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Appendix A. Search Strategy

KQ 1a.

Ovid
Database(s): Embase 1988 to 2016 Week 30, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 20, 2016
Search Strategy:

#	Searches	Results
1	exp Asthma/	308141
2	asthma*.mp.	387608
3	1 or 2	387722
4	("airway nitric oxide" or "airway NO" or "airway oxide" or "breath nitric oxide" or "breath NO" or "breath oxide" or "breathed nitric oxide" or "breathed NO" or "breathed oxide" or "breathing nitric oxide" or "breathing NO" or "breathing oxide" or "exhaled nitric oxide" or "exhaled NO" or "exhaled oxide" or FeNO or "lung nitric oxide" or "lung NO" or "lung oxide" or "pulmonary nitric oxide" or "pulmonary NO" or "pulmonary oxide" or "respiration nitric oxide" or "respiration NO" or "respiration oxide" or "respiratory nitric oxide" or "respiratory NO" or "respiratory oxide").mp.	100229
5	exp diagnostic accuracy/	202333
6	exp Spirometry/	48927
7	exp methacholine/	15852
8	exp Eosinophils/	55216
9	exp Eosinophil/	55216
10	exp eosinophil count/	7771
11	exp Peak Expiratory Flow Rate/	17248
12	(("respired air" adj3 pressure) or ((hyperreactiv* or hyperrespons* or respons*) adj3 (SABA or "short-acting beta2 agonist*")) or (breath adj3 measur*) or (diagnos* adj3 (accuracy or accurate)) or bronchoprovocat* or eosinophil* or mecholine or mecholyl or metacholine or methacholine or methacholinium or methylcholine or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*" or spirometr*).mp.	605846
13	or/5-12	606514
14	3 and 4 and 13	8599
15	exp Blood/	2555329
16	blood.fs.	1571711
17	exp Heart/	879900
18	exp Blood Vessels/	1373624

19	exp Heart Diseases/	2263854
20	exp Vascular Diseases/	3255967
21	(arter* or blood or cardiac or cardial or heart or plasma or plasmas or serum or vascular* or vein* or vessel*).mp.	11139543
22	or/15-21	13473717
23	14 not 22	5081
24	exp evidence based medicine/	904342
25	exp meta analysis/	183265
26	exp Meta-Analysis as Topic/	43341
27	exp "systematic review"/	110642
28	exp controlled study/	5161226
29	exp Randomized Controlled Trial/	821123
30	exp triple blind procedure/	132
31	exp Double-Blind Method/	375029
32	exp Single-Blind Method/	59663
33	exp latin square design/	330
34	exp Placebos/	302126
35	exp Placebo Effect/	9028
36	exp comparative study/	2625586
37	exp Cohort Studies/	1940158
38	exp longitudinal study/	303249
39	exp retrospective study/	1069095
40	exp prospective study/	836601
41	case report/	3441589
42	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case adj3 report)).mp,pt.	17709671
43	or/24-42	19397581
44	23 and 43	4197
45	limit 44 to ("preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or	4118

	"young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	
46	limit 45 to (preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	3736
47	from 46 keep 1-1225	1225
48	(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) adj2 (year or years)).mp.	2161044
49	48 and child*.mp.	744191
50	(adult or adults or "middle age" or "middle aged" or elderly or geriatric*).mp.	12223883
51	44 and (49 or 50)	3087
52	47 or 51	3303
53	remove duplicates from 52	2782

Scopus
TITLE-ABS-KEY(asthma*)
TITLE-ABS-KEY("airway nitric oxide" OR "airway NO" OR "airway oxide" OR "breath nitric oxide" OR "breath NO" OR "breath oxide" OR "breathed nitric oxide" OR "breathed NO" OR "breathed oxide" OR "breathing nitric oxide" OR "breathing NO" OR "breathing oxide" OR "exhaled nitric oxide" OR "exhaled NO" OR "exhaled oxide" OR FeNO OR "lung nitric oxide" OR "lung NO" OR "lung oxide" OR "pulmonary nitric oxide" OR "pulmonary NO" OR "pulmonary oxide" OR "respiration nitric oxide" OR "respiration NO" OR "respiration oxide" OR "respiratory nitric oxide" OR "respiratory NO" OR "respiratory oxide")
TITLE-ABS-KEY(("respired air" W/3 pressure) or ((hyperreactiv* or hyperrespons* or respons*) W/3 (SABA or "short-acting beta2 agonist*")) or (breath W/3 measur*) or (diagnos* W/3 (accuracy or accurate)) or bronchoprovocat* or eosinophil* or mecholine or mecholyl or metacholine or methacholine or methacholinium or methylcholine or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*" or spirometr*)
1 and 2 and 3
TITLE-ABS-KEY(arter* OR blood OR cardiac OR cardial OR heart OR plasma OR plasmas OR serum OR vascular* OR vein* OR vessel*)
4 and not 5
TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or

"prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case W/3 report))
TITLE-ABS-KEY(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) W/2 (year or years))
TITLE-ABS-KEY(child*)
TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" or elderly or geriatric*)
6 and 7 and ((8 and 9) or 10)
DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
11 not 12
PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
13 not 14

KQ 1b

Ovid

Database(s): Embase 1988 to 2016 Week 30, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 20, 2016
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5	exp Spirometry/	48927
6	exp Peak Expiratory Flow Rate/	17248
7	exp symptom assessment/	5377
8	(("respired air" adj3 pressure) or ((assess* or evaluat*) adj3 (symptom* or asthma* or control*)) or (breath adj3 measur*) or ACQ or "Asthma Control Questionnaire" or monitor* or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*"	2011076

	or spirometr*).mp.	
9	5 or 6 or 7 or 8	2011755
10	3 and 4 and 9	7945
11	exp Blood/	2555329
12	blood.fs.	1571711
13	exp Heart/	879900
14	exp Blood Vessels/	1373624
15	exp Heart Diseases/	2263854
16	exp Vascular Diseases/	3255967
17	(arter* or blood or cardiac or cardial or heart or plasma or plasmas or serum or vascular* or vein* or vessel*).mp.	11139543
18	or/11-17	13473717
19	10 not 18	5245
20	exp evidence based medicine/	904342
21	exp meta analysis/	183265
22	exp Meta-Analysis as Topic/	43341
23	exp "systematic review"/	110642
24	exp controlled study/	5161226
25	exp Randomized Controlled Trial/	821123
26	exp triple blind procedure/	132
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35	exp retrospective study/	1069095
36	exp prospective study/	836601
37	case report/	3441589
38	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3	17709671

	(study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case adj3 report)).mp,pt.	
39	or/20-38	19397581
40	19 and 39	4326
41	limit 40 to ("preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	4252
42	limit 41 to (preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	3857
43	from 42 keep 1-1267	1267
44	(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) adj2 (year or years)).mp.	2161044
45	44 and child*.mp.	744191
46	(adult or adults or "middle age" or "middle aged" or elderly or geriatric*).mp.	12223883
47	40 and (45 or 46)	3101
48	43 or 47	3346
49	remove duplicates from 48	2797

Scopus
TITLE-ABS-KEY(asthma*)
TITLE-ABS-KEY("airway nitric oxide" OR "airway NO" OR "airway oxide" OR "breath nitric oxide" OR "breath NO" OR "breath oxide" OR "breathed nitric oxide" OR "breathed NO" OR "breathed oxide" OR "breathing nitric oxide" OR "breathing NO" OR "breathing oxide" OR "exhaled nitric oxide" OR "exhaled NO" OR "exhaled oxide" OR FeNO OR "lung nitric oxide" OR "lung NO" OR "lung oxide" OR "pulmonary nitric oxide" OR "pulmonary NO" OR "pulmonary oxide" OR "respiration nitric oxide" OR "respiration NO" OR "respiration oxide" OR "respiratory nitric oxide" OR "respiratory NO" OR "respiratory oxide")
TITLE-ABS-KEY(("respired air" W/3 pressure) or ((assess* or evaluat*) W/3 (symptom* or asthma* or control*)) or (breath W/3 measur*) or ACQ or "Asthma Control Questionnaire" or monitor* or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*" or spirometr*)
1 and 2 and 3
TITLE-ABS-KEY(arter* OR blood OR cardiac OR cardial OR heart OR plasma OR plasmas OR serum OR vascular* OR vein* OR vessel*)
4 and not 5
TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3

trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case W/3 report))
TITLE-ABS-KEY(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) W/2 (year or years))
TITLE-ABS-KEY(child*)
TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" or elderly or geriatric*)
6 and 7 and ((8 and 9) or 10)
DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
11 and not 12
PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
#13 and not #14

KQ 1c

Ovid

Database(s): Embase 1988 to 2016 Week 30, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 20, 2016
Search Strategy:

