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Change in FEV_1 and FeNO measurements as predictors of future asthma outcomes in children

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ABSTRACT (word count 249)

Background. Repeated measurements of spirometry and fractional exhaled nitric oxide (FeNO) are recommended as part of the management of childhood asthma, but the evidence base for such recommendations is small. We tested the hypothesis that reducing spirometric indices or increasing FeNO will predict poor future asthma outcomes.

Methods. A one-stage individual patient data meta-analysis used data from seven randomised controlled trials where FeNO was used to guide asthma treatment, and where spirometric indices were also measured. Change in $\%FEV_1$ and % change in FeNO between baseline and three months were related to having poor asthma control and to having an asthma exacerbation between three and six months after baseline.

Results. Data were available from 1112 children (mean age 12.6 years, mean $\%FEV_1$ 94%). A 10% reduction in $\%FEV_1$ between baseline and three months was associated with 28% increased odds for asthma exacerbation [95% CI 3, 58] and with 21% increased odds for having poor asthma control [95% CI 1, 45] six months after baseline. A 50% increase in FeNO between baseline and three months was associated with 11% increase in odds for poor asthma control six months after baseline [95% CI 0, 16]. Baseline FeNO and $\%FEV_1$ were not related to asthma outcomes at three months.

Conclusions. Repeated measurements of $\%FEV_1$ which are typically within the "normal" range add to clinical risk assessment of future asthma outcomes in children. The role of repeated FeNO measurements is less certain since large changes were associated with small changes in outcome risk.

Keywords: Asthma, Child, Monitoring, Nitric oxide, Spirometry

ABBREVIATION LIST

BUD Budesonide

ERS European Respiratory Society

FeNO Fractional Exhaled Nitric Oxide

FEF_{25-75} Forced Expiratory Flow at 25-75% of FVC

FEV_1 Forced Expiratory Volume in one second

FVC Forced Vital Capacity

GLI Global Lung Initiative

ICS Inhaled corticosteroid

IPD Individual Patient Data Analysis

IQR Inter-quartile range

LABA Long Acting Beta Agonist

LTRA Leukotriene Receptor Antagonist

NHANES National Health and Nutrition Examination Survey

OR Odds ratio

ppb Parts per billion

RCT Randomised Controlled Trial

SD Standard deviation

UK United Kingdom

USA United States of America

INTRODUCTION

Asthma is a common condition affecting 1 million children in the UK[1] and 6 million in the USA[2]. Guidelines recommend that objective markers of respiratory function (e.g. forced Expiratory Volume in one second (FEV_1)) and airway inflammation (e.g. fractional exhaled nitric oxide, FeNO) may be used in conjunction with symptoms to guide asthma preventive treatment in children. However these recommendations differ between guidelines, and none gives clinicians advice how to interpret changes in spirometry when values fall within the normal range, yet FEV_1 (the most commonly used spirometric index) is usually within normal limits [3].

One guideline recommends that lung function should be "monitored and recorded" only in children aged over 12 years[4]. Two guidelines recommend that FEV_1 may be useful for monitoring of asthma for children aged over five to seven years[5, 6]. A fourth guideline[7] recommends that lung function should be measured three-to-six months after treatment is started and "periodically" thereafter, and that $\%FEV_1$ less than 60% identifies a patient at risk for future asthma exacerbations. A fifth guideline[8] recommends that lung function should be measured every one to two years (more frequently when symptoms are poorly controlled) and suggests that treatment might be stepped up if $\%FEV_1$ is below 80% or 60%. Some guidelines suggest that a 20% drop in FEV_1 relative to personal best identifies an individual at risk for future asthma exacerbations[5, 7].

Although FeNO is recommended by the US Food and Drug Administration for monitoring asthma[9] there is no consensus on how results should be interpreted; one international guidelines states that a change in FeNO of 10 parts per billion or 20% may be clinically relevant[10].

To understand the relationship between change in spirometry and FeNO and asthma outcomes we obtained individual patient data (IPD) from seven FeNO randomised controlled trials (RCTs) where details of spirometry, FeNO, asthma control and the occurrence of asthma exacerbations were collected longitudinally [11-17]. Our primary hypothesis was that falling spirometric indices (with $\%FEV_1$ as the primary index) and/or rising FeNO between randomisation and three months follow up will be

associated with increased risk for asthma being uncontrolled and for an asthma exacerbation between three and six months follow up. The secondary hypothesis was that at baseline, low spirometric indices and high FeNO will be associated with increased risk for asthma being uncontrolled and for an asthma exacerbation between baseline and three months follow up.

METHODS

Study design

Authors of published RCTs where measurements of FeNO was used to guide asthma treatment in children[18] were invited to provide anonymised data for IPD[19]. The outcomes were asthma exacerbation (defined as a prescription of prednisolone during the follow-up period and derived using data provided by study authors) and poor asthma control (defined by per trial protocol by symptom score, and including FEV_1 cut off values in some trials[11, 12, 16] but not including an asthma exacerbation). The supplement provides definitions of being uncontrolled. For all RCTs, prescribing of oral corticosteroids for asthma exacerbations was at the discretion of the attending doctor. The explanatory variables between baseline and three months follow up were absolute change and %change in FeNO and absolute change in percentage of predicted (%) spirometry; the analysis of change in % spirometry and % change in FeNO included the corresponding baseline measurement. The relationship between outcomes and the following explanatory variables at baseline were sought: FeNO and $\%FEV_1$, $\%FEV_1/FVC$, $\%FEF_{25-75}$ and %FVC. Figure one shows which physiological measurements (and changes) were linked to later asthma outcomes in this study. Additional covariates collected at baseline and included in the models were: age, gender, height, weight, ethnicity, trial arm, dose of inhaled corticosteroid (ICS, as daily budesonide equivalent dose, BUD), prescribed long acting beta agonist (LABA) or not, prescribed leukotriene receptor agonist (LTRA) or not, asthma control and treatment compliance. For each follow up visit, the following variables were collected: FeNO, FEV_1, height, dose of ICS, asthma control and asthma exacerbation since the

previous visit. The focus of this study was follow up at three and six months since these are typically used in asthma clinics; for trials where there was no three or six month assessment, the assessment closest to these time points was used. In all but two studies[14, 15], absolute spirometry data were available and expressed as percentage of predicted to the Global Lung Initiative standard[20]; where absolute data were not available, the % predicted value provided by the local team was used for analysis. Whilst $\%FEV_1$ was the primary spirometric index of interest, $\%FEV_1/FVC$, $\%FEF_{25-75}$ and %FVC were also considered to determine which index had the greatest precision for future outcomes. For completeness, FEV_1 was also expressed as a Z scores and centile (standardised to the Global Lung Initiative standard[20]). Additionally, as a sensitivity analysis, $\%FEV_1$ was derived using National Asthma Education and Prevention Program (NHANES) III standard[21] to determine whether any relationship between $\%FEV_1$ and later outcome was dependent on the standard used. Body Mass Index (BMI) was derived and International Obesity Task Force weight categories created[22]. In each trial, FeNO was measured in accordance with the 2005 guideline[23]. Ethical approval was obtained for each individual study but was not required for the IPD.

Individual patient data analysis

Demographic and baseline characteristics were obtained for each study. A one-stage IPD meta-analysis was undertaken using the melogit command in STATA with study included as a random effect. All models were adjusted for the baseline variables of age, gender, LABA, LTRA, asthma control, ICS dose, arm of trial and where relevant baseline FeNO or baseline FEV_1. A one-stage approach was used rather than a two-stage as some of the studies had low event counts (few asthma exacerbations) and adoption of one-stage in this instance is recommended by Burke *et al*[24]. Sensitivity analyses considered separately outcomes for individuals in FeNO intervention and standard care arms of the trials, and also excluding data from trials where $\%FEV_1$ was used to guide treatment decisions [11, 12, 16]. STATA version 14 was used for analysis.

RESULTS

Study subjects

Data from seven paediatric RCT were analysed [11-17], data from an eighth RCT could not be obtained [25]. Details of population inclusion and exclusion criteria are presented in the supplement. The IPD included data on 1112 participants. In two studies[14, 17] spirometry was only measured at baseline and at 12 months and change in $\%FEV_1$ between baseline and three months could not be calculated. There was a predominance of male participants (58%) and mean (standard deviation(SD)) age was 12.6 (3.1) years, table 2. Median values of FeNO varied between 18 and 34 parts per billion (ppb) with an overall median (interquartile range (IQR)) of 22ppb (12, 43). Mean $\%FEV_1$ values at baseline varied between 89% and 98% predicted with an overall mean (SD) of 94% (18). Details of mean FEV_1 z scores and centile are presented in supplemental table 1. The Pearson correlation coefficient between FeNO and $\%FEV_1$ at baseline was -0.184 (n=1025, p <0.001) and between % change in FeNO (baseline to 3 months) and change in $\%FEV_1$ (baseline to 3 months) was -0.127 (n=759, p <0.001). Overall 7% of participants had an asthma exacerbation during the first 3 months and 12% in the second three months, while 27% were uncontrolled at baseline, 25% at 3 months, and 23% at six months, table 3. An asthma exacerbation occurred between baseline and three months in 47 (7%) of the 718 participants with controlled symptoms at baseline and in 27 (12%) of 230 with uncontrolled symptoms at baseline.

