeen. Kokeen jälkeen lapsille annettiin salbutamolia, ja spirometria toistettiin. Metakoliinialtistus sisälsi alkuvaiheen spirometriamittauksen, jonka jälkeen potilaat hengittivät suolaliuosta ilman metakoliinia ja spirometria toistettiin. Tämän jälkeen annettiin kumulatiiviset metakoliiniannokset, joiden suuruudet olivat 18, 72, 270, 810 ja 2600 µg, viiden minuutin välein, ja spirometria toistettiin jokaisen annoksen yhteydessä. Altistuksen jälkeen annettiin salbutamolia, ja lopuksi tehtiin vielä yksi spirometriamittaus. PEF- ja FEV<sub>1</sub>-muutosten vertailuun vasteparametreina käytettiin regressioanalyysia, Pearsonin korrelaatiokerrointa, Bland–Altman-kaaviota, receiver operating

characteristic (ROC) -analyysiä, herkkyyttä, tarkkuutta, positiivista ennustearvoa (PPV), negatiivista ennustearvoa (NPV) ja Cohenin kappakerrointa.

Teknisesti epäluotettavat mittaukset suljettiin pois analyysistä, minkä jälkeen jäljelle jäi 326 lasten juoksurasituskoetta ja 878 aikuisten metakoliinialtistuskoea. Lapsista 326 ja aikuisista 869 tuotti luotettavia bronkodilataatiotuloksia. PEF- ja FEV<sub>1</sub>-muutosten välinen korrelaatio vaihteli kohtalaisesta vahvaan, korrelaatiokertoimien ollessa välillä 0,67–0,79. Vaikka ROC-analyysit saavuttivat erinomaisia tai hyviä AUC-arvoja (area under the curve), PEF- ja FEV<sub>1</sub>-mittaukset tunnistivat suurelta osin eri yksilöitä. Cohenin kappakertoimen arvot olivat välillä 0,199–0,680 eli PEF- ja FEV<sub>1</sub>-muutosten välinen yhtenevyys vaihteli vähäisestä merkittävään.

Nykyisin suositeltu 15 %:n PEF-laskun raja-arvo lasten juoksurasituskokeessa ei ollut optimaalinen 15 %:n FEV<sub>1</sub>-laskun havaitsemisessa, sillä yli puolet positiivisista tuloksista oli väärä. Kappa-arvon perusteella paras yhtenevyys saavutettiin 25 %:n raja-arvolla, mutta silläkin yli viidennes positiivisista tuloksista oli väärä. Tämä korkeampi raja-arvo johti myös heikentyneeseen herkkyyteen (73 %), mutta parempaan tarkkuuteen (94 %) ja NPV:hen (92 %). Aikuisten metakoliinialtistuskokeessa PEF-laskun tarkkuus oli yleensä parempi kuin herkkyyden, ja NPV oli korkeampi kuin PPV 15 %:n FEV<sub>1</sub>-laskun havaitsemisessa. Kappakertoimen perusteella parhaan yhtenevyyden antoi 15 %:n PEF-laskun raja-arvo, jolla 15 %:n FEV<sub>1</sub>-laskun havaitsemisen PPV oli vain 59 %, kun taas NPV oli huomattavasti korkeampi (94 %). Herkkyyden ja tarkkuuden olivat vastaavasti 66 % ja 92 %.

Lasten bronkodilataatiokokeessa PEF-arvon nousun tarkkuus oli yleensä parempi kuin herkkyyden, ja NPV oli korkeampi kuin PPV. Kappakertoimen perusteella parhaan yhtenevyyden 12 %:n ja 0.2 litran FEV<sub>1</sub>-nousun havaitsemisessa antoi 20 %:n PEF-suureneminen. Tällä raja-arvolla herkkyyden (61 %) ja PPV (70 %) olivat matalia, mutta tarkkuus (88 %) ja NPV (83 %) suhteellisesti korkeampia. Aikuisten bronkodilataatiokokeessa havaitsimme, että PEF-arvon nousulla oli parempi tarkkuus ja PPV kuin herkkyyden ja NPV kaikilla tutkituilla raja-arvoilla. Kappakertoimen perusteella parhaan yhtenevyyden 12 %:n ja 0.2 litran FEV<sub>1</sub>-nousun havaitsemisessa antoi 10 %:n PEF-suureneminen, jolla saavutettiin suhteellisen alhaiset ja keskenään samankaltaiset arvot herkkyydessä (75 %), tarkkuudessa (79 %), PPV:ssä (77 %) ja NPV:ssä (77 %).

Johtopäätöksenä, PEF-muutos ei ole luotettava parametri keuhkofunktion vaihteluiden havaitsemiseksi, kun ne määritellään FEV<sub>1</sub>-muutoksen perusteella. Lasten juoksurasituskokeeseen suositeltu PEF-raja-arvo ei ole optimaalinen ja johtaa

suureen väärin positiivisten tulosten osuuteen. Koska PEF-muutos ei ole luotettava keuhkofunktion vaihteluiden havaitsemisessa ja pieniä kannettavia spirometreja on nykyään saatavilla, kotispirometriaseuranta tulisi tutkia tarkemmin mahdollisena vaihtoehtona PEF-seurannalle.

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# ABBREVIATIONS

ASL	Airway surface liquid
ASM	Airway smooth muscle
AUC	Area under the curve
BDR	Bronchodilator response
$\beta_2$	Beta-2 adrenergic receptor
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
EIB	Exercise-induced bronchoconstriction
ERS	European Respiratory Society
FEV <sub>1</sub>	Forced expiratory volume in one second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
IgE	Immunoglobulin E
IL	Interleukin
ILC2	Group 2 innate lymphoid cell
IOS	Impulse oscillometry
NPV	Negative predictive value
PC <sub>20</sub> FEV <sub>1</sub>	Provocative concentration causing a 20% decrease in FEV <sub>1</sub>
PD <sub>20</sub> FEV <sub>1</sub>	Provocative dose causing a 20% decrease in FEV <sub>1</sub>
PEF	Peak expiratory flow
pMDI	Pressurized metered-dose inhaler
PPV	Positive predictive value
r	Pearson correlation coefficient
ROC	Receiver operating characteristic
SD	Standard deviation
Th2	Type 2 helper lymphocyte

# LIST OF ORIGINAL PUBLICATIONS

- I        **Csonka L**, Tikkakoski A, Tikkakoski AP, Karjalainen J, Lehtimäki L.  
Relation of changes in PEF and FEV<sub>1</sub> in exercise challenge in children.  
*Clinical Physiology and Functional Imaging*. 2024 Mar;44(2):179–185.
- II        **Csonka LL**, Tikkakoski A, Vuotari L, Karjalainen J, Lehtimäki L.  
Relation of changes in peak expiratory flow (PEF) and forced expiratory  
volume in 1 s (FEV<sub>1</sub>) during bronchoconstriction. *Clinical Physiology and  
Functional Imaging*. 2024 Nov;44(6):447–453.
- III       **Csonka LL**, Tikkakoski A, Tikkakoski AP, Karjalainen J, Lehtimäki L.  
Relation of changes in PEF and FEV<sub>1</sub> during bronchodilation in  
children. Submitted.
- IV       **Csonka LL**, Tikkakoski A, Vuotari L, Karjalainen J, Lehtimäki L.  
Relation of Changes in PEF and FEV<sub>1</sub> During Salbutamol-Induced  
Bronchodilation After Methacholine Challenge Test. *Pulmonary Medicine*.  
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# AUTHOR'S CONTRIBUTION

The author collaborated with the supervisor and other research group members in designing all studies. The literature review was conducted solely by the author. The author was responsible for the statistical analysis of the data and wrote the first drafts of all manuscripts. Additionally, the author took part in revising all studies alongside the supervisor and group members. The author also contributed to the acquisition of funding.



# 1 INTRODUCTION

Asthma is among the most common chronic diseases, affecting approximately 340 million individuals globally (1). Each day, asthma claims the lives of over a thousand people, primarily in low- to middle-income countries, with the majority of these fatalities being avoidable (2,3). Asthma is attributed to bronchial hyperreactivity, a state characterized by easily triggered contraction of the bronchial smooth muscle, leading to narrowing of the airways. Bronchial hyperreactivity induces symptoms such as wheezing, difficulty breathing, chest tightness, breathlessness, and coughing, together with variable expiratory airflow limitation that bronchodilators can resolve. The symptoms vary over time and in intensity, with one or more symptoms potentially predominating (4). As a heterogeneous inflammatory disease, asthma manifests many clinically different phenotypes and endotypes, with various underlying pathophysiological mechanisms (5).

Bronchial obstruction in asthma can be triggered by different stimuli, including chemical exposures, air pollutants, allergens, respiratory infections, changes in weather, and physical exercise. No singular optimal diagnostic approach exists for asthma, and a multitude of tests are commonly used. Different diagnostic tests often induce airway obstruction by either direct or indirect stimuli or rely on reversing existing obstruction using bronchodilators. Additionally, daily fluctuations in lung function associated with asthma can be followed via home monitoring. Some commonly used diagnostic tests include exercise challenge, methacholine challenge, bronchodilator response (BDR) detection, and monitoring diurnal variation in peak expiratory flow (PEF) (4,6)

From 1994 to 2004, Finland implemented a national asthma program aimed at enhancing asthma care and shifting the primary responsibility for diagnosing and treating adult asthma to primary healthcare services. Following the incorporation of objective lung function measures as a standard practice, diagnostic accuracy improved notably, accompanied by favorable changes in several indicators of the national asthma burden. In Finnish primary care settings, the principal diagnostic tools available are spirometry with BDR testing and two-week home PEF monitoring (7).

Despite forced expiratory volume in one second (FEV<sub>1</sub>) measured by spirometry being the gold standard in lung function assessment, home PEF monitoring has been advocated as a tool for diagnosing and managing asthma for several decades (8,9). The affordability and simplicity of handheld PEF meters have enabled the observation of bronchial obstruction and dilation over time. Nevertheless, the European Respiratory Society (ERS) does not endorse PEF monitoring as the sole or primary diagnostic method. Instead, it suggests using it as a supplementary method, especially in cases with normal spirometry, particularly when access to bronchial challenge testing is limited (6). For children in particular, exercise challenge testing aimed at detecting exercise-induced bronchoconstriction (EIB) is often utilized and recommended (4,10). Despite oscillometry or spirometry typically being preferred in the context of exercise challenge testing in children, Global Initiative for Asthma (GINA) guidelines still recommend PEF as an alternative and offer the relevant cut-off value (4).

In recent years, small and reliable handheld spirometers have been developed for home monitoring. However, the effectiveness and usability of home spirometry monitoring in the context of asthma diagnostics and management are not well understood. Currently, all guideline-based diagnostic thresholds for lung function variation in home monitoring are based on PEF (4,6,10). Some concerns have emerged regarding the reliability of PEF change in assessing changes in lung function (9,11,12). Nevertheless, the relationship between changes in PEF and FEV<sub>1</sub> during bronchoconstriction and bronchodilation remains unclear.

Therefore, this study aimed to use exercise challenge and methacholine challenge, both followed by subsequent salbutamol administration, as models of induced airway obstruction and dilation to assess how well change in PEF reflects airway obstruction and relaxation, as defined by change in FEV<sub>1</sub>, in children and adults. Additionally, we sought to evaluate the justification for the current recommendation of using PEF in children's exercise challenge testing and to assess whether the suggested cut-off value is optimal. We hypothesized that PEF is not an accurate parameter for evaluating changes in lung function, as defined by FEV<sub>1</sub> change, and that the currently recommended cut-off value for PEF change in detecting EIB in children is too low.

## 2 REVIEW OF THE LITERATURE

### 2.1 Asthma

#### 2.1.1 History

The first documented account of respiratory distress, recorded in China circa 2600 BC, described the condition as “noisy breathing.” Anti-asthmatic herbal remedies were also first used during the same period. Hippocrates, the ancient Greek physician, first noted a characteristic hunched posture in asthma patients and explored the relationship between respiratory distress and environmental factors. In the 17th century, chemist Jean Baptiste Van Helmont described asthma as originating “in the pipes of the lungs.” By the 18th century, it was recognized that exercise could trigger asthmatic exacerbations. Subsequent centuries uncovered the connections between asthma and various allergenic irritants. During the 1960s and 1970s, the introduction of PEF meters, along with advancements in other technology and the development of new corticosteroid medications, significantly improved the accuracy and effectiveness of asthma diagnostics and management (13).

#### 2.1.2 Definition

The declared definitions for asthma vary slightly between different organizations, but all definitions include the same core symptoms. Some organizations’ definitions include the required observation of specific lung function measurements, which attempt to assess the severity of bronchial obstruction (6), while others’ definitions are more centered on the pathophysiological mechanisms of asthma (14).

According to GINA guidelines, asthma is defined as follows: “Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough, which vary over time and intensity, together with variable

airflow limitation.” Patients under 12 years old are classified as children for diagnostic and treatment purposes (4). Finnish guidelines utilize the definition of asthma provided by GINA (10).

The National Institutes of Health guidelines employ a more extensive and comprehensive, mechanism-focused definition: “Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma.” (14). This definition underscores the multifactorial nature of asthma and its varied clinical presentations.

The more diagnostics-focused “operating definition of asthma” presented by ERS begins by stating, “Typical symptoms including breathlessness, wheezing, cough, chest tightness and objective demonstration of excessive airway caliber fluctuation with at least one of the following define asthma both in primary and secondary care.” The definition then lists four PEF- or FEV<sub>1</sub>-based criteria (6). In ERS guidelines, the limit between adults and children is 16 years (15).

### 2.1.3 Epidemiology

Asthma prevalence, severity, and mortality vary substantially across geographical regions. It is estimated that approximately 340 million people suffer from asthma globally (1), and more than one thousand people die from the disease each day (2). The majority of these deaths occur in low- to middle-income countries and are preventable (3). In Finland, asthma is the third most prevalent condition qualifying for special medication reimbursement, with over 282,000 individuals holding active asthma medication prescriptions in 2019. A small minority of these prescriptions were for chronic obstructive pulmonary disease (COPD) (10). According to some estimates, up to 55% of COPD patients also have asthma (16). During 2019, asthma claimed the lives of 63 individuals in Finland (10).

Although asthma often begins in childhood, morbidity and mortality are higher among adults with asthma. Boys are more commonly affected by childhood asthma,

whereas in adulthood, asthma is more prevalent among women (17). The prevalence of asthma and asthma-like symptoms among young people in Finland had been increasing, but this trend plateaued in the early 2010s. The requirement for hospitalization due to asthma has also decreased among children. Currently, the prevalence of physician-diagnosed asthma among children and young adults varies from 3% to 6%, depending on the age group (10).

#### 2.1.4 Etiology

The exact cause of asthma remains unknown, but several risk factors have been identified. Estimates of the significance of genetic contribution to the pathogenesis of asthma range from 35% to 95% (18). Several individual genes, as well as certain epigenetic variations, have been identified as potential risk factors (19,20). The most substantial risk factor for asthma is atopy, and allergic reactions to diverse stimuli are major triggers of asthma symptoms (21). Disturbances to the gut microbiome, smoking, air pollutants, prenatal stress, and vitamin D deficiency have all been linked to a higher incidence of asthma (22). Severe respiratory infections in childhood are also known to increase the risk of asthma (23). It is conceivable that additional risk factors have yet to be identified.

#### 2.1.5 Pathophysiology

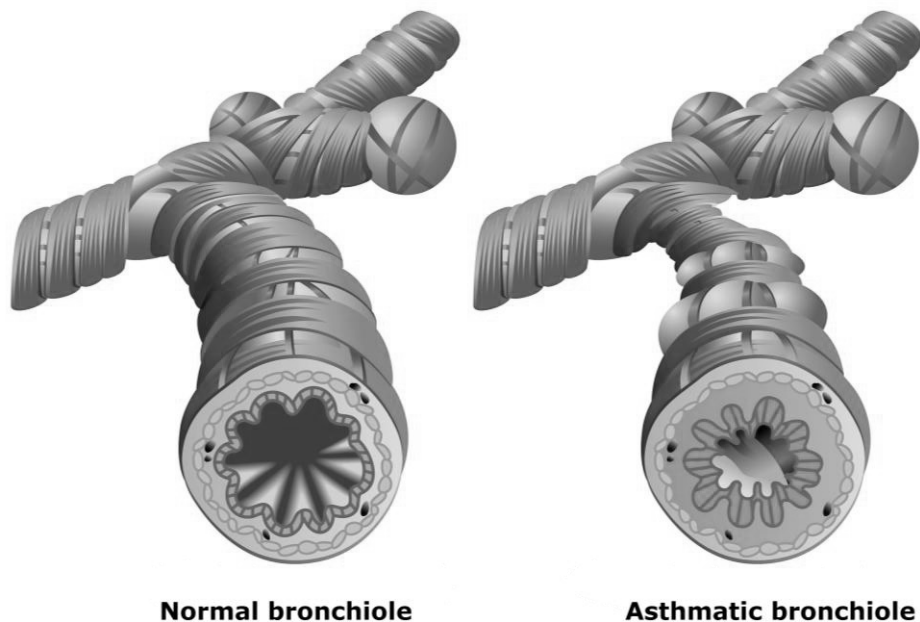
The pathophysiology of asthma centers on the inflammatory process, which arises from a multitude of genetic and environmental factors (18,21–23). It is essential to understand the histological structure of the airways to comprehend which tissues and cell types are responsible for and affected by the inflammatory processes underlying asthma. The respiratory tract comprises multiple histological layers. The layer in contact with the lumen of the bronchi is the respiratory mucosa, which includes the epithelium supported by the lamina propria. The deeper layers include the submucosa, cartilage and/or muscular layer, and adventitia (24).

The type of inflammation present varies among different endotypes of asthma, but most asthmatics suffer from type 2 inflammation, named after the type 2 helper lymphocyte (Th2). Alongside Th2 cells, type 2 inflammation is driven by group 2 innate lymphoid cells (ILC2) (25). Type 2 inflammation is typically found in allergic diseases and parasitic infections. It is generally accepted that epithelial cells lining the airway walls play a central role in initiating type 2 inflammation through the release

of interleukins (ILs) and other cytokines (IL-25, IL-33, and thymic stromal lymphopoietin), proteins that regulate the inflammatory process along with other functions. This induces a pathogenic cascade, resulting in increased levels of other inflammatory cytokines, including IL-4, IL-5, and IL-13, which in turn trigger subsequent processes. During type 2 inflammation, an increase in eosinophils, basophils, mast cells, and immunoglobulin E (IgE)-producing plasma cells, in addition to Th2 and ILC2 cells, can also be observed (26).

In addition to the role of the airway epithelium in regulating asthmatic inflammation, there is also evidence pointing toward airway smooth muscle (ASM) being an active participant in the inflammatory process, not just a bystander. Inflammatory molecular signals are both released by ASM and act upon it (27). Because the inflammation underlying asthma is chronic, it may be present, even in the absence of clinical symptoms. However, asthma symptoms tend to worsen at night, a pattern that correlates with fluctuations in endogenous cortisol levels (28). Another factor contributing to the diurnal variation in asthma symptom severity is the shifting balance between sympathetic and parasympathetic nervous system activation. Acetylcholine released by the parasympathetic nervous system acts on the muscarinic receptors of the airways, inducing ASM contraction and increased mucous production (29).

The inflammation cascade present in asthma triggers clinical symptoms in several ways, the most significant being airway hyperresponsiveness. During this state, ASM becomes overly sensitive to stimuli and contracts excessively, even with minimal provocation, leading to bronchoconstriction and airway obstruction (Figure 1). Factors such as respiratory heat and water loss during exercise, as well as contractile agents like methacholine, are among the triggers that can induce ASM contraction (27).



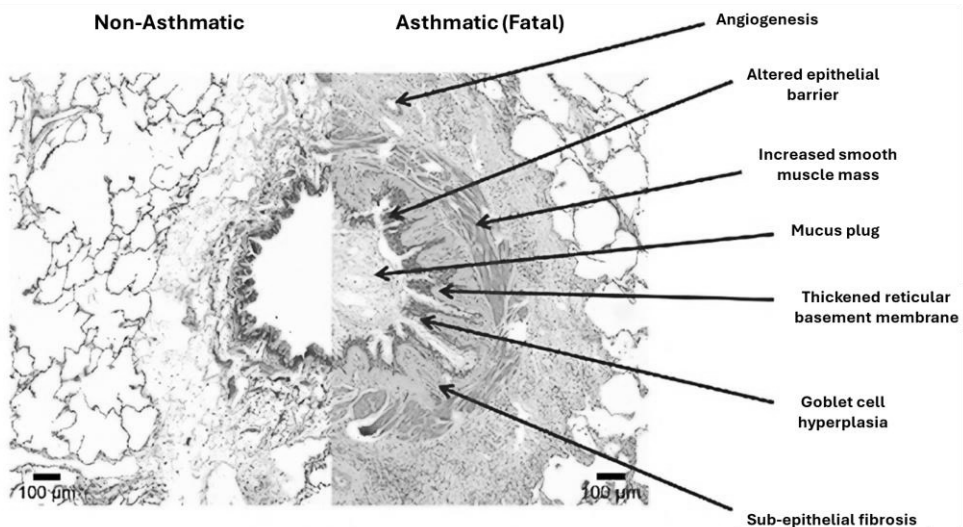
**Figure 1.** Illustration comparing the bronchioles of a healthy person with those of a patient suffering from airway obstruction caused by bronchoconstriction. Modified from a stock image.

The mechanisms by which inflammation causes hyperresponsiveness are complex. One crucial factor is the increased availability of histamine, a contractile agonist released from mast cells, which enhances the contraction of ASM (30). Inflammatory cytokines raise the levels of free intracellular calcium, intensifying the contractility of ASM (31). Amplified activity of the vagus nerve and stimulation of the Rho kinase pathway also contribute to the development of hyperresponsiveness. Additionally, the inflammatory process not only leads to an increase in ASM mass, resulting in greater contractile force, but the breathing difficulties associated with asthma also contribute to stiffening the muscle (27).

Another muscle-related cause of asthmatic airway obstruction is the inadequate relaxation of ASM. In most mammals, cholinergic-parasympathetic nerves induce contractions, while adrenergic-sympathetic and non-cholinergic parasympathetic nerves promote relaxation. However, histological examinations suggest that the direct sympathetic-adrenergic nerve supply to human ASM is scarce or absent, having minimal to no impact on controlling airway dilation. In humans, non-cholinergic parasympathetic nerves, regulated by distinct reflex pathways, are

responsible for direct nerve-mediated ASM relaxation (32). Beta-2 adrenergic receptor ( $\beta_2$ ) agonist medications act as bronchodilators because, despite the limited sympathetic innervation in ASM, the receptors remain abundant and functional (33). During heightened sympathetic nervous system activation, adrenaline released into the bloodstream by the adrenal medulla induces bronchodilation through the same mechanism (34). Yet, it has been observed that prolonged exposure to  $\beta_2$  agonists may result in the downregulation of the  $\beta_2$ -adrenergic receptors in ASM, consequently leading to poorer treatment outcomes. This effect is exacerbated by the presence of certain inflammatory cytokines (IL-1 $\beta$  and IL-13) (27).

Tissue remodeling refers to pathological changes in the various layers of the bronchial walls caused by the inflammatory processes associated with asthma (Figure 2). Alterations in the epithelial layer involve metaplasia and hyperplasia of goblet cells, as well as increases in epithelial mucin stores. Beneath the mucosa, subepithelial fibrosis develops within the submucosa. The submucosal glands, responsible for storing and secreting mucus, expand in volume, and angiogenesis promotes the formation of new blood vessels. Additionally, submucosal edema is also present. ASM mass and thickness increase due to both hyperplasia and hypertrophy. These changes lead to a reduction in the airway caliber combined with increased production of mucus (26). If asthma progresses untreated, extensive tissue remodeling may occur, leading to irreversible fixed airway obstruction (35).



**Figure 2.** Histological comparison of the airway wall of a healthy individual versus a fatal asthma case, highlighting the typical features of tissue remodeling. Modified from Hsieh et al. 2023 (36).

## 2.1.6 Phenotypes and Endotypes

Asthma can be classified into phenotypes based on clinical features, such as onset age, severity, frequency of exacerbations, and related diseases. However, to truly understand the disease mechanisms and identify the optimal treatment for each individual, the critical distinctions between asthma types lie in the differences in their inflammatory processes (10). The different endotypes of asthma can be broadly divided into two groups: type 2 inflammatory and non-type 2 inflammatory (5). The process of type 2 inflammation is described in Section 2.1.5. Some overlap exists between different types, and patients may sometimes exhibit immune signatures characteristic of multiple endotypes (37).

The more common type 2 inflammatory asthma is marked by airway eosinophilia and, in some cases, systemic eosinophilia (26). It is further divided into allergic eosinophilic asthma, typically onset in childhood or early adulthood, and non-allergic eosinophilic asthma, which emerges more often in later adulthood. There are distinctions in the inflammatory mechanisms between allergic and non-allergic eosinophilic asthma. Exposure to allergens or irritants in allergic asthma prompts Th2 cells to produce cytokines, stimulating allergen-specific B lymphocytes to synthesize IgE. These IgE antibodies subsequently induce asthma symptoms upon re-encounter with the triggering antigen by activating basophils and mast cells. This process, alongside the accumulation of eosinophils in the airway wall and heightened mucus production, contributes to the characteristic features of allergic asthma (38).

Despite the absence of allergy, type 2 inflammation plays a major role in non-allergic eosinophilic asthma. The disease mechanism of late-onset eosinophilic asthma is also likely more complex than allergic asthma (39). It is mainly driven by ILC2 cells, which produce many of the same inflammatory cytokines as Th2 cells and, in doing so, activate eosinophils and mast cells (40). ILC2 cells do not possess antigen-specific receptors. Instead, they respond to cytokines released by epithelial cells, triggering inflammation in the airways without the need for antigen involvement (25). Non-allergic eosinophilic asthma commonly exhibits elevated eosinophil levels compared to allergic asthma, and it frequently presents with greater severity than its allergic counterpart (38). Eosinophils typically exhibit an excellent response to corticosteroid treatment, consequently leading to apoptosis. This explains why allergic asthma generally responds well to corticosteroid treatment. However, in late-onset eosinophilic asthma, significant eosinophilia persists in about half of the patients, despite corticosteroid therapy. This suggests that the ILC2-driven mechanism in this form of asthma is less responsive to corticosteroids (39).

Non-eosinophilic endotypes of asthma include neutrophilic and paucigranulocytic asthma. It is believed that a high neutrophilic signature in asthma could arise from type 1 inflammation mediated by Th1 and/or Th17 helper lymphocytes (37). Th1 and Th17 cells are well known to counter-regulate each other, yet they also appear to cooperate in driving pathological processes (41). Neutrophilic asthma is associated with systemic inflammation, which may help explain its prevalence among patients with poor metabolic health, such as the elderly and obese (42). However, obesity-related asthma can occur with a variety of inflammatory subtypes. Additionally, it is often resistant to glucocorticoid treatment (43).

The pathophysiological mechanisms of the inflammation underlying paucigranulocytic asthma are not well known. Evidence suggests that leukocyte levels around the airways in patients with paucigranulocytic asthma are comparable to those in healthy individuals. Despite the lack of excess immune cells, the airways of these patients are still subject to tissue remodeling. The airway hyperresponsiveness and tissue remodeling seen in paucigranulocytic asthma may result from pollutants, oxidative stress, or dysregulated neuronal control of ASM (37).

### 2.1.7 Treatment

The treatment of asthma focuses on achieving an asymptomatic state, maintaining normal lung function, preventing exacerbations, and using only the necessary medications required to meet these objectives. Appropriate treatment is guided by monitoring asthma control with a symptom diary and regular objective lung function testing (10).