#	Searches	Results
1	exp Asthma/dh, dt, rt, su, th [Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	47695
2	exp asthma/dm, dt, rt, su, th [Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	56442
3	asthma*.mp.	387624
4	(drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or microbicid* or prevent* or radiotherap* or surg* or resect* or operat* or repair* or reconstruction* or therap* or treat*).mp.	24384025
5	3 and 4	249963
6	1 or 2 or 5	261247
7	("airway nitric oxide" or "airway NO" or "airway oxide" or "breath nitric oxide" or	100229

	"breath NO" or "breath oxide" or "breathed nitric oxide" or "breathed NO" or "breathed oxide" or "breathing nitric oxide" or "breathing NO" or "breathing oxide" or "exhaled nitric oxide" or "exhaled NO" or "exhaled oxide" or FeNO or "lung nitric oxide" or "lung NO" or "lung oxide" or "pulmonary nitric oxide" or "pulmonary NO" or "pulmonary oxide" or "respiration nitric oxide" or "respiration NO" or "respiration oxide" or "respiratory nitric oxide" or "respiratory NO" or "respiratory oxide").mp.	
8	exp Eosinophils/	55216
9	exp Eosinophil/	55216
10	exp eosinophil count/	7771
11	exp sputum examination/ or exp sputum/ or exp sputum level/ or exp sputum analysis/	53693
12	exp Bronchoalveolar Lavage Fluid/	66065
13	exp Skin Tests/	109868
14	exp Hypersensitivity/di [Diagnosis]	94630
15	exp sensitization/	49920
16	exp allergy test/	3670
17	exp Immunoglobulin E/	95525
18	(((allerg* or skin or hypersensitivit* or sensitiz*) adj3 test*) or "alveolar lavage" or "bronchial lavage" or "bronchoalveolar lavage" or eosinophil* or expectorate or IgE or "immunoglobulin e" or "lung lavage" or "lung washing" or "pulmonary lavage" or "pulmonary washing" or sputum).mp.	495523
19	or/8-18	619799
20	6 and 7 and 19	4530
21	exp Blood/	2555329
22	blood.fs.	1571711
23	exp Heart/	879900
24	exp Blood Vessels/	1373624
25	exp Heart Diseases/	2263854
26	exp Vascular Diseases/	3255967
27	(arter* or blood or cardiac or cardial or heart or plasma or plasmas or serum or vascular* or vein* or vessel*).mp.	11140330
28	or/21-27	13474504
29	20 not 28	2127
30	exp evidence based medicine/	904342
31	exp meta analysis/	183265
32	exp Meta-Analysis as Topic/	43341
33	exp "systematic review"/	110642
34	exp controlled study/	5161226
35	exp Randomized Controlled Trial/	821123

36	exp triple blind procedure/	132
37	exp Double-Blind Method/	375029
38	exp Single-Blind Method/	59663
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40	exp Placebos/	302126
41	exp Placebo Effect/	9028
42	exp comparative study/	2625586
43	exp Cohort Studies/	1940158
44	exp longitudinal study/	303249
45	exp retrospective study/	1069095
46	exp prospective study/	836601
47	case report/	3441591
48	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case adj3 report)).mp,pt.	17710846
49	or/30-48	19398758
50	29 and 49	1584
51	limit 50 to ("preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	1527
52	limit 51 to (preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	1324
53	from 52 keep 1-652	652
54	(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) adj2 (year or years)).mp.	2161258
55	54 and child*.mp.	744238
56	(adult or adults or "middle age" or "middle aged" or elderly or geriatric*).mp.	12224142

57 50 and (55 or 56)	1050
58 53 or 57	1191
59 remove duplicates from 58	1007

Scopus
TITLE-ABS-KEY(asthma*)
TITLE-ABS-KEY(drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or microbicid* or prevent* or radiotherap* or surg* or resect* or operat* or repair* or reconstruction* or therap* or treat*)
TITLE-ABS-KEY("airway nitric oxide" OR "airway NO" OR "airway oxide" OR "breath nitric oxide" OR "breath NO" OR "breath oxide" OR "breathed nitric oxide" OR "breathed NO" OR "breathed oxide" OR "breathing nitric oxide" OR "breathing NO" OR "breathing oxide" OR "exhaled nitric oxide" OR "exhaled NO" OR "exhaled oxide" OR FeNO OR "lung nitric oxide" OR "lung NO" OR "lung oxide" OR "pulmonary nitric oxide" OR "pulmonary NO" OR "pulmonary oxide" OR "respiration nitric oxide" OR "respiration NO" OR "respiration oxide" OR "respiratory nitric oxide" OR "respiratory NO" OR "respiratory oxide")
TITLE-ABS-KEY(((allerg* or skin or hypersensitivit* or sensitiz*) W/3 test*) or "alveolar lavage" or "bronchial lavage" or "bronchoalveolar lavage" or eosinophil* or expectorate or IgE or "immunoglobulin e" or "lung lavage" or "lung washing" or "pulmonary lavage" or "pulmonary washing" or sputum)
1 and 2 and 3 and 4
TITLE-ABS-KEY(arter* OR blood OR cardiac OR cardial OR heart OR plasma OR plasmas OR serum OR vascular* OR vein* OR vessel*)
5 and not 6
TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case W/3 report))
TITLE-ABS-KEY(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) W/2 (year or years))
TITLE-ABS-KEY(child*)
TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" or elderly or geriatric*)
7 and 8 and ((9 and 10) or 11)
DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
12 and not 13

PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
14 and not 15

KQ 1d

Ovid

Database(s): Embase 1988 to 2016 Week 30, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 20, 2016
Search Strategy:

#	Searches	Results
1	exp Asthma/dh, dt, rt, su, th [Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	47695
2	exp asthma/dm, dt, rt, su, th [Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	56442
3	asthma*.mp.	387624
4	(drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or microbicid* or prevent* or radiotherap* or surg* or resect* or operat* or repair* or reconstruction* or therap* or treat*).mp.	24384025
5	3 and 4	249963
6	1 or 2 or 5	261247
7	("airway nitric oxide" or "airway NO" or "airway oxide" or "breath nitric oxide" or "breath NO" or "breath oxide" or "breathed nitric oxide" or "breathed NO" or "breathed oxide" or "breathing nitric oxide" or "breathing NO" or "breathing oxide" or "exhaled nitric oxide" or "exhaled NO" or "exhaled oxide" or FeNO or "lung nitric oxide" or "lung NO" or "lung oxide" or "pulmonary nitric oxide" or "pulmonary NO" or "pulmonary oxide" or "respiration nitric oxide" or "respiration NO" or "respiration oxide" or "respiratory nitric oxide" or "respiratory NO" or "respiratory oxide").mp.	100229
8	exp Spirometry/	48927
9	exp Peak Expiratory Flow Rate/	17248
10	exp symptom assessment/	5377
11	(("respired air" adj3 pressure) or ((assess* or evaluat*) adj3 (symptom* or asthma* or control*)) or (breath adj3 measur*) or ACQ or "Asthma Control Questionnaire" or monitor* or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*" or spirometr*).mp.	2011281
12	8 or 9 or 10 or 11	2011960
13	6 and 7 and 12	6539
14	exp Blood/	2555329
15	blood.fs.	1571711

16	exp Heart/	879900
17	exp Blood Vessels/	1373624
18	exp Heart Diseases/	2263854
19	exp Vascular Diseases/	3255967
20	(arter* or blood or cardiac or cardial or heart or plasma or plasmas or serum or vascular* or vein* or vessel*).mp.	11140330
21	or/14-20	13474504
22	13 not 21	4246
23	exp evidence based medicine/	904342
24	exp meta analysis/	183265
25	exp Meta-Analysis as Topic/	43341
26	exp "systematic review"/	110642
27	exp controlled study/	5161226
28	exp Randomized Controlled Trial/	821123
29	exp triple blind procedure/	132
30	exp Double-Blind Method/	375029
31	exp Single-Blind Method/	59663
32	exp latin square design/	330
33	exp Placebos/	302126
34	exp Placebo Effect/	9028
35	exp comparative study/	2625586
36	exp Cohort Studies/	1940158
37	exp longitudinal study/	303249
38	exp retrospective study/	1069095
39	exp prospective study/	836601
40	case report/	3441591
41	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case adj3 report)).mp,pt.	17710846
42	or/23-41	19398758

43	22 and 42	3621
44	limit 43 to ("preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	3567
45	limit 44 to (preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	3268
46	from 45 keep 1-897	897
47	(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) adj2 (year or years)).mp.	2161258
48	47 and child*.mp.	744238
49	(adult or adults or "middle age" or "middle aged" or elderly or geriatric*).mp.	12224142
50	43 and (48 or 49)	2627
51	46 or 50	2789
52	remove duplicates from 51	2389

Scopus

TITLE-ABS-KEY(asthma*)

TITLE-ABS-KEY(drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or microbicid* or prevent* or radiotherap* or surg* or resect* or operat* or repair* or reconstruction* or therap* or treat*)