Relationship between change in spirometry and percentage change in FeNO between baseline and three months and outcomes between three and six months

Between baseline and 3 months, the mean (SD) change in $\%FEV_1$ was -0.17 (10.4), the median absolute change in FeNO was 0.6 ppb (IQR -7.9, 12.2) and the median % change in FeNO (interquartile range) was 3.7% (IQR -30.4, 66.7). A fall in $\%FEV_1$ was related to increased odds of an asthma exacerbation over the following three months (e.g. a reduction of 10% FEV_1 between baseline and three months was associated with increased odds ratio (OR) for future exacerbation

between three and six months of 1.3 [1.0, 1.6], p=0.027) and loss of future asthma control (e.g. a reduction of 10% FEV_1 was associated with increased odds ratio for uncontrolled asthma 1.2 [96% CI 1.0, 1.5], p=0.046), table 4. A reduction of 10% FVC was also associated with increased odds for a future exacerbation (OR 1.40 [1.04, 1.88], p=0.026), supplemental table 2. A 50% increase in FeNO between baseline and three months was associated with 11% increased odds of asthma being uncontrolled at six months [95% 0, 16] (p=0.014) but not odds of an exacerbation between three and six months, table 4. When both change in $\%FEV_1$ and %change in FeNO were considered in the same model, the odds ratio for asthma being uncontrolled remained significant for FeNO (p=0.036) but not for $\%FEV_1$ (p=0.061). Neither change in $\%FEV_1$/FVC or $\%FEF_{25-75}$ (supplemental table 2) nor absolute change in FeNO (table 4) were associated with outcomes. The associations between change in $\%FEV_1$ and % change in FeNO did not achieve significance when each trial arm was considered separately (supplemental table 3). When the RCTs where $\%FEV_1$ was used to guide treatment were excluded there was an association between rising FeNO and future asthma exacerbation (p=0.029) but associations between change in FEV_1 and outcomes were not significant, supplemental table 4. Among the subset of RCT where FEV_1 z score and centile values could be derived, falling z scores were associated with increased odds for both asthma exacerbations and being uncontrolled and falling centile score with being uncontrolled, supplemental table 5. The results seen with change in % FEV_1 using the Global Lung Initiative (GLI) standard were also seen when the NHANES III standard was used, supplemental table 6.

Relationship between baseline FeNO and spirometric indices and outcomes at three months

Percentage of predicted FEV_1/FVC at baseline (but no other spirometric index) was related to the odds of asthma exacerbation at three months during this interval (p=0.016), table 5. No index of spirometry at baseline was related to having uncontrolled asthma at three months. FeNO at baseline was not related to asthma outcomes at three months (table 5). Supplementary table 6 demonstrates that when FEV_1 was standardised to the NHANES III data, reducing $\%FEV_1$ at baseline

was associated with increased odds for future asthma exacerbation (p=0.033) and a trend for reduced odds for asthma not being controlled in future (p=0.055). Baseline FEV_1 z score or centile were not related to outcomes (supplemental table 7).

DISCUSSION

This study sought to understand the relationship between changes in spirometric measurements and FeNO and future asthma outcomes. The first finding was that, independent of all factors which might influence treatment decisions, falling $\%FEV_1$ (even within the range of 80-120% commonly considered as "normal") was associated with increased odds for future asthma exacerbation and having uncontrolled asthma. A second finding was that an absolute change in FeNO (table 4) did not predict outcomes, and only a large rise in % change in FeNO was related to a small increase in the odds for having uncontrolled asthma in future. We also observed that at baseline, a "one off" $\%FEV_1$/FVC ratio (but not $\%FEV_1$) was associated with future odds for asthma exacerbation. Together the results suggest that change in $\%FEV_1$ can be used as part of risk assessment for asthma outcomes. The role of change in FeNO is less clear and future clinical trials could include % change in FeNO as part of a treatment algorithm for children with asthma.

The individuals whose data contributed to this study were participating in RCTs, and this could mean that the results are not necessarily generalisable for at least two reasons. First, participants in RCTs often have to fulfil specific eligibility criteria, receive more clinical contact than standard care and often have better outcomes such as fewer asthma exacerbations, but these differences are likely to weaken any association between FeNO or $\%FEV_1$ and asthma outcomes by narrowing the phenotype of participants and improving outcomes. Secondly, the participants in our study had treatment guided by FeNO (and $\%FEV_1$ in three studies) and thus the predictive variables in our study may have affected the outcome (e.g. rising FeNO leading to increased ICS resulting in good asthma control). We justify inclusion of data from these trials because firstly FeNO and, in all but one study[14], $\%FEV_1$

did not differ between trial arms and secondly, if FeNO or $\%FEV_1$ did improve asthma outcomes by protocol-driven treatment changes this would have weakened any association between FeNO or $\%FEV_1$ and asthma control or asthma exacerbations. Our inclusion of participants in RCTs may therefore have weakened the associations described, and in "real life" change in $\%FEV_1$ and % change in FeNO may have greater precision for outcomes than indicated by our results.

There are some limitations to our study. First, the methodologies of the RCTs were different and in particular in three of the RCTs[15-17] the intervals between assessments did not include multiples of three months, and this heterogeneity may have weakened the associations described, assuming that the relationship between FeNO and FEV_1 and outcomes changes over time. Different methods were used to assess asthma control; again this would weaken and not strengthen the associations described between baseline $\%FEV_1$ or %change in FeNO and being uncontrolled in future. A second limitation is that the range of $\%FEV_1$ values was relatively narrow and the incidence of asthma exacerbations was relatively low and this could make the relationship between physiological measurement and clinical outcome difficult to detect, but nonetheless we were still able to observe an association between $\%FEV_1$ and future asthma exacerbations. A third limitation is that we did not have an objective measure of adherence and could not consider how non-adherence may have influenced asthma control and exacerbations, however this information is not available for most clinicians and thus our study reflects "real world". A fourth limitation is that none of the RCTs included an assessment of short-term variability of pulmonary function, such as peak expiratory flow variability or bronchodilator response, and we are not able to say how short-term variability in pulmonary function might be related to future asthma outcomes.

The magnitude of the change in odds ratio for an asthma exacerbation or being uncontrolled in future in the context of changing $\%FEV_1$ and FeNO were relatively small, and this is partly due to our including RCT participants as previously discussed and partly due to the fact that the model

considered many other factors which might predict poor asthma outcomes, e.g. current symptom control, treatment level, current %FEV_1.

In our sensitivity analyses we excluded the three studies where %FEV_1 was used to guide treatment and the results seen in the whole population were no longer significant and this is most likely explained by lack of power. We when split results by trial arm, and the significant associations seen between change in %FEV_1 and %change in FeNO for the whole population were also non-significant and this is also most likely due to lack of power in the analysis.

We are not aware of published studies which relate change in spirometry to future asthma outcomes, but there are several studies where spirometry on a single occasion has been related to subsequent asthma outcomes in children. One study reported an inverse relationship between reduced %FEV_1 and increased risk for asthma exacerbation in the next 12 months[26]. Two further studies[27, 28] (data from one[27] contributed to the present IPD) reported that reduced FEV_1/FVC ratio was associated with increased risk for future exacerbation.

The 2015 European Respiratory Society (ERS) Task Force on Monitoring Asthma in Children[29] stated that "the meaning of significant changes in FeNO in a longitudinal setting is still unclear and needs further attention, and that "the use of 'personal best' cut-off points in FeNO algorithms requires further investigation". Our study findings suggest that a % relatively large rise (50%) in FeNO over three months (independent of treatment and initial symptoms) may be a useful predictor of having uncontrolled asthma in future but not for asthma exacerbations. Additionally, our results suggest that a single FeNO value and absolute change in FeNO over time are unlikely to be clinically useful.

In summary our results suggest that %FEV_1 within the "normal" range over three month periods could assist with risk assessment in childhood asthma and these findings now need replicating elsewhere. A fall in %FEV_1 and a rise in FeNO should prompt an evaluation of medication adherence, inhaler technique, perception of symptoms and exposure to either allergens or viral infection. The

relationship between changes in FeNO measurements and asthma outcomes is less clear and requires further evaluation.

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ST conceived the idea for the study, wrote the first draft of the manuscript and is the guarantor of the study. ST and SF designed the study. All authors other than ST and SF contributed data for the analysis. SF undertook the analysis. All authors made contributions to the final manuscript.

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FIGURE LEGEND

Figure one. A diagram showing how different physiological measurements were linked to later asthma outcomes in the study's analyses. The analyses used data collected at recruitment to seven clinical trials and at follow up assessments three and six months after recruitment.*Although % FEV_1 was the primary spirometric index, the following were also considered: %FEV_1/FVC, %FEF_{25-75} and %FVC.