All patients with a confirmed asthma diagnosis should have a fast-acting bronchodilator available as a symptom reliever, typically a  $\beta_2$  agonist such as salbutamol or terbutaline. In addition to as-needed relievers, various types of maintenance medications may be used if necessary, depending on the severity of asthma; these are usually inhaled corticosteroids. Certain biological medications can be used in severe cases, provided that specific rigorous criteria are met (10,44). If asthma has been well controlled for 6–12 months, gradually stepping down the maintenance medication may be attempted (10).

## 2.2 Diagnostics of Asthma

### 2.2.1 General Principles

The diagnosis of asthma is based on a history of characteristic symptoms and the presence of variable expiratory airflow limitation, which can be resolved by bronchodilators. Symptoms may vary over time and between patients but are usually paroxysmal, often worsening at night or in the morning. They are frequently triggered by exercise, allergens, cold air, stress, and infections. Common symptoms include wheezing, difficulty breathing, chest tightness, breathlessness, cough, and increased mucus production. Bronchial hyperreactivity and the resulting variable airflow obstruction can be documented through various objective lung function tests, including spirometry to detect BDR, different bronchial challenge tests, and monitoring of diurnal variation in PEF (4,6,10).

Usually, treatment is not initiated until a diagnosis of asthma is confirmed. However, sometimes the response to treatment can be utilized as a separate diagnostic method by itself. Although spirometry is preferred over PEF recording in settings other than home monitoring, access to spirometry can be limited, especially globally. Therefore, cut-off values for PEF are recommended as alternatives to FEV<sub>1</sub> in various tests (4,6,10).

Since both the symptoms and expiratory airflow limitation are variable, initial examination may reveal a normal clinical status when symptoms are absent. In the lung auscultation of symptomatic patients, expiratory wheezing and coarse crackles can frequently be heard. In severe asthma, wheezing and other lung sounds may occasionally become silent, with accessory respiratory muscles being recruited for breathing. This life-threatening state arises from obstruction of the small airways, leading to air entrapment in the distal parts of the airways. It warrants immediate action (4,10).

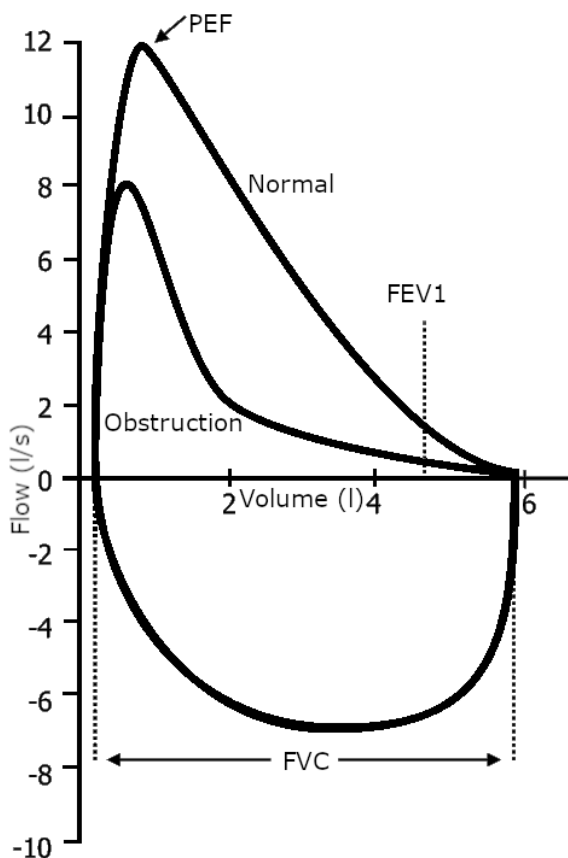
Once the initial diagnosis of asthma is confirmed, it is essential to identify the specific inflammatory endotype present, as it influences the selection of the appropriate treatment regimen. This investigation involves assessing allergies, measuring blood eosinophil count, and, in some instances, measuring exhaled nitric oxide levels or counting inflammatory cells in sputum or mucosal biopsy (10).

While asthma cannot be diagnosed through imaging, a chest X-ray can be valuable in ruling out potential differential diagnoses. Similarly, imaging of the nasal sinuses may be required in some cases for the same purpose. The most important

differential diagnoses include COPD, chronic bronchitis, sinusitis, cystic fibrosis, cardiovascular diseases, laryngeal dysfunction, large airway collapse tendency, sleep apnea, hyperventilation syndrome, an inhaled foreign body, and panic disorder (4,10).

## 2.2.2 Measuring Lung Function

Since it is often difficult to predict the degree of airway obstruction based on clinical symptoms alone, measuring lung function in a reliable way is necessary (45). Lung function assessment is usually performed using spirometry, PEF measurement, or, in the case of small children, impulse oscillometry (IOS). Spirometry is an objective, non-invasive, sensitive, and reproducible physiological pulmonary function test. It measures airflow as a function of time during maximal exhalation followed by full inhalation; however, current practice typically involves displaying a graph of flow as a function of volume. A spirometry graph is generated, allowing for visual assessment of the reliability of the blowing technique (Figure 3). The key variables obtained from spirometry include forced vital capacity (FVC), defined as the total volume of air exhaled during a forceful exhalation; FEV<sub>1</sub>, which measures the volume of air exhaled in the first second of exhalation; and the FEV<sub>1</sub>/FVC ratio, which compares the two parameters (46,47). Spirometry can be attempted in children as young as five years old, but it is generally considered reliable from school age onwards (9,10).



**Figure 3.** Comparison of a flow–volume graph generated during spirometry from a healthy individual versus a patient experiencing significant airway obstruction. Modified from Binks 2020 (48).

PEF measurements can be taken using a dedicated PEF meter, which records only a single value: the fastest speed at which air exits the lungs during forceful exhalation (49). PEF measurements can also be obtained through spirometry. When measured by spirometry, PEF is customarily expressed in L/s, whereas with portable instruments, it is typically reported in L/min. (50). PEF can be accurately assessed in children aged 12 years and older (10).

PEF is rapidly reached at the start of exhalation, when lung volume is near its maximum (Figure 3). At this point, the result is strongly influenced by the force exerted by the respiratory muscles and the effort applied during exhalation. In contrast, FEV<sub>1</sub> is measured over the first full second of exhalation, by the end of which the lung volume has already decreased significantly. Consequently, PEF may be more sensitive to limitations in respiratory muscle strength or reductions in

thoracic elasticity. It is also commonly believed that PEF more accurately represents the function of the large airways, while FEV<sub>1</sub> provides a better indication of activity within the smaller airways (9). Nevertheless, the evidence for this theory is rather unsatisfactory.

IOS works by superimposing sound waves on normal tidal breathing. The resulting disturbances in flow and pressure caused by these external waves are used to calculate parameters that reflect airflow resistance and reactive properties, describing the lung's efficiency in storing and returning energy (51). The passive nature of IOS makes it a highly suitable method for assessing lung function in small children from three years of age onwards (10,52).

### 2.2.3 Bronchodilator Reversibility

In asthmatics, inhalation of  $\beta_2$  agonists during bronchial obstruction stimulates  $\beta_2$  receptors located on the airway walls, leading to ASM relaxation and a subsequent increase in airway caliber (53). Upon stimulation of  $\beta_2$  receptors, there is an increase in intracellular cyclic adenosine monophosphate (cAMP) and the activation of protein kinase A, which phosphorylates various cellular proteins, leading to relaxation. Additionally,  $\beta_2$  agonists affect membrane K<sup>+</sup> channels, inducing smooth muscle relaxation independent of cAMP elevation (54). Non-asthmatic individuals can experience airway obstruction due to other conditions, such as COPD or cystic fibrosis (55). However, obstruction caused by conditions other than asthma is usually due to irreversible tissue remodeling, which renders it unresponsive to  $\beta_2$  agonists. Conversely, asthma can also advance to a state of irreversible obstruction if left untreated for an extended period (56).

Identifying significant BDR often aids in distinguishing asthma from other obstructive lung diseases. Thus, asthma can be diagnosed by measuring the extent of the airway's reaction to  $\beta_2$  agonist inhalation by assessing improvement in lung function via spirometry (10). In bronchodilator reversibility testing, lung function is first evaluated at baseline. A  $\beta_2$  agonist is then administered, and lung function is reassessed after a 15-minute interval (57). If spirometry is not available, GINA recommends measuring lung function using a PEF meter instead (4).

For both children and adults, an increase in FEV<sub>1</sub> or FVC of at least 12% and 0.2 L after bronchodilation is often considered diagnostic for asthma, including according to the Finnish guideline (6,10,15). GINA recommends using a threshold of 12% and 0.2 L for adults, while for children, it recommends an increase of 12%

of the predicted FEV<sub>1</sub> value (4). Other proposed cut-off criteria include a 10% increase in predicted FEV<sub>1</sub> (58) and a 12% increase from baseline without an absolute volume requirement (59). The diagnostic cut-off values recommended by GINA for detecting BDR using PEF are an increase of 20% for adults and 15% for children, respectively (4). ERS guidelines do not provide PEF cut-off values for BDR testing, whereas Finnish guidelines only include them for home PEF monitoring, which will be discussed separately in Section 2.2.6 (6,10,15).

If lung function measured at baseline indicates signs of obstruction (z-score of FEV<sub>1</sub>/FVC ratio of less than -1.65), the likelihood of asthma is higher, although not certain (10). Bronchial reversibility testing appears to be highly specific but not very sensitive. Correspondingly, it has a high positive predictive value (PPV) and a relatively poor negative predictive value (NPV) (60,61). Therefore, confirmed BDR significantly enhances the probability of asthma, but a negative test result does not necessarily rule it out. Thus, BDR testing is more effective for establishing an asthma diagnosis than for excluding it.

## 2.2.4 Direct Bronchial Challenge

Detecting the bronchial hyperreactivity characteristic of asthma can be achieved through direct or indirect bronchial challenge testing. A methacholine challenge is the most used type of test, although histamine can also be utilized. Methacholine is preferred due to its fewer systemic side effects compared to histamine (62). Direct stimuli, including methacholine and histamine, are cholinergic agonists that trigger bronchoconstriction. Methacholine exerts its effects by binding to muscarinic receptors on ASM, resulting in muscle contraction and a subsequent decrease in airway caliber (63). Patients with airway hyperresponsiveness exhibit increased sensitivity to muscarinic agonists, a steeper dose–response curve slope, and a greater maximal response. The less methacholine needed to induce a certain level of airway obstruction, the more hyperreactive the airways are (64,65).

Before administration of methacholine, baseline lung function is assessed using spirometry. This is followed by a diluent step with a saline solution. After the diluent, progressively increasing doses of methacholine are administered at 5-minute intervals, with spirometry measurements performed concurrently. After the methacholine challenge, bronchodilator medication is administered. The results are determined by calculating the cumulative dose of methacholine that caused a 20% reduction in FEV<sub>1</sub> from baseline (PD<sub>20</sub>FEV<sub>1</sub>) (65). Additionally, some sources

calculate the provocative concentration that causes a 20% decrease in FEV<sub>1</sub> (PC<sub>20</sub>FEV<sub>1</sub>) instead of using a cumulative dose (6,15).

The results from the methacholine challenge can be used to classify individuals into four categories. A PD<sub>20</sub>FEV<sub>1</sub> greater than 2600 µg is categorized as no hyperresponsiveness, a PD<sub>20</sub>FEV<sub>1</sub> of 601-2600 µg indicates mild hyperresponsiveness, a PD<sub>20</sub>FEV<sub>1</sub> of 151-600 µg suggests moderate hyperresponsiveness, and a PD<sub>20</sub>FEV<sub>1</sub> of 150 µg or less signifies marked hyperresponsiveness (65). A PD<sub>20</sub>FEV<sub>1</sub> of 600 µg or less is considered diagnostic for asthma, according to Finnish guidelines (10).

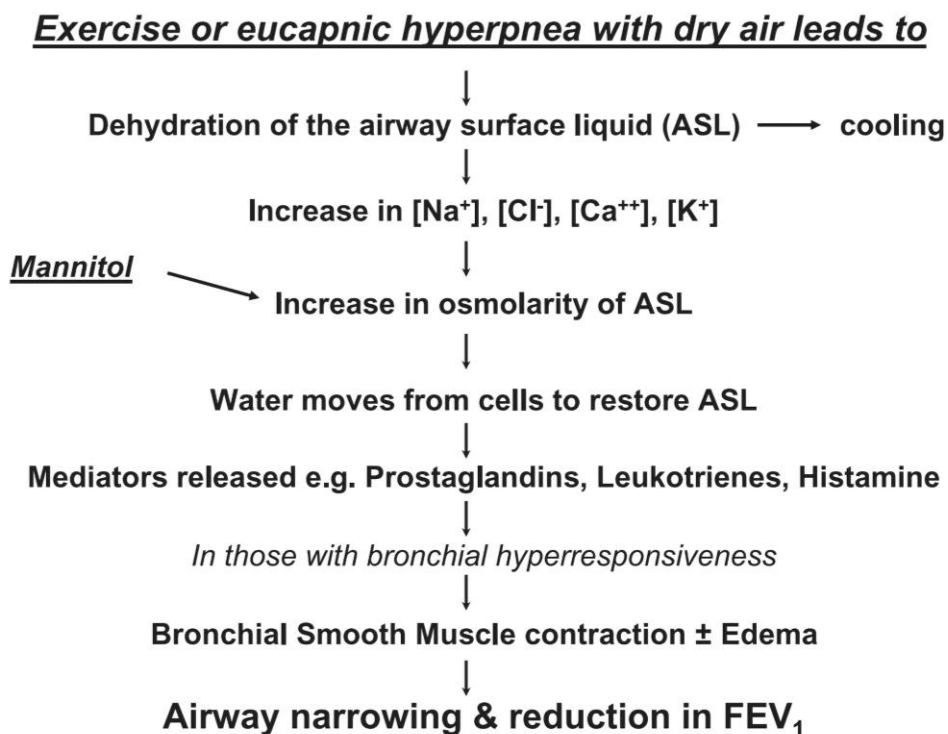
The recommendations from GINA are less rigorous regarding methacholine challenge testing. They only suggest a cut-off value of a 20% decrease in FEV<sub>1</sub> using “standard doses” of methacholine as a positive result but do not specify the exact definition of these “standard doses” (4). ERS recommends a diagnostic cut-off PC<sub>20</sub>FEV<sub>1</sub> value of 8 mg/ml or less for the methacholine challenge test in both adults and children aged five years or older (6,15). In contrast, GINA and Finnish guidelines do not recommend a methacholine challenge for children under 12 years old, and there is limited research on the optimal diagnostic cut-off value for this population (4,10).

Absence of bronchial hyperresponsiveness (PD<sub>20</sub>FEV<sub>1</sub> > 2600 µg) typically excludes a diagnosis of asthma. However, in some cases, hyperreactivity may not yet be present in the early stages of asthma (10). The methacholine challenge test is very sensitive and has high NPV, which makes it a valuable instrument for excluding the possibility of asthma (61,66). Nevertheless, airway hyperresponsiveness to methacholine has also been described in several other airway diseases, such as rhinitis, chronic bronchitis, and cystic fibrosis (67–69). Coupled with the observation that direct bronchial challenge testing generally lacks specificity and has lower PPV compared to indirect challenges, the methacholine challenge may not be optimal for confirming a diagnosis of asthma. Yet, if significant methacholine-induced airway obstruction is achieved using low doses, specificity and PPV increase to levels comparable to those of indirect challenge testing (4,70).

## 2.2.5 Indirect Bronchial Challenge

Indirect bronchial challenge testing reveals the propensity for airway hyperresponsiveness through a mechanism involving the release of endogenous mediators, which cause ASM to contract (Figure 4). Indirect stimuli, such as exercise

or eucapnic voluntary hyperpnea, lead to airway dehydration because large volumes of air must be warmed and moisturized. Water evaporation from the epithelial lining fluid cools the airway surfaces and increases the osmolarity of the airway surface liquid (ASL). The mannitol test similarly raises the osmolarity of ASL. The resulting increase in osmolarity, whether due to ventilation or mannitol, causes water to move out of the cells lining the airways via an osmotic gradient. This shift in cell volume is thought to activate mast cells, basophils, and eosinophils to release inflammatory mediators, such as prostaglandins, leukotrienes, and histamine. In individuals with bronchial hyperresponsiveness, these mediators act on ASM, leading to airway obstruction (71). Cooling of the bronchial surface may also contribute to airway narrowing through reactive hyperemia (72). However, evidence indicates that cooling alone may not be a sufficient stimulus for bronchoconstriction (73). The reduction in lung function caused by indirect bronchial challenge testing can be quantified via spirometry and used to support the diagnosis of asthma (10).



**Figure 4.** The pathophysiological mechanism of airway obstruction induced by indirect bronchial challenge testing. Modified from Anderson 2010 (74).

Exercise challenge testing relies on the detection of EIB (75,76). In children, it is usually the most sensitive diagnostic tool available for asthma (10). For adults, exercise challenge testing is ideally performed indoors on a treadmill, while outdoor free running is used for children. Spiroergometry may also be used for this purpose, although it demonstrates lower sensitivity than running due to the lower level of ventilation achieved. After exercise begins, intensity is rapidly increased to near-maximal levels within 1–3 minutes. The intense exercise continues for a total of 6–8 minutes. A satisfactory level of intensity is confirmed by monitoring heart rate, with the last 4–6 minutes required to exceed 85% of the theoretical maximum (77). To obtain reliable results, the air passing through the lungs needs to have a low level of absolute humidity (78).

Lung function is initially assessed at baseline using spirometry before exercise. Measurements are repeated immediately after the cessation of running and subsequently at varying time intervals afterward or until spontaneous resolution of airway obstruction is observed. A bronchodilator is then administered, and spirometry is repeated after 10–15 minutes (77).

According to Finnish guidelines, the cut-off value for significant EIB is a 15% decrease in FEV<sub>1</sub> for both children and adults. A reduction in FEV<sub>1</sub> of 10%–14% suggests possible asthma but is not diagnostic (10). The diagnostic cut-off values provided by GINA for exercise challenge are a 10% and 0.2 L decrease in FEV<sub>1</sub> for adults and a reduction of 12% in predicted FEV<sub>1</sub> for children (4). ERS recommends a cut-off value of a 10% decrease in FEV<sub>1</sub> as diagnostic for both adults and children (6,15). Additionally, GINA recommends using a 20% reduction in PEF for adults and a 15% decrease in PEF for children as alternatives to spirometry (4).

It has been theorized that, since naturally occurring stimuli in asthma act through indirect mechanisms, airway responsiveness detected by indirect challenge testing should correlate more closely with the clinical manifestations of the disease (79). Indirect airway hyperresponsiveness correlates more strongly with eosinophilic airway inflammation than direct airway hyperresponsiveness. Furthermore, indirect bronchial challenge testing typically exhibits greater specificity and higher PPV. This may make it a more reliable method for confirming an asthma diagnosis than for excluding it (80).

## 2.2.6 Diurnal Home PEF Monitoring

Lung function in asthma patients is widely known to follow a circadian rhythm, with symptoms commonly worsening at night or early in the morning (10). Even in healthy individuals, lung function typically reaches its lowest point around 4:00 a.m. and peaks around noon (81). Asthma patients who experience early-morning flare-ups have been identified as having reduced levels of epinephrine in their serum at corresponding times. This is coupled with increases in vagus nerve tone, cholinergic activity, esophageal reflux, and eosinophils in the bloodstream during the night and morning hours. These observations could shed light on the underlying mechanisms that cause the detected effects (82). Home monitoring allows for, over time, continuous observation of the diurnal variation of lung function characteristic of asthma. Currently, all relevant guidelines recommend the use of PEF meters for this purpose, at least in certain situations (4,6,10,15). In children, home PEF monitoring is suitable from 12 years onwards (10).

Over a period of two weeks, measurements are systematically recorded twice daily, first upon awakening and then in the evening. Ideally, these measurements should be conducted at identical times each day. Each measurement point involves recording three consecutive forceful exhalations. Following this, 400 µg of salbutamol or 1000 µg of terbutaline is inhaled, and three additional measurements are recorded 15–20 minutes after drug administration. The highest PEF value from each set of three exhalations is selected for analysis. If significant symptoms of airway obstruction occur, additional measurements beyond the standard twice-daily recordings are performed. The PEF values reported by the meter are manually documented in a form, along with a symptom diary (83).

According to Finnish guidelines, the diagnosis of asthma is confirmed when the diurnal PEF variation observed over a two-week monitoring period reaches a minimum of 20% and 60 L/min on at least three separate occasions (83). In contrast, GINA recommends a different set of cut-off values. They suggest an average diurnal PEF variation of 10% for adults and 13% for children across a two-week monitoring period (4). ERS recommends a diagnostic cut-off value of 20% for diurnal PEF variation in adults and 12% in children. However, it remains unspecified whether this value pertains to an average taken over multiple days or a single instance (6,15).

Globally, the assessment of BDR is not very common in the context of home PEF monitoring. Nevertheless, in Finland, the detection of BDR through PEF monitoring is also used in the diagnosis of asthma. For adults, a minimum increase of 15% and 60 L/min in PEF after bronchodilator administration must be observed

at least three times during the monitoring period to establish a diagnosis of asthma using this criterion. In children, the diagnostic threshold requires only a 15% increase in PEF on at least three occasions during the monitoring period, with no specific volume requirement (83).

One of the benefits of using home PEF monitoring as a diagnostic method is its ability to track changes in lung function over longer periods. This allows for a more comprehensive view of the variability present in lung function rather than a single measurement at one time point. However, a significant challenge to the reliability of home PEF monitoring is the relatively low compliance rate observed in some studies. There have even been reports of fabrication rates of up to 60% for the results. Nonetheless, it is worth noting that the monitoring periods in these studies were significantly longer than the typical two-week duration (84,85). Some evidence indicates that connecting an electronic PEF meter to a smartphone application, which enables self-monitoring, could potentially enhance compliance (86). Diurnal variability in home PEF monitoring yields high specificity and PPV, although sensitivity and NPV seem to achieve less impressive values (87). This suggests that home PEF monitoring may be more suitable for confirming, rather than excluding, a diagnosis of asthma.

## 2.3 Measuring Equipment and Technique

### 2.3.1 Spirometry Equipment

Spirometers are generally categorized into closed- and open-circuit designs and are usually situated in laboratory settings due to their considerable size. Closed-circuit spirometers collect air using a piston or bellow, while measurements are captured by a moving recording system. Open-circuit spirometers, in contrast, do not collect air but instead utilize various methods to measure airflow and calculate parameters from those measurements. A turbine flow meter is the most common type of open-circuit spirometer. It records the rate at which turbines inside the device rotate and uses this information, through proportionality, to derive the flow measurement. Hotwire spirometers use a heated metal wire; as air flows through, it cools the wire. This cooling effect is then used to calculate various lung function parameters. Pneumotachographs measure differences in pressure created by airflow passing

through a specific resistance, while ultrasound spirometers can operate using any of the previously mentioned open-circuit methods (46).

A spirometer must be capable of measuring volume continuously for at least 15 seconds. It should have a volume measurement capacity of at least 8 liters, with a maximum permissible error of  $\pm 2.5\%$ . While it is recommended that a spirometer display both flow–volume and volume–time graphs, the flow–volume curve offers more profound insights into the first second of the expiratory maneuver, during which FEV<sub>1</sub> and PEF are recorded. The flow–volume curve generated during spirometry serves as a critical tool for evaluating the intensity of effort exerted by the patient during exhalation. This assessment is vital for determining the technical reliability of the measurements obtained (50,88).

Traditionally, spirometry has been conducted in clinics due to the large and non-portable nature of laboratory spirometers, limiting its availability for home monitoring. However, in recent years, compact handheld spirometers have emerged for this purpose (49,89). Conflicting findings have been reported regarding the accuracy of handheld spirometers, with evidence suggesting that the manufacturer may also influence performance. Some studies report that portable microspirometers yield high compliance and reliable results comparable to those of gold-standard laboratory spirometers, while others indicate that the results from handheld spirometers may not be interchangeable with those obtained from traditional laboratory spirometry (90–99). While home spirometry monitoring appears to hold promise as a tool for remote over-time monitoring of lung function, its effectiveness is unclear, and it is undeniable that more research is needed, particularly in assessing its clinical usefulness for diagnosing asthma.

### 2.3.2 Peak Flow Meters

The peak flow meter is a small, portable handheld device that only measures the highest rate of airflow and cannot calculate other lung function parameters. PEF meters are routinely used for home monitoring because they are easy to use, affordable, and widely available. The most common PEF meters are designed as plastic cylinders with a mouthpiece attached to one end. The cylinder's body includes a display that presents the recorded measurements (49). A PEF meter should have an accuracy and intra-device reproducibility of less than  $\pm 10\%$  or  $\pm 0.3$  L/s (20 L/min), whichever is larger (50).

Many PEF meters from different manufacturers exhibit significant variation in the results they produce, and results obtained using different PEF meters are therefore usually not interchangeable (100–102). Some observations also suggest that PEF values obtained from a spirometer and a PEF meter may not always be directly comparable (103). It is possible that differences in the devices themselves could contribute to this observed discrepancy, and there is some research to support this theory (104). Our research group’s previous findings demonstrated that using the same blowing technique, whether with a laboratory spirometer or a PEF meter, resulted in small but statistically significant differences in PEF outcomes. However, further analysis indicated that these differences were too small to be clinically relevant (unpublished). It is worth noting that due to the wide variety of technologies used in different spirometers and PEF meters, a difference observed in one pair of devices does not necessarily imply a difference in other comparisons.

PEF meters do not generate any graphical representation of the expiratory maneuver. This limitation makes it difficult to assess the quality of the blows, preventing the exclusion of faulty measurements that could potentially skew results.

### 2.3.3 Blowing Technique

The blowing technique used for spirometry differs slightly from the technique typically utilized for PEF monitoring. Both spirometry and PEF recording begin with the patient sitting in good posture and the head slightly elevated. A nose clip is attached for spirometry, which is not required for PEF measurement. The patient places the mouthpiece of either device in their mouth and closes their lips securely around the mouthpiece to prevent any air from escaping during breathing. The patient then rapidly inhales to total lung capacity and exhales as forcefully as possible. The pause at total lung capacity should be as brief as possible, with a requirement of under one second being standard. During spirometry, exhalation continues until no more air flows out of the lungs. For PEF recording, the exhalation maneuver is more explosive and does not need to extend long after PEF is reached. Both spirometry and PEF measurements are performed at least three times in one sitting, with some recovery time between blows (50).

The data regarding the extent to which varying blowing technique affects PEF recordings obtained from the same device, whether a spirometer or a PEF meter, are inconclusive. Most evidence suggests that employing a prolonged spirometry-style expiratory maneuver may yield PEF values that are lower than those produced

by a short and explosive blowing technique associated with PEF recording. In some studies, the difference is quite significant, while in others, it is minimal (105,106). Therefore, whether the observed discrepancies between long and short blows carry clinical significance and should affect decision-making is unclear. Nevertheless, this may help explain some of the previously discussed differences between PEF measurements obtained using spirometry and a PEF meter (103).

## 2.4 Relationship Between PEF and FEV<sub>1</sub>

### 2.4.1 Comparison of Diagnostic Parameters

The gold standard for measuring lung function in the context of BDR testing and bronchial challenge testing is FEV<sub>1</sub> measured by spirometry, while PEF is usually recommended as an alternative. Home monitoring guidelines rely exclusively on PEF monitoring (4,6,10). It is essential to understand the differences in the sensitivity, specificity, PPV, and NPV of the available diagnostic parameters across various situations, considering each metric independently. This enables clinicians to select the most appropriate tools for accurate diagnosis in different contexts. However, it is equally important to study how these variables behave in relation to one another. Even when two parameters show similar performance relative to a third metric, they may still identify substantially different patient populations due to various underlying factors. Considering current diagnostic guidelines, understanding how changes in PEF reflect changes in FEV<sub>1</sub> is crucial.

