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Change in FEV_1 and F_{ENO} Measurements as Predictors of Future Asthma Outcomes in Children

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e-Appendix 1.

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].

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e-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)

e-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)

e-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

e-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

e-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)

e-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)

e-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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