Table 1. Details of the randomised controlled trials included in this individual patient data analysis

	Mean age, y		Intervals at follow up after baseline when FeNO was measured (months). Zero corresponds to baseline.	Intervals at follow up after baseline when spirometry was measured (months). Zero corresponds to baseline	Were absolute spirometry data available?	Which spirometric indices were available?	Was there a run in period?	Was atopy an inclusion criteria?	What measure of asthma control was used?
	FeNO arm	Control arm							
Fritsch[11]	11.3	12.1	0, 1.5, 3, 4.5, 6	0, 1.5, 3, 4.5, 6	Yes	FEV_1, FVC	Yes	Yes	Unvalidated symptom diary
Peirsman[12]	10.6	10.7	0, 3, 6, 9, 12	0, 3, 6, 9, 12	Yes	FEV_1	No	Yes	First four (of seven) questions on CACT*†
Petsky[13]	9.9	10.1	0, 1, 2, 3, 4, 6, 8, 10, 12	0, 1, 2, 3, 4, 6, 8, 10, 12	Yes	FEV_1, FEF_{25-75}, FVC	Yes	No	Validated symptom diary
Pijnenburg[14]	11.9	12.6	0, 3, 6, 9, 12	0, 12	No	FEV_1, FEF_{50}, FVC	Yes	Yes	Validated symptom diary
Pike[15]	10.5	11.4	0, 2, 4, 6, 7, 10, 12	0, 2, 4, 6, 7, 10, 12	No	FEV_1, FVC	No	No	Modified validated symptom diary†
Szefler[16]	14.4	14.4	0, 1.5, 3.2, 5, 7, 8.5, 10.5	0, 1.5, 3.2, 5, 7, 8.5, 10.5	Yes	FEV_1, FEF_{25-75}, FVC	Yes	No	ACT*‡ plus FEV_1
Voorend-van Bergen[17]	10.3	10.2	0, 4, 8, 12	0, 12	Yes	FEV_1, FEF_{75}, FVC	Yes	Yes	ACT and C-ACT*

*ACT = asthma control test, C-ACT=Childhood Asthma Control Test

†reliever medication use and FEV_1 or ¶FEV_1 alone were used in the treatment algorithm for both arms of the RCT but were not used to define being uncontrolled in the present study

Table 2. Characteristic of study participants at the baseline visit in each study

		Fritsch[11]	Peirsman[12]	Petsky[13]	Pijnenburg[14]	Pike[15]	Szefler[16]	Voorend-van Bergen[17]	All populations combined
Total number of participants		47	99	63	86	90	546	181	1112
%(number) male		60% (28)	67% (66)	49% (31)	65% (56)	57% (51)	53% (288)	68% (123)	58% (643)
Age	mean (SD)	11.5(3.1)	10.7 (2.1)	10.0 (3.2)	12.3 (2.8)	10.9 (2.6)	14.4 (2.1)	10.2 (3.0)	12.6 (3.1)
	range	6 to 17	5 to 14	4 to 16	6 to 18	5 to 16	12 to 19	4 to 18	4 to 19
Trial arm	Standard	25	50	32	46	46	270	92	561
	FeNO	22	49	31	40	44	276	89	551
FeNO	Number of observations	46	49	61	86	90	546	179	1057
	Median (ppb)	33.9	31.3	25.6	32	25.5	20.1	18.2	21.9
	IQR (ppb)	(18.6, 58.6)	(14, 69)	(12.2, 47.5)	(16.6, 52.5)	(10, 48)	(11.2, 40.6)	(10.2, 30.4)	(11.6, 43.0)
% predicted FEV_1	Number of observations	47	98	54	86	90	546	157	1078
	mean (SD)	93.5 (15.7)	91.4 (15.7)	90.7 (15.6)	97.5 (17.5)	89.2 (14.3)	90.9 (16.6)	93.8 (13.0)	93.5 (18.1)
% predicted FEV_1/FVC	Number of observations	47	0	0	0	0	546	156	749
	mean (SD)	90.1 (10.6)	-	-	-	-	91.3 (9.9)	93.4 (9.4)	91.7 (9.9)
% with positive skin prick test		100%	100%	38% (24/63)	100%	76% (68/90)	88% (467/531)	100%	89% (972/1097)
Mean Centile BMI (SD)	Number of observations	47	99	58	86	89	546	181	1106
	mean (SD)	67.6 (27.0)	52.1 (30.1)	48.5 (32.4)	60.8 (27.3)	64.2 (32.2)	83.1 (23.5)	58.9 (29.9)	70.7 (29.8)
Obese	Number of observations	47	99	58	85	89	526	181	1085
	% (number) overweight	28% (13)	12% (12)	16% (9)	14% (12)	25% (22)	28% (145)	20% (36)	23% (249)
	% (number) obese	8% (4)	1% (1)	2% (1)	4% (4)	8% (7)	31% (165)	3% (5)	17% (187)
LTRA treatment prescribed	Number of observations	47	99	58	86	90	546	181	1107
	% (number) yes	28% (13)	60% (59)	10% (6)	0	51% (46)	15% (80)	13% (23)	21% (227)
LABA	Number of observations	47	99	58	86	90	546	181	1107

treatment prescribed	% (number) yes	38% (18)	32% (32)	67% (39)	38% (33)	76% (68)	66% (360)	46% (84)	57% (634)
Median dose of inhaled corticosteroids (IQR)		400 (0, 800)	320 (200, 400)	400 (250, 500)	800 (400, 1000)	800 (400, 1000)	1000 (400, 2000)	400 (400, 800)	400 (400, 1000)
Ethnic group	Number of observations	0	84	20	0	90	526	179	889
	White		82% (69)			92% (83)		89% (160)	35% (312)
	Hispanic						65% (340)		38% (340)
	Other		18% (15)	100% (20)		8% (7)	35% (186)	11% (19)	28% (247)
Asthma control status	Number of observations	47	65	57	77	90	528	181	1045
	Asthma controlled	49% (23)	75% (49)	72% (41)	57% (44)	68% (62)	80% (421)	67% (122)	73% (762)
	Asthma not Controlled	51% (24)	25% (16)	28% (16)	43% (33)	31% (28)	20% (107)	33% (59)	27% (283)

Table 3. Frequency of outcomes between baseline and three months and between three and six months post baseline.

	Exacerbation between baseline and three months	Exacerbation between three and six months	Asthma not controlled at three months	Asthma not controlled at six months
	% (n)	% (n)	% (n)	n (%)
Fritsch[11]	2% (1/47)	6% (3/47)	54% (25/46)	53% (25/47)
Peirsman[12]	4% (4/99)	0%	25% (21/83)	21% (18/86)
Petsky[13]	5% (3/63)	8% (5/63)	not available	not available
Pijnenburg[14]	9% (8/86)	8% (7/86)	40% (32/81)	40% (31/78)
Pike[15]	17% (15/90)	30% (27/90)	26% (23/90)	32% (29/90)
Szefler[16]	7% (35/522)	15% (78/505)	21% (111/541)	17% (86/513)
Voorend-van Bergen[17]	7% (12/181)	7% (12/181)	21% (38/179)	20% (36/178)
Overall	7% (78/1088)	12% (132/1071)	25% (250/1010)	23% (225/992)

Table 4. Relationship between falling % FEV_1 or rising %change in FeNO over a three month period and odds of having an asthma attack or uncontrolled asthma during the next three months. Results are from a one stage individual patient data analysis. All models adjusted for sex, age, treatment with long acting beta agonists at baseline, treatment with leukotriene receptor antagonist at baseline, asthma control at baseline, change in dose of inhaled corticosteroid between baseline and three months. *For change in $\%FEV_1$, "per unit" means for each percentage change (e.g. from 98% to 97% FEV_1) and for %change in FeNO means for each percent change (e.g. from 100 to 101ppb) and absolute change in FeNO "per unit" means per part per billion change (e.g. from 35 to 36ppb). †Odds ratio for outcomes were derived from the odds ratio per unit change, for example odds ratio for asthma attack after a reduction in $\%FEV_1$ of 5 is 1.025 to the power of 5. ‡The model also includes asthma attack between baseline and 3 months. The change in FeNO model included FeNO at baseline and the change in FEV_1 model included FEV_1 at baseline.

Change in measurement of respiratory function	Asthma outcome	Odds Ratio per unit change in FEV_1 or FeNO*	Odds Ratio per 5, 10 and 20 reduction in $\%FEV_1$†			Odds Ratio per 20 and 50% increase in FeNO†		Odds Ratio per 20 and 50ppb increase in FeNO†	
			$\%FEV_1$ reduced by 5	$\%FEV_1$ reduced by 10	$\%FEV_1$ reduced by 20	20% increase in FeNO	50% increase in FeNO	20ppb increase in FeNO	50ppb increase in FeNO
Change (baseline to 3m) in% FEV_1	≥1 asthma attack between three and six months‡	1.025 (1.003, 1.047) p=0.027 n=716 (5 trials)	1.131 [1.015, 1.258]	1.280 [1.030, 1.583]	1.639 [1.062, 2.506]				
	Asthma uncontrolled at six months	1.019 (1.000, 1.038) p=0.046 n=693 (4 trials)	1.099 [1.000, 1.205]	1.207 [1.000, 1.452]	1.457 [1.000, 2.108]				
% change in FeNO (baseline to 3m)	≥1 asthma attack between three and six months‡	1.001 (0.999, 1.003) p=0.228 n=929 (7 trials)				1.020 [0.980, 1.062]	1.051 [0.951, 1.162]		
	Asthma uncontrolled at six months	1.002 (1.000, 1.003) p=0.014 n=897 (6 trials)				1.041 [1.000, 1.062]	1.105 [1.00, 1.162]		
Absolute change in FeNO (baseline to 3m), ppb	≥1 asthma attack between three and six months‡	1.004 (0.998, 1.010) p=0.197 n=929 (7 trials)						1.083 [0.961, 1.220]	1.221 [0.905, 1.645]
	Asthma uncontrolled at six months	1.002 (0.997, 1.008) p=0.407 n=897 (6 trials)						1.041 [0.942, 1.173]	1.105 [0.861, 1.489]

Table 5. Relationship between baseline % FEV_1 or baseline FeNO and odds of asthma attack or asthma being uncontrolled during the next three months. Results are from a one stage individual patient data analysis. All models adjusted for sex, age, treatment with long acting beta agonists at baseline, treatment with leukotriene receptor antagonist at baseline, asthma control at baseline and change in dose of inhaled corticosteroid between baseline and three months. *For $\%FEV_1$, "per unit" means for each percentage reduction (e.g. from 98% to 97% FEV_1) and for FeNO "per unit" means per part per billion change (e.g. from 35 to 36ppb).