### 2.4.2 During Baseline Lung Function

When lung function is measured without induced bronchoconstriction or bronchodilation, the baseline state of the bronchi can be observed. In people with asthma, this baseline can vary drastically over time. In many patients, some degree of airway constriction will be present and observable, allowing the relationship between PEF and FEV<sub>1</sub> to be studied during obstruction (107). Obstruction detection at baseline is typically accomplished by comparing measurements to the relevant reference values, with the diagnostic cut-off being a specific percentage of the predicted value. Understanding the relationship between PEF and FEV<sub>1</sub> at baseline is particularly relevant for home monitoring, as it primarily captures

spontaneous asthma-related diurnal changes in lung function rather than responses to externally induced stimuli.

A correlation coefficient ranging from 0.00 to 0.30 is considered negligible, 0.31 to 0.50 is weak, 0.51 to 0.70 is moderate, 0.71 to 0.90 is strong, and 0.91 to 1.00 is very strong (108). Multiple studies have suggested that the correlation between PEF and FEV<sub>1</sub> in adults at baseline ranges from strong to very strong, with correlation coefficients between 0.73 and 0.91. While the correlation between PEF and FEV<sub>1</sub> at baseline is generally high at the group level, considerable variation exists in the populations identified by each parameter. This is because many patients exhibit significant discrepancies between their PEF and FEV<sub>1</sub> values at the individual level (109–114). Interestingly, one study found that the correlation between PEF and FEV<sub>1</sub> measured at baseline in females was slightly weaker compared to males, with correlation coefficients of 0.73 and 0.77, respectively (109). One study found that in adults, the baseline percent predicted values for PEF were significantly higher than those for FEV<sub>1</sub> (11). Baseline PEF has also been reported to overestimate mild obstruction but underestimate severe obstruction in adults (109).

The correlation between PEF and FEV<sub>1</sub> measured at baseline has been studied less in children. One study found a large discrepancy between the correlation of absolute PEF and FEV<sub>1</sub> values and the correlation of percent predicted values of PEF and FEV<sub>1</sub> in children. The correlation between absolute PEF and FEV<sub>1</sub> values measured at baseline was weak, with a correlation coefficient of 0.36. In contrast, the correlation between the percent predicted values of PEF and FEV<sub>1</sub> measured at baseline was very strong, with a coefficient of 0.91 (115). In children, the correlation between FEV<sub>1</sub> measured at baseline and the severity of asthma seems more substantial than the correlation between PEF measured at baseline and the severity of asthma (12).

The ability of various explicitly defined cut-off values for PEF decrease from the predicted baseline value to detect obstruction, defined as a sufficient reduction in FEV<sub>1</sub> relative to the predicted value, can be expressed in terms of sensitivity, specificity, PPV, and NPV. One study found that in adults, low PEF measured at baseline had a sensitivity of 83%, specificity of 76%, PPV of 47%, and NPV of 94% in detecting low FEV<sub>1</sub> measured at baseline (111). For children, two relevant studies were identified, showing sensitivities ranging from 36% to 87%, specificities from 73% to 97%, PPVs from 33% to 71%, and NPVs from 88% to 96% (110,115). The data are conflicting since two studies (one in children and one in adults) indicate that detection of low PEF at baseline has higher sensitivity than specificity (110,111), while one study (in children) shows that low PEF at baseline has much higher

specificity than sensitivity (115). NPV was significantly higher than PPV in all three studies (110,111,115).

Evidence suggests that the ability of PEF to detect airway obstruction is maximized when multiple measurements are conducted over time, such as during home monitoring (9). Some studies have found the accuracy of PEF to be as high as that of FEV<sub>1</sub> in diagnosing bronchial obstruction during long-term monitoring (116,117). However, substantial evidence also highlights certain limitations of PEF, even within this framework (118).

### 2.4.3 During Induced Bronchoconstriction

Changes in PEF and FEV<sub>1</sub> can be assessed during induced airway obstruction via bronchial challenge testing. Since obstruction induced by external stimuli is typically more severe than that caused by natural diurnal variation, the relationship between changes in PEF and FEV<sub>1</sub> may differ depending on the underlying cause. Reduction in lung function is typically quantified either as the change expressed relative to the predicted value or as the change expressed relative to the baseline value. Sometimes, absolute changes in PEF and FEV<sub>1</sub> before and after a bronchial challenge are also compared.

In one study, the correlation between changes in PEF and FEV<sub>1</sub> in adults ranged from negligible to moderate, with correlation coefficients between 0.27 and 0.69, depending on the type of challenge (119). During children's indirect bronchial challenge testing, the correlation between maximal relative changes in PEF and FEV<sub>1</sub> was found to be moderate in one study, with a correlation coefficient of 0.65 (120). In children, during a direct bronchial challenge with histamine, the correlation between the cumulative dose of histamine that causes a 20% decrease in PEF from baseline (PD<sub>20</sub>PEF) and PD<sub>20</sub>FEV<sub>1</sub> was strong, with a correlation coefficient of 0.76 (121). Change in PEF was, on average, less than change in FEV<sub>1</sub> in both children and adults (119,121)

In adults, during direct bronchial challenge testing, PEF decrease demonstrated sensitivities ranging from 44% to 74% and specificities from 71% to 100% in detecting a decrease in FEV<sub>1</sub>, depending on the chosen cut-off value. The corresponding PPV ranged from 60% to 80%, while NPV varied from 50% to 84% (119,122). A study of direct bronchial challenge testing in children concluded that changes in PEF have poor sensitivity for detecting obstruction compared to changes in FEV<sub>1</sub>. However, that study did not assess the ability of PEF reduction to detect a

decrease in FEV<sub>1</sub>. Instead, it compared the two variables independently and, as such, did not truly examine the relationship between them (121).

In adults, during indirect bronchial challenge testing, decrease in PEF achieved sensitivities ranging from 12% to 100% and specificities from 66% to 100% in detecting decrease in FEV<sub>1</sub> (119,123,124). Only one study examined the PPV and NPV of PEF changes in detecting a decrease in FEV<sub>1</sub> in adults, showing that PPV across different PEF cut-off values ranged from 96% to 100% and NPV from 66% to 90% (124). No data were found on the relationship between changes in PEF and FEV<sub>1</sub> during indirect bronchial challenge testing in children. Overall, during bronchial challenge testing, change in PEF generally displays higher specificity compared to sensitivity, and PPV often exceeds NPV. However, not all studies concur with these findings (119,122–125).

#### 2.4.4 During Bronchodilation

The relationship between changes in PEF and FEV<sub>1</sub> may differ when lung function improves rather than deteriorates. Examining these lung function parameters during BDR testing enables the evaluation of this relationship. Improvement in lung function is usually quantified either as the change expressed relative to the predicted value or as the change expressed relative to the baseline value. In some cases, absolute changes in PEF and FEV<sub>1</sub> from baseline are also compared.

In adults, the correlation between relative increases in PEF and FEV<sub>1</sub> during BDR testing varied from negligible to moderate, with correlation coefficients ranging from 0.28 to 0.67 (111,126–128). In children, the same correlation was observed to be moderate, with correlation coefficients ranging from 0.48 to 0.54 (115,129). One study showed that the average relative improvement in PEF and FEV<sub>1</sub> was comparable after bronchodilation (128).

In adults, during BDR testing, PEF increase demonstrated sensitivities ranging from 6% to 85%, specificities from 43% to 99%, PPVs from 14% to 92%, and NPVs from 40% to 98% in detecting improvement in FEV<sub>1</sub> (111,122,126–128). In children, one relevant study reported that different cut-off levels in PEF change had sensitivities ranging from 20% to 67%, specificities from 81% to 97%, PPVs from 70% to 85%, and NPVs from 65% to 79% (115). In general, PEF increase during bronchodilation seems to have low sensitivity but a high degree of specificity, while NPV is often higher than PPV. However, there is a significant level of disagreement between the different studies (111,115,126–128).

## 2.4.5 Explanatory Factors

The relationship between PEF and FEV<sub>1</sub> appears to vary depending on the context, such as whether lung function is assessed at baseline, during induced obstruction, or after bronchodilation. It also differs based on whether absolute values or relative changes over time are evaluated. Many studies have reported conflicting and sometimes even opposite results, even within the same setting. A multitude of factors may help explain these observations.

The populations studied varied significantly; some studies only included individuals with obstructive pulmonary diseases (115,128), while others completely excluded people with asthma (111,126), and some encompassed both groups (119,122). Various age groups have also been utilized in various studies. Children's airways are narrower and more prone to obstruction (130). The pediatric chest wall, airways, and surrounding structures are also more compliant than those of adults (131). Consequently, the relationship between changes in PEF and FEV<sub>1</sub> during obstruction or bronchodilation may vary substantially with the degree of airway maturation. Even within adult populations, age may influence results since respiratory muscle strength and PEF are known to decline with age. One study even observed significant differences in the relation of changes in PEF and FEV<sub>1</sub> between older and younger adults, with the usefulness of PEF declining with age (126).

The equipment, and most likely also the blowing technique used to record PEF and FEV<sub>1</sub>, varied across studies. In some cases, PEF and FEV<sub>1</sub> were recorded using separate devices (119,123), while others recorded measurements on the same device from the same exhalation (111). In addition to the potential inaccuracies and systematic errors associated with using different devices, it is particularly important to consider that correct blowing technique cannot be assessed from PEF values alone. When PEF is recorded with a spirometer, unreliable measurements can be identified and excluded by visually analyzing the flow–volume curve produced. This becomes impossible when using PEF meters. Additionally, in the context of BDR testing, some studies used recommended doses of bronchodilator agents (111,127), while others used non-standard doses (115).

Different studies have used a wide range of cut-off values for both PEF and FEV<sub>1</sub> (115,119,122,124,126,127). Generally, the higher the cut-off value for PEF, the lower the sensitivity and NPV, and the higher the corresponding specificity and PPV. It is also important to note that the current guidelines regarding cut-off values for FEV<sub>1</sub>, at least in the context of BDR testing, may not be optimal (132). Changes in PEF and FEV<sub>1</sub> were calculated in various ways across studies. Some studies

expressed changes in lung function relative to predicted values (111,126,128), while others calculated changes relative to pre-stimulus values (119,124,127); still others only assessed changes in absolute values (123).

## 2.4.6 Interpretation and Knowledge Gaps

To accurately interpret the findings of the studies discussed, it is essential to understand that sensitivity and specificity are inherent properties of the test itself, while PPV and NPV are influenced by the prevalence of the condition within the population being examined. Therefore, while PPV and NPV can offer valuable insights into the diagnostic accuracy of PEF, they are context-dependent and likely to vary across studies based on population characteristics (133).

For baseline lung function assessment, the few studies available found that, in relation to FEV<sub>1</sub>, PEF achieved higher NPVs than PPVs, suggesting that it may be more suitable for ruling out rather than confirming a diagnosis of asthma (110,111,115). However, data on sensitivity and specificity were conflicting and remain inconclusive due to limited evidence in both children and adults, preventing reliable conclusions at this time.

During induced obstruction, PEF change appeared to confirm the presence of asthma more accurately than to exclude it, due to the high specificity and PPV reported in some studies (119,123,124). Nevertheless, inconsistencies remain in the data, and currently, no PPV or NPV data are available for direct bronchial challenge testing. In children, the diagnostic characteristics of PEF decrease during direct bronchial challenges are poorly documented, and there is a complete absence of data on indirect bronchial challenge testing. This is particularly notable given that GINA recommends PEF as an alternative to FEV<sub>1</sub> for exercise challenge testing in children, and provides a corresponding cut-off value (4).

Data on bronchodilation mostly point to PEF change having high specificity relative to its sensitivity, suggesting that PEF may be more useful for confirming an asthma diagnosis (115,128). However, several studies have also found significantly higher NPVs than PPVs (111,127). There is variation in findings across studies, reflecting ongoing disagreement. Particularly in children, there is insufficient evidence regarding the ability of PEF increase to detect improvement in FEV<sub>1</sub>.

As highlighted in the literature review, the relationship between PEF and FEV<sub>1</sub>, and the changes in these parameters during bronchoconstriction and bronchodilation, remain unclear across both adult and pediatric populations. Further

research is needed to evaluate how accurately PEF change reflects changes in FEV<sub>1</sub> and in bronchial caliber across different contexts. This research should explore both the currently recommended cut-off values and the potential for more effective ones. It should adhere to the recommended bronchodilator medication doses, include sufficiently large patient populations representative of real-world clinical practice, and measure PEF from the same exhalation as FEV<sub>1</sub> using reliable equipment.

### 3 AIMS OF THE STUDY

The aim of this dissertation was to evaluate the relationship between changes in PEF and FEV<sub>1</sub> during bronchoconstriction and bronchodilation through various types of bronchial challenges and bronchodilator tests in both adults and children. The specific aims were as follows:

1. To assess how accurately change in PEF reflects airway obstruction, as defined by decrease in FEV<sub>1</sub>, in children during an exercise challenge test, and to determine whether the currently recommended cut-off value for PEF decrease is optimal for accurate diagnosis of EIB (Study I).
2. To assess how accurately change in PEF reflects airway obstruction, as defined by decrease in FEV<sub>1</sub>, in adults during a methacholine challenge test (Study II).
3. To assess how accurately change in PEF reflects bronchodilation, as defined by increase in FEV<sub>1</sub>, in children following the administration of salbutamol after an exercise challenge test (Study III).
4. To assess how accurately change in PEF reflects bronchodilation, as defined by increase in FEV<sub>1</sub>, in adults following the administration of salbutamol after a methacholine challenge test (Study IV).

## 4 METHODS

### 4.1 Study Design

This dissertation comprises four separate retrospective chart reviews. The medical histories of all study subjects were obtained from patient records.

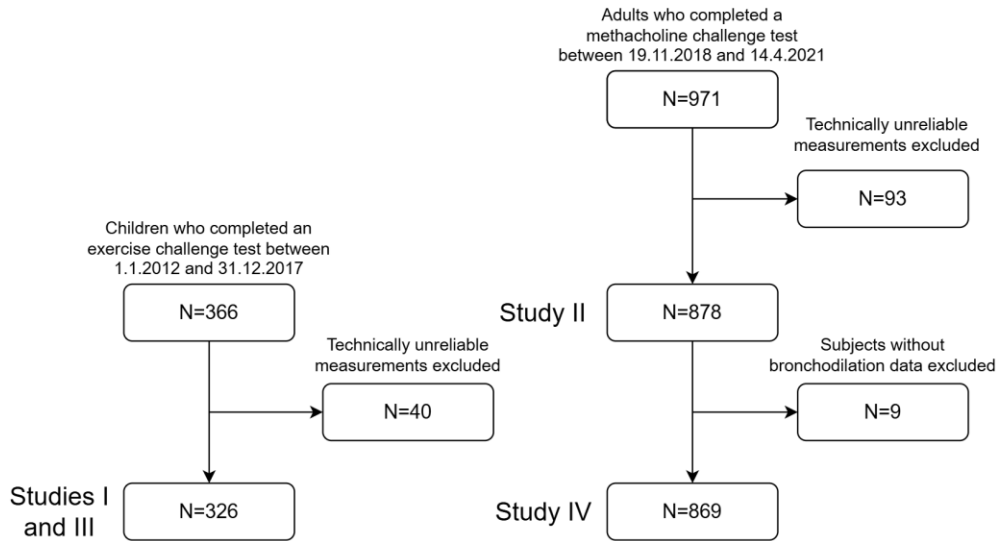
#### 4.1.1 Exercise Challenge Subjects

For Studies I and III, we retrospectively collected all free-running exercise challenge tests with spirometry conducted for children at Tampere University Hospital between January 1, 2012, and December 31, 2017. To determine the appropriate sample size for statistical significance, our primary analysis was “What are the sensitivity and specificity of a PEF decrease  $\geq 15\%$  in identifying EIB, defined as a decrease in FEV<sub>1</sub> of  $\geq 15\%$ ?” We estimated the sensitivity and specificity to be 0.85 and 0.65, respectively. Based on our research group’s previous project, we know that approximately 20% of exercise challenge tests are positive (i.e., FEV<sub>1</sub> decreases by at least 15%). Using a precision margin of 0.1 and an alpha error of 5%, the required sample size was 245 tests. We identified 366 exercise challenge tests conducted on children from our data sources during the study period, thus fulfilling the necessary sample size. After assessing the technical reliability of the spirometry measurements and excluding technically unreliable ones, 326 subjects remained (Figure 5).

#### 4.1.2 Methacholine Challenge Subjects

For Studies II and IV, we retrospectively collected all methacholine challenge tests with spirometry conducted for adults at Tampere University Hospital between November 19, 2018, and April 14, 2021. Due to the similarity in the analysis planned for Studies II and IV compared to Studies I and III, the required sample size was also similar. We identified 971 methacholine challenge tests conducted on adults

from our data sources during the study period, which clearly exceeded the required sample size. Patients with technically unreliable spirometry measurements were excluded, leaving 878 study subjects. For Study IV, patients with missing bronchodilation data were excluded, resulting in a total of 869 subjects (Figure 5).



**Figure 5.** A flowchart visualizing the selection process of study subjects. The designated population of each study is specified.

## 4.2 Protocols

### 4.2.1 Spirometry

Spirometry (measured with Vyntus® Pneumo, Vyair Medical Inc., Illinois, USA) was performed according to international guidelines (88). Trained physicians visually evaluated the patients’ blowing technique and the technical reliability and reproducibility of the measurements. Measurements were deemed technically reliable if the spirometry maneuvers before and after the stimulus met the quality standards set by international guidelines (50,88). We excluded data that were clearly faulty due to human or technical error. Outliers were not excluded if they were technically reliable. We collected FEV<sub>1</sub>, PEF, and FVC from all spirometries.

## 4.2.2 Exercise Challenge Protocol

The exercise challenge test was performed according to international guidelines (76). First, spirometry was performed inside the hospital laboratory. Then, the subjects were taken outdoors for the exercise challenge, which consisted of running in the hospital yard. The mean values for air humidity, temperature, and relative humidity of outdoor air during the tests were 5 g/m<sup>3</sup>, 4 °C, and 77%, respectively. Experienced nurses monitored heart rate and exercise intensity. The exercise level was considered sufficient if the heart rate (measured with FT4, Polar Ltd, Kempele, Finland) exceeded 85% of the theoretical maximum (205 – age/2 beats per minute), and the exercise duration was over 6 minutes or if symptoms appeared. Afterward, the subjects returned to the laboratory for additional spirometry measurements conducted at 2, 5, 10, and 15 minutes post-exercise. EIB was defined as a 15% reduction in FEV<sub>1</sub>. Children under 10 years of age received 300 µg, and those 10 years or over received 400 µg of salbutamol via a pressurized metered-dose inhaler (pMDI) with a spacer (Ventoline Evohaler and Volumatic, GSK). Spirometry was repeated 15 minutes after salbutamol inhalation. BDR was defined as a 12% and 0.2 L increase in FEV<sub>1</sub> (10,15).

## 4.2.3 Methacholine Challenge Protocol

Experienced technicians conducted the methacholine challenge test using the dosimetric method of Nieminen et al. in accordance with Finnish and international guidelines (65,66,134). Spirometry was first performed at baseline. After the initial measurements, a diluent step with saline solution was applied, and spirometry was repeated. Then, methacholine doses of 18, 72, 270, 810, and 2600 µg were administered (using Vyntus® APS, Vyaire Medical Inc., Illinois, USA) at 5-minute intervals. Spirometry measurements were performed concurrently after each methacholine dose. The methacholine challenge results were calculated using PD<sub>20</sub>FEV<sub>1</sub>. After the challenge, 400 µg of salbutamol was administered using a pMDI with a spacer (Ventoline Evohaler and Volumatic, GSK), and a final spirometry measurement was recorded 10 minutes later. BDR was defined as a 12% and 0.2 L increase in FEV<sub>1</sub> (4,6,10).

### 4.3 Statistics

IBM SPSS Statistics for Windows, Version 27 (IBM Corp., NY, USA) and R, Version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria), were used for the data analysis. Additionally, some calculations were performed using Microsoft Excel for Microsoft 365 MSO, Version 2110 (Microsoft Corp., WA, USA). Regression analysis was used to assess the relationship between relative changes in PEF and FEV<sub>1</sub> during airway obstruction and relaxation, and a Pearson correlation coefficient was calculated (108). To better visualize the differences between the relative changes of the two variables, a Bland–Altman plot was constructed (135). Receiver operating characteristic (ROC) analysis,

$$\text{sensitivity} \left( \frac{\text{(true positive)}}{\text{(true positive)} + \text{(false negative)}} * 100 \right),$$

$$\text{specificity} \left( \frac{\text{(true negative)}}{\text{(false positive)} + \text{(true negative)}} * 100 \right),$$

$$\text{PPV} \left( \frac{\text{(true positive)}}{\text{(true positive)} + \text{(false positive)}} * 100 \right),$$

$$\text{NPV} \left( \frac{\text{(true negative)}}{\text{(false negative)} + \text{(true negative)}} * 100 \right),$$

and Cohen’s kappa coefficient were used to compare changes in PEF and FEV<sub>1</sub> as outcome measures (136,137).

In Studies I and II, the relative decreases in PEF and FEV<sub>1</sub> during obstruction were calculated as follows:

$$\frac{\text{(pre – challenge PEF or FEV1)} - \text{(post – challenge PEF or FEV1)}}{\text{(pre – challenge PEF or FEV1)}} * 100$$

In Study I, each recorded PEF and FEV<sub>1</sub> measurement after exercise but before bronchodilation (up to four measurements per child) was included in the regression analysis, Bland–Altman plot, and ROC curve. Consequently, the total number of data points (n = 1237) was significantly larger than the number of study subjects (n = 326). Since the results of the exercise challenge test in clinical practice (EIB or not) are independent of the time point at which a certain decrease in PEF or FEV<sub>1</sub> is reached, we conducted sensitivity, specificity, PPV, NPV, and kappa analyses independently of the time point. We assessed how accurately decreases in PEF (10%,

15%, 20%, 25%, and 30%) at any time point after the exercise detected the presence of a decrease in FEV<sub>1</sub> (10% or 15%) at any time point after the exercise. Additionally, considering that the reliability of the measurement is often unverifiable when using a PEF meter, we repeated the analyses while including unreliable measurements to determine whether their inclusion affected the results. In Study II, after each step of the methacholine challenge (a maximum of five steps), decreases in PEF (10%, 15%, and 20%) and FEV<sub>1</sub> (10% and 15%) were recorded and included in the analyses. Therefore, the total number of measurements included in the analyses (n = 4066) in Study II was far greater than the number of individual subjects (n = 878).

In Studies III and IV, various increases in PEF (10%, 15%, 15% and 60 L/min, 20%, and 25%) were compared against improvement in FEV<sub>1</sub> (12% and 0.2 L). The relative increases in PEF and FEV<sub>1</sub> during bronchodilation were calculated as follows:

$$\frac{(\text{post} - \text{bronchodilator PEF or FEV}_1) - (\text{pre} - \text{bronchodilator PEF or FEV}_1)}{(\text{pre} - \text{bronchodilator PEF or FEV}_1)} * 100$$

In Studies I and III, to examine whether the relationship between changes in PEF and FEV<sub>1</sub> differed by age or sex, we split the population by median age (11 years) and sex and conducted the analyses separately in these subgroups. In Study III, additional subanalyses were performed by stratifying subjects by median baseline FEV<sub>1</sub> (95% of predicted) and by asthma diagnosis status. In Study IV, which involved adult patients, we conducted subanalyses by dividing the population by median age (47 years), sex, and pre-bronchodilator FEV<sub>1</sub> (80% of predicted), as well as by whether patients experienced at least a 20% decrease or less than a 20% decrease in FEV<sub>1</sub> following methacholine inhalation.

## 4.4 Ethical Considerations

Due to the retrospective nature of all the studies, the subjects remained anonymous and uncontacted; hence, ethical approval was not required. The research was funded by non-profit foundations, with no commercial funding involved. All authors of the original articles declare no conflicts of interest.

## 5 RESULTS

### 5.1 Patient Characteristics

#### 5.1.1 Exercise Challenge

Of the 366 children who underwent the exercise challenge test during the study period, 326 produced technically reliable spirometry data and were included in the primary analyses. The average age of the children was 11 years, with a higher proportion of males than females. More than half of the children had a clinical diagnosis of asthma, and on average, their lung function was normal before exercise. Less than one-fourth of the children had a positive test result (Table 1).

**Table 1.** Patient characteristics of 326 children with technically reliable spirometry measurements in the exercise challenge test. Modified from Studies I and III.

<b>Characteristics</b>	<b>Value</b>
<b>Age (yr)</b>	11.0 (2.6)
<b>Gender</b>	
Female	140 (42.9)
Male	186 (57.1)
<b>Height (cm)</b>	146.6 (15.8)
<b>Weight (kg)</b>	43.1 (15.5)
<b>Clinical diagnosis of asthma</b>	183 (56.1)
<b>Allergic sensitization to pollen or animal allergens</b>	
Not tested or data unavailable	140 (42.9)
Positive	126 (38.7)
Negative	60 (18.4)
<b>Max heart rate during exercise (bpm)</b>	195.2 (9.0)
<b>Duration of exercise (min)</b>	7.8 (0.7)
<b>Lung function at baseline</b>	
FVC (% predicted)	100.7 (12.0)
FEV <sub>1</sub> (% predicted)	94.2 (12.1)
FEV <sub>1</sub> /FVC (% predicted)	93.4 (8.2)
<b>Outcome of the exercise challenge</b>	
No EIB	250 (76.7)
EIB	76 (23.3)

The results are presented as mean (SD) for continuous variables and n (%) for categorical variables.

### 5.1.2 Methacholine Challenge

During the study period, 971 adult patients completed the methacholine challenge test. Of these, 878 patients provided technically reliable measurements during the challenge, and 869 provided reliable measurements with bronchodilation data. The exclusion of these nine subjects in Study IV in comparison to Study II did not significantly alter the characteristics of the study population. The average age was 47 years, with two-thirds of the participants being female. Over one-third of the patients were either former or current smokers, and on average, they were slightly overweight according to body mass index (BMI). On average, they had normal lung function

before the administration of methacholine. Fewer than one in seven patients had a positive test result (Table 2).

**Table 2.** Patient characteristics of 878 adults with technically reliable spirometry measurements in the methacholine challenge test. Modified from Studies II and IV.

<b>Characteristics</b>	<b>Value</b>
<b>Age (yr)</b>	47.4 (16.4)
<b>Gender</b>	
Female	587 (66.9)
Male	291 (33.1)
<b>Height (cm)</b>	169.2 (9.4)
<b>Weight (kg)</b>	80.8 (18.4)
<b>BMI (kg/m<sup>2</sup>)</b>	28.2 (6.1)
<b>Smoking status</b>	
Data not available	164 (18.7)
Current smoker	56 (6.4)
Ex-smoker	208 (23.7)
Never smoker	450 (51.3)
<b>Lung function at baseline</b>	
FVC (% predicted)	96.2 (13.1)
FEV <sub>1</sub> (% predicted)	93.7 (13.6)
FEV <sub>1</sub> /FVC (% predicted)	97.4 (8.1)
PEF (% predicted)	94.8 (15.2)
<b>Outcome of the methacholine challenge</b>	
No hyperresponsiveness	582 (66.3)
Mild hyperresponsiveness (PD <sub>20</sub> FEV <sub>1</sub> 601-2610 µg)	148 (16.9)
Moderate hyperresponsiveness (PD <sub>20</sub> FEV <sub>1</sub> 151-600 µg)	95 (10.2)
Marked hyperresponsiveness (PD <sub>20</sub> FEV <sub>1</sub> ≤ 150 µg)	53 (6.0)

The results are presented as mean (SD) for continuous variables and n (%) for categorical variables.