TITLE-ABS-KEY("airway nitric oxide" OR "airway NO" OR "airway oxide" OR "breath nitric oxide" OR "breath NO" OR "breath oxide" OR "breathed nitric oxide" OR "breathed NO" OR "breathed oxide" OR "breathing nitric oxide" OR "breathing NO" OR "breathing oxide" OR "exhaled nitric oxide" OR "exhaled NO" OR "exhaled oxide" OR FeNO OR "lung nitric oxide" OR "lung NO" OR "lung oxide" OR "pulmonary nitric oxide" OR "pulmonary NO" OR "pulmonary oxide" OR "respiration nitric oxide" OR "respiration NO" OR "respiration oxide" OR "respiratory nitric oxide" OR "respiratory NO" OR "respiratory oxide")

TITLE-ABS-KEY(("respired air" W/3 pressure) or ((assess* or evaluat*) W/3 (symptom* or asthma* or control*)) or (breath W/3 measur*) or ACQ or "Asthma Control Questionnaire" or monitor* or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*" or spirometr*)

1 and 2 and 3 and 4

TITLE-ABS-KEY(arter* OR blood OR cardiac OR cardial OR heart OR plasma OR plasmas OR serum OR vascular* OR vein* OR vessel*)

5 and not 6

TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative

analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case W/3 report))
TITLE-ABS-KEY(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) W/2 (year or years))
TITLE-ABS-KEY(child*)
TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" or elderly or geriatric*)
7 and 8 and ((9 and 10) or 11)
DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
12 and not 13
PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
14 and not 15

KQ 1e

Ovid

Database(s): Embase 1988 to 2016 Week 30, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 20, 2016
Search Strategy:

#	Searches	Results
1	("airway nitric oxide" or "airway NO" or "airway oxide" or "breath nitric oxide" or "breath NO" or "breath oxide" or "breathed nitric oxide" or "breathed NO" or "breathed oxide" or "breathing nitric oxide" or "breathing NO" or "breathing oxide" or "exhaled nitric oxide" or "exhaled NO" or "exhaled oxide" or FeNO or "lung nitric oxide" or "lung NO" or "lung oxide" or "pulmonary nitric oxide" or "pulmonary NO" or "pulmonary oxide" or "respiration nitric oxide" or "respiration NO" or "respiration oxide" or "respiratory nitric oxide" or "respiratory NO" or "respiratory oxide").mp.	100229
2	exp Respiratory Sounds/	51820
3	(rhonchi or rhonchus or wheez*).mp.	37161
4	2 or 3	64711
5	exp "Predictive Value of Tests"/	269135
6	(predict* or API).mp.	2747478
7	5 or 6	2747478
8	1 and 4 and 7	499
9	exp Blood/	2555329

10	blood.fs.	1571711
11	exp Heart/	879900
12	exp Blood Vessels/	1373624
13	exp Heart Diseases/	2263854
14	exp Vascular Diseases/	3255967
15	(arter* or blood or cardiac or cardial or heart or plasma or plasmas or serum or vascular* or vein* or vessel*).mp.	11140330
16	or/9-15	13474504
17	8 not 16	282
18	exp evidence based medicine/	904342
19	exp meta analysis/	183265
20	exp Meta-Analysis as Topic/	43341
21	exp "systematic review"/	110642
22	exp controlled study/	5161226
23	exp Randomized Controlled Trial/	821123
24	exp triple blind procedure/	132
25	exp Double-Blind Method/	375029
26	exp Single-Blind Method/	59663
27	exp latin square design/	330
28	exp Placebos/	302126
29	exp Placebo Effect/	9028
30	exp comparative study/	2625586
31	exp Cohort Studies/	1940158
32	exp longitudinal study/	303249
33	exp retrospective study/	1069095
34	exp prospective study/	836601
35	case report/	3441591
36	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case adj3 report)).mp,pt.	17710846

37	or/18-36	19398758
38	17 and 37	247
39	limit 38 to ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	234
40	limit 39 to (infant or preschool child <1 to 6 years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	182
41	from 40 keep 1-31	31
42	(("1" or "2" or "3" or "4" or one or two or three or four) adj2 (year or years)).mp.	1727622
43	42 and child*.mp.	432826
44	(newborn* or neonat* or infant* or toddler*).mp.	2225413
45	38 and (43 or 44)	113
46	41 or 45	117
47	remove duplicates from 46	105