Measurement of respiratory function	Asthma outcome	Odds Ratio per unit* reduction in FEV_1 or rise in FeNO
$\%FEV_1$ at baseline	≥1 asthma attack between baseline and three months	1.011(0.997, 1.026) p=0.118 n=973 (7 trials)
	Asthma uncontrolled at three months	0.993 (0.984, 1.001) p=0.098 n=939 (6 trials)
$\%FEV_1$/FVC at baseline	≥1 asthma attack between baseline and three months	1.037 (1.007, 1.067) p=0.016 n=706 (3 trials)
	Asthma uncontrolled at three months	0.993 (0.973, 1.012) p=0.451 n=715 (3 trials)
FeNO (ppb) at baseline	≥1 asthma attack between baseline and three months	1.001 (0.995, 1.008) p=0.682 n=966 (7 trials)
	Asthma uncontrolled at three months	1.002 (0.997, 1.007) p=0.476 n=929 (6 trials)

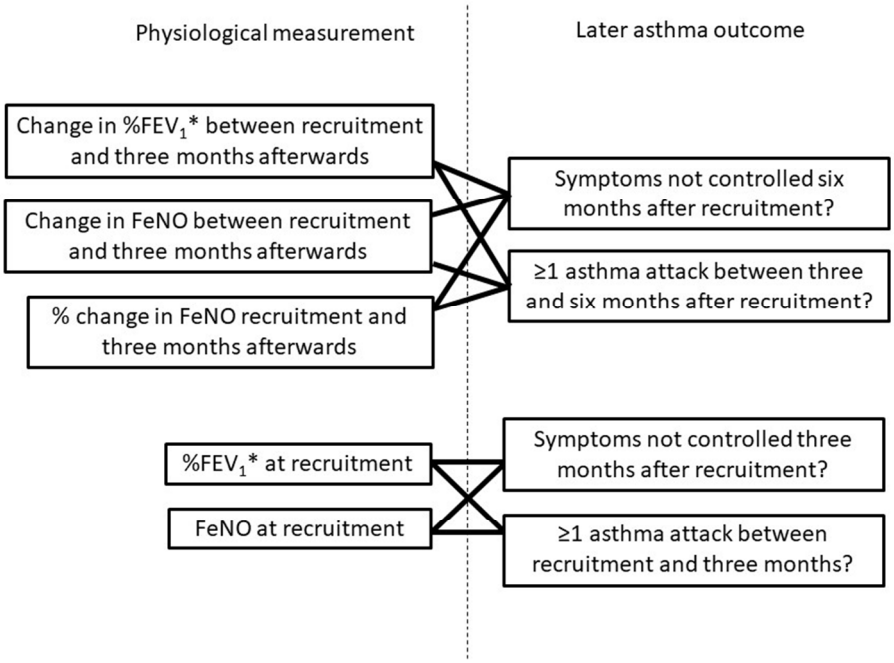

Figure one. A diagram showing how different physiological measurements were linked to later asthma outcomes in the study's analyses. The analyses used data collected at recruitment to seven clinical trials and at follow up assessments three and six months after recruitment.*Although % FEV1 was the primary spirometric index, the following were also considered: %FEV1/FVC, %FEF25-75 and %FVC.

254x190mm (96 x 96 DPI)

SUPPLEMENT

Details of each population

Fritsch *et al*[1] undertook a study of 47 children with asthma attending a hospital asthma clinic in Vienna, Austria and collected data at baseline, 1.5, 3, 4.5 and 6 months (see table 1). The intervention compared treatment guided by symptom and FEV_1 (applying a cut off of 80% of predicted) versus symptoms, FEV_1 and FeNO (applying a cut off of 20 parts per billion, ppb). The data collected at baseline, three and six months were used for the IPD. FeNO was measured using a NIOX chemiluminescence analyser (Aerocrine AB, Solna, Sweden). Sensitisation to inhaled allergen was an inclusion criterion and children treated with oral or intravenous corticosteroids within four weeks prior to the baseline visit were excluded. Reported asthma symptoms over a four week period were scored as 0 (no symptoms, i.e. controlled), 1 (mild symptoms, i.e. controlled) and 2 (severe symptoms, i.e. uncontrolled). Prescribing of oral corticosteroids for asthma attacks was at the discretion of the attending doctor.

Peirsman *et al*[2] recruited 99 participants with persistent asthma attending one of seven hospital asthma clinics across Belgium and collected data at baseline, three, six, nine and twelve months (see table 1). The intervention compared treatment guided by symptoms plus $\%FEV_1$ (applying a cut off of 80% predicted) against symptoms, $\%FEV_1$ and FeNO (with a cut off of 20ppb). FeNO was measured using the NIOX MINO device (Aerocrine AB, Solna, Sweden). All participants were sensitised to inhaled allergens. Inclusion criteria included mild to severe persistent asthma and sensitised to inhaled allergen. Children with an asthma attack in the previous four weeks or who had received treatment with oral corticosteroids in the previous twelve weeks were ineligible. The first four questions of the children Asthma Control Test were used to ascertain asthma control. Prescribing of oral corticosteroids for asthma attacks was at the discretion of the attending doctor.

Petsky *et al*[3] recruited 63 children in Australia and Hong Kong and data were collected at baseline, one, two, three, four, six, eight, ten and twelve months. If three month data were missing, two month data were used, and if six month data were missing, the four month information was used in the IPD. The intervention compared asthma treatment guided by symptoms versus symptoms plus FeNO (applying a cut off of 10ppb for non-atopic children, 12ppb for those with one positive skin test and 20ppb for those with >one positive skin test). FeNO was measured with a chemiluminescence analyser (Sievers NOA 280i, Colorado, USA). Inclusion criteria included age > four years, attending a hospital asthma clinic, having persistent asthma and being prescribed regular asthma preventer treatment. Exclusion criteria included poor treatment adherence and not being able to take inhaled medication. The following questions were scored 0 (no symptoms/normal activity) to 6 (greatest symptoms/disruption of activity): How often did you experience asthma symptoms? How much did your asthma symptoms bother you today? How much activity could you do today? How often did your asthma affect your usual activities today? Being uncontrolled was defined as an increased in symptoms score of ≥15% since the previous visit. The symptom score could only be identified for the baseline assessment but not for the three and six month visits. Prescribing of oral corticosteroids for asthma attacks was at the discretion of the attending doctor.

Pijnenburg *et al* [4] included 86 participants in the Netherlands and data were collected at baseline, three, six, nine and twelve months. The intervention compared asthma treatment guided by symptoms versus symptoms plus FeNO (applying a cut off of 30 ppb). Spirometry was not measured at the three and six month follow ups. FeNO was measured using the using the NIOX chemiluminescence analyzer (Aerocrine AB, Solna, Sweden). Inclusion criteria were age 6-18 years, being atopic and having had no change to ICS dose for the three months prior to recruitment. There were no exclusion criteria. A daily symptom diary scored the following as 0 (none) to 3 (greatest symptoms): daytime dyspnoea, daytime wheezing, daytime cough, night time dyspnoea, night time wheezing, night time cough and being uncontrolled was defined as a mean of the symptoms score over two weeks of >14.

Pike *et al* [5] recruited 90 participants in the UK and collected data at baseline, two, four, six, eight, ten and twelve months. The two month data was used to represent three months, and if six month data were missing then the four month data were used. The intervention compared asthma treatment guided by symptoms versus symptoms plus FeNO (applying a cut off of 25ppb). FeNO was measured using the NIOX MINO device (Aerocrine AB, Solna, Sweden). Inclusion criteria were age 6-17 years, diagnosed asthma, attending one of three hospital asthma clinics and being prescribed ≥400 microg BUD. Exclusion criteria were being unable to provide FeNO or FEV_1 measurements, active smoking, poor treatment adherence, a history of a life-threatening asthma attack or requirement for maintenance oral corticosteroids. Symptoms were scored none, trivial, mild, moderate or severe for the following outcomes: cough, wheeze, sputum production, shortness of breath while walking, waking due to night time cough, waking due to night time cough, waking due to night time sputum production and waking due to shortness of breath. The blinded clinician categorised each participant's asthma as well controlled (symptoms and reliever inhaler <1/week and FEV1 >90% predicted); controlled (symptoms or reliever inhaler use 1-2/week, or FEV1 >80% predicted), or poorly controlled (symptoms or reliever inhaler use >2/week, or FEV1 <80% predicted) (modified from Smith *et al*[6]).

Szefler *et al*[7] recruited 546 participants in the USA and collected information at baseline, 1.5, 3.2, 5, 7, 8.5 and 10.5 months. We utilised the baseline information, 3.2 month assessment to represent three months and the seven month assessment to represent six months. If data were missing at these time points, data from the 1.5 month assessment was used to represent three month assessment, and the five month assessment used to impute at six months. The intervention compared asthma treatment guided by symptoms plus FEV_1 (applying a cut off of 80% predicted) versus symptoms, FEV_1 and FeNO (applying cut offs of 20, 30 and 40 ppb). FeNO was measured using a rapid-response chemiluminescent analyser (NIOX, Aerocrine AB, Sweden). Inclusion criteria were age 12-20 years, living in a household where ≥20% of resident's income was below the federal poverty threshold, physician diagnosed asthma

which required long-term treatment and was persistent and/or uncontrolled. Individuals with cotinine confirmed active smoking were excluded. Having uncontrolled asthma was defined as a score of <19 on the asthma control test[8].

Voorend-van Bergen *et al*[9] undertook a study of 181 participants and collected data at baseline, 4, 8 and 12 months. We assigned the four and eight month data to represent three and six month assessments respectively. Spirometry was only measured at baseline and twelve months. The intervention compared asthma treatment guided by symptoms versus symptoms plus FeNO (applying cut offs of 20 and 50 ppb). Participants in a third arm of this trial (a web-based intervention) were not included. FeNO was measured using a NIOX chemiluminescence analyzer or NIOX MINO (Aerocrine AB, Stockholm, Sweden). Inclusion criteria were age 4-18 years, diagnosed asthma, sensitisation to inhaled allergen, bronchodilator response of 9%, attending one of seven hospital clinics in the Netherlands and being prescribed inhaled corticosteroids for more than three months. Exclusion criteria included active smoking, admission to intensive care for asthma, inability to provide FeNO measurement and use of omalizumab. Having uncontrolled asthma was defined as a score of <19 on the asthma control test[8].