### 5.1.3 Prevalence of Bronchoconstriction

Nearly half of the 326 children who completed the exercise challenge and produced reliable spirometry measurements experienced a decrease in FEV<sub>1</sub> of at least 10%, while fewer than a quarter had a reduction of at least 15%. Depending on the chosen cut-off value, a significant decrease in PEF was observed in 14.7%–66.3% of the children. Using the PEF cut-off value of 15%, which is recommended for children by GINA, nearly half of the study subjects had EIB (Table 3).

Among the 878 adults who completed the methacholine challenge and produced reliable spirometry measurements, 4066 unique data points were generated. A 10% decrease in FEV<sub>1</sub> compared to baseline was observed in a quarter of these measurement points, while a 15% reduction was seen in 14.1% of the data points. Depending on the chosen cut-off value, a significant decrease in PEF was observed in 1.7%–32.1% of patients (Table 3).

**Table 3.** Proportions of 326 children in the exercise challenge and 4066 measurement points of 878 adults in the methacholine challenge meeting varying criteria for significant airway obstruction. Modified from Studies I and II.

<b>Lung function decline</b>	<b>Children</b>	<b>Measurement points of adults</b>
≥10% decrease in FEV <sub>1</sub>	140 (42.9)	1094 (26.8)
≥15% decrease in FEV <sub>1</sub>	76 (23.3)	575 (14.1)
≥10% decrease in PEF	216 (66.3)	1304 (32.1)
≥15% decrease in PEF	161 (49.4)	638 (15.7)
≥20% decrease in PEF	102 (31.3)	317 (7.8)
≥25% decrease in PEF	66 (20.2)	148 (3.6)
≥30% decrease in PEF	48 (14.7)	69 (1.7)

The results are presented as n (%).

### 5.1.4 Prevalence of Bronchodilation

Nearly a third of the 326 children who completed the exercise challenge and produced reliable spirometry measurements exhibited BDR based on FEV<sub>1</sub> increase. Only four more children were categorized as having BDR using a 12% improvement in FEV<sub>1</sub> compared to the Finnish recommended 12% and 0.2 L for all ages. Depending on the chosen cut-off value, a significant increase in PEF was measured in 18.4%–54.9% of the children. Using the 15% improvement in PEF cut-off recommended for children in home PEF monitoring, 38.0% of patients had BDR. In comparison, only 18.4% met the 15% and 60 L/min increase cut-off recommended for adults (Table 4).

Of the 869 adults who completed the methacholine challenge and produced reliable spirometry measurements, almost half experienced BDR after salbutamol inhalation, as defined by FEV<sub>1</sub> increase. Depending on the chosen cut-off value, a significant improvement in PEF was measured in 17.1%–49.6% of patients. Using the 15% and 60 L/min cut-off, 27.5% of patients were classified as having BDR (Table 4).

**Table 4.** Proportions of 326 children and 869 adults meeting varying criteria for significant bronchodilator response after salbutamol inhalation following bronchial challenge testing. Modified from Studies III and IV.

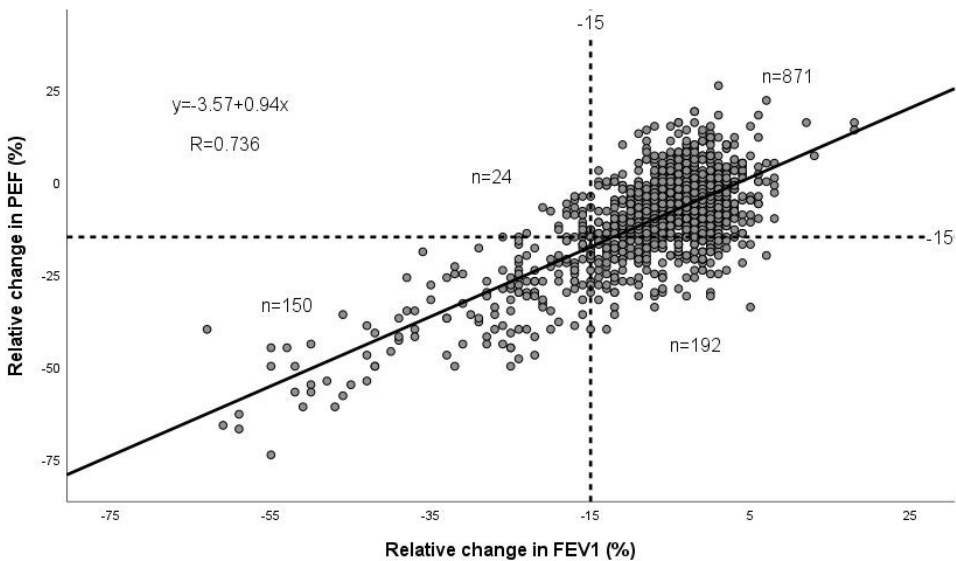
<b>Lung function improvement</b>	<b>Children</b>	<b>Adults</b>
≥12% increase in FEV <sub>1</sub>	109 (33.4)	431 (49.6)
≥12% and 0.2 L increase in FEV <sub>1</sub>	105 (32.2)	425 (48.9)
≥10% increase in PEF	179 (54.9)	412 (47.4)
≥15% increase in PEF	124 (38.0)	291 (33.5)
≥15% and 60 L/min increase in PEF	60 (18.4)	239 (27.5)
≥20% increase in PEF	91 (27.9)	210 (24.2)
≥25% increase in PEF	64 (19.6)	149 (17.1)

The results are presented as n (%).

## 5.2 Correlation Between Changes in PEF and FEV<sub>1</sub>

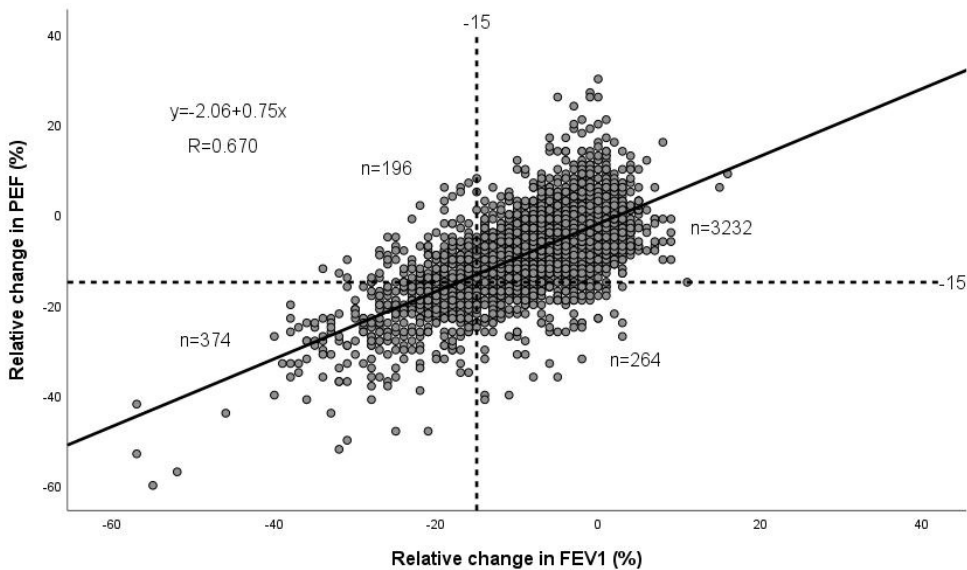
### 5.2.1 During Bronchoconstriction

Figure 6 presents the correlation between the 1237 measurement points of relative changes in PEF and FEV<sub>1</sub> in 326 children during the exercise challenge test. There was a strong positive linear correlation between the relative changes in PEF and FEV<sub>1</sub> with a Pearson correlation coefficient of 0.736 (108). According to the regression equation  $y = -3.57 + 0.94x$ , the model predicts that the average decrease in PEF will exceed the decrease in FEV<sub>1</sub> until the FEV<sub>1</sub> reduction reaches approximately 60%. The difference between the rates of decline was statistically significant ( $p < 0.01$ ). In the majority of measurements ( $n = 871$ ), neither PEF nor FEV<sub>1</sub> reduced by 15%. There were 150 measurement points where both PEF and FEV<sub>1</sub> decreased by at least 15%. Additionally, 192 data points showed a 15% reduction in PEF without a corresponding 15% decrease in FEV<sub>1</sub>, and 24 data points showed a 15% reduction in FEV<sub>1</sub> without a 15% decrease in PEF. The decreases in PEF and FEV<sub>1</sub> therefore agreed in 82.5% of cases using these thresholds.



**Figure 6.** Correlation between 1237 measurement points of relative changes in PEF and FEV<sub>1</sub> in 326 children during the exercise challenge test. Modified from Study I.

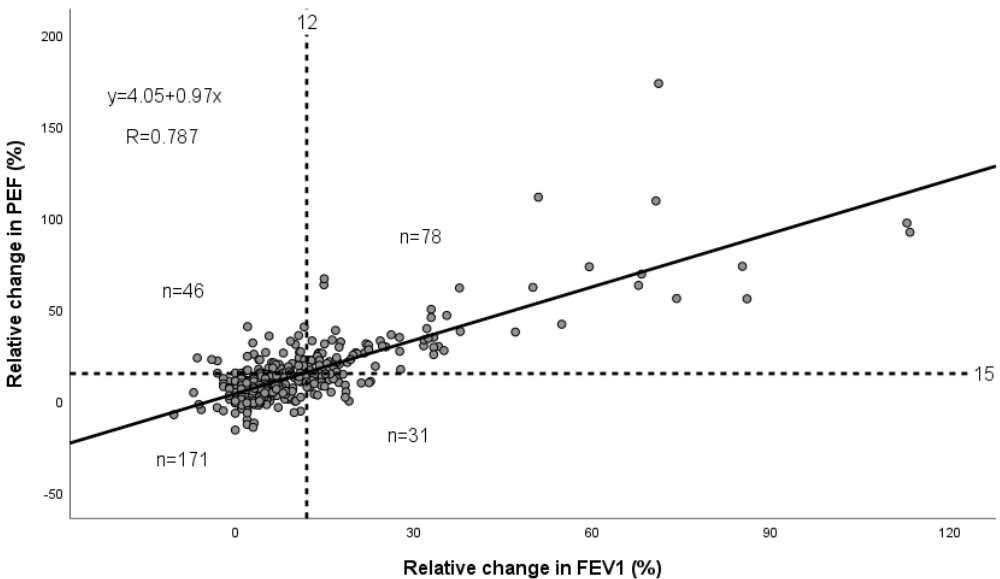
Figure 7 illustrates the correlation between the 4066 measurement points of relative changes in PEF and FEV<sub>1</sub> in 878 adults during the methacholine challenge test. There was a moderate positive linear correlation between the relative changes in PEF and FEV<sub>1</sub>, with a Pearson correlation coefficient of 0.670. According to the regression equation  $y = -2.06 + 0.75x$ , the model predicts that the average decrease in PEF exceeds the decrease in FEV<sub>1</sub> until the FEV<sub>1</sub> reduction reaches approximately 8%. The difference between the rates of decline was statistically significant ( $p < 0.01$ ). In most measurements ( $n = 3232$ ), neither PEF nor FEV<sub>1</sub> decreased by 15%. There were 374 measurement points where both PEF and FEV<sub>1</sub> decreased by at least 15%. Additionally, 264 data points showed a 15% reduction in PEF without a corresponding 15% decrease in FEV<sub>1</sub>, and 196 data points showed a 15% reduction in FEV<sub>1</sub> without a 15% decrease in PEF. Using these thresholds, decreases in PEF and FEV<sub>1</sub> identified the same cases in 88.7% of instances.



**Figure 7.** Correlation between 4066 measurement points of relative changes in PEF and FEV<sub>1</sub> in 878 adults during the methacholine challenge test. Modified from Study II.

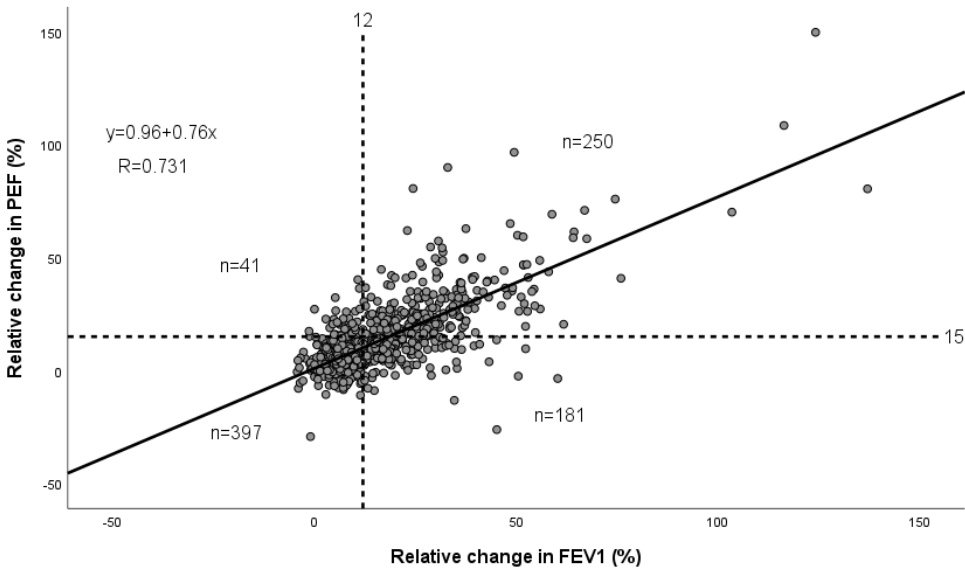
## 5.2.2 During Bronchodilation

Figure 8 shows the correlation between the relative changes in PEF and FEV<sub>1</sub> in 326 children during bronchodilation after the exercise challenge test. There was a strong positive linear correlation between the relative changes in PEF and FEV<sub>1</sub>, with a Pearson correlation coefficient of 0.787. According to the regression equation  $y = 4.05 + 0.97x$ , the model predicts that the relative increase in PEF will exceed the relative increase in FEV<sub>1</sub> until the FEV<sub>1</sub> increase reaches approximately 135%. The difference between the rates of improvement was statistically significant ( $p < 0.01$ ). Of the 326 children examined, 171 did not meet the criteria for either a 12% increase in FEV<sub>1</sub> or a 15% improvement in PEF. Additionally, 78 children met both requirements, 46 achieved a 15% increase in PEF without a corresponding 12% improvement in FEV<sub>1</sub>, and 31 met a 12% increase in FEV<sub>1</sub> without a 15% improvement in PEF. The increases in PEF and FEV<sub>1</sub> therefore identified the same patients in 76.4% of cases when these thresholds were applied.



**Figure 8.** Correlation between the relative changes in PEF and FEV<sub>1</sub> in 326 children during bronchodilation after the exercise challenge test. Modified from Study III.

Figure 9 describes the correlation between the relative changes in PEF and FEV<sub>1</sub> in 869 adults during bronchodilation after the methacholine challenge test. There was a strong positive linear correlation between the relative changes in PEF and FEV<sub>1</sub>, with a Pearson correlation coefficient of 0.731. According to the regression equation  $y = 0.96 + 0.76x$ , the model predicts that the relative increase in FEV<sub>1</sub> will exceed the relative increase in PEF once the FEV<sub>1</sub> increase surpasses approximately 4%. The difference between the rates of improvement was statistically significant ( $p < 0.01$ ). Of the 869 patients examined, 397 did not meet the criteria for either a 12% increase in FEV<sub>1</sub> or a 15% improvement in PEF. Additionally, 250 patients met both requirements, while 41 achieved a 15% increase in PEF without a corresponding 12% improvement in FEV<sub>1</sub>, and 181 achieved a 12% increase in FEV<sub>1</sub> without a 15% improvement in PEF. This resulted in agreement between increases in PEF and FEV<sub>1</sub> in 74.5% of cases using these thresholds.

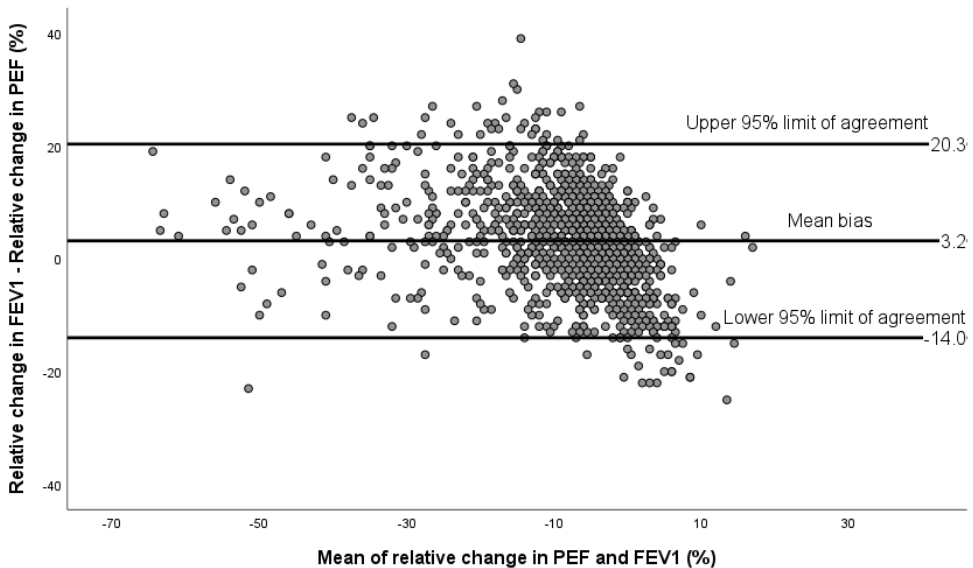


**Figure 9.** Correlation between the relative changes in PEF and FEV<sub>1</sub> in 869 adults during bronchodilation after the methacholine challenge test. Original from Study IV.

## 5.3 Bland–Altman Plot of Changes in PEF and FEV<sub>1</sub>

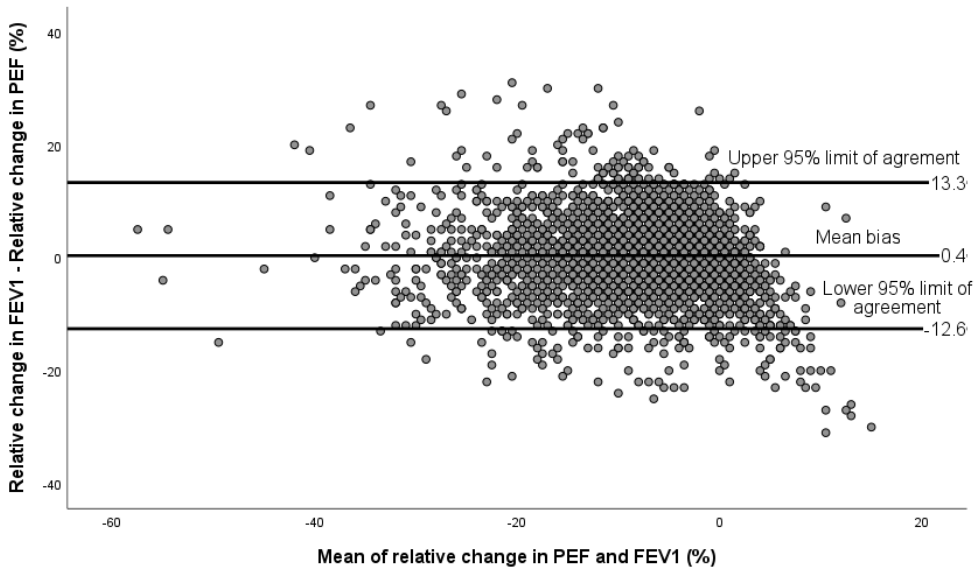
### 5.3.1 During Bronchoconstriction

Figure 10 presents the difference between the relative changes in PEF and FEV<sub>1</sub> plotted against their mean (a Bland–Altman plot) in 1237 measurement points of 326 children during the exercise challenge test (135). The mean bias between the changes in PEF and FEV<sub>1</sub> was 3.2%, indicating a larger decrease in PEF on average. The limits of agreement (-14.0%–20.3%) were wide, suggesting poor interchangeability of PEF and FEV<sub>1</sub> for assessing EIB in individual children. Most patients experienced at least a slight decrease in lung function during the exercise challenge; thus, the majority of data points have shifted to the left on the x-axis, indicating some level of bronchoconstriction.



**Figure 10.** Bland–Altman plot of 1237 measurement points of relative change in PEF and FEV<sub>1</sub> in 326 children during the exercise challenge test. Created using the data from Study I.

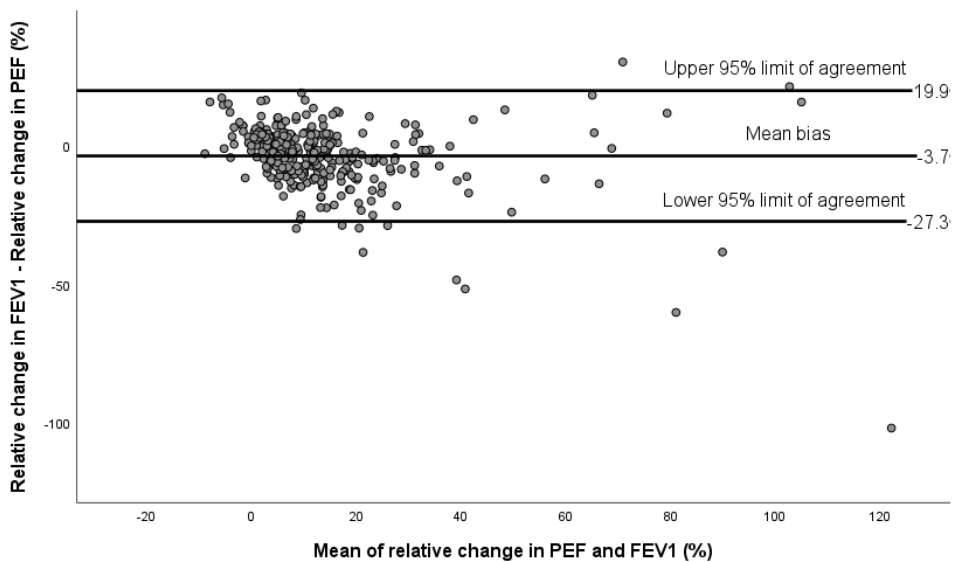
Figure 11 displays a Bland–Altman plot of the relative changes in PEF and FEV<sub>1</sub> in 4066 measurement points of adults during the methacholine challenge test. The mean bias between the changes in PEF and FEV<sub>1</sub> was 0.4%, indicating a similar decrease in both parameters on average. The limits of agreement (-12.6%–13.3%) were wide, suggesting poor interchangeability of PEF and FEV<sub>1</sub> for assessing obstruction in individual adults. Most patients experienced at least a slight decrease in lung function during the methacholine challenge, resulting in most data points shifting to the left on the x-axis, indicating some level of bronchoconstriction.



**Figure 11.** Bland–Altman plot of 4066 measurement points of relative change in PEF and FEV<sub>1</sub> in 878 adults during the methacholine challenge test. Original form from Study II.

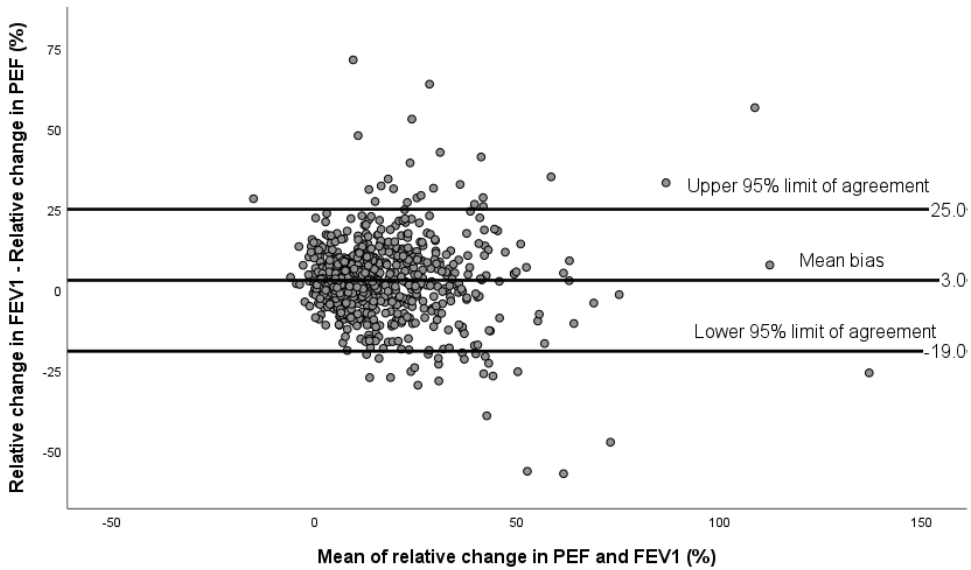
### 5.3.2 During Bronchodilation

Figure 12 shows a Bland–Altman plot of the relative changes in PEF and FEV<sub>1</sub> in 326 children during bronchodilation after the exercise challenge test. The mean bias between the changes in PEF and FEV<sub>1</sub> was -3.7%, indicating a larger increase in PEF on average. The limits of agreement (-27.3%–19.9%) were wide, suggesting poor interchangeability of PEF and FEV<sub>1</sub> for assessing BDR in individual children. Most patients experienced at least a slight improvement in lung function after the inhalation of salbutamol; thus, the majority of data points have shifted to the right on the x-axis, indicating some level of bronchodilation.



**Figure 12.** Bland–Altman plot of the relative change in PEF and FEV<sub>1</sub> in 326 children during bronchodilation after the exercise challenge test. Original from Study III.

Figure 13 describes a Bland–Altman plot of the relative changes in PEF and FEV<sub>1</sub> in 869 adults during bronchodilation after the methacholine challenge test. The mean bias between the changes in PEF and FEV<sub>1</sub> was 3.0%, indicating a larger increase in FEV<sub>1</sub> on average. The limits of agreement (-19.0%–25.0%) were wide, suggesting poor interchangeability of PEF and FEV<sub>1</sub> for assessing BDR in individual adults. Most patients experienced at least a slight improvement in lung function after the inhalation of salbutamol, resulting in most data points shifting to the right on the x-axis, indicating some level of bronchodilation.

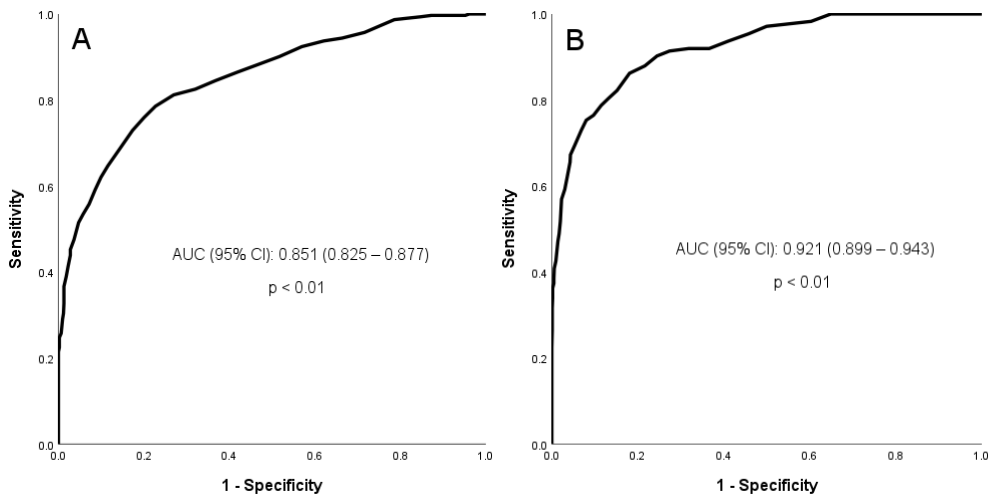


**Figure 13.** Bland–Altman plot of the relative change in PEF and FEV<sub>1</sub> in 869 adults during bronchodilation after the methacholine challenge test. Original from Study IV.