Scopus
TITLE-ABS-KEY("airway nitric oxide" OR "airway NO" OR "airway oxide" OR "breath nitric oxide" OR "breath NO" OR "breath oxide" OR "breathed nitric oxide" OR "breathed NO" OR "breathed oxide" OR "breathing nitric oxide" OR "breathing NO" OR "breathing oxide" OR "exhaled nitric oxide" OR "exhaled NO" OR "exhaled oxide" OR FeNO OR "lung nitric oxide" OR "lung NO" OR "lung oxide" OR "pulmonary nitric oxide" OR "pulmonary NO" OR "pulmonary oxide" OR "respiration nitric oxide" OR "respiration NO" OR "respiration oxide" OR "respiratory nitric oxide" OR "respiratory NO" OR "respiratory oxide")
TITLE-ABS-KEY(rhonchi or rhonchus or wheez*)
TITLE-ABS-KEY(predict* or API)
1 and 2 and 3
TITLE-ABS-KEY(arter* OR blood OR cardiac OR cardial OR heart OR plasma OR plasmas OR serum OR vascular* OR vein* OR vessel*)
4 and not 5
TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case W/3 report))
TITLE-ABS-KEY (("1" or "2" or "3" or "4" or one or two or three or four) W/2 (year or years))
TITLE-ABS-KEY(child*)

TITLE-ABS-KEY(newborn* or neonat* or infant* or toddler*)
6 and 7 and ((8 and 9) or 10)
DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
11 and not 12
PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
13 and not 14

Appendix B. Excluded Studies

Abuzayan, I, Turner, et al. Changes in exhaled nitric oxide after ingestion of L-arginine in children: A pilot study. Pediatric Pulmonology. 2010 March;45(3):236-40. PMID: 2010136401. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Acouetey, Dovi S, Zmirou N, et al. Genetic predictors of inflammation in the risk of occupational asthma in young apprentices.[Erratum appears in Ann Allergy Asthma Immunol. 2013 Aug;111(2):149 Note: Avogbe, Patrice [corrected to Avogbe, Patrice Hodonou]]. Annals of Allergy, Asthma, & Immunology. 2013 Jun;110(6):423-8.e5. PMID: 23706710. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Adar, Sara D, D'Souza, et al. Adopting Clean Fuels and Technologies on School Buses. Pollution and Health Impacts in Children. American Journal of Respiratory & Critical Care Medicine. 2015 Jun 15;191(12):1413-21. PMID: 25867003. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Adema, A Y, Verwey, et al. Effect of a short-term stay in a high altitude clinic. Tijdschrift voor Kindergeneeskunde. 2009;77(1):30-6. The study does not evaluate FeNO

Adisesh, L A, Kharitonov, et al. Exhaled and nasal nitric oxide is increased in laboratory animal allergy. Clinical and Experimental Allergy. 1998;28(7):876-80. PMID: 1998243666. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Akamatsu, Taisuke, Shirai, et al. Effect of switching from salmeterol/fluticasone to formoterol/ budesonide combinations in patients with uncontrolled asthma. Allergology International. 2012 Jun;61(2):323-9. PMID: 22441635. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Akamatsu, Taisuke, Shirai, et al. Switching from salmeterol/fluticasone to formoterol/budesonide combinations improves peripheral airway/alveolar inflammation in asthma. Pulmonary Pharmacology & Therapeutics. 2014 Feb;27(1):52-6. PMID: 23583566. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Akashi, Kenichi, Mezawa, et al. Optimal step-down approach for pediatric asthma controlled by salmeterol/fluticasone: A randomized, controlled trial (OSCAR study). Allergology International. 2016 Jul;65(3):306-11. PMID: 27155753. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Al A, M K, Eames, et al. Exhaled nitric oxide; Relationship to clinicophysiological markers of asthma severity. Respiratory Medicine. 1998 July;92(7):908-13. PMID: 1998294224. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Al A, M K, Howarth, et al. Exhaled nitric oxide levels in exacerbations of asthma, chronic obstructive pulmonary disease and pneumonia. Saudi Medical Journal. 2001 Mar;22(3):249-53. PMID: 11307112. *The study does not have a comparison group (studies must have a comparison group or pre/post design)*