Supplemental table 1. Details of FEV_1 z scores and centile scores both for individual trials and all trials combined. Raw data were not available for the trials by Peirsman et al or Pijnenburg et al.

		Fritsch[1]	Peirsman[2]	Petsky[3]	Pijnenburg[4]	Pike[5]	Szefler[7]	Voorend-van Bergen[9]	All populations combined
Total number of participants		47	99	63	86	90	546	181	1112
FEV_1 z score	Number of observations	47	-	54	-	90	546	157	894
	mean (SD)	-0.61 (1.28)	-	-0.07 (1.41)	-	-0.51 (1.34)	-0.58(1.66)	-0.49 (1.09)	-0.53 (1.51)
FEV_1 centile score	Number of observations	47	-	54	-	90	546	157	894
	Median(IQR)	28.1 (7.4, 58.0)	-	48.2 (22.1, 75.4)	-	27.2 (7.2, 66.2)	22.5 (4.01, 71.9)	31.3 (12.6, 58.4)	27.9 (5.9, 66.9)

Supplemental table 2. Relationship between falling % FEV_1/FVC or $\%FEF_{25-75}$ over a three month period and odds of asthma attack or loss of asthma control during the next three months. Results are from a one stage individual patient data analysis. All models adjusted for sex, age, treatment with long acting beta agonists at baseline, treatment with leukotriene receptor antagonist at baseline, asthma control at baseline, change in dose of inhaled corticosteroid between baseline and three months. †The model also includes asthma attack between baseline and 3 months. The change in $\%FEV_1$/FVC or $\%FEF_{25-75}$ model included $\%FEV_1$/FVC or $\%FEF_{25-75}$ at baseline. *For change in $\%FEV_1$/FVC "per unit" means for each percentage change (e.g. from 98% to 97% FEV_1/FVC).

Measurement of respiratory function	Asthma outcome	Odds Ratio per unit* reduction in $\%FEV_1$/FVC, $\%FEF_{25-75}$ or FVC
Change (baseline to 3m) in $\%FEV_1$/FVC	≥1 asthma attack between baseline and three months	1.013(0.977, 1.050) p=0.492 n=526 (2 trials)
	Asthma uncontrolled at three months	1.026 (0.99, 1.061) p=0.166 n=544 (2 trials)
Change (baseline to 3m) in $\%FEF_{25-75}$	≥1 asthma attack between baseline and three months	1.009 (0.995, 1.024) p=0.200 n=480 (1 trial)
	Asthma uncontrolled at three months	1.006 (0.993, 1.020) p=0.353 n=498 (1 trial)
Change (baseline to 3m) in %FVC	≥1 asthma attack between baseline and three months	1.034 (1.034, 1.065) p=0.026 n=542 (3 trials)
	Asthma uncontrolled at three months	1.023 (0.994, 1.053) p=0.126 n=544 (2 trials)

Supplemental table 3. Relationship between baseline % FEV_1 or baseline FeNO or change in %FEV_1 or %change in FeNO and risk of asthma attack or loss of asthma control during the next three months. Results are from a one stage individual patient data analysis and are stratified by trial arm.

		Only children in standard treatment arm	Only children in FeNO treatment arm
Per unit fall in % FEV_1 between baseline and three months	≥1 asthma attack between three and six months	1.026 (0.994, 1.058) p = 0.119 n = 366	1.014 (0.987, 1.043) p = 0.314 n = 359
	Asthma uncontrolled at six months	1.006 (0.981, 1.033) p = 0.632 n = 363	1.023 (0.999, 1.048) p = 0.061 n = 349
Per % rise in FeNO between baseline and three months	≥1 asthma attack between three and six months	1.001 (0.998, 1.003) p=0.574 n=463	1.001 (0.998, 1.003) p=0.431 n=475
	Asthma uncontrolled at six months	1.001 (0.999, 1.004) p=0.173 n=456	1.000 (0.998, 1.003) p=0.633 n=462
Per unit reduction %FEV_1 at baseline	Odds ratio for ≥1 asthma attack between baseline and three months	0.999 (0.980, 1.019) p = 0.971 n=493	1.026 (1.005, 1.049) p = 0.017 n = 480
	Asthma uncontrolled at three months	1.001 (0.989, 1.013) p = 0.846 n = 479	0.981 (0.967, 0.995) p = 0.008 n = 460
Per ppb increase in FeNO at baseline	Odds ratio for ≥1 asthma attack between baseline and three months	1.002 (0.993, 1.012) p=0.650 n=476	1.001 (0.992, 1.010) p=0.771 n=490
	Asthma uncontrolled at three months	1.002 (0.996, 1.008) p=0.591 n=460	0.996 (0.988, 1.003) p=0.296 n=469

Supplemental table 4. Relationship between falling % FEV_1 or rising %change in FeNO over a three month period and risk of asthma attack or loss of asthma control during the next three months where data from the cohorts[1, 2, 7] where FEV_1 was used to guide treatment were excluded.

Change in measurement of respiratory function	Asthma outcome	Odds Ratio per unit change in FEV_1 or FeNO
Change (baseline to 3m) in % FEV_1	Loss of control	0.973 (0.926, 1.021) p =0.266
	Asthma attack	1.029 (0.986, 1.074) p = 0.194
% change in FeNO (baseline to 3m)	Loss of control	0.999 (0.996, 1.002) p = 0.507
	Asthma attack	1.004 (1.000, 1.008) p = 0.029
% FEV_1 at baseline	Loss of control	0.998 [0.988, 1.008] p = 0.737
	Asthma attack	1.001 [0.989, 1.013] p = 0.925
FeNO at baseline	Loss of control	0.989 [0.971, 1.008] p = 0.273
	Asthma attack	1.027 [0.999, 1.055] p = 0.054

Supplemental table 5. Relationship between falling FEV_1 z score or FEV_1 centile over a three month period and the odds of an asthma attack or having poor asthma control during the next three months. *For change in FEV_1, "per unit" means for each percentage change (e.g. 1 z score decrease in FEV_1 or a decrease of one FEV_1 centile).

Change in measurement of respiratory function	Asthma outcome	Odds Ratio per unit change in FEV_1*
Change (baseline to 3m) in FEV_1 z score	≥1 asthma attack between three and six months†	1.417 (1.036, 1.939) p=0.029 n=625 (4 trials)
	Asthma uncontrolled at six months	1.394 (1.086, 1.790) p=0.009 n=602 (3 trials)
change in FEV_1 centile (baseline to 3m)	≥1 asthma attack between three and six months†	1.011 (0.9996, 1.027) p=0.157 n=625 (4 trials)
	Asthma uncontrolled at six months	1.017 (1.005, 1.031) p=0.006 n=602 (3 trials)

Supplemental table 6. Relationship between falling % FEV_1 (standardised to NHANESIII) over a three month period and risk of asthma attack or loss of asthma control during the next three months. Results are from a one stage individual patient data analysis. All models adjusted for sex, age, treatment with long acting beta agonists at baseline, treatment with leukotriene receptor antagonist at baseline, control at baseline, change in dose of inhaled corticosteroid between baseline and three months

Change in measurement of respiratory function	Asthma outcome	Odds Ratio per unit change in FEV_1
Change (baseline to 3m) in% FEV_1	≥1 asthma attack between three and six months	1.025 (1.002, 1.047) p=0.031 n=716 (5 trials)
	Asthma uncontrolled at six months	0.981 (1.0, 0.993) p=0.055 n=693 (4 trials)
%FEV_1 at baseline	≥1 asthma attack between baseline and three months	1.017(1.001, 1.034) p=0.039 n=974 (7 trials)
	Asthma uncontrolled at three months	1.012 (1.001, 1.021) p=0.033 n=940 (6 trials)

Supplemental table 7. Relationship between baseline FEV_1 z score and centile and odds of asthma attack or asthma being uncontrolled during the next three months. Results are from a one stage individual patient data analysis. All models adjusted for sex, age, treatment with long acting beta agonists at baseline, treatment with leukotriene receptor antagonist at baseline, asthma control at baseline and change in dose of inhaled corticosteroid between baseline and three months. *"Per unit" means for each z score or centile percentage reduction.

Measurement of respiratory function	Asthma outcome	Odds Ratio per unit* reduction in FEV_1
FEV_1 z score at baseline	≥1 asthma attack between baseline and three months	1.065 (0.87, 1.30), p = 0.537 n=807 (5 trials)
	Asthma uncontrolled at three months	0.945 (0.841, 1.062) p =0.344 n=777 (4 trials)
FEV_1 centile at baseline	≥1 asthma attack between baseline and three months	1.002 (0.993, 1.011) p =0.669 n=807 (5 trials)
	Asthma uncontrolled at three months	0.999 (0.993, 1.004) p = 0.668 n=777 (4 trials)

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Change in FEV_1 and FeNO measurements as predictors of future asthma outcomes in children

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ABSTRACT (word count 249)

Background. Repeated measurements of spirometry and fractional exhaled nitric oxide (FeNO) are recommended as part of the management of childhood asthma, but the evidence base for such recommendations is small. We tested the hypothesis that reducing spirometric indices or increasing FeNO will predict poor future asthma outcomes.

Methods. A one-stage individual patient data meta-analysis used data from seven randomised controlled trials where FeNO was used to guide asthma treatment, and where spirometric indices were also measured. Change in $\%FEV_1$ and % change in FeNO between baseline and three months were related to having poor asthma control and to having an asthma exacerbation between three and six months after baseline.