## 5.4 Receiver Operating Characteristic Analysis of PEF Change and Categorical FEV<sub>1</sub> Changes

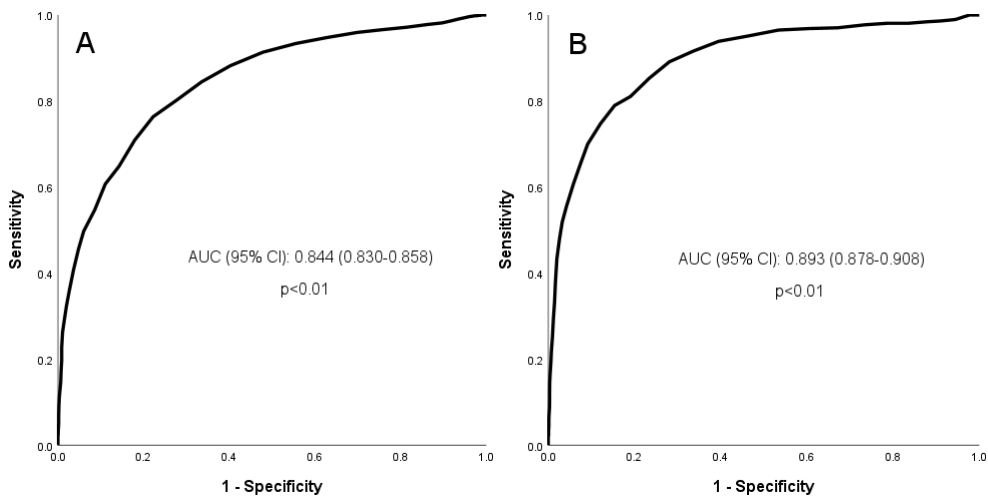
### 5.4.1 During Bronchoconstriction

Figures 14A and 14B present ROC curves of the relative change in PEF in 1237 measurement points of 326 children during the exercise challenge test, compared against a 10% and a 15% decrease in FEV<sub>1</sub>, respectively. With an area under the curve (AUC) of 0.921, the change in PEF was a better predictor of a 15% reduction in FEV<sub>1</sub> than of a 10% decrease, which had an AUC of 0.851. According to the AUC, the ability of PEF change to detect a 15% reduction in FEV<sub>1</sub> was excellent, although the lower limit of the 95% confidence interval (CI) would only be classified as good (136). The optimal operating point based on Youden's index for detecting a 10% decrease in FEV<sub>1</sub> corresponded to a 12.5% (95% CI, 10.5–15.5%; Youden's J = 0.559) reduction in PEF, yielding a sensitivity of 75.9% and a specificity of 80.0%. To detect a 15% decrease in FEV<sub>1</sub>, the optimal operating point was a 14.5% reduction in PEF (95% CI, 12.5–20.5%; Youden's J = 0.681), with a sensitivity of 86.2% and a specificity of 81.9%.



**Figure 14.** ROC curves presenting the ability of PEF change to detect a 10% (A) and a 15% (B) decrease in FEV<sub>1</sub> in 1237 measurement points of 326 children during the exercise challenge test. Modified from Study I.

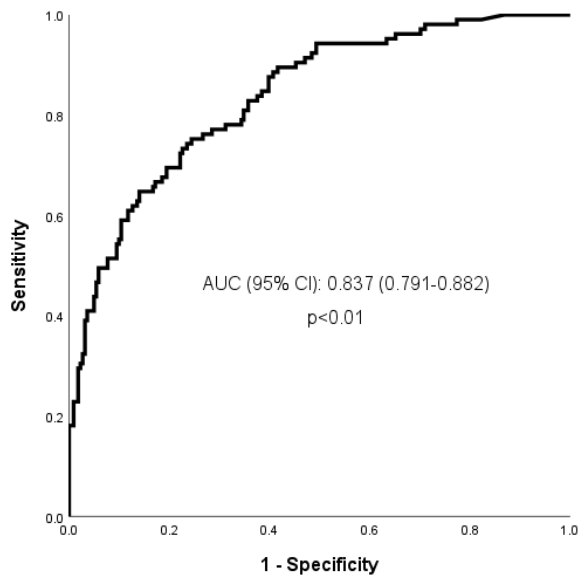
Figures 15A and 15B show ROC curves of the relative change in PEF in 4066 measurement points of 878 adults during the methacholine challenge test, compared against a 10% and a 15% decrease in FEV<sub>1</sub>, respectively. With an AUC of 0.893, the change in PEF was a better predictor of a 15% reduction in FEV<sub>1</sub> than of a 10% decrease, which had an AUC of 0.844. An AUC of 0.893 is considered good. The optimal operating point based on Youden's index for detecting a 10% decrease in FEV<sub>1</sub> corresponded to an 8.5% (95% CI, 8.5–9.5%; Youden's J = 0.541) reduction in PEF, yielding a sensitivity of 76.3% and a specificity of 77.8%. To detect a 15% decrease in FEV<sub>1</sub>, the optimal operating point was a 11.5% reduction in PEF (95% CI, 9.5–12.5%; Youden's J = 0.636), with a sensitivity of 78.9% and a specificity of 84.6%.



**Figure 15.** ROC curves presenting the ability of PEF change to detect a 10% (A) and a 15% (B) decrease in FEV<sub>1</sub> in 4066 measurement points of 878 adults during the methacholine challenge test. Modified from Study II.

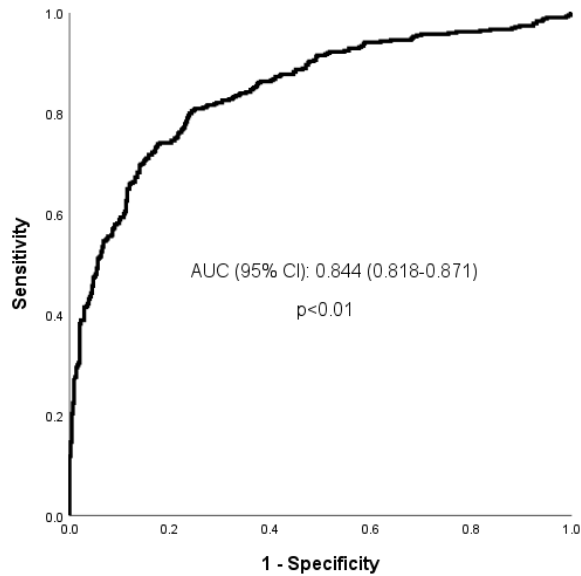
## 5.4.2 During Bronchodilation

Figure 16 displays the ROC curve of the relative change in PEF in 326 children during bronchodilation after the exercise challenge test, compared against a 12% and 0.2 L increase in FEV<sub>1</sub>. With an AUC of 0.837, the ability of PEF change to detect a 12% and 0.2 L improvement in FEV<sub>1</sub> was just above the threshold to be classified as good, although the lower limit of the 95% CI would be classified as poor. The optimal operating point by Youden's index was a 14.5% (95% CI, 7.5–21.0%; Youden's J = 0.499) increase in PEF, yielding a sensitivity of 74.3% and a specificity of 75.6%.



**Figure 16.** ROC curve presenting the ability of PEF change to detect a 12% and 0.2 L increase in FEV<sub>1</sub> in 326 children during bronchodilation after the exercise challenge test. Modified from Study III.

Figure 17 illustrates the ROC curve of the relative change in PEF in 869 adults during bronchodilation after the methacholine challenge test, compared against a 12% and 0.2 L increase in FEV<sub>1</sub>. With an AUC of 0.844, the ability of PEF change to detect a 12% and 0.2 L improvement in FEV<sub>1</sub> was classified as good. The optimal operating point by Youden's index was a 11.5% (95% CI, 8.5–12.5%; Youden's J = 0.555) increase in PEF, yielding a sensitivity of 71.1% and a specificity of 84.5%.



**Figure 17.** ROC curve presenting the ability of PEF change to detect a 12% and 0.2 L increase in FEV<sub>1</sub> in 869 adults during bronchodilation after the methacholine challenge test. Original from Study IV.

## 5.5 Accuracy of PEF Change in Detecting FEV<sub>1</sub> Changes

### 5.5.1 During Bronchoconstriction

Table 5 presents the sensitivity, specificity, PPV, NPV, and Cohen's kappa coefficient for different cut-off values of PEF decrease in detecting a 10% or a 15% reduction in FEV<sub>1</sub> in 326 children measured at any time point during the exercise challenge test. As expected for diagnostic cut-offs, a lower PEF decrease threshold was associated with higher sensitivity and NPV, while a higher cut-off value was associated with better specificity and PPV. Based on the kappa coefficient, agreement ranged from fair to moderate (0.332–0.505) for detecting a 10% decrease in FEV<sub>1</sub> and from slight to substantial (0.199–0.680) for detecting a 15% reduction in FEV<sub>1</sub> (138). According to the kappa value, a 20% decrease in PEF showed the best agreement for detecting a 10% reduction in FEV<sub>1</sub>, while a 25% decrease in PEF showed the best agreement for detecting a 15% reduction in FEV<sub>1</sub>. The 25% PEF cut-off value achieved low sensitivity (72.9%) and PPV (77.3%) but relatively higher specificity (93.7%) and NPV (92.2%) for detecting a 15% reduction in FEV<sub>1</sub>. The currently recommended PEF cut-off value of 15% had high sensitivity (90.8%) and NPV (95.6%) but lower specificity (62.4%) and PPV (42.9%) for detecting a 15% decrease in FEV<sub>1</sub>.

We found no significant differences in the relationship between changes in PEF and FEV<sub>1</sub> when stratified by median age (11 years) or sex. Additionally, repeating the analyses to include unreliable measurements did not significantly change the results, with differences in any given percentage being only a few points at most (data not presented).

**Table 5.** The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Cohen's kappa coefficient of different cut-off values of PEF decrease in detecting a 10% or a 15% reduction in FEV<sub>1</sub> in 326 children measured at any time point during the exercise challenge test. Modified from Study I.

<b>Change in lung function</b>	<b>Sensitivity (%)</b>	<b>Specificity (%)</b>	<b>PPV (%)</b>	<b>NPV (%)</b>	<b>Cohen's kappa</b>
<b>10% decrease in PEF</b>					
10% decrease in FEV <sub>1</sub>	87.1	48.1	56.5	82.9	0.332
15% decrease in FEV <sub>1</sub>	92.1	40.4	32.4	94.3	0.199
<b>15% decrease in PEF</b>					
10% decrease in FEV <sub>1</sub>	77.9	71.3	67.7	80.6	0.483
15% decrease in FEV <sub>1</sub>	90.8	62.4	42.9	95.6	0.384
<b>20% decrease in PEF</b>					
10% decrease in FEV <sub>1</sub>	60.3	88.8	80.4	74.5	0.505
15% decrease in FEV <sub>1</sub>	84.9	83.4	60.8	94.8	0.600
<b>25% decrease in PEF</b>					
10% decrease in FEV <sub>1</sub>	44.3	95.5	87.8	70.0	0.426
15% decrease in FEV <sub>1</sub>	72.9	93.7	77.3	92.2	0.680
<b>30% decrease in PEF</b>					
10% decrease in FEV <sub>1</sub>	34.4	97.8	91.7	67.4	0.352
15% decrease in FEV <sub>1</sub>	61.2	97.1	85.4	89.9	0.649

Table 6 displays the sensitivity, specificity, PPV, NPV, and Cohen's kappa coefficient for different cut-off values of PEF decrease in detecting a 10% or a 15% reduction in FEV<sub>1</sub> in 4066 measurement points of 878 adults during the methacholine challenge test. Again, a lower cut-off value for PEF decrease resulted in higher sensitivity and NPV, while a higher cut-off produced better specificity and PPV. Based on the kappa coefficient, agreement ranged from fair to moderate (0.325–0.498) for detecting a 10% decrease in FEV<sub>1</sub> and was moderate (0.402–0.553) for detecting a 15% reduction in FEV<sub>1</sub>. According to the kappa value, a 10% decrease in PEF showed the best agreement for detecting a 10% reduction in FEV<sub>1</sub>, while a 15% decrease in PEF showed the best agreement for detecting a 15% reduction in FEV<sub>1</sub>. The 15% PEF cut-off value achieved low sensitivity (65.6%) and PPV (58.6%) but higher specificity (92.4%) and NPV (94.3%) in detecting a 15% reduction in FEV<sub>1</sub>.

**Table 6.** The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Cohen's kappa coefficient of different cut-off values of PEF decrease in detecting a 10% or a 15% reduction in FEV<sub>1</sub> in 4066 measurement points of 878 adults during the methacholine challenge test. Modified from Study II.

Change in lung function	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cohen's kappa
<b>10% decrease in PEF</b>					
10% decrease in FEV <sub>1</sub>	70.9	82.1	59.0	88.6	0.498
15% decrease in FEV <sub>1</sub>	85.3	76.6	37.3	97.0	0.402
<b>15% decrease in PEF</b>					
10% decrease in FEV <sub>1</sub>	45.6	95.2	77.6	82.8	0.469
15% decrease in FEV <sub>1</sub>	65.6	92.4	58.6	94.3	0.553
<b>20% decrease in PEF</b>					
10% decrease in FEV <sub>1</sub>	26.2	98.9	89.9	78.6	0.325
15% decrease in FEV <sub>1</sub>	43.3	98.0	77.9	91.4	0.508

## 5.5.2 During Bronchodilation

Table 7 presents the sensitivity, specificity, PPV, NPV, and Cohen's kappa coefficient for different cut-off values of PEF increase in detecting a 12% and 0.2 L improvement in FEV<sub>1</sub> in 326 children following salbutamol inhalation after the exercise challenge test. The same sensitivity–specificity trade-off associated with the magnitude of the cut-off value was observed as before. Based on the kappa coefficient, agreement ranged from fair to moderate (0.395–0.505) for detecting a 12% and 0.2 L increase in FEV<sub>1</sub>. According to the kappa value, a 20% improvement in PEF showed the best agreement for detecting a 12% and 0.2 L increase in FEV<sub>1</sub>. The 20% PEF cut-off value achieved low sensitivity (61.0%) and PPV (70.3%) but relatively higher specificity (87.8%) and NPV (82.6%). The currently recommended 15% increase cut-off for detecting BDR in children during home PEF monitoring had lower sensitivity (71.4%) and PPV (60.5%) than specificity (77.8%) and NPV (85.1%). The PEF cut-off value recommended for adults, a 15% and 60 L/min increase, had very low sensitivity (42.9%), while specificity, PPV, and NPV were 93.2%, 75.0%, and 77.4%, respectively.

We also repeated every analysis while defining BDR as a 12% increase in FEV<sub>1</sub> and found the results to be practically identical to using the more commonly recommended threshold of 12% and 0.2 L. We also divided the patients by median

age (11 years), sex, median baseline FEV<sub>1</sub> (95% of predicted), and asthma diagnosis status and repeated the analyses. These subgroup analyses revealed no clear differences between children with better and worse baseline lung function, between males and females, or between those with and without a doctor’s diagnosis of asthma. For age, there were likewise no clear differences in sensitivity, specificity, PPV, NPV, or kappa between younger and older children, as indicated by overlapping 95% CIs. However, within the age subgroups, the PEF cut-off with the highest agreement differed: 20%–25% provided the best agreement in younger children, whereas 10%–15% performed best in older children (data not presented).

**Table 7.** The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Cohen’s kappa coefficient of different cut-off values of PEF increase in detecting a 12% and 0.2 L improvement in FEV<sub>1</sub> in 326 children during bronchodilation after the exercise challenge test. Modified from Study III.

Improvement in PEF	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cohen’s kappa
10%	86.7	60.2	50.8	90.5	0.395
15%	71.4	77.8	60.5	85.1	0.470
15% and 60 L/min	42.9	93.2	75.0	77.4	0.406
20%	61.0	87.8	70.3	82.6	0.505
25%	48.6	94.1	79.7	79.4	0.476

Table 8 presents the sensitivity, specificity, PPV, NPV, and Cohen’s kappa coefficient for different cut-off values of PEF increase in detecting a 12% and 0.2 L improvement in FEV<sub>1</sub> in 869 adults following salbutamol inhalation after the methacholine challenge test. The trade-off between sensitivity and specificity, depending on the cut-off value, was again evident. Based on the kappa coefficient, agreement ranged from fair to moderate (0.313–0.541) for detecting a 12% and 0.2 L increase in FEV<sub>1</sub>. According to the kappa value, a 10% improvement in PEF showed the best agreement for detecting a 12% and 0.2 L increase in FEV<sub>1</sub>. The 10% PEF cut-off achieved relatively similar values in sensitivity (75.1%), specificity (79.1%), PPV (77.4%), and NPV (76.8%). The cut-off value recommended for adults during home PEF monitoring, an increase of 15% and 60 L/min, had low sensitivity (49.6%) and NPV (66.0%), while specificity (93.7%) and PPV (88.3%) remained significantly higher.

After splitting the population by median age (47 years), sex, and median pre-bronchodilator FEV<sub>1</sub> (80% of predicted), we found no marked differences in the

relationship between PEF and FEV<sub>1</sub> changes across the groups in these subanalyses. After comparing those who experienced a reduction of at least 20% in FEV<sub>1</sub> after methacholine inhalation, and those who experienced less than a 20% decrease, we found that PEF increase was overall less accurate at identifying bronchodilation in patients with more severe obstruction before bronchodilation. The different PEF cut-off values ranked similarly by agreement across both groups, with a 10% improvement in PEF having the highest kappa value (data not presented).

**Table 8.** The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Cohen's kappa coefficient of different cut-off values of PEF increase in detecting a 12% and 0.2 L improvement in FEV<sub>1</sub> in 869 adults during bronchodilation after the methacholine challenge test. Modified from Study IV.

Improvement in PEF	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cohen's kappa
10%	75.1	79.1	77.4	76.8	0.541
15%	58.1	90.1	84.9	69.2	0.485
15% and 60 L/min	49.6	93.7	88.3	66.0	0.438
20%	44.7	95.5	90.5	64.3	0.406
25%	32.9	98.0	94.0	60.4	0.313

## 6 DISCUSSION

### 6.1 Relationship Between Changes in PEF and FEV<sub>1</sub> During Bronchoconstriction

#### 6.1.1 Indirect Bronchial Challenge Testing

Although the correlation between the changes in PEF and FEV<sub>1</sub> during exercise challenge testing in children was strong, PEF was a poor metric for diagnosing EIB, as defined by a 15% decrease in FEV<sub>1</sub>. On average, PEF decreased more than FEV<sub>1</sub>. Although the ROC analyses resulted in excellent or good AUCs, the individuals identified as positive by each parameter only partially overlapped. The predominance of either sensitivity or specificity, as well as the higher value between PPV and NPV, varied widely depending on the selected cut-off value. The currently recommended cut-off value of a 15% reduction in PEF was unreliable because over half of the positive tests were false. Even when using a cut-off value of 25%, which showed the highest agreement according to the kappa value, over a fifth of the positives were still false. Such a high cut-off value also led to significantly diminished sensitivity (73%) but better specificity (94%) and NPV (92%).

The performance of the predetermined cut-offs was assessed independently of time point, meaning that we analyzed how accurately decreases in PEF occurring at any time point after the challenge detected the presence of a decrease in FEV<sub>1</sub> (10% or 15%) at any time point after the challenge. This approach was considered the most appropriate for evaluating the clinically relevant performance of PEF in the exercise challenge since a positive test result in clinical practice is not tied to a specific time point. Furthermore, PEF and FEV<sub>1</sub> may not reach their lowest point simultaneously due to inherent physiological differences between the parameters. Therefore, extending the observation beyond fixed time points is essential when examining clinical implications.

However, this time-independent design does not allow for the construction of ROC curves. The ROC curves were instead constructed using data from single time-specific observations of PEF and FEV<sub>1</sub> change. Using this approach, the optimal

operating point based on Youden's index for detecting a 15% decrease in FEV<sub>1</sub> was a 14.5% decrease in PEF. This value is lower than the 25% cut-off, which showed the best agreement according to the kappa value in the time-independent analysis (Table 5). While the diagnostic characteristics derived from time-independent analyses are more relevant in the clinical context, time-specific analyses may provide better insight into the physiological relationship between changes in PEF and FEV<sub>1</sub> during bronchoconstriction in children.

Akar et al. found the correlation between changes in PEF and FEV<sub>1</sub> during children's exercise challenge testing to be moderate instead of strong. However, their correlation coefficient ( $r = 0.65$ ) was quite close to ours ( $r = 0.74$ ). The results are not entirely comparable since Akar et al. only measured the correlation between maximal change and not at every measurement point during the challenge. Their study population was significantly smaller compared to ours, and all their subjects had been diagnosed with asthma. This could substantially impact the results, as patients with obstructive pulmonary diseases experience a higher incidence of obstruction, which also tends to be more severe (120).

To the best of our knowledge, the diagnostic accuracy of PEF in detecting airway obstruction during indirect bronchial challenge testing in children, defined as a decrease in FEV<sub>1</sub>, has not been previously investigated. Malmberg et al. studied PEF and FEV<sub>1</sub> in the context of direct challenge testing in children. They found that PEF decreases significantly less than FEV<sub>1</sub> during induced obstruction and that the sensitivity of PEF decrease is worse than that of FEV<sub>1</sub>. However, they did not quantify sensitivity, specificity, PPV, or NPV, nor did they study the ability of PEF reduction to detect FEV<sub>1</sub> decrease. Instead, they concluded that PEF decrease has poor sensitivity based on the observation that when normalized to the within-subject baseline reproducibility of each parameter, PEF decreases less. At the higher cut-off values according to the kappa coefficient, our findings regarding the low sensitivity of PEF were consistent with theirs (121).

Some research exists concerning the relationship between changes in PEF and FEV<sub>1</sub> during indirect bronchial challenge testing in adults. Giannini et al. found that in the context of exercise challenge testing in adults, a 15% decrease in PEF had low sensitivity (18%) but high specificity (95%) in detecting a 15% reduction in FEV<sub>1</sub>. In contrast, our study in children showed that a 15% decrease in PEF achieved sensitivity and specificity of 91% and 62%, respectively. One factor that may explain the observed differences is the small sample size in Giannini et al.'s study ( $n = 30$ ), with only 15 patients experiencing airway obstruction. Additionally, they measured

PEF and FEV<sub>1</sub> using separate devices, which could introduce systematic errors stemming from differing equipment or blowing technique (119).

In another study, Weytjens et al. analyzed the sensitivity, specificity, PPV, and NPV of PEF decrease in relation to FEV<sub>1</sub> reduction in adults undergoing indirect challenge testing using occupational agents. They found a 15% PEF decrease to be relatively accurate in assessing diminishing airway caliber, as defined by a 20% reduction in FEV<sub>1</sub>, with a sensitivity of 95%, specificity of 95%, PPV of 97%, and NPV of 90%. Generally, across multiple cut-off values, they found specificity and PPV to be higher than the corresponding sensitivity and NPV. However, their study population was comparatively small, with only 57 patients, which could have introduced more room for error. They also employed a higher cut-off value for FEV<sub>1</sub> decrease compared to ours. Additionally, the inhalation of occupational irritants, such as wood dust or flour, is a dissimilar method of inducing obstruction compared to exercise, even though both fall under the category of indirect challenge testing (124).

Moscato et al. investigated the effectiveness of PEF change in detecting a 15% decrease in FEV<sub>1</sub> among adults exposed to various indirect challenge stimuli. They analyzed absolute reductions in PEF between 40 and 100 L/min and found that a decrease of 70 L/min provided the highest combination of sensitivity and specificity, with values of 69% and 92%, respectively. The corresponding PPV was 90%, and the NPV was 75%. These results closely align with our findings using a cut-off of a 25% reduction in PEF, which we identified as having the best agreement in detecting a 15% decrease in FEV<sub>1</sub>. Moscato et al. generally reported higher specificity than sensitivity, and NPV exceeded PPV across different PEF cut-off values. While their study included a considerable sample size of 150 patients, they used a wide range of methods to induce obstruction and did not explore whether the relationship between PEF and FEV<sub>1</sub> varied with different stimuli. Additionally, they focused solely on absolute PEF values and used separate devices to measure PEF and FEV<sub>1</sub> (123). Lastly, it is important to note that the physiological differences between the airways of children and adults mean that conclusions drawn from the studies by Giannini et al., Weytjens et al., and Moscato et al. cannot be directly applied to children (119,123,124).

## 6.1.2 Direct Bronchial Challenge Testing

We found that while PEF change has a moderate positive correlation with change in FEV<sub>1</sub> during direct bronchial challenge testing in adults, PEF decrease shows poor accuracy in assessing bronchial obstruction, as defined by decrease in FEV<sub>1</sub>. Overall, the magnitudes of change in PEF and FEV<sub>1</sub> were similar; however, PEF tended to decrease relatively more when the corresponding FEV<sub>1</sub> reduction was lower, and vice versa. Although our ROC curves achieved good AUCs, changes in PEF and FEV<sub>1</sub> did not identify the same individuals, indicating limited overlap between the two measures. This discrepancy is unsurprising, as PEF is thought to primarily reflect large airway function, whereas FEV<sub>1</sub> reflects both large and small airways.

The selected cut-off value influenced whether sensitivity or specificity predominated and whether PPV or NPV was higher. However, in general, specificity was higher than sensitivity, and NPV was higher than PPV. According to Youden's index, the optimal operating point for detecting a 15% decrease in FEV<sub>1</sub> was 11.5%. When using a cut-off value of a 15% decrease in PEF, which showed the best agreement, as indicated by the kappa coefficient, PPV for detecting a 15% reduction in FEV<sub>1</sub> was low at 59%. In comparison, NPV was significantly higher at 94%. This indicates a significant risk of false-positive interpretations of airway obstruction when using PEF but a more negligible risk of false-negative interpretations. The corresponding sensitivity and specificity were 66% and 92%, respectively.

In Giannini et al.'s study, in the context of methacholine challenge testing in adults, the sensitivity and specificity of a 15% PEF decrease in detecting a 15% reduction in FEV<sub>1</sub> were 44% and 100%, respectively. These results align reasonably well with our findings, although their sensitivity was lower and specificity slightly higher. The minor differences observed may be attributable to the small population size ( $n = 36$ ) of the methacholine arm in Giannini et al.'s study and to the fact that they recorded PEF and FEV<sub>1</sub> using separate devices (119).

Pino et al. examined the ability of PEF decrease to detect a 20% reduction in FEV<sub>1</sub> following a methacholine challenge in adults. They identified a 12% reduction in PEF as the optimal cut-off value. However, even at this threshold, PEF demonstrated limited accuracy, with a sensitivity of 74%, specificity of 71%, PPV of 77%, and NPV of 67%. Comparing the results of Pino et al. with ours is challenging due to the different cut-off values used in each study. One counterintuitive finding is that Pino et al.'s study, despite detecting a larger reduction in FEV<sub>1</sub> compared to our study, identified a similar optimal PEF cut-off value. Key methodological differences between their study and ours that may help explain the conflicting results

include their small sample size of 40 patients in the methacholine arm compared to our 878, their use of a different methacholine dosing regimen than the one recommended, and the fact that they recorded PEF and FEV<sub>1</sub> from separate exhalations using different equipment (122).