Alcazar N, B, Romero P, et al. Diagnostic performance of the measurement of nitric oxide in exhaled air in the diagnosis of COPD phenotypes. Nitric Oxide - Biology and Chemistry. 2016 01 Apr;54:67-72. PMID: 20160251434. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Ali, May, Khoo, et al. NOS1 polymorphism is associated with atopy but not exhaled nitric oxide levels in healthy children. Pediatric Allergy & Immunology. 2003 Aug;14(4):261-5. PMID: 12911502. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Allen, R W, Mar, et al. Changes in lung function and airway inflammation among asthmatic children residing in a woodsmoke-impacted urban area. Inhalation Toxicology. 2008 February;20(4):423-33. PMID: 2008106146. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Alvarez G, Francisco J, Medina G, et al. [Comparison of the Asthma Control Test (ACT) with lung function, levels of exhaled nitric oxide and control according to the Global Initiative for Asthma (GINA)]. Archivos de Bronconeumologia. 2010 Jul;46(7):370-7. PMID: 20605310. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Alvarez P, M J, Olaguibel, et al. Mannitol versus hypertonic saline: Safety and efficacy of mannitol and hypertonic saline in sputum induction and bronchial hyperreactivity assessment. Chronic respiratory disease. 2015;12(3):197-203. PMID: CN-01084977 NEW. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Amer, M, Cowan, et al. Effect of inhaled beta<inf>2</inf>-agonist on exhaled nitric oxide in chronic obstructive pulmonary disease. PLoS ONE. 2016 01 Jun;11 (6) (no pagination)(e0157019) PMID: 20160431719. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Amimoto, Y, Arakaki, et al. Relationship between compliance with inhaled corticosteroids and changes in the fraction of exhaled nitric oxide during summer camp for asthmatic children. Japanese Journal of Allergology. 2011;60(12):1641-5. The study is not original (commentaries, letters, etc. should be excluded)

Amore, M, Antonucci, et al. Disease Control in Patients with Asthma is Associated with Alexithymia but not with Depression or Anxiety. Behavioral Medicine. 2013 01 Oct;39(4):138-45. PMID: 2013757256. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Anderson, W J, Lipworth, et al. Relationship of mannitol challenge to methacholine challenge and inflammatory markers in persistent asthmatics receiving inhaled corticosteroids. Lung. 2012 October;190(5):513-21. PMID: 2012567692. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Anderson, William J, Lipworth, et al. Does body mass index influence responsiveness to inhaled corticosteroids in persistent asthma? Annals of Allergy, Asthma, & Immunology. 2012 Apr;108(4):237-42. PMID: 22469442. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Ansarin, K, Chatkin, et al. Exhaled nitric oxide in chronic obstructive pulmonary disease: Relationship to pulmonary function. European Respiratory Journal. 2001;17(5):934-8. PMID: 2001232784. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

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Appendix C. Description of Included Studies