Results. Data were available from 1112 children (mean age 12.6 years, mean $\%FEV_1$ 94%). A 10% reduction in $\%FEV_1$ between baseline and three months was associated with 28% increased odds for asthma exacerbation [95% CI 3, 58] and with 21% increased odds for having poor asthma control [95% CI 1, 45] six months after baseline. A 50% increase in FeNO between baseline and three months was associated with 11% increase in odds for poor asthma control six months after baseline [95% CI 0, 16]. Baseline FeNO and $\%FEV_1$ were not related to asthma outcomes at three months.

Conclusions. Repeated measurements of $\%FEV_1$ which are typically within the "normal" range add to clinical risk assessment of future asthma outcomes in children. The role of repeated FeNO measurements is less certain since large changes were associated with small changes in outcome risk.

Keywords: Asthma, Child, Monitoring, Nitric oxide, Spirometry

ABBREVIATION LIST

BUD Budesonide

ERS European Respiratory Society

FeNO Fractional Exhaled Nitric Oxide

FEF_{25-75} Forced Expiratory Flow at 25-75% of FVC

FEV_1 Forced Expiratory Volume in one second

FVC Forced Vital Capacity

GLI Global Lung Initiative

ICS Inhaled corticosteroid

IPD Individual Patient Data Analysis

IQR Inter-quartile range

LABA Long Acting Beta Agonist

LTRA Leukotriene Receptor Antagonist

NHANES National Health and Nutrition Examination Survey

OR Odds ratio

ppb Parts per billion

RCT Randomised Controlled Trial

SD Standard deviation

UK United Kingdom

USA United States of America

INTRODUCTION

Asthma is a common condition affecting 1 million children in the UK[1] and 6 million in the USA[2]. Guidelines recommend that objective markers of respiratory function (e.g. forced Expiratory Volume in one second (FEV_1)) and airway inflammation (e.g. fractional exhaled nitric oxide, FeNO) may be used in conjunction with symptoms to guide asthma preventive treatment in children. However these recommendations differ between guidelines, and none gives clinicians advice how to interpret changes in spirometry when values fall within the normal range, yet FEV_1 (the most commonly used spirometric index) is usually within normal limits [3].

One guideline recommends that lung function should be "monitored and recorded" only in children aged over 12 years[4]. Two guidelines recommend that FEV_1 may be useful for monitoring of asthma for children aged over five to seven years[5, 6]. A fourth guideline[7] recommends that lung function should be measured three-to-six months after treatment is started and "periodically" thereafter, and that $\%FEV_1$ less than 60% identifies a patient at risk for future asthma exacerbations. A fifth guideline[8] recommends that lung function should be measured every one to two years (more frequently when symptoms are poorly controlled) and suggests that treatment might be stepped up if $\%FEV_1$ is below 80% or 60%. Some guidelines suggest that a 20% drop in FEV_1 relative to personal best identifies an individual at risk for future asthma exacerbations[5, 7].

Although FeNO is recommended by the US Food and Drug Administration for monitoring asthma[9] there is no consensus on how results should be interpreted; one international guidelines states that a change in FeNO of 10 parts per billion or 20% may be clinically relevant[10].

To understand the relationship between change in spirometry and FeNO and asthma outcomes we obtained individual patient data (IPD) from seven FeNO randomised controlled trials (RCTs) where details of spirometry, FeNO, asthma control and the occurrence of asthma exacerbations were collected longitudinally [11-17]. Our primary hypothesis was that falling spirometric indices (with $\%FEV_1$ as the primary index) and/or rising FeNO between randomisation and three months follow up will be

associated with increased risk for asthma being uncontrolled and for an asthma exacerbation between three and six months follow up. The secondary hypothesis was that at baseline, low spirometric indices and high FeNO will be associated with increased risk for asthma being uncontrolled and for an asthma exacerbation between baseline and three months follow up.

METHODS

Study design

Authors of published RCTs where measurements of FeNO was used to guide asthma treatment in children[18] were invited to provide anonymised data for IPD[19]. The outcomes were asthma exacerbation (defined as a prescription of prednisolone during the follow-up period and derived using data provided by study authors) and poor asthma control (defined by per trial protocol by symptom score, and including FEV_1 cut off values in some trials[11, 12, 16] but not including an asthma exacerbation). The supplement provides definitions of being uncontrolled. For all RCTs, prescribing of oral corticosteroids for asthma exacerbations was at the discretion of the attending doctor. The explanatory variables between baseline and three months follow up were absolute change and %change in FeNO and absolute change in percentage of predicted (%) spirometry; the analysis of change in % spirometry and % change in FeNO included the corresponding baseline measurement. The relationship between outcomes and the following explanatory variables at baseline were sought: FeNO and $\%FEV_1$, $\%FEV_1/FVC$, $\%FEF_{25-75}$ and %FVC. Figure one shows which physiological measurements (and changes) were linked to later asthma outcomes in this study. Additional covariates collected at baseline and included in the models were: age, gender, height, weight, ethnicity, trial arm, dose of inhaled corticosteroid (ICS, as daily budesonide equivalent dose, BUD), prescribed long acting beta agonist (LABA) or not, prescribed leukotriene receptor agonist (LTRA) or not, asthma control and treatment compliance. For each follow up visit, the following variables were collected: FeNO, FEV_1, height, dose of ICS, asthma control and asthma exacerbation since the

previous visit. The focus of this study was follow up at three and six months since these are typically used in asthma clinics; for trials where there was no three or six month assessment, the assessment closest to these time points was used. In all but two studies[14, 15], absolute spirometry data were available and expressed as percentage of predicted to the Global Lung Initiative standard[20]; where absolute data were not available, the % predicted value provided by the local team was used for analysis. Whilst $\%FEV_1$ was the primary spirometric index of interest, $\%FEV_1/FVC$, $\%FEF_{25-75}$ and %FVC were also considered to determine which index had the greatest precision for future outcomes. For completeness, FEV_1 was also expressed as a Z scores and centile (standardised to the Global Lung Initiative standard[20]). Additionally, as a sensitivity analysis, $\%FEV_1$ was derived using National Asthma Education and Prevention Program (NHANES) III standard[21] to determine whether any relationship between $\%FEV_1$ and later outcome was dependent on the standard used. Body Mass Index (BMI) was derived and International Obesity Task Force weight categories created[22]. In each trial, FeNO was measured in accordance with the 2005 guideline[23]. Ethical approval was obtained for each individual study but was not required for the IPD.

Individual patient data analysis

Demographic and baseline characteristics were obtained for each study. A one-stage IPD meta-analysis was undertaken using the melogit command in STATA with study included as a random effect. All models were adjusted for the baseline variables of age, gender, LABA, LTRA, asthma control, ICS dose, arm of trial and where relevant baseline FeNO or baseline FEV_1. A one-stage approach was used rather than a two-stage as some of the studies had low event counts (few asthma exacerbations) and adoption of one-stage in this instance is recommended by Burke *et al*[24]. Sensitivity analyses considered separately outcomes for individuals in FeNO intervention and standard care arms of the trials, and also excluding data from trials where $\%FEV_1$ was used to guide treatment decisions [11, 12, 16]. STATA version 14 was used for analysis.

RESULTS

Study subjects

Data from seven paediatric RCT were analysed [11-17], data from an eighth RCT could not be obtained [25]. Details of population inclusion and exclusion criteria are presented in the supplement. The IPD included data on 1112 participants. In two studies[14, 17] spirometry was only measured at baseline and at 12 months and change in $\%FEV_1$ between baseline and three months could not be calculated. There was a predominance of male participants (58%) and mean (standard deviation(SD)) age was 12.6 (3.1) years, table 2. Median values of FeNO varied between 18 and 34 parts per billion (ppb) with an overall median (interquartile range (IQR)) of 22ppb (12, 43). Mean $\%FEV_1$ values at baseline varied between 89% and 98% predicted with an overall mean (SD) of 94% (18). Details of mean FEV_1 z scores and centile are presented in supplemental table 1. The Pearson correlation coefficient between FeNO and $\%FEV_1$ at baseline was -0.184 (n=1025, p <0.001) and between % change in FeNO (baseline to 3 months) and change in $\%FEV_1$ (baseline to 3 months) was -0.127 (n=759, p <0.001). Overall 7% of participants had an asthma exacerbation during the first 3 months and 12% in the second three months, while 27% were uncontrolled at baseline, 25% at 3 months, and 23% at six months, table 3. An asthma exacerbation occurred between baseline and three months in 47 (7%) of the 718 participants with controlled symptoms at baseline and in 27 (12%) of 230 with uncontrolled symptoms at baseline.