## 6.2 Relationship Between Changes in PEF and FEV<sub>1</sub> During Bronchodilation

### 6.2.1 Children

We found that when defined as an increase in FEV<sub>1</sub>, BDR is not accurately detected by relative improvement in PEF in children. Although there was a strong positive correlation between the changes in PEF and FEV<sub>1</sub>, on average, PEF increased more than FEV<sub>1</sub>. Our ROC analysis achieved a good AUC, but the individuals identified as positive based on PEF improvement only partially overlapped with those identified using FEV<sub>1</sub> increase. The choice of cut-off value determined whether sensitivity, specificity, PPV, or NPV emerged as the most prominent characteristic of test performance. However, in general, specificity was higher than sensitivity, and NPV was higher than PPV. According to Youden's index, the optimal operating point for detecting BDR was 14.5%. The currently recommended cut-off value for detecting BDR in the context of home PEF monitoring, a 15% increase in PEF, detected slightly over two-thirds of the true positives, while almost 40% of all positives according to PEF were false when judged by FEV<sub>1</sub> improvement. Using a cut-off value of a 20% increase in PEF, which showed the best agreement according to the kappa coefficient, sensitivity was even lower, detecting noticeably fewer than two-thirds of all the true positives, and PPV remained suboptimal, with almost one-third of all positives being false. The corresponding specificity and NPV of the 20% cut-off were higher, at 88% and 83%, respectively. Our subgroup analysis revealed that in younger children, higher PEF cut-offs were associated with better agreement, whereas in older children, lower cut-offs showed better agreement. This finding is consistent with adult bronchodilation data, which demonstrate that lower cut-offs yield better agreement in adults.

We identified one previous study investigating the relationship between changes in PEF and FEV<sub>1</sub> during bronchodilation in children. Sliker and van der Ent found the correlation coefficient between changes in PEF and FEV<sub>1</sub> (% predicted) during

bronchodilation to be 0.54, in contrast to our significantly higher 0.79. They observed that across cut-off values for PEF increase ranging from 10% to 25%, the specificity of PEF improvement in detecting a 9% predicted increase in FEV<sub>1</sub> was consistently higher than the corresponding sensitivity. Using a cut-off value of a 20% increase in PEF, they achieved low sensitivity (33%) and NPV (69%) but higher specificity (96%) and PPV (85%). These results conflict somewhat with ours, but the general trends were similar. While the size of their study population was sufficient (n = 176), they included patients aged 4–20 years, meaning some were not children. Additionally, all participants were diagnosed with asthma, which was not the case in our study. Although they calculated PEF change similarly to us, FEV<sub>1</sub> change was calculated differently. They measured PEF and FEV<sub>1</sub> separately using different equipment and administered double the recommended amount of salbutamol, potentially inducing a more robust bronchial reaction (115).

## 6.2.2 Adults

We found that PEF increase is not an accurate parameter for detecting BDR in adults, as defined by improvement in FEV<sub>1</sub>. While the correlation between changes in PEF and FEV<sub>1</sub> was strong, FEV<sub>1</sub> increased more on average. Although our ROC curve achieved a good AUC, the overlap between individuals identified based on PEF improvement and those identified using FEV<sub>1</sub> improvement was limited. We found PEF increase to have better specificity and PPV than sensitivity and NPV across all cut-off values studied. According to Youden's index, the optimal operating point for detecting BDR was 11.5%. The currently recommended cut-off for detecting BDR in the context of home PEF monitoring of a 15% and 60 L/min increase identified under half of the true positives based on FEV<sub>1</sub> improvement. Using the same cut-off value, over one-third of the negative results were false. With a cut-off of 10%, which showed the best agreement according to the kappa value, the diagnostic characteristics of PEF increase remained relatively poor, with sensitivity, specificity, PPV, and NPV all between 75% and 79%.

We found several previous studies focusing on the relationship between changes in PEF and FEV<sub>1</sub> during bronchodilation in adults. The correlation between changes in PEF and FEV<sub>1</sub> in these studies ranged from negligible to moderate, with correlation coefficients between 0.28 and 0.67, in contrast to our 0.73. The methodological differences and possible explanations underlying the observed variations in the findings are dissected below (111,126–128).

Dekker et al. studied the ability of an absolute increase in PEF of 60 L/min to detect either a 9% predicted improvement in FEV<sub>1</sub> or an absolute increase in FEV<sub>1</sub> of 0.19 L. Their findings aligned with ours, showing that the specificity and PPV of PEF change were significantly higher than the corresponding sensitivity and NPV for detecting improvement in FEV<sub>1</sub>. They recorded PEF and FEV<sub>1</sub> on separate devices, which could introduce variability. Their study population was relatively small, with 73 participants, and had a considerably higher average age of 62 years compared to ours. Notably, they included only patients with confirmed diagnoses of asthma or COPD. These factors, together with significant differences in cut-off values and calculation methods, suggest that although their results support ours, they should be interpreted with caution (128).

Aggarwal et al. investigated the accuracy of various increases in PEF in detecting a 12% improvement in FEV<sub>1</sub>. Their findings were similar to ours, with one notable difference—PEF consistently achieved a higher NPV than PPV in their study—which contrasted with our results. They also found that the sensitivity of the recommended PEF increase of 15% and 60 L/min was very poor, while specificity was better. Overall, their results indicated PEF increase to have slightly worse diagnostic characteristics compared to ours, except for NPV. Aggarwal et al.'s study had a large population that well-represented the general population and used the recommended dose of salbutamol. However, their definition of BDR did not include the recommended absolute FEV<sub>1</sub> increase of 0.2 L. Additionally, they recorded FEV<sub>1</sub> and PEF on different devices, which could introduce systematic error (127).

Thiadens et al. studied the effectiveness of various PEF increases in detecting a 12% predicted and 0.2 L improvement in FEV<sub>1</sub>. Their findings primarily aligned with ours, but similar to those of Aggarwal et al., they found that the NPV of PEF increase was higher than the PPV. Their sensitivities and specificities were comparable to ours across most cut-off values; however, at higher cut-offs, the decline in sensitivity was steeper in their results. For a 15% increase in PEF, they reported a sensitivity of 42% and a specificity of 93%, closely matching our results. However, their PPV was 37% compared to our 85%, and their NPV was 93% compared to our 69%. This difference may arise because, unlike sensitivity and specificity, PPV and NPV are influenced by the prevalence of the condition being detected. In contrast to our study, Thiadens et al. did not induce airway obstruction before administering bronchodilators and excluded all patients with COPD or asthma, a group known to exhibit stronger BDRs. These methodological differences led to a much lower BDR prevalence in their sample, likely explaining the observed discrepancies in PPV and NPV. They administered the recommended dose of

salbutamol and measured PEF and FEV<sub>1</sub> using the same device and expiratory maneuver. However, the spirometer they used, a Microlab 3300 turbine spirometer, has been reported to consistently yield lower PEF values than typical PEF meters (104). Thiadens et al. calculated relative change in FEV<sub>1</sub> as a percentage of the predicted value, rather than in relation to pre-bronchodilator values. Notably, they also excluded all patients with asthma or COPD (111).

Ozturk et al. examined the ability of two relative PEF increases, 15% and 20%, to detect a 12% predicted increase FEV<sub>1</sub> while dividing the participants into two age groups: under and over 60 years. The diagnostic accuracy of PEF varied significantly with age and the chosen cut-off value, resulting in conflicting outcomes between the groups. These results also contradicted our findings. In patients over 60, sensitivity, specificity, and PPV were lower compared to those under 60, while NPV was slightly better. For a 15% PEF cut-off, sensitivity exceeded specificity in both age groups. PPV was higher than NPV in subjects under 60, whereas NPV was higher in those over 60. Ozturk et al. recorded PEF and FEV<sub>1</sub> using separate equipment. The relatively small population, further divided into smaller groups, may also account for some discrepancies observed in our results. Additionally, they excluded individuals with asthma or COPD and did not require absolute values alongside relative changes in their cut-off values for PEF and FEV<sub>1</sub>. They also calculated FEV<sub>1</sub> change differently from us (126).

Pino et al. investigated the accuracy of different relative increases in PEF in detecting a 15% improvement in FEV<sub>1</sub> following bronchodilation in adults. They determined that an 18% increase in PEF was the optimal cut-off value, with a sensitivity of 85%, specificity of 79%, PPV of 77%, and NPV of 86%. Direct comparison with our study is challenging due to differences in the cut-off values used. However, we observed similar accuracy in detecting a 12% and 0.2 L increase in FEV<sub>1</sub> using a 10% PEF improvement. As expected, their findings were consistent with ours in that a lower optimal PEF cut-off was identified when detecting a smaller improvement in FEV<sub>1</sub>. The differences in our results may be attributed to the relatively small sample size of 44 patients in the bronchodilation arm of Pino et al.'s study and to their use of separate exhalations and different equipment to measure PEF and FEV<sub>1</sub> (122).

## 6.3 Implications for Home Monitoring

Since recording FEV<sub>1</sub> via spirometry is considered the gold standard for lung function assessment, and PEF seems to reflect changes in FEV<sub>1</sub> poorly, it is reasonable to question the accuracy of any diagnostic method that relies exclusively on measuring PEF. Home monitoring of asthma relies solely on detecting bronchial obstruction and relaxation using PEF; however, PEF has been clearly shown to be inaccurate in detecting both. Our study excluded unreliable measurements, which was possible because PEF was recorded using a spirometer. However, since recording lung function using a PEF meter does not allow for the consistent exclusion of unreliable measurements, PEF may be even more inaccurate in a home monitoring scenario due to the inevitable inclusion of such data. This raises the question of whether an alternative method of home monitoring should be considered.

In recent years, increasingly affordable handheld spirometers have become available, allowing spirometry to be performed and FEV<sub>1</sub> to be recorded at home. As discussed in Section 2.3.1, the reliability and feasibility of home spirometry monitoring remain unclear but hold considerable promise. The literature on this issue is conflicting, primarily due to the limited amount of research available. Based on the findings of this dissertation, it is concluded that the technical feasibility of home spirometry monitoring should be evaluated next. Specifically, it is essential to determine whether patients can perform technically reliable and repeatable spirometry measurements in a home setting and whether compliance with home spirometry monitoring is adequate. If these prerequisites are met, the next phase would ideally be to evaluate the diagnostic accuracy, specifically the sensitivity, specificity, PPV, and NPV, of home FEV<sub>1</sub> monitoring compared to home PEF monitoring.

## 6.4 Strengths and Weaknesses of the Study

One of the strengths of our study was the use of two large study populations, which provided significant statistical power. In both populations, patient ages were well distributed, and each included patients with and without asthma. This diversity enhances the applicability of our results. Moreover, the characteristics of these patients were primarily representative of the population commonly encountered in the context of asthma diagnostics and management. Additionally, a careful screening

process for each measurement ensured that the relationship between changes in PEF and FEV<sub>1</sub> could be assessed under ideal conditions. Furthermore, only 10.9% of exercise challenge patients and 9.6% of methacholine challenge patients were excluded due to unreliable measurements, further underscoring the high quality of our spirometry measurements. All equipment used for recording measurements and administering stimuli was reliable and met the relevant technical standards. The bronchial challenge protocols were performed according to the current guidelines, and bronchodilation was conducted using the currently recommended medication doses. We used the most commonly recommended cut-off values for defining EIB and BDR in children and adults, further enhancing the clinical relevance of our results.

Various statistical approaches were used to compare different cut-off values of PEF change in detecting FEV<sub>1</sub> change. Cohen's kappa coefficient was applied to identify which of the predetermined PEF change cut-offs showed the greatest agreement with a given FEV<sub>1</sub> change cut-off, whereas calculation of the optimal operating point from ROC curves identified the cut-off that maximized the sum of sensitivity and specificity. Both approaches provide valuable but slightly different perspectives on which cut-off may be most useful, and together, they offer a more comprehensive understanding of the relationship between PEF and FEV<sub>1</sub> changes.

As explored in Section 2.3.2, spirometers and PEF meters may yield non-comparable results for PEF. Thus, measuring PEF and FEV<sub>1</sub> from the same blow and therefore the same device should have minimized any systematic errors. This approach also eliminated the potential effect of varying blowing techniques often used with PEF meters and spirometry. Given the unclear magnitude of this possible effect, as discussed in Section 2.3.3, we decided to evaluate this aspect as part of Study II. Our investigation revealed that while there were minor statistically significant differences between the mean PEF values using varying blowing techniques, the differences were so small that they are likely clinically irrelevant. However, variations may exist among different types of PEF meters, and our evaluation was limited to only one type.

Due to the poor repeatability of measurements obtained using earlier, less advanced spirometers, it was originally recommended that the threshold for BDR when assessing PEF values from spirometry be set at 23% rather than the lower thresholds recommended for PEF meters (139). To investigate the basis for this recommendation, we conducted a supplementary analysis for Study III and found that the spirometer used in our study actually provided statistically significantly better repeatability than the Mini Wright PEF meter. Therefore, we considered it

appropriate to use the same PEF threshold for bronchodilation, even though we measured PEF with a spirometer.

While the diversity of our study populations enhances the generalizability of our findings, the results might differ in populations composed exclusively of patients with severe asthma or other specific groups. We investigated the potential effect of varying patient characteristics, such as age or sex, on the results of Studies I, III, and IV but did not perform additional analyses with patients divided by age, smoking status, BMI, or other subgroups in Study II. The prevalence of airway obstruction was higher in the exercise challenge sample compared to the methacholine challenge population, whereas the prevalence of BDR was higher in the latter. Although prevalence does not affect sensitivity or specificity, it mathematically influences PPV, NPV, and Cohen's kappa coefficient. Consequently, studying populations with varying prevalences of airway caliber change may yield different results for PPV, NPV, and kappa value.

Given that two studies included only children and the other two exclusively included adults, the results from children may not be directly applicable to adults, and vice versa, even when the same challenge protocol was used. Overall, we observed that to detect a given change in FEV<sub>1</sub>, a larger change in PEF was required in children than in adults. This is likely explained by physiological differences in airway mechanics between children and adults. However, because the method used to induce obstruction varied between the pediatric and adult studies, the observed difference could also partly reflect that obstruction induced by methacholine is not biologically identical to that induced by exercise, which should be considered a limitation.

In the exercise challenge tests, the target exercise intensity was based on achieving at least 85% of the predicted maximal heart rate, calculated using the equation  $(205 - \text{age}/2)$ . Although this formula is commonly used in pediatric exercise testing in Finland, it has not been formally validated and may therefore be considered a limitation. However, the widely used formula  $(220 - \text{age})$  is known to be inaccurate in children, typically overestimating the maximal heart rate. The Tanaka equation  $(208 - 0.7 * \text{age})$ , which is more commonly recommended, provides very similar estimates in children aged 6–16 years compared with  $(205 - \text{age}/2)$ , with differences of only 0–2 beats per minute (140). Therefore, the use of this formula is unlikely to have adversely affected the degree of exertion achieved during testing in our study population.

Our studies were conducted at a single medical center, and the findings could have varied if the analyses were based on samples from other centers utilizing

differing equipment, bronchial challenge protocols, or bronchodilation protocols. In both of our study populations, the exercise group and the methacholine group, a higher proportion of pronounced obstruction and bronchodilator effects was observed compared to what could be anticipated in routine spirometry or IOS BDR tests, allowing for a higher signal-to-noise ratio. However, since we investigated only two methods of inducing obstruction and one of bronchodilation, the results may not fully generalize to natural diurnal variation in lung function or to other stimuli, such as infections or allergens.

Study I comprehensively focused on the clinical value of PEF in the context of exercise challenge testing, as recommended by GINA. However, a diagnosis of asthma is typically not established using PEF during methacholine challenge testing or by measuring BDR with PEF after any type of bronchial challenge. Nevertheless, the objectives of Studies II–IV were not to strictly evaluate the clinical value of PEF change within the context of obstruction induced by a methacholine challenge or bronchodilation induced after said bronchial challenge tests. Instead, the aim was to assess the technical relationship between changes in PEF and FEV<sub>1</sub> during airway obstruction and bronchodilation.

## 7 CONCLUSIONS

Corresponding to the previously defined aims of the study, the following conclusions were drawn:

1. Change in PEF is not a reliable parameter for detecting airway obstruction in children, as defined by decrease in FEV<sub>1</sub>, and there was marked discordance between subjects fulfilling EIB criteria according to PEF versus FEV<sub>1</sub>. The recommended PEF cut-off value of a 15% reduction is too low, leading to a significant false positive rate. If spirometry is unavailable and PEF is used, we recommend using a cut-off value of a 25% decrease instead of 15%.
2. Change in PEF is not a reliable parameter for detecting airway obstruction in adults, as defined by decrease in FEV<sub>1</sub>. Agreement between PEF- and FEV<sub>1</sub>-based criteria for obstruction was limited, indicating that the two parameters often classify individuals differently.
3. Change in PEF is not a reliable parameter for detecting bronchodilation in children, as defined by increase in FEV<sub>1</sub>. Agreement between PEF- and FEV<sub>1</sub>-based criteria for bronchodilation was limited, indicating that the two parameters often classify individuals differently.
4. Change in PEF is not a reliable parameter for detecting bronchodilation in adults, as defined by increase in FEV<sub>1</sub>. Agreement between PEF- and FEV<sub>1</sub>-based criteria for bronchodilation was limited, indicating that the two parameters often classify individuals differently.

Given the unreliability of PEF change in detecting variation in lung function, home spirometry monitoring should be further investigated as an alternative to home PEF monitoring.

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# PUBLICATION

I

## **Relation of changes in PEF and FEV<sub>1</sub> in exercise challenge in children**

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## ORIGINAL ARTICLE

# Relation of changes in PEF and FEV<sub>1</sub> in exercise challenge in children

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## Abstract

Decrease in forced expiratory volume in one second (FEV<sub>1</sub>) 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<sub>1</sub>.

We retrospectively studied 326 free running exercise challenge tests with spirometry in children 6–16 years old. FEV<sub>1</sub> 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  $\kappa$ -coefficient were used to analyse how decrease in PEF predicts decrease of 10% or 15% in FEV<sub>1</sub>.

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<sub>1</sub>, respectively. The agreement between changes in PEF and FEV<sub>1</sub> varied from slight to substantial ( $\kappa$  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<sub>1</sub>, 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<sub>1</sub> 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

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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<sub>1</sub>) 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 (Thiagens et al., 1999). PEF also seems to have poor reliability as a single measure in assessing lung function (Llewellyn 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<sub>1</sub> is recommended over PEF, the relation between change in PEF and change in FEV<sub>1</sub> 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 FEV<sub>1</sub> (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<sub>1</sub> during exercise challenge and to evaluate the accuracy of different PEF cut off points to diagnose EIB in comparison to FEV<sub>1</sub>. Our hypothesis was that PEF would not be very accurate in representing changes in lung function assessed by FEV<sub>1</sub>. 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  $\geq 15\%$  to find EIB defined as FEV<sub>1</sub> decrease  $\geq 15\%$ '. 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., FEV<sub>1</sub> decreases at least 15%). Using precision margin of 0.1 and  $\alpha$  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<sup>3</sup>, 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<sub>1</sub>, 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  $\mu\text{g}$  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))  $\times 100$ ], specificity [(true negative/(false positive + true negative))  $\times 100$ ], positive predictive values (PPV) [(true positive/(true positive + false positive))  $\times 100$ ], NPV [(true negative/(false negative + true negative))  $\times 100$ ] and  $\kappa$  coefficient were used to compare decrease in PEF and decrease in FEV<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> (10% or 15%) *at any time point after the challenge*. To check if the relation between change in PEF and change in FEV<sub>1</sub> 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 <sub>1</sub> (% predicted)	94.2 (12.3)
FEV <sub>1</sub> z-score	-0.82 (3.7)
FEV <sub>1</sub> /FVC (% predicted)	93.7 (8.3)
FEV <sub>1</sub> /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 <sub>1</sub>	140 (42.9)
≥15% decrease in FEV <sub>1</sub>	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<sub>1</sub>, 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<sub>1</sub> of at least 10%, but only less than a quarter had a decrease in FEV<sub>1</sub> 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<sub>1</sub> and percentage change of PEF. There was a strong positive linear correlation between changes in FEV<sub>1</sub> and PEF. The relative change in PEF is on average slightly less than the relative change in FEV<sub>1</sub>, 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<sub>1</sub>. 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<sub>1</sub>. On the other hand, not all children with EIB had any significant reductions in PEF.

#### 3.1 | Changes in PEF and FEV<sub>1</sub> and interpretation of exercise challenge test

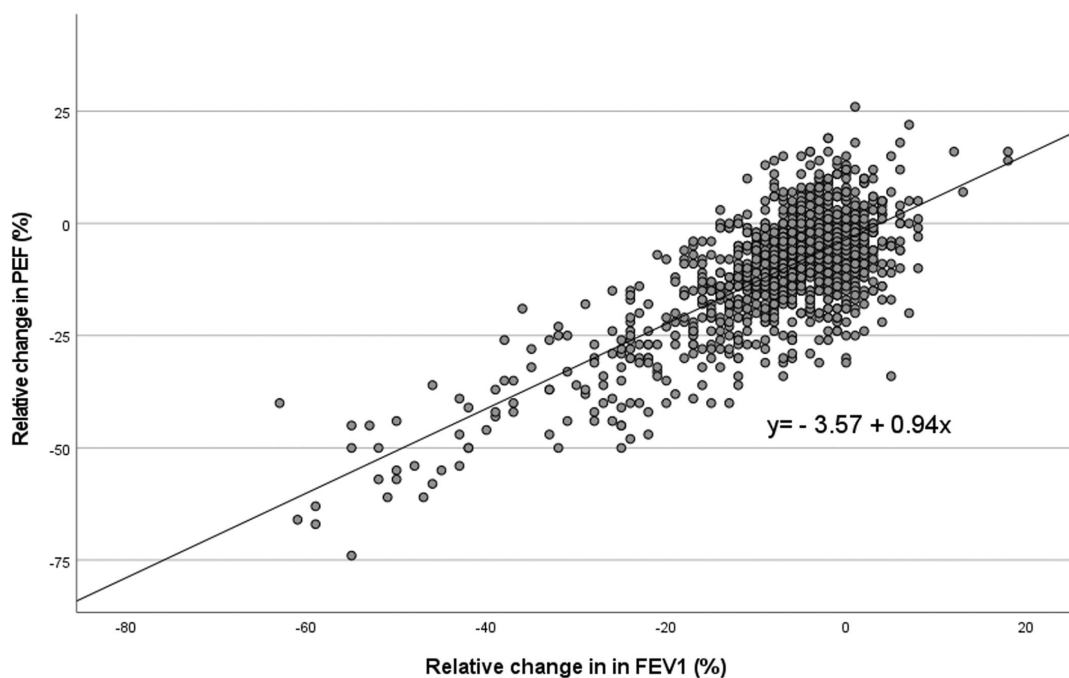
In clinical practice, exercise challenge test is considered positive if a certain decrease in lung function is achieved at any time point after the challenge. Figure 3a,b presents ROC-curves of PEF change compared against EIB defined as a 10% or a 15% decrease in FEV<sub>1</sub>, respectively. PEF change seemed to represent EIB slightly better when defined with a 15% decrease in FEV<sub>1</sub> compared to a cut-off value of 10% decrease in FEV<sub>1</sub>.

Table 2 presents the sensitivity, specificity, PPV, NPV and Cohen's  $\kappa$  coefficient for different cut-points of PEF decrease in predicting a 10% or a 15% decrease in FEV<sub>1</sub> 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<sub>1</sub>, and 25% decrease in PEF seemed to be the best to predict a 15% decrease in FEV<sub>1</sub>. 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub>. FEV<sub>1</sub>, 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.

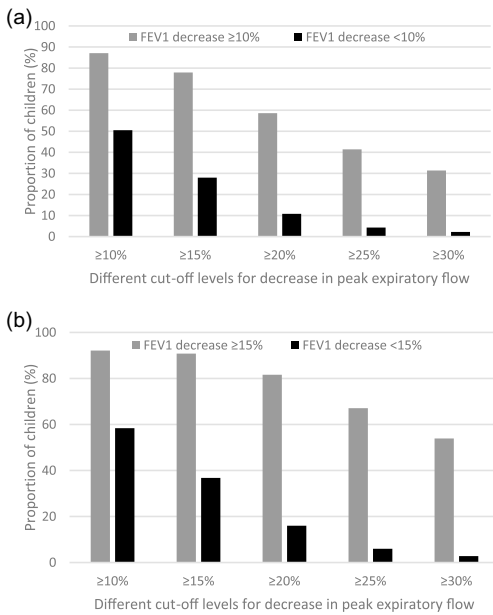
#### 4 | DISCUSSION

In this retrospective study, we found that compared to FEV<sub>1</sub>, PEF is a suboptimal metric for diagnosing EIB. 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<sub>1</sub>. 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  $\kappa$ -value of using PEF instead of FEV<sub>1</sub> 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<sub>1</sub>. 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<sub>1</sub>, 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.

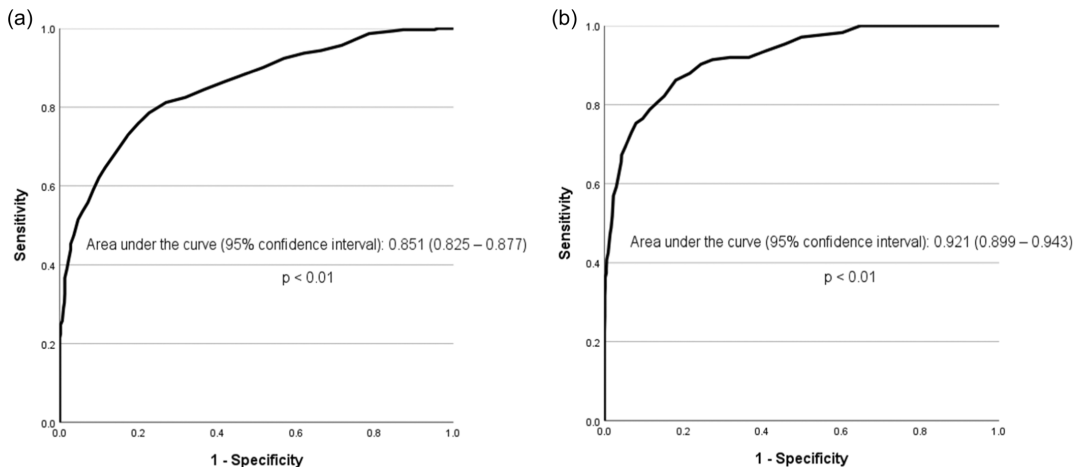
We found two studies assessing the correlation between changes in FEV<sub>1</sub> and PEF in children with EIB, but these papers did not calculate the same variables as we did (Akar et al., 2015; Gharagozlou et al., 2007). Both studies found changes in FEV<sub>1</sub> and PEF to have a 'strong' or a '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<sub>1</sub> 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<sub>1</sub>. In some studies, the cut-off for decrease in FEV<sub>1</sub> 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<sub>1</sub>. FEV<sub>1</sub>, 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub>. FEV<sub>1</sub>, 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<sub>1</sub> measured at any time point after the exercise challenge.