Relationship between change in spirometry and percentage change in FeNO between baseline and three months and outcomes between three and six months

Between baseline and 3 months, the mean (SD) change in $\%FEV_1$ was -0.17 (10.4), the median absolute change in FeNO was 0.6 ppb (IQR -7.9, 12.2) and the median % change in FeNO (interquartile range) was 3.7% (IQR -30.4, 66.7). A fall in $\%FEV_1$ was related to increased odds of an asthma exacerbation over the following three months (e.g. a reduction of 10% FEV_1 between baseline and three months was associated with increased odds ratio (OR) for future exacerbation

between three and six months of 1.3 [1.0, 1.6], p=0.027) and loss of future asthma control (e.g. a reduction of 10% FEV_1 was associated with increased odds ratio for uncontrolled asthma 1.2 [96% CI 1.0, 1.5], p=0.046), table 4. A reduction of 10% FVC was also associated with increased odds for a future exacerbation (OR 1.40 [1.04, 1.88], p=0.026), supplemental table 2. A 50% increase in FeNO between baseline and three months was associated with 11% increased odds of asthma being uncontrolled at six months [95% 0, 16] (p=0.014) but not odds of an exacerbation between three and six months, table 4. When both change in $\%FEV_1$ and %change in FeNO were considered in the same model, the odds ratio for asthma being uncontrolled remained significant for FeNO (p=0.036) but not for $\%FEV_1$ (p=0.061). Neither change in $\%FEV_1$/FVC or $\%FEF_{25-75}$ (supplemental table 2) nor absolute change in FeNO (table 4) were associated with outcomes. The associations between change in $\%FEV_1$ and % change in FeNO did not achieve significance when each trial arm was considered separately (supplemental table 3). When the RCTs where $\%FEV_1$ was used to guide treatment were excluded there was an association between rising FeNO and future asthma exacerbation (p=0.029) but associations between change in FEV_1 and outcomes were not significant, supplemental table 4. Among the subset of RCT where FEV_1 z score and centile values could be derived, falling z scores were associated with increased odds for both asthma exacerbations and being uncontrolled and falling centile score with being uncontrolled, supplemental table 5. The results seen with change in % FEV_1 using the Global Lung Initiative (GLI) standard were also seen when the NHANES III standard was used, supplemental table 6.

Relationship between baseline FeNO and spirometric indices and outcomes at three months

Percentage of predicted FEV_1/FVC at baseline (but no other spirometric index) was related to the odds of asthma exacerbation at three months during this interval (p=0.016), table 5. No index of spirometry at baseline was related to having uncontrolled asthma at three months. FeNO at baseline was not related to asthma outcomes at three months (table 5). Supplementary table 6 demonstrates that when FEV_1 was standardised to the NHANES III data, reducing $\%FEV_1$ at baseline

was associated with increased odds for future asthma exacerbation (p=0.033) and a trend for reduced odds for asthma not being controlled in future (p=0.055). Baseline FEV_1 z score or centile were not related to outcomes (supplemental table 7).

DISCUSSION

This study sought to understand the relationship between changes in spirometric measurements and FeNO and future asthma outcomes. The first finding was that, independent of all factors which might influence treatment decisions, falling $\%FEV_1$ (even within the range of 80-120% commonly considered as "normal") was associated with increased odds for future asthma exacerbation and having uncontrolled asthma. A second finding was that an absolute change in FeNO (table 4) did not predict outcomes, and only a large rise in % change in FeNO was related to a small increase in the odds for having uncontrolled asthma in future. We also observed that at baseline, a "one off" $\%FEV_1$/FVC ratio (but not $\%FEV_1$) was associated with future odds for asthma exacerbation. Together the results suggest that change in $\%FEV_1$ can be used as part of risk assessment for asthma outcomes. The role of change in FeNO is less clear and future clinical trials could include % change in FeNO as part of a treatment algorithm for children with asthma.

The individuals whose data contributed to this study were participating in RCTs, and this could mean that the results are not necessarily generalisable for at least two reasons. First, participants in RCTs often have to fulfil specific eligibility criteria, receive more clinical contact than standard care and often have better outcomes such as fewer asthma exacerbations, but these differences are likely to weaken any association between FeNO or $\%FEV_1$ and asthma outcomes by narrowing the phenotype of participants and improving outcomes. Secondly, the participants in our study had treatment guided by FeNO (and $\%FEV_1$ in three studies) and thus the predictive variables in our study may have affected the outcome (e.g. rising FeNO leading to increased ICS resulting in good asthma control). We justify inclusion of data from these trials because firstly FeNO and, in all but one study[14], $\%FEV_1$

did not differ between trial arms and secondly, if FeNO or %FEV_1 did improve asthma outcomes by protocol-driven treatment changes this would have weakened any association between FeNO or %FEV_1 and asthma control or asthma exacerbations. Our inclusion of participants in RCTs may therefore have weakened the associations described, and in "real life" change in %FEV_1 and % change in FeNO may have greater precision for outcomes than indicated by our results.

There are some limitations to our study. First, the methodologies of the RCTs were different and in particular in three of the RCTs[15-17] the intervals between assessments did not include multiples of three months, and this heterogeneity may have weakened the associations described, assuming that the relationship between FeNO and FEV_1 and outcomes changes over time. Different methods were used to assess asthma control; again this would weaken and not strengthen the associations described between baseline %FEV_1 or %change in FeNO and being uncontrolled in future. A second~~further~~ limitation is that the range of %FEV_1 values was relatively narrow and the incidence of asthma exacerbations was relatively low and this could make the relationship between physiological measurement and clinical outcome difficult to detect, but nonetheless we were still able to observe an association between %FEV_1 and future asthma exacerbations. A third~~final~~ limitation is that we did not have an objective measure of adherence and could not consider how non-adherence may have influenced asthma control and exacerbations, however this information is not available for most clinicians and thus our study reflects "real world". A fourth limitation is that none of the RCTs included an assessment of short-term variability of pulmonary function, such as peak expiratory flow variability or bronchodilator response, and we are not able to say how short-term variability in pulmonary function might be related to future asthma outcomes.

The magnitude of the change in odds ratio for an asthma exacerbation or being uncontrolled in future in the context of changing %FEV_1 and FeNO were relatively small, and this is partly due to our including RCT participants as previously discussed and partly due to the fact that the model

considered many other factors which might predict poor asthma outcomes, e.g. current symptom control, treatment level, current %FEV_1.

In our sensitivity analyses we excluded the three studies where %FEV_1 was used to guide treatment and the results seen in the whole population were no longer significant and this is most likely explained by lack of power. We when split results by trial arm, and the significant associations seen between change in %FEV_1 and %change in FeNO for the whole population were also non-significant and this is also most likely due to lack of power in the analysis.

We are not aware of published studies which relate change in spirometry to future asthma outcomes, but there are several studies where spirometry on a single occasion has been related to subsequent asthma outcomes in children. One study reported an inverse relationship between reduced %FEV_1 and increased risk for asthma exacerbation in the next 12 months[26]. Two further studies[27, 28] (data from one[27] contributed to the present IPD) reported that reduced FEV_1/FVC ratio was associated with increased risk for future exacerbation.

The 2015 European Respiratory Society (ERS) Task Force on Monitoring Asthma in Children[29] stated that "the meaning of significant changes in FeNO in a longitudinal setting is still unclear and needs further attention, and that "the use of 'personal best' cut-off points in FeNO algorithms requires further investigation". Our study findings suggest that a % relatively large rise (50%) in FeNO over three months (independent of treatment and initial symptoms) may be a useful predictor of having uncontrolled asthma in future but not for asthma exacerbations. Additionally, our results suggest that a single FeNO value and absolute change in FeNO over time are unlikely to be clinically useful.

In summary our results suggest that %FEV_1 within the "normal" range over three month periods could assist with risk assessment in childhood asthma and these findings now need replicating elsewhere. A fall in %FEV_1 and a rise in FeNO should prompt an evaluation of medication adherence, inhaler technique, perception of symptoms and exposure to either allergens or viral infection. The

relationship between changes in FeNO measurements and asthma outcomes is less clear and requires further evaluation.

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ST conceived the idea for the study, wrote the first draft of the manuscript and is the guarantor of the study. ST and SF designed the study. All authors other than ST and SF contributed data for the analysis. SF undertook the analysis. All authors made contributions to the final manuscript.

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FIGURE LEGEND

Figure one. A diagram showing how different physiological measurements were linked to later asthma outcomes in the study's analyses. The analyses used data collected at recruitment to seven clinical trials and at follow up assessments three and six months after recruitment.*Although % FEV_1 was the primary spirometric index, the following were also considered: %FEV_1/FVC, %FEF_{25-75} and %FVC.

Table 1. Details of the randomised controlled trials included in this individual patient data analysis

	Mean age, y		Intervals at follow up after baseline when FeNO was measured (months). Zero corresponds to baseline.	Intervals at follow up after baseline when spirometry was measured (months). Zero corresponds to baseline	Were absolute spirometry data available?	Which spirometric indices were available?	Was there a run in period?	Was atopy an inclusion criteria?	What measure of asthma control was used?
	FeNO arm	Control arm							
Fritsch[11]	11.3	12.1	0, 1.5, 3, 4.5, 6	0, 1.5, 3, 4.5, 6	Yes	FEV_1, FVC	Yes	Yes	Unvalidated symptom diary
Peirsman[12]	10.6	10.7	0, 3, 6, 9, 12	0, 3, 6, 9, 12	Yes	FEV_1	No	Yes	First four (of seven) questions on CACT*†
Petsky[13]	9.9	10.1	0, 1, 2, 3, 4, 6, 8, 10, 12	0, 1, 2, 3, 4, 6, 8, 10, 12	Yes	FEV_1, FEF_{25-75}, FVC	Yes	No	Validated symptom diary
Pijnenburg[14]	11.9	12.6	0, 3, 6, 9, 12	0, 12	No	FEV_1, FEF_{50}, FVC	Yes	Yes	Validated symptom diary
Pike[15]	10.5	11.4	0, 2, 4, 6, 7, 10, 12	0, 2, 4, 6, 7, 10, 12	No	FEV_1, FVC	No	No	Modified validated symptom diary†
Szefler[16]	14.4	14.4	0, 1.5, 3.2, 5, 7, 8.5, 10.5	0, 1.5, 3.2, 5, 7, 8.5, 10.5	Yes	FEV_1, FEF_{25-75}, FVC	Yes	No	ACT*‡ plus FEV_1
Voorend-van Bergen[17]	10.3	10.2	0, 4, 8, 12	0, 12	Yes	FEV_1, FEF_{75}, FVC	Yes	Yes	ACT and C-ACT*

*ACT = asthma control test, C-ACT=Childhood Asthma Control Test

†reliever medication use and FEV_1 or ¶FEV_1 alone were used in the treatment algorithm for both arms of the RCT but were not used to define being uncontrolled in the present study

Table 2. Characteristic of study participants at the baseline visit in each study

		Fritsch[11]	Peirsman[12]	Petsky[13]	Pijnenburg[14]	Pike[15]	Szefler[16]	Voorend-van Bergen[17]	All populations combined
Total number of participants		47	99	63	86	90	546	181	1112
%(number) male		60% (28)	67% (66)	49% (31)	65% (56)	57% (51)	53% (288)	68% (123)	58% (643)
Age	mean (SD)	11.5(3.1)	10.7 (2.1)	10.0 (3.2)	12.3 (2.8)	10.9 (2.6)	14.4 (2.1)	10.2 (3.0)	12.6 (3.1)
	range	6 to 17	5 to 14	4 to 16	6 to 18	5 to 16	12 to 19	4 to 18	4 to 19
Trial arm	Standard	25	50	32	46	46	270	92	561
	FeNO	22	49	31	40	44	276	89	551
FeNO	Number of observations	46	49	61	86	90	546	179	1057
	Median (ppb)	33.9	31.3	25.6	32	25.5	20.1	18.2	21.9
	IQR (ppb)	(18.6, 58.6)	(14, 69)	(12.2, 47.5)	(16.6, 52.5)	(10, 48)	(11.2, 40.6)	(10.2, 30.4)	(11.6, 43.0)
% predicted FEV_1	Number of observations	47	98	54	86	90	546	157	1078
	mean (SD)	93.5 (15.7)	91.4 (15.7)	90.7 (15.6)	97.5 (17.5)	89.2 (14.3)	90.9 (16.6)	93.8 (13.0)	93.5 (18.1)
% predicted FEV_1/FVC	Number of observations	47	0	0	0	0	546	156	749
	mean (SD)	90.1 (10.6)	-	-	-	-	91.3 (9.9)	93.4 (9.4)	91.7 (9.9)
% with positive skin prick test		100%	100%	38% (24/63)	100%	76% (68/90)	88% (467/531)	100%	89% (972/1097)
Mean Centile BMI (SD)	Number of observations	47	99	58	86	89	546	181	1106
	mean (SD)	67.6 (27.0)	52.1 (30.1)	48.5 (32.4)	60.8 (27.3)	64.2 (32.2)	83.1 (23.5)	58.9 (29.9)	70.7 (29.8)
Obese	Number of observations	47	99	58	85	89	526	181	1085
	% (number) overweight	28% (13)	12% (12)	16% (9)	14% (12)	25% (22)	28% (145)	20% (36)	23% (249)
	% (number) obese	8% (4)	1% (1)	2% (1)	4% (4)	8% (7)	31% (165)	3% (5)	17% (187)
LTRA treatment prescribed	Number of observations	47	99	58	86	90	546	181	1107
	% (number) yes	28% (13)	60% (59)	10% (6)	0	51% (46)	15% (80)	13% (23)	21% (227)
LABA	Number of observations	47	99	58	86	90	546	181	1107

treatment prescribed	% (number) yes	38% (18)	32% (32)	67% (39)	38% (33)	76% (68)	66% (360)	46% (84)	57% (634)
Median dose of inhaled corticosteroids (IQR)		400 (0, 800)	320 (200, 400)	400 (250, 500)	800 (400, 1000)	800 (400, 1000)	1000 (400, 2000)	400 (400, 800)	400 (400, 1000)
Ethnic group	Number of observations	0	84	20	0	90	526	179	889
	White		82% (69)			92% (83)		89% (160)	35% (312)
	Hispanic						65% (340)		38% (340)
	Other		18% (15)	100% (20)		8% (7)	35% (186)	11% (19)	28% (247)
Asthma control status	Number of observations	47	65	57	77	90	528	181	1045
	Asthma controlled	49% (23)	75% (49)	72% (41)	57% (44)	68% (62)	80% (421)	67% (122)	73% (762)
	Asthma not Controlled	51% (24)	25% (16)	28% (16)	43% (33)	31% (28)	20% (107)	33% (59)	27% (283)

Table 3. Frequency of outcomes between baseline and three months and between three and six months post baseline.

	Exacerbation between baseline and three months	Exacerbation between three and six months	Asthma not controlled at three months	Asthma not controlled at six months
	% (n)	% (n)	% (n)	n (%)
Fritsch[11]	2% (1/47)	6% (3/47)	54% (25/46)	53% (25/47)
Peirsman[12]	4% (4/99)	0%	25% (21/83)	21% (18/86)
Petsky[13]	5% (3/63)	8% (5/63)	not available	not available
Pijnenburg[14]	9% (8/86)	8% (7/86)	40% (32/81)	40% (31/78)
Pike[15]	17% (15/90)	30% (27/90)	26% (23/90)	32% (29/90)
Szefler[16]	7% (35/522)	15% (78/505)	21% (111/541)	17% (86/513)
Voorend-van Bergen[17]	7% (12/181)	7% (12/181)	21% (38/179)	20% (36/178)
Overall	7% (78/1088)	12% (132/1071)	25% (250/1010)	23% (225/992)

Table 4. Relationship between falling % FEV_1 or rising %change in FeNO over a three month period and odds of having an asthma attack or uncontrolled asthma during the next three months. Results are from a one stage individual patient data analysis. All models adjusted for sex, age, treatment with long acting beta agonists at baseline, treatment with leukotriene receptor antagonist at baseline, asthma control at baseline, change in dose of inhaled corticosteroid between baseline and three months. *For change in $\%FEV_1$, "per unit" means for each percentage change (e.g. from 98% to 97% FEV_1) and for %change in FeNO means for each percent change (e.g. from 100 to 101ppb) and absolute change in FeNO "per unit" means per part per billion change (e.g. from 35 to 36ppb). †Odds ratio for outcomes were derived from the odds ratio per unit change, for example odds ratio for asthma attack after a reduction in $\%FEV_1$ of 5 is 1.025 to the power of 5. ‡The model also includes asthma attack between baseline and 3 months. The change in FeNO model included FeNO at baseline and the change in FEV_1 model included FEV_1 at baseline.

Change in measurement of respiratory function	Asthma outcome	Odds Ratio per unit change in FEV_1 or FeNO*	Odds Ratio per 5, 10 and 20 reduction in $\%FEV_1$†			Odds Ratio per 20 and 50% increase in FeNO†		Odds Ratio per 20 and 50ppb increase in FeNO†	
			$\%FEV_1$ reduced by 5	$\%FEV_1$ reduced by 10	$\%FEV_1$ reduced by 20	20% increase in FeNO	50% increase in FeNO	20ppb increase in FeNO	50ppb increase in FeNO
Change (baseline to 3m) in% FEV_1	≥1 asthma attack between three and six months‡	1.025 (1.003, 1.047) p=0.027 n=716 (5 trials)	1.131 [1.015, 1.258]	1.280 [1.030, 1.583]	1.639 [1.062, 2.506]				
	Asthma uncontrolled at six months	1.019 (1.000, 1.038) p=0.046 n=693 (4 trials)	1.099 [1.000, 1.205]	1.207 [1.000, 1.452]	1.457 [1.000, 2.108]				
% change in FeNO (baseline to 3m)	≥1 asthma attack between three and six months‡	1.001 (0.999, 1.003) p=0.228 n=929 (7 trials)				1.020 [0.980, 1.062]	1.051 [0.951, 1.162]		
	Asthma uncontrolled at six months	1.002 (1.000, 1.003) p=0.014 n=897 (6 trials)				1.041 [1.000, 1.062]	1.105 [1.00, 1.162]		
Absolute change in FeNO (baseline to 3m), ppb	≥1 asthma attack between three and six months‡	1.004 (0.998, 1.010) p=0.197 n=929 (7 trials)						1.083 [0.961, 1.220]	1.221 [0.905, 1.645]
	Asthma uncontrolled at six months	1.002 (0.997, 1.008) p=0.407 n=897 (6 trials)						1.041 [0.942, 1.173]	1.105 [0.861, 1.489]

Table 5. Relationship between baseline % FEV_1 or baseline FeNO and odds of asthma attack or asthma being uncontrolled during the next three months. Results are from a one stage individual patient data analysis. All models adjusted for sex, age, treatment with long acting beta agonists at baseline, treatment with leukotriene receptor antagonist at baseline, asthma control at baseline and change in dose of inhaled corticosteroid between baseline and three months. *For $\%FEV_1$, "per unit" means for each percentage reduction (e.g. from 98% to 97% FEV_1) and for FeNO "per unit" means per part per billion change (e.g. from 35 to 36ppb).

Measurement of respiratory function	Asthma outcome	Odds Ratio per unit* reduction in FEV_1 or rise in FeNO
$\%FEV_1$ at baseline	≥1 asthma attack between baseline and three months	1.011(0.997, 1.026) p=0.118 n=973 (7 trials)
	Asthma uncontrolled at three months	0.993 (0.984, 1.001) p=0.098 n=939 (6 trials)
$\%FEV_1$/FVC at baseline	≥1 asthma attack between baseline and three months	1.037 (1.007, 1.067) p=0.016 n=706 (3 trials)
	Asthma uncontrolled at three months	0.993 (0.973, 1.012) p=0.451 n=715 (3 trials)
FeNO (ppb) at baseline	≥1 asthma attack between baseline and three months	1.001 (0.995, 1.008) p=0.682 n=966 (7 trials)
	Asthma uncontrolled at three months	1.002 (0.997, 1.007) p=0.476 n=929 (6 trials)