Decrease in PEF	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
10%					
EIB defined as	87.1	48.1	56.5	82.9	0.332
A 10% decrease in FEV <sub>1</sub>					
EIB defined as	92.1	40.4	32.4	94.3	0.199
A 15% decrease in FEV <sub>1</sub>					
15%					
EIB defined as	77.9	71.3	67.7	80.6	0.483
A 10% decrease in FEV <sub>1</sub>					
EIB defined as	90.8	62.4	42.9	95.6	0.384
A 15% decrease in FEV <sub>1</sub>					
20%					
EIB defined as	60.3	88.8	80.4	74.5	0.505
A 10% decrease in FEV <sub>1</sub>					
EIB defined as	84.9	83.4	60.8	94.8	0.600
A 15% decrease in FEV <sub>1</sub>					
25%					
EIB defined as	44.3	95.5	87.8	70.0	0.426
A 10% decrease in FEV <sub>1</sub>					
EIB defined as	72.9	93.7	77.3	92.2	0.680
A 15% decrease in FEV <sub>1</sub>					
30%					
EIB defined as	34.4	97.8	91.7	67.4	0.352
A 10% decrease in FEV <sub>1</sub>					
EIB defined as	61.2	97.1	85.4	89.9	0.649
A 15% decrease in FEV <sub>1</sub>					

Abbreviations: EIB, exercise induced bronchoconstriction; FEV<sub>1</sub>, 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub>. 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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# PUBLICATION

## II

### **Relation of changes in peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV<sub>1</sub>) during bronchoconstriction**

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## ORIGINAL ARTICLE

# Relation of changes in peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV<sub>1</sub>) during bronchoconstriction

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## Abstract

Diagnosis of asthma can be confirmed based on variability in peak expiratory flow (PEF) or changes in forced expiratory volume in 1 s (FEV<sub>1</sub>) measured with spirometry. Our aim was to use methacholine challenge as a model of induced airway obstruction to assess how well relative changes in PEF reflect airway obstruction in comparison to relative changes in FEV<sub>1</sub>. We retrospectively studied 878 patients who completed a methacholine challenge test. To assess congruency along with differences between relative changes in FEV<sub>1</sub> and PEF during airway obstruction, a regression analysis was performed, and a Bland & Altman plot was constructed. ROC analysis, sensitivity, specificity, positive and negative predictive values and  $\kappa$ -coefficient were used to analyze how decrease in PEF predicts decrease of 10% or 15% in FEV<sub>1</sub>. The relative change in PEF was on average less than the relative change in FEV<sub>1</sub>. In the ROC analysis areas under the curve were 0.844 and 0.893 for PEF decrease to predict a 10% and 15% decrease in FEV<sub>1</sub>, respectively. The agreement between changes in PEF and FEV<sub>1</sub> varied from fair to moderate. Airway obstruction detected by change in PEF was false in about 40% of cases when compared to change in FEV<sub>1</sub>. Change in PEF is not a very accurate measure of airway obstruction when compared to change in FEV<sub>1</sub>. Replacing peak flow metre with a handheld spirometer might improve diagnostic accuracy of home monitoring in asthma.

## KEYWORDS

asthma, diagnostics, home monitoring, methacholine, obstruction, spirometry

## 1 | INTRODUCTION

Asthma is one of the most common chronic diseases affecting about 339 million people globally (Vos et al. 2017). Asthma is attributed to bronchial hyperreactivity, a state characterized by easily triggered contraction of the bronchial smooth muscle

leading to narrowing of the airways. Bronchial hyperreactivity leads to symptoms including wheeze, chest tightness, breathlessness and cough together with variable expiratory airflow limitation that can be resolved by bronchodilators. The severity of the symptoms and airflow obstruction vary over time, and they are often triggered by different exposures and physical exercise

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(GINA, 2022). No one universally optimal approach exists for diagnosing asthma and a multitude of tests are commonly used. Asthma can for instance be diagnosed by bronchodilation response with spirometry, diurnal variation in peak expiratory flow or hyperreactivity discovered utilizing different bronchial challenge tests (GINA, 2022; Louis et al., 2022).

A national asthma programme was conducted in Finland from 1994 to 2004 which sought to improve asthma care and, also, to direct the main responsibility of diagnostics and treatment of adult asthma to primary health care. The main diagnostic tools available in primary care in Finland are spirometry with bronchodilation test and a 2-week home peak flow (PEF) monitoring. As the diagnosis of asthma in Finnish primary care after the asthma programme is always based on objective lung function measures, diagnostic accuracy was improved together with various indicators of the burden of asthma on the national level (Haahela, 2006). Home PEF-monitoring has been advocated as a test to diagnose and manage the treatment of asthma for several decades (Reddel et al. 2009). However, the European respiratory society does not recommend PEF-monitoring as a sole and primary diagnostic method, but as a complementary method in cases with normal spirometry particularly if access to bronchial challenge tests is limited (Louis et al., 2022).

PEF seems to have poor reliability as a single reading in assessing lung function (Llewellyn et al., 2002) and it is not optimal in assessing bronchodilator response (Thiadens et al., 1999). Nevertheless, the simplicity and low cost of handheld peak flow metres have enabled home monitoring and thus allowed for observation of variability in bronchial obstruction over time. PEF does seem more useful in situations where multiple measurements are made over time, such as in home peak flow monitoring that has been studied more (Mueller & Eigen, 1992). However, even in the context of home monitoring, some studies suggest PEF to be unreliable (Brouwer & Brand, 2008). The sensitivity and specificity of home PEF-monitoring in diagnosing asthma is greatly affected by the chosen method of calculating PEF variability (Goldstein et al., 2001). In addition, the technical reliability of measurements cannot be accurately assessed in the context of home PEF-monitoring, and unreliable data stemming from poor blowing technique may thus negatively impact the reliability of the test.

In the recent years, small and reliable handheld spirometers have been developed for the purpose of home monitoring. Usability of home spirometry monitoring in the context of asthma diagnostics and management is not well known and so far all the guideline based diagnostic thresholds on variation in home monitoring are based on PEF (GINA, 2022; Louis et al., 2022). Furthermore, the relation between change in PEF and change in FEV<sub>1</sub> at bronchoconstriction is not clear. Our aim was therefore to use methacholine challenge as a model of induced airway obstruction to assess how well relative changes in PEF reflect airway obstruction in comparison to relative changes in FEV<sub>1</sub>.

## 2 | METHODS

### 2.1 | Study design

We retrospectively collected all methacholine challenge tests with spirometry conducted at Tampere university hospital between dates 19 November 2018 and 14 April 2021. Medical history was gathered from patient records. Due to the retrospective nature of this study, no ethical approval was needed.

### 2.2 | Spirometry measurements and methacholine challenge

Spirometry was performed according to international recommendations (Miller, 2005). A trained physician visually assessed technical reliability and the patients' spirometry technique and evaluated reproducibility of the parameters according to international guidelines (Graham et al., 2019). Measurements were considered technically reliable if spirometry maneuvers before and after methacholine inhalation were of reliable quality according to international guidelines.

Methacholine challenge test was carried out with Vyntus Pneumo spirometer and Carefusion Vyntus APS -dosimeter (Vyaire Medical) according to latest European respiratory society guidelines (Coates et al., 2017). The methacholine test was performed by experienced technicians. After initial spirometry measurements diluent step was applied with saline solution. After the diluent, methacholine doses of 18, 72, 270, 810 and 2600 µg were administered at 5-min intervals, and spirometry measurements were performed concurrently using the dosimetric method by Nieminen et al. (Nieminen et al., 1988) according to Finnish guidelines (Malmberg et al., 2018). Results were calculated using cumulative dose that causes a 20% fall in FEV<sub>1</sub> (PD20). After the methacholine challenge, bronchodilator was administered (Salbutamol 400 µg).

### 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). After each step of methacholine challenge (maximum of five steps) changes in PEF and FEV<sub>1</sub> compared to baseline were recorded and included in the analyses. Therefore, the total number of measurements included in the analyses was far greater than the number of patients. To assess congruency between relative changes in FEV<sub>1</sub> and PEF during airway obstruction, a regression analysis was performed. To better visualize differences in relative changes of the two variables, a Bland & Altman plot was constructed (Bland & Altman, 1995, 2010). Receiver operating characteristics (ROC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Cohen's

$\kappa$  coefficient were used to compare decrease in PEF and decrease in FEV<sub>1</sub> as outcome measures.

### 3 | RESULTS

During the study period, 971 adult patients completed a methacholine challenge test. Altogether 878 patients produced technically reliable measurements and a total of 4066 technically reliable data points (changes in PEF and FEV<sub>1</sub> after each dose of methacholine in comparison to baseline) were collected. On average, the subjects were 47.4 years old (Table 1). Over a third of the patients had smoked or were current smokers. Two thirds of the participants were females, and they had on average normal lung function before the administration of methacholine. A quarter of the measurement points had at least a 10% decrease in FEV<sub>1</sub> compared to baseline and almost a third of the measurement points had a decrease of 10% or more in PEF.

Figure 1 shows the relation between relative change in PEF and relative change in FEV<sub>1</sub> in the 4066 measurement points. There was a positive linear correlation between changes in PEF and FEV<sub>1</sub>. The relative change in PEF was on average less than the relative change in FEV<sub>1</sub>, and the slope was 0.75 instead of 1.0. The correlation coefficient was 0.670. In the majority of measurements ( $n = 3232$ ) neither PEF nor FEV<sub>1</sub> decreased by 15%. There were 374 measurement points where both PEF and FEV<sub>1</sub> had decreased at least 15%, but in 460 measurement points there was a discrepancy between the changes in PEF and FEV<sub>1</sub> such that only one of the parameters had decreased by at least 15%.

Figure 2 shows the difference between the relative changes in FEV<sub>1</sub> and PEF plotted against their mean (a Bland & Altman plot) in the 4066 measurement points. The mean difference between changes in PEF and FEV<sub>1</sub> was only 0.4% but the 95% confidence interval (CI) of the difference varied from -12.6% to 13.3%. Most patients experienced at least a slight decrease in lung function during the methacholine test, and thus most data points have shifted to the left on the  $x$ -axis, indicating some level of bronchoconstriction.

Figure 3a,b present the ability of change in PEF to predict a 10% and a 15% decrease in FEV<sub>1</sub>, respectively, by using ROC curves. The area under the curve (AUC) was slightly better for predicting a 15% (0.893) than a 10% decrease in FEV<sub>1</sub> (0.844).

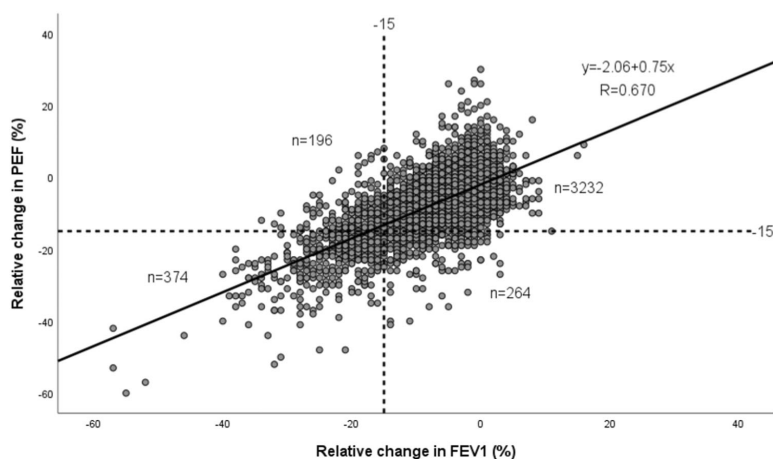
Table 2 presents the sensitivity, specificity, PPV, NPV and Cohen's  $\kappa$  coefficient for different cut-points of relative PEF decrease in predicting a 10% or a 15% decrease in FEV<sub>1</sub>. In both detecting a 10% or a 15% FEV<sub>1</sub> decrease, a lower cut-off value for decrease in PEF was associated with higher sensitivity and NPV, while a higher cut-off value for decrease in PEF was associated with better specificity and PPV. The Cohen's  $\kappa$  coefficient values ranged from 0.325 to 0.498 for detecting a 10% FEV<sub>1</sub> decrease and from 0.402 to 0.553 for detecting a 15% FEV<sub>1</sub> decrease. Cut-off values of 10% and

**TABLE 1** Patient characteristics in 878 subjects with technically reliable measurements in methacholine challenge test.

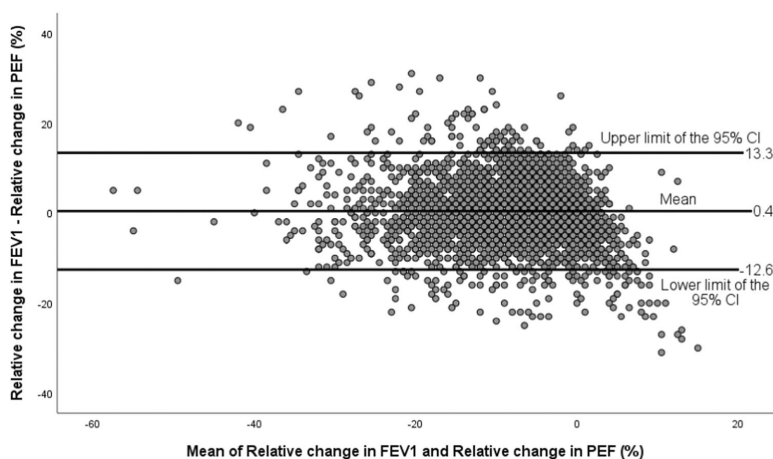
Characteristics	Value
Age (year)	47.4 (16.4)
Gender	
Female	587 (66.9)
Male	291 (33.1)
Height (cm)	169.2 (9.4)
Weight (kg)	80.8 (18.4)
BMI (kg/m <sup>2</sup> )	28.2 (6.1)
Smoking status	
Data not available	164 (18.7)
Current smoker	56 (6.4)
Ex-smoker	208 (23.7)
Never smoker	450 (51.3)
Lung function at baseline	
FVC (% predicted)	96.2 (13.1)
FEV <sub>1</sub> (% predicted)	93.7 (13.6)
FEV <sub>1</sub> /FVC (% predicted)	97.4 (8.1)
PEF (% predicted)	94.8 (15.2)
Outcome of methacholine challenge	
No hyperresponsiveness	582 (66.3)
Mild hyperresponsiveness (PD20FEV <sub>1</sub> 601–2610 $\mu$ g)	148 (16.9)
Moderate hyperresponsiveness (PD20FEV <sub>1</sub> 151–600 $\mu$ g)	95 (10.2)
Marked hyperresponsiveness (PD20FEV <sub>1</sub> $\leq$ 150 $\mu$ g)	53 (6.0)
Technically reliable measurement points	4066 (100.0)
Measurements with $\geq$ 10% decrease in FEV <sub>1</sub>	1094 (26.8)
Measurements with $\geq$ 15% decrease in FEV <sub>1</sub>	575 (14.1)
Measurements with $\geq$ 10% decrease in PEF	1304 (32.1)
Measurements with $\geq$ 15% decrease in PEF	638 (15.7)
Measurements with $\geq$ 20% decrease in PEF	317 (7.8)

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

15% decrease in PEF seemed most accurate for detecting decreases of 10% and 15% in FEV<sub>1</sub>, respectively. Even with these cut-offs, PPV was slightly less than 60% indicating that airway obstruction detected by PEF was false in about 40% of cases when compared to change in FEV<sub>1</sub>. NPV of these PEF cut points was better, about 90%, indicating that if airway obstruction is ruled out by change in PEF it is present only in about 10% of cases determined by simultaneous change in FEV<sub>1</sub>.



**FIGURE 1** Relative changes in PEF and FEV<sub>1</sub> in 4066 measurement points after methacholine administration. The solid black line represents regression line with  $r = 0.670$ . The dotted horizontal and vertical lines represent 15% decrease in PEF and FEV<sub>1</sub>, respectively. The majority of measurement points ( $n = 3232$ ) had both PEF and FEV<sub>1</sub> decrease less than 15% and in 374 measurement points both FEV<sub>1</sub> and PEF had decreased more than 15%. In 264 measurement points PEF had decreased more than 15% and FEV<sub>1</sub> less than 15%, and vice versa in 196 measurement points.



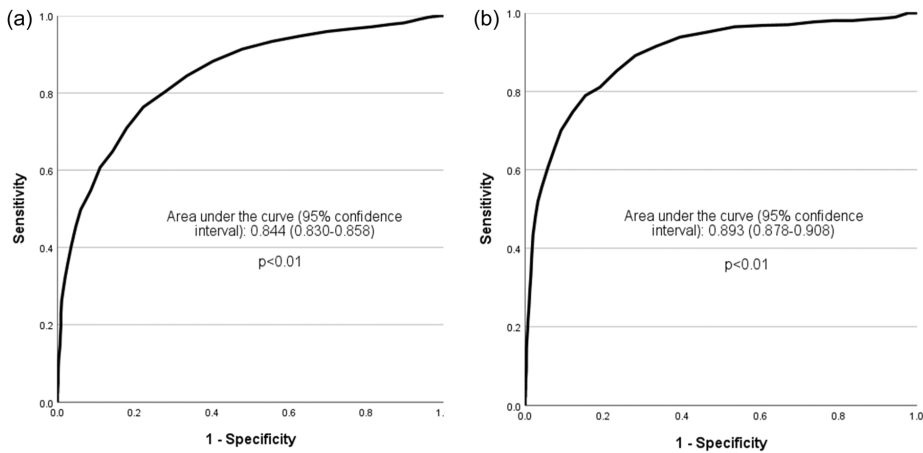
**FIGURE 2** Bland & Altman plot of relative change in PEF and FEV<sub>1</sub> in 4066 measurement points. The mean difference between changes in PEF and FEV<sub>1</sub> was only 0.4% but the 95% confidence interval (CI) varied from -12.6% to 13.3%.

#### 4 | DISCUSSION

In this retrospective study we found that while relative change in PEF has a positive correlation with relative change in FEV<sub>1</sub> during airway obstruction, the difference between change in PEF and change in FEV<sub>1</sub> has a large 95% CI. Furthermore, PEF seems to have poor accuracy in assessing obstruction defined by decrease in FEV<sub>1</sub>. Even with the best cut-off values PPV was only about 60% while NPV was better around 90% indicating a significant risk of false positive

interpretation of airway obstruction by using PEF but a smaller risk for false negative interpretations.

Previous research already exists examining the relation of changes in PEF and FEV<sub>1</sub> during bronchoconstriction. One study found PEF to generally have worse sensitivity compared to specificity for detecting a 15% or 20% decrease in FEV<sub>1</sub> (Giannini et al., 1997). In accordance with our findings, they concluded that in the context of mild bronchoconstriction induced by varying stimuli, PEF and FEV<sub>1</sub> changes relate poorly. In another study with a very large patient



**FIGURE 3** ROC analysis presenting the relationship between PEF change and a 10% decrease (a) or a 15% decrease (b) in FEV<sub>1</sub> in 4066 measurement points after methacholine administration.

**TABLE 2** Characteristics of different cut-off values in PEF decrease to predict a decrease of 10% or 15% in FEV<sub>1</sub> measured in the 4066 measurement points during methacholine challenge.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	κ
10% decrease in PEF					
10% decrease in FEV <sub>1</sub>	70.9	82.1	59.0	88.6	0.498
15% decrease in FEV <sub>1</sub>	85.3	76.6	37.3	97.0	0.402
15% decrease in PEF					
10% decrease in FEV <sub>1</sub>	45.6	95.2	77.6	82.8	0.469
15% decrease in FEV <sub>1</sub>	65.6	92.4	58.6	94.3	0.553
20% decrease in PEF					
10% decrease in FEV <sub>1</sub>	26.2	98.9	89.9	78.6	0.325
15% decrease in FEV <sub>1</sub>	43.3	98.0	77.9	91.4	0.508

population, percentage of predicted PEF was found not to be equivalent with percentage of predicted FEV<sub>1</sub> during obstruction. The authors of this study found PEF to underestimate the level of obstruction in less severe cases and overestimate it in more severe obstruction compared to FEV<sub>1</sub> (Aggarwal et al., 2006). In a study comparing the diagnostic accuracy of changes in PEF to detect immediate asthmatic reactions due to occupational agents, change in PEF was found satisfactory for detecting a 20% decrease in FEV<sub>1</sub>. Both sensitivity and specificity reached values of over 90% for PEF change cut off values of 15% and 20%, corrected for device inaccuracies by the Miller equation. However, using noncorrected PEF change values, sensitivity and NPV were significantly worse and PEF changes were in fact not equal to FEV<sub>1</sub> changes (Weytjens et al., 1999). The transformative calculations undertaken in this study as well as the different FEV<sub>1</sub> cut off value chosen for detection could explain the differences to our results.

PEF is often used and reasonably well studied in the context of home peak flow monitoring and almost exclusively used over spirometry in a home setting. Exaggerated diurnal variation of PEF can be used to diagnose asthma (Louis et al., 2022). The handheld peak flow metres used for this purpose do not allow for the assessment of technical reliability. Thus, it becomes impossible to exclude measurements that could possibly skew the results of the home monitoring. This combined with the evidence indicating PEF to have suboptimal sensitivity and specificity in detecting bronchoconstriction when compared to FEV<sub>1</sub> (Csonka et al., 2023) raises a question for the future of home monitoring with peak flow metres. If change in FEV<sub>1</sub> is diagnostically more accurate in other settings, could it also be superior in a home monitoring context, and could home peak flow monitoring be possibly replaced with home spirometry? Peak flow metres have the advantage of lower cost compared to microspirometers but this cost difference could

eventually be offset by better allocation of resources due to more accurate diagnostics.

In the recent years, multiple feasibility studies have been conducted regarding home spirometry monitoring. Two studies found home spirometry monitoring to be safe, feasible and satisfactory (Kupczyk et al., 2021) and the patients to have high compliance (Bindler et al., 2023). However, in one study, spirometry was found to be significantly less consistent and of inferior quality compared to spirometry performed in a clinical setting under supervision (Oppenheimer et al., 2023). We are currently not aware of any studies successfully ascertaining the sensitivity, specificity and other diagnostic parameters for home spirometry monitoring compared to home PEF monitoring. More research is currently needed to determine the feasibility and efficacy of home spirometry monitoring.

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. Data on smoking was not available for all patients but we have no reason to expect the proportion of smokers to be significantly different in the population with missing data. In this study, bronchoconstriction was induced by inhalation of methacholine. It is possible that the method of inducing obstruction could affect the relation of changes in PEF and FEV<sub>1</sub> and the results may be different in the context of diurnal variation or exercise challenge, for example. However, previous research supports the hypothesis that changes in PEF relate poorly to changes in FEV<sub>1</sub> during obstruction in different contexts (Csonka et al., 2023; Giannini et al., 1997). It is thought that PEF reflects mainly the patency of large airways while FEV<sub>1</sub> would reflect both small and large airways. This might explain some of the differences found in this study. However, there is limited experimental data on which parts of the airways these parameters reflect.

The strengths of our study were a large population size of 878 patients and a careful screening process in which every measurement was assessed individually to ensure technical reliability. Patients deemed unreliable were excluded to observe the relationship between PEF change and FEV<sub>1</sub> change in ideal conditions more effectively. Patient age was generally well distributed with children excluded. This makes our results well applicable to the general adult population. 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. 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 (Supporting Information: 1).

In conclusion, we showed in a methacholine induced airway obstruction that change in PEF is not a very accurate measure of airway obstruction when compared to change in FEV<sub>1</sub>. Use of PEF monitoring in asthma has the advantage of being able to detect variability over time, but changes in PEF may not be very reliable in comparison to changes in FEV<sub>1</sub>. Replacing the measuring device with

a handheld spirometer might improve diagnostic accuracy of home monitoring in asthma.

#### AUTHOR CONTRIBUTIONS

All authors participated in designing this study and participated in the revision process. The data was collected by Antti Tikkakoski and Liisa Vuotari. The data was analyzed by Leon L. Csonka and Lauri Lehtimäki. Leon L. 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

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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PUBLICATION  
III

**Relation of changes in PEF and FEV<sub>1</sub> during bronchodilation in children**

Csonka LL, Tikkakoski A, Tikkakoski AP, Karjalainen J, Lehtimäki L

Submitted



# PUBLICATION IV

## **Relation of Changes in PEF and FEV<sub>1</sub> During Salbutamol-Induced Bronchodilation After Methacholine Challenge Test**

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## Research Article

# Relation of Changes in PEF and FEV<sub>1</sub> During Salbutamol-Induced Bronchodilation After Methacholine Challenge Test

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Asthma diagnosis can be confirmed by observing significant bronchodilator response (BDR) through peak expiratory flow (PEF) at home or forced expiratory volume in 1 s (FEV<sub>1</sub>) via spirometry in a clinical setting. We aimed to use the administration of salbutamol after a methacholine challenge test as a model of bronchodilation to study how accurately the change in PEF predicts improvement in lung function, as defined by an increase in FEV<sub>1</sub>. We analyzed 869 adult patients who were administered salbutamol after a methacholine challenge. To compare relative changes in PEF and FEV<sub>1</sub> during bronchodilation, we used regression analysis and constructed a Bland and Altman plot. ROC analysis, sensitivity, specificity, positive and negative predictive values, and kappa coefficient assessed how precisely increases in PEF detected a 12% and 0.2-L improvement in FEV<sub>1</sub>. The average relative increase in FEV<sub>1</sub> was significantly greater than that in PEF. The area under the curve in the ROC analysis was 0.844 for PEF change to detect a 12% and 0.2-L increase in FEV<sub>1</sub>. The kappa values for changes in PEF and FEV<sub>1</sub> ranged from fair to moderate. BDR detected by the recommended 15% and 60L/min cut-off for PEF identified less than half of true positives, while a 10% cut-off correctly identified close to 75% of them. PEF increase is not a reliable measure of BDR in comparison to FEV<sub>1</sub> increase, and a 10% improvement in PEF was the least inaccurate cut-off. Substituting the PEF meter with a handheld spirometer should be further investigated for asthma home monitoring.

**Keywords:** asthma; bronchodilation; diagnostics; home monitoring; methacholine; spirometry

## 1. Introduction

Asthma stands as one of the most common chronic diseases, impacting almost 340 million individuals worldwide [1]. Asthma typically presents with breathlessness, cough, wheeze, and chest tightness, along with variable expiratory airflow limitation relieved by bronchodilators [2]. The diagnostic framework for asthma remains devoid of universal standardization, resulting in the utilization of a diverse array of different tests. Diagnosing asthma may encompass evaluating bronchodilator response (BDR) using spirometry, monitoring daily fluctuations in peak expiratory flow (PEF), or identifying bronchial hyperreactivity through diverse challenge tests [2, 3].

Following the adoption of objective lung function measures such as home PEF monitoring as a standard practice for diagnosing asthma in Finnish primary care, diagnostic precision saw a marked improvement, alongside positive shifts in various metrics reflecting the national asthma burden [4]. While home PEF monitoring has been well recognized for its utility in asthma diagnosis and management over the years [5], the European Respiratory Society (ERS) takes a nuanced stance. It refrains from promoting PEF monitoring as the primary or solitary diagnostic method. Instead, it emphasizes PEF monitoring as an adjunctive measure, particularly in cases where spirometry outcomes appear normal, especially if access to bronchial challenge testing is not available [3].

Various studies have indicated the limited reliability of PEF as a single reading for assessing lung function during obstruction [6–10]. However, the affordability and simplicity of handheld PEF meters have facilitated home monitoring. This enables the observation of bronchial obstruction and dilation over time. The usefulness of PEF in monitoring asthma is better proved when multiple daily values are recorded over time [9]. While PEF monitoring proves useful in this setting, some studies indicate potential unreliability, even within the home monitoring framework [11]. Different PEF meters are known to yield noncomparable results [12–14]. Furthermore, the method chosen for calculating PEF variability significantly impacts the sensitivity and specificity of PEF monitoring [15]. Accurately assessing the technical reliability of home PEF measurements is challenging, and unreliable measurements due to inadequate technique can consequently compromise the reliability of home PEF monitoring.

For adults, within the framework of home PEF monitoring, the Finnish national asthma guideline defines a significant BDR as PEF increasing at least 15% and 60 L/min following the administration of bronchodilators. To establish a diagnosis of asthma, BDR must occur at least three times during the monitoring period. GINA recommends a 20% improvement in PEF as the threshold for in-clinic BDR testing as an alternative to FEV<sub>1</sub>, but it currently does not recommend BDR testing in the context of home PEF monitoring. According to the Finnish national asthma guideline, ERS asthma guideline, and GINA, during a bronchodilation test conducted with a spirometer, BDR is defined as an increase of at least 12% and 0.2 L in FEV<sub>1</sub> [2, 3, 16]. GINA and the Finnish national guideline also recommend an increase of at least 12% and 0.2 L in forced vital capacity (FVC) as an alternative definition for BDR, with a 15% and 0.4-L increase providing greater confidence [2, 16]. The joint American Thoracic Society (ATS) and ERS spirometry technical standard guideline recommends using a cut-off value of at least 10% increase in the predicted value for FEV<sub>1</sub> or FVC [17].

The little existing research investigating the relation between changes in PEF and FEV<sub>1</sub> during bronchodilation suggests that the accuracy of PEF change in detecting BDR is questionable [18–21]. Additionally, no study directly compared the recommended BDR cut-off values of 15% and 60-L/min PEF increase and 12% and 0.2-L FEV<sub>1</sub> improvement. Recently, the availability of compact and reliable handheld spirometers tailored for home monitoring has increased, but the applicability of home spirometry monitoring with bronchodilation testing in asthma diagnostics is not well studied yet. Thus, our goal was to utilize salbutamol administration after a methacholine challenge test as a bronchodilation model to study how accurately PEF changes represent airway relaxation, as defined by an improvement in FEV<sub>1</sub>.

## 2. Methods

**2.1. Study Design.** We gathered all methacholine challenge tests with spirometry performed at Tampere University Hospital between November 19, 2018, and April 14, 2021.

The subjects had been sent for a methacholine challenge test due to suspected asthma. The exclusion criteria were the standard contraindications for the methacholine challenge test [22]. Additionally, all patients under 18 years of age and those with technically unreliable measurements were excluded from the study. Patient medical history was collected from records. As this was a retrospective study, ethical approval was not required.

**2.2. Spirometry and Methacholine Challenge Protocol.** Spirometry was performed according to international guidelines [23], using reference values for Finnish adults [24]. The patients' blowing technique, along with the technical reliability and reproducibility of the measurements, was visually evaluated by trained physicians in accordance with international guidelines [25]. Reliability of measurements was established if all spirometry blows during the methacholine challenge met the quality standards outlined in international guidelines [25]. A Vyntus Pneumo spirometer and Carefusion Vyntus APS dosimeter (Vyair Medical, Illinois, United States) were used to perform the methacholine challenge, in accordance with ERS recommendations [26]. Experienced technicians conducted the methacholine challenge. Following the first spirometry measurements, a saline solution was administered as a diluent step. Subsequently, methacholine doses of 18, 72, 270, 810, and 2600 µg were given at 5-min intervals. After each methacholine dose, spirometry measurements were repeated using the dosimetric method by Nieminen et al. [27] according to Finnish guidelines [22]. Following the challenge, bronchodilator medication (salbutamol 400 µg) was administered using a pMDI and a spacer (Ventoline Evohaler and Volumatic, GSK), and a final spirometry measurement was recorded.

**2.3. Statistics.** Data analysis was performed using IBM SPSS Statistics for Windows, Version 27 (IBM Corp, New York, United States). Microsoft Excel for Microsoft 365 MSO (Version 2110 Build 16.0.14527.20234) (Washington, United States) was used for additional calculations. The relative decrease in FEV<sub>1</sub> and PEF after methacholine was calculated as follows:  $\frac{((\text{premethacholine FEV}_1 \text{ or PEF}) - (\text{postmethacholine FEV}_1 \text{ or PEF}))}{(\text{premethacholine FEV}_1 \text{ or PEF})} \times 100$ . The relative increase in FEV<sub>1</sub> and PEF after bronchodilation was calculated as follows:  $\frac{((\text{postbronchodilator FEV}_1 \text{ or PEF}) - (\text{prebronchodilator FEV}_1 \text{ or PEF}))}{(\text{prebronchodilator FEV}_1 \text{ or PEF})} \times 100$ . A regression analysis was carried out to examine the correlation between relative changes in FEV<sub>1</sub> and PEF during bronchodilation. A Bland-Altman plot was used to illustrate the differences in relative changes between FEV<sub>1</sub> and PEF [28, 29]. Receiver operating characteristic (ROC), sensitivity  $\frac{(\text{true positive}/(\text{true positive} + \text{false negative})) \times 100$ , specificity  $\frac{(\text{true negative}/(\text{false positive} + \text{true negative})) \times 100$ , PPV  $\frac{(\text{true positive}/(\text{true positive} + \text{false positive})) \times 100$ , NPV  $\frac{(\text{true negative}/(\text{false negative} + \text{true negative})) \times 100$ , and Cohen's kappa coefficient were employed to compare the increases in FEV<sub>1</sub> and PEF as outcome measures. An additional analysis based on the ATS/ERS technical spirometry standard recommendation to use an increase in FEV<sub>1</sub> of at least 10% of predicted value as

the definition for BDR was performed as a supplementary analysis [17]. Increase in FEV<sub>1</sub> % predicted was calculated as  $\frac{((\text{postbronchodilator FEV}_1) - (\text{prebronchodilator FEV}_1))}{(\text{predicted FEV}_1)} * 100$ . Increase in PEF % predicted was calculated as follows:  $\frac{((\text{postbronchodilator PEF}) - (\text{prebronchodilator PEF}))}{(\text{predicted PEF})} * 100$  (Supporting Information). To assess whether the relationship between changes in PEF and FEV<sub>1</sub> is influenced by age, sex, prebronchodilator lung function, or degree of response to methacholine, we divided the population by sex, median age, and median prebronchodilator FEV<sub>1</sub> % predicted, as well as into groups who experienced either at least a 20% decrease or less than a 20% decrease in FEV<sub>1</sub> following methacholine inhalation. We then analyzed whether the differences in sensitivity, specificity, PPV, and NPV between these subgroups were significant using a two-sample test for equality of proportions.

### 3. Results

Throughout the study duration, 971 adults participated in a methacholine challenge test. After excluding 102 tests due to technical unreliability, 869 patients with reliable measurements remained. The average age of the participants was 47 years. One-third of the participants were male, and more than one-third had a history of smoking or were active smokers. On average, the patients had normal lung function prior to the methacholine challenge. After the highest dose of methacholine was administered, lung function significantly worsened, and the relative decrease was slightly larger in FEV<sub>1</sub> compared to PEF. After salbutamol inhalation, almost half of the patients experienced BDR, as defined by a 12% and 0.2-L increase in FEV<sub>1</sub>. Contingent upon the cut-off value, a significant PEF increase was observed in 17.1%–47.4% of the participants. Using the Finnish recommended 15% and 60-L/min cut-off value, 27.5% of patients were classified as having BDR, while the GINA recommended 20% increase in PEF categorized 24.2% of patients as having BDR (Table 1).

Figure 1 presents the relation between relative change in FEV<sub>1</sub> and relative change in PEF during bronchodilation. A strong positive linear relationship was observed between changes in FEV<sub>1</sub> and PEF. The formula of the correlation line was  $y = 0.96 + 0.76x$ , meaning the relative change in FEV<sub>1</sub> was, on average, more than the relative change in PEF after a 4% increase in FEV<sub>1</sub>. The correlation coefficient was 0.731. Of the 869 patients examined, 397 did not meet the criteria for either a 12% increase in FEV<sub>1</sub> or a 15% improvement in PEF. Moreover, 250 patients achieved both criteria, while 41 attained a 15% increase in PEF without a corresponding 12% improvement in FEV<sub>1</sub>, and 181 achieved a 12% increase in FEV<sub>1</sub> without a 15% improvement in PEF.

Figure 2 presents a Bland and Altman plot of the relative changes in FEV<sub>1</sub> and PEF during bronchodilation. The mean signed difference between changes in FEV<sub>1</sub> and PEF was 3.0%, indicating a larger average increase in FEV<sub>1</sub> compared to PEF. This concurs with the findings from Figure 1, showing that the relative FEV<sub>1</sub> increase was mostly greater than the relative PEF improvement. The 95% confidence interval (CI) for the difference between changes in FEV<sub>1</sub>

**TABLE 1:** Characteristics of 869 study subjects with technically reliable measurements in the methacholine challenge and BDR tests.

Characteristics	Value
Age (years)	47.4 (16.4)
Gender ( <i>n</i> )	
Female	581 (66.9)
Male	288 (33.1)
Height (cm)	169.2 (9.4)
Weight (kg)	80.9 (18.4)
BMI (kg/m <sup>2</sup> )	28.2 (6.1)
Smoking status ( <i>n</i> )	
Data not available	162 (18.6)
Current smoker	56 (6.4)
Ex-smoker	207 (23.8)
Never smoker	444 (51.1)
Lung function at baseline (% predicted)	
FVC	96.2 (13.1)
FEV <sub>1</sub>	93.7 (13.6)
FEV <sub>1</sub> /FVC	97.4 (8.0)
PEF	91.5 (21.0)
FEV <sub>1</sub> after last dose of methacholine (% predicted)	80.1 (16.6)
PEF after last dose of methacholine (% predicted)	82.0 (16.8)
Relative decrease in FEV <sub>1</sub> after last dose of methacholine (%)	14.9 (9.6)
Relative decrease in PEF after last dose of methacholine (%)	13.2 (9.7)
Subjects with a ≥ 20% decrease in FEV <sub>1</sub> after last dose of methacholine ( <i>n</i> )	265 (30.5)
Bronchodilator response ( <i>n</i> )	
≥ 12% improvement in FEV <sub>1</sub>	431 (49.6)
≥ 12% and 0.2-L improvement in FEV <sub>1</sub>	425 (48.9)
≥ 10% improvement in PEF	412 (47.4)
≥ 15% improvement in PEF	291 (33.5)
≥ 15% and 60 L/min improvement in PEF	239 (27.5)
≥ 20% improvement in PEF	210 (24.2)
≥ 25% improvement in PEF	149 (17.1)

Note: Continuous variables are shown as mean (SD) and categorical variables as *n* (%).

and PEF was large and varied from −19.0% to 25.0%. The majority of study participants showed some degree of improvement in lung function following salbutamol administration. Most data points reflect this shift to the right on the *x*-axis, signifying some amount of bronchodilation.

Figure 3 shows a ROC curve comparing changes in PEF with a 12% and 0.2-L increase in FEV<sub>1</sub> during bronchodilation. The area under the curve (AUC) was 0.844, and the 95% CI ranged from 0.818 to 0.871 ( $p < 0.01$ ). According to the AUC, the ability of PEF change to predict a 12% and 0.2-L increase in FEV<sub>1</sub> was classified as good [30].

Table 2 shows the sensitivity, specificity, PPV, NPV, and Cohen's kappa coefficient for various PEF increase cut-offs in detecting a 12% and 0.2-L improvement in FEV<sub>1</sub> after salbutamol inhalation. Lower cut-off values were associated

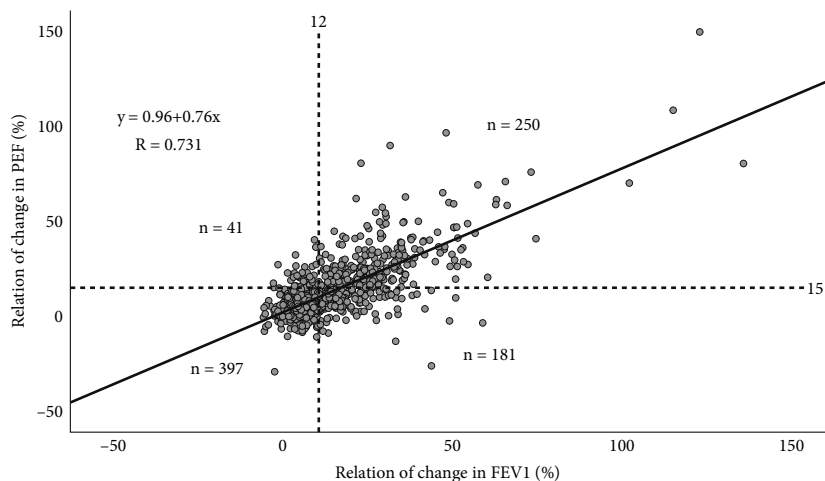


FIGURE 1: Relative change in PEF in relation to relative change in FEV<sub>1</sub> during bronchodilation. Horizontal and vertical dotted lines represent increases of 15% and 12% in PEF and FEV<sub>1</sub>, respectively.

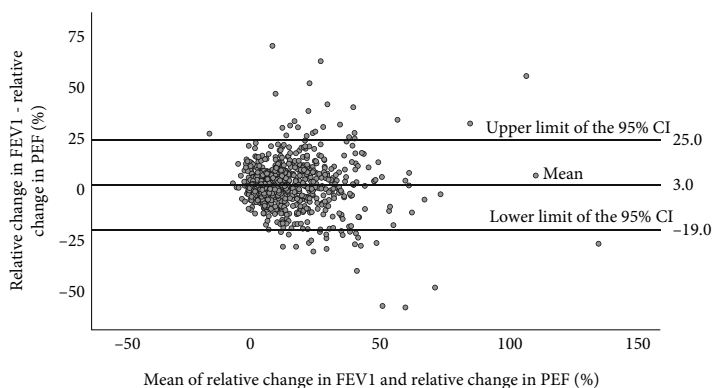


FIGURE 2: Bland and Altman plot of relative change in PEF and FEV<sub>1</sub> during bronchodilation. While the mean difference between changes in PEF and FEV<sub>1</sub> only reached 3.0%, the 95% confidence interval (CI) ranged from -19.0% to 25.0%.

with higher sensitivity and NPV in detecting a 12% and 0.2-L improvement in FEV<sub>1</sub>. In comparison, higher cut-off values achieved improved specificity and PPV. Cohen's kappa ranged between fair and moderate, with values between 0.313 and 0.541 [31]. Judging by kappa value, 10% seemed to be the most accurate PEF cut-off for detecting a 12% and 0.2-L improvement in FEV<sub>1</sub>.

We performed additional analyses based on the ATS/ERS technical spirometry standard recommendation to use an increase in FEV<sub>1</sub> of at least 10% of predicted value as the definition for BDR [17]. The results of this analysis were similar to those using a BDR definition based on change in relation to baseline, as presented in Table 2, with no critical differences, except that PEF was slightly less accurate when BDR was defined in relation to predicted values (Tables S1 and S2).

We found that after splitting the population based on the prebronchodilator FEV<sub>1</sub> median value (80% of predicted),

median age (47 years), or sex, there were no marked differences in the relation between PEF and FEV<sub>1</sub> changes across the groups in these subanalyses. We also compared those who experienced a reduction of at least 20% in FEV<sub>1</sub> after methacholine inhalation, and those who experienced less than a 20% decrease, and found that PEF increase was less accurate at correctly identifying bronchodilation in patients with more severe obstruction before bronchodilation. The different PEF cut-off values were ranked similarly by accuracy across both groups, with a 10% improvement in PEF being the least inaccurate, based on the kappa coefficient (data not shown).

#### 4. Discussion

We found that PEF increase was not accurate at detecting bronchodilation as defined by an improvement in FEV<sub>1</sub>. Increase in PEF had especially poor accuracy in patients with

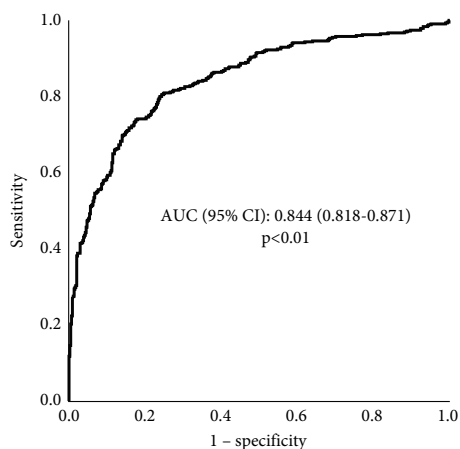


FIGURE 3: ROC analysis illustrating the association between PEF change and a 12% and 0.2-L increase in FEV<sub>1</sub> during bronchodilation.

more severe obstruction prior to bronchodilation. While the correlation between relative change in FEV<sub>1</sub> and relative change in PEF was strong, FEV<sub>1</sub> increased significantly more after bronchodilation. We found increase in PEF to have better specificity and PPV than sensitivity and NPV. The two different cut-off values recommended by the Finnish national asthma guideline and GINA achieved similar results in terms of diagnostic accuracy. Both currently recommended cut-off values identified under half of the true positives based on FEV<sub>1</sub> improvement. Using the same PEF cut-offs, over one-third of the negative results were false in both cases [2, 16]. Even when using the 10% cut-off for PEF increase, which yielded the best kappa value, the diagnostic characteristics of PEF change remained relatively poor. Although our ROC analysis achieved a good AUC, there was a significant difference in the population detected based on increase in PEF compared to the group selected using improvement in FEV<sub>1</sub>.

Dekker et al. studied the ability of an absolute increase in PEF of 60 L/min in bronchodilation test to predict either a 9% improvement in FEV<sub>1</sub> percent predicted or an absolute increase in FEV<sub>1</sub> of 0.19 L. Their findings aligned with ours, showing that the specificity and PPV of PEF change were significantly higher than the sensitivity and NPV for detecting increases in FEV<sub>1</sub>. Although they used the recommended 400 µg of salbutamol, they recorded FEV<sub>1</sub> and PEF on separate devices, which could introduce variability. Their study population was relatively small, with 73 participants, and had a significantly higher average age of 62 years compared to ours. Notably, they also included only patients with diagnoses of asthma or COPD. These factors, along with the significant differences in cut-off values and calculation methods, may lead to variation in the results [19].

Aggarwal et al. investigated the accuracy of various increases in PEF in detecting a 12% improvement in FEV<sub>1</sub>. Their findings were similar to ours, with one notable difference: PEF consistently achieved a higher NPV than PPV in their study, which contrasted with our results. They also

found that the sensitivity of the recommended PEF increase of 15% and 60-L/min was very poor, while the specificity was better. Overall, their results indicated slightly worse diagnostic characteristics for PEF compared to ours, except for NPV. Aggarwal et al.'s study had a large population that well-represented the general population, and they used the recommended dose of salbutamol. However, their definition of BDR did not include the recommended absolute FEV<sub>1</sub> increase of 0.2 L. Additionally, they recorded FEV<sub>1</sub> and PEF on different devices, which could affect the results [32].

Thiadens et al. studied the effectiveness of various PEF increases in predicting a 12% and 0.2-L improvement in FEV<sub>1</sub>. Their findings largely aligned with ours, but similar to Aggarwal et al., they found that the NPV of PEF increase was higher than the PPV. Sensitivities and specificities were comparable across most cut-off values; however, at higher cut-offs, sensitivity declined more significantly in their results. For a 15% increase in PEF, they reported a sensitivity of 42% and a specificity of 93%, closely matching our results. However, their PPV was 37%, significantly lower than our 85%, while their NPV was 93%, compared to our 69% for detecting a 12% and 0.2-L improvement in FEV<sub>1</sub>. This difference may stem from the fact that PPV and NPV, unlike sensitivity and specificity, are influenced by the prevalence of the condition the test is designed to detect. In contrast to our study, Thiadens et al. did not induce airway obstruction before administering bronchodilators, and they excluded all patients with COPD or asthma, a population known to show stronger BDRs. These factors resulted in a BDR prevalence manyfold lower than in our sample, likely contributing to the observed differences in PPV and NPV. They administered the recommended dose of salbutamol and measured FEV<sub>1</sub> and PEF using the same device and expiratory maneuver, minimizing potential result skewing. While they used the recommended cut-off value for FEV<sub>1</sub>, they did not evaluate PEF cut-off values that combine relative and absolute changes, such as the Finnish recommended 15% and 60 L/min. Relative change in lung function was also calculated using percent predicted values instead of comparing prebronchodilator measurements to postbronchodilator values [21].

Ozturk et al. examined the ability of two relative PEF increases, 15% and 20%, to detect a 12% improvement in FEV<sub>1</sub>, dividing the participants into two age groups: under and over 60 years. The diagnostic accuracy of PEF change varied significantly with age and the chosen cut-off value, resulting in conflicting outcomes between groups. Those results also largely contradicted our findings. In patients over 60, sensitivity, specificity, and PPV were lower compared to those under 60, while NPV was slightly better. For a 15% PEF cut-off, sensitivity exceeded specificity in both age groups. PPV was higher than NPV in subjects under 60, whereas NPV was higher in those over 60. Although they used the recommended dose of salbutamol, FEV<sub>1</sub> and PEF were measured with different equipment. The relatively small population, further divided into smaller groups, may account for some discrepancies with our results. Additionally, they excluded individuals with asthma and COPD and did not include absolute values alongside the relative change in their cut-off values for FEV<sub>1</sub> and PEF [20].

**TABLE 2:** Characteristics of different PEF increase cut-offs in detecting a 12% and 0.2-L improvement in FEV<sub>1</sub> during bronchodilation.

Increase in PEF	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
10%	75.1	79.1	77.4	76.8	0.541
15%	58.1	90.1	84.9	69.2	0.485
15% and 60 L/min	49.6	93.7	88.3	66.0	0.438
20%	44.7	95.5	90.5	64.3	0.406
25%	32.9	98.0	94.0	60.4	0.313

Home PEF monitoring has been researched extensively and is commonly utilized and recommended. In contrast, home spirometry is neither widely practiced nor recommended [2, 3, 16]. In Finland, home PEF monitoring involves measurements twice daily for 2 weeks, both before and after inhalation of a bronchodilator, typically salbutamol. Asthma can be diagnosed if BDR is observed at least thrice during this period [16]. Internationally, however, home PEF monitoring typically focuses on measuring natural diurnal PEF variability alone, without assessing BDR [2, 3]. It is known that the sensitivity and specificity of PEF change are less than ideal in identifying bronchoconstriction, which is another method for diagnosing asthma during home PEF monitoring [6, 7].

Monitoring PEF with a PEF meter rather than a spirometer complicates quality control. While consistent PEF values are required, spirometry allows for visual assessment of flow volume curves, identifying potential technical issues during exhalation. Our study excluded unreliable measurements, but this would be nearly impossible in a home setting with only PEF values. Consequently, increase in PEF may be an even less reliable indicator of BDR during home monitoring. We have also studied the relationship between changes in PEF and FEV<sub>1</sub> in children during bronchodilation after an exercise challenge, and those findings further indicate that PEF is inaccurate in detecting BDR (in review). However, because children's airways are smaller, less rigid, and more prone to obstruction, the relationship between changes in FEV<sub>1</sub> and PEF during bronchodilation may differ from adults. Even in adults, the relationship between changes in FEV<sub>1</sub> and PEF seems to behave differently depending on age, and it is known that respiratory muscle strength and PEF decline with age [20].

The factors discussed above call into question the future of PEF meters in home monitoring. Since change in PEF seems to reflect lung function poorly in other settings, spirometry could also be more accurate for home settings. Replacing PEF meters with handheld microspirometers should be considered. PEF meters are generally more affordable than microspirometers, providing a cost advantage. However, the increased diagnostic accuracy of microspirometers may enhance resource allocation, potentially offsetting the initial cost difference over time.

Findings on the accuracy of handheld spirometers are mixed, with the chosen manufacturer influencing results. Some studies suggest that portable microspirometers provide accurate results comparable to gold-standard laboratory spirometers [33–35], while others indicate that their results may not be interchangeable with traditional laboratory

spirometry [36, 37]. Additionally, studies on the feasibility of home spirometry monitoring have yielded conflicting results. Some found it highly efficacious, useful, and well-received with high compliance [38–40]. However, other research indicated that home spirometry is inconsistent and of lower quality than spirometry performed in supervised clinical settings or that its usefulness in the asthma diagnostic process is limited [41, 42]. While home spirometry shows promise for remote monitoring of lung function, its effectiveness remains unclear, highlighting the need for further research, particularly in evaluating its clinical usefulness for diagnosing asthma.

Our study was performed at one hospital, and there could be variation in the results if the analysis was based on samples from other medical centers employing different bronchodilation protocols or equipment. While smoking data were unavailable for some patients, there is no evidence to suggest that the fraction of smokers differed significantly among those without this data. Additionally, it is essential to note that not all participants in our study had asthma, which could introduce variability in the relationship between changes in PEF and FEV<sub>1</sub> among individuals with and without asthma. In our population, obstruction was directly induced prior to bronchodilation. While this approach could be considered a limitation, as induced obstruction may behave differently during bronchodilation compared to naturally occurring obstruction associated with exercise, allergens, or infections, it also offers distinct advantages. Specifically, studying a population with induced obstruction allowed us to achieve a high proportion of fairly marked bronchodilator effects and thereby a higher signal-to-noise ratio.

Typically, a diagnosis of asthma based on BDR is not established during methacholine challenge testing [2, 3, 16]. However, our aim was not to evaluate the clinical value of PEF change in this context but rather to study the technical relationship between increase in PEF and improvement in FEV<sub>1</sub> during bronchodilation. It should be noted that while we did utilize the recommended cut-off value of 12% and 0.2-L increase in FEV<sub>1</sub>, the evidential basis for this recommendation lacks strong support. Current research is insufficient to thoroughly assess the sensitivity of different FEV<sub>1</sub> cut-off values for BDR in distinguishing patients with asthma from healthy individuals [43]. PEF is believed to primarily indicate the level of dilation in the large airways, whereas FEV<sub>1</sub> is thought to represent both small and large airways [9]. This distinction may help explain some of the variations observed in this investigation. Nevertheless, there is a lack of experimental data on the specific airway regions to which PEF and FEV<sub>1</sub> and their changes correspond.

Our study had several notable strengths. We had a large sample of 869 subjects and a meticulous selection process whereby each measurement was individually analyzed for technical reliability. We excluded all unreliable measurements, which enabled us to more accurately examine the relationship between changes in PEF and FEV<sub>1</sub>. Our findings are relevant to the general adult population, as the age distribution of participants in our study was broad and children were excluded. We performed additional analyses using an alternative definition of BDR, and the similarity of these results to our main analyses further confirmed our findings and increased confidence in their validity [17]. Using a PEF meter for PEF measurements might have yielded different results due to the variation between device types [44]. Our previous findings showed that using the same blowing technique with either a laboratory spirometer or a PEF meter resulted in small but statistically significant differences in PEF outcomes. However, further analysis revealed that these differences were not clinically relevant (unpublished).

Blowing technique may also vary depending on the device type. In typical PEF recordings, the exhalation is shorter than the longer blow required for spirometry. Some studies indicate that a prolonged, spirometry-style expiratory maneuver may produce lower PEF values compared to the brief, explosive technique associated with PEF meters. The magnitude of this difference varies, with some studies reporting significant discrepancies while others find minimal differences [45, 46]. Our previous investigation demonstrated that both short and long expiratory efforts yield clinically similar PEF measurements, regardless of whether a PEF meter or a spirometer is used [7]. This highlights that PEF measurements are likely consistent enough from a clinical perspective, whether recorded with the spirometer used in our study or a PEF meter. However, variations may exist among different types of PEF meters, and our evaluation was limited to one type [12, 14].

In conclusion, we demonstrated in relation to salbutamol administration after a methacholine challenge test that the increase in PEF after bronchodilation is not an accurate method of measuring improvement in lung function, as defined by the increase in FEV<sub>1</sub>. PEF increase appears to have greater specificity than sensitivity, with higher PPV compared to NPV. The recommended cut-off for PEF increase, 15% and 60 L/min, has poor sensitivity for detecting improvement in FEV<sub>1</sub>, while a 10% cut-off value was found to be better overall. Incorporating PEF monitoring in asthma diagnostics and management allows for the detection of variability and improvement in lung function. However, it is essential to acknowledge that PEF increase may not reliably indicate reversibility of airway obstruction. Replacing the PEF meter with a portable spirometer could enhance the accuracy of asthma home monitoring and should thus be investigated further.

### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### Ethics Statement

Due to the retrospective nature of the study, no ethical approval was required in accordance with Finnish law.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Author Contributions

All authors participated in designing this study. The data was collected by A.T. and L.V. The data was analyzed by L.L.C. and L.L. L.L.C. wrote the first draft of the manuscript, and all authors participated in the revision process.

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### Supporting Information

Additional supporting information can be found online in the Supporting Information section. (*Supporting Information*) The characteristics of different PEF cut-off values when BDR is defined as an increase in FEV<sub>1</sub> of at least 10% of predicted value, according to the ATS/ERS technical spirometry standard recommendation.

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