Table C.1. Characteristics of the included studies in KQ 1a

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
Arora, 2006[1]	United States, cross section study, low risk of bias.	Reference test; Positive bronchial challenge Histamine broncho-provocation, N= 172	138 asthmatic patients; mean age of 20 years, 47% males. 34 non-asthmatic patients a mean age of 21 years, 59% males.	Histamine challenge used to confirm or refute asthma diagnosis in subjects with compatible symptoms; i.e. used as part of gold standard Dx. PC20 <8 mg/mL.	FeNO at 17 ppb cut-off, compared with histamine broncho-provocation test had sensitivity: 63%, specificity: 59%, PPV: 86%, NPV: 28%. AUC=0.63. FeNO at 20 ppb cut-off, compared with histamine broncho-provocation test had sensitivity: 53%, specificity: 68%, PPV: 87%, NPV: 26%.
		FeNO, N= 172		Measured by NIOX system (Aerocrine AB, Stockholm, Sweden) at a flow rate of 50 mL/sec. FeNO measurement occurred before start of the standard asthma evaluation, including spirometry, to avoid any influence of baseline spirometry on FeNO values.	
Avital, 2001[2]	Israel, longitudinal nonrandomized, outpatient setting, medium risk of bias.	Reference test; Positive bronchial challenge Adenosine-5' monophosphate (AMP) challenge test, N= 71	36 children with mild intermittent asthma Mean age 4.4 years (SD: 0.2). 20 non-asthmatic children with chronic cough with a mean age of 4.2 years (SD: 0.3) and 15 healthy children with a mean age of 5.1 years (SD: 0.2).	Positive test was defined as a clear wheeze heard over the chest by auscultation, a drop in oxygen saturation of 5% or more from baseline, or an increase of >50% over the baseline respiratory rate.	Mild intermittent asthma vs. Chronic cough: Compared to AMP challenge test, FeNO 3.8 ppb had sensitivity 77% and specificity 77%. Mild intermittent asthma vs. healthy children: Compared to AMP challenge test, FeNO 2.9 ppb had sensitivity 88% and specificity 88%.
		FeNO, N= 71		Measured using chemiluminescence analyzer (LR 2000, Logan Research, Rochester, UK). FeNO measured before bronchial challenge. Salbutamol inhalation was administered at end of test ex. beta-agonist was given at end of bronchoprovocation challenge and after FeNO measured.	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
Backer, 2014[3]	Denmark. Retrospective study, outpatient setting, medium risk of bias.	Reference test; Positive bronchial challenge Mannitol challenge test, N= 141	Overall mean age 28.3 years, 41% males, 4% current smokers, 90% atopic.	Positive challenge test when >15% reduction in FEV1. Negative challenge, max dose reached (635 mg). PD15 computed by interpolation.	FeNO at 25 ppb cut-off, compared with mannitol with PD15 <635 mg had sensitivity of 64% and specificity of 87% to diagnose asthma.
		FeNO, N= 141		Aerocrine (NioxMinor, Solna, Sweden) following the recommendations of the ERS and ATS.	
Berkman, 2005[4]	Israel, Cross-sectional study, outpatient setting, low risk of bias.	Reference test; Positive bronchial challenge Adenosine 5 'monophosphate (AMP), N= 85	40 asthmatics Mean age 21.9 years (SD: 1.6), 60% males. 45 healthy subjects Mean age 29.3 years (SD: 2.4), 53.3% males.	Musing Sigma-Aldridge, Rehovot, Israel. The test was positive if AMP 150 < mg/ml.	FeNO 7 ppb vs. AMP had sensitivity 86.5% and specificity 81.5%
		Reference test; clinical diagnosis, N= 85		Determined 24 months after performing FeNO and provocation studies.	FeNO 7 ppb vs. clinical diagnosis had sensitivity 88.9% and specificity 82.5%
		Reference test; Positive bronchial challenge Exercise-induced bronchochonstriction		The test was positive if exercise change FEV_1 >10%.	FeNO 7 ppb vs. Exercise-induced bronchoconstriction had sensitivity 91.3% and specificity 70.1%
		Reference test; Positive bronchial challenge Methacoline challenge, N= 85		Using (Spectrum Chemical Corp, Gardena, CA, USA). The test was considered positive if MCH < 3 mg/ml.	FeNO 7 ppb vs. MCH had sensitivity 66.7% and specificity 72.9%

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
		FeNO, N= 85		Measured using a chemiluminescence analyser (LR 2000, Logan Research, Rochester, UK). Resistance, mouth pressure (5 cm H2O), and flow rate (250 ml/s) Three successive recordings were made and the mean value was recorded.	
Berlyne, 2000[5]	Canada, cross sectional study, outpatient setting, high risk of bias.	Reference test; Combined (Positive bronchial challenge + Bronchodilator response) airway hyperresponsiveness and methacholine challenge test, N= 123	Healthy (N= 50) and patients (N=73) Overall mean age 38.1 years, 42% males, 85% atopic.	Methacholine airway hyperresponsiveness with a PC20 of less than 8 mg/mL if the FEV_1/FVC was 70% or greater or an improvement of the FEV_1 from predicted of 15% or greater after 200 µg of inhaled salbutamol if the FEV_1/FVC was less than 70%.	Compared with airway hyperresponsiveness and methacholine challenge test, FeNO levels of 17.1 ppb had a sensitivity of 81% and a specificity of 90% for diagnosing asthma in patients without steroid treatment. However, the sensitivity and specificity were lower when the patients were taking ICSs (sensitivity and specificity of FeNO at 15.1 ppb were 51% and 86%, respectively.
		FeNO, N= 123		Measured by rapid linear-response chemiluminescence analyzer (Sievers 240, Boulder, Colo) at fixed flow of 45 mL/s. FeNO was not used to diagnose asthma, but to distinguish asthmatics (steroid naive or on ICS) from atopic non-asthmatics, and to distinguish these groups from the healthy nonatopic group.	
Bommarito, 2007[6]	Italy, Cross sectional study, low risk of bias.	Reference test; Clinical Diagnosis European Community Respiratory Health Survey II (ECRHS II)	13 asthmatic, mean age 43.6 years (SD: 0.72), 46.2% males, 23.1% current smokers. 42 controls (rhinitis and atopics)	A short, self-completed questionnaire identical to that used for stage 1 in the ECRHS I. Subjects with 'current asthma' were defined as those reporting asthma in life + at least 1 of these asthma-like symptoms in the last 12 months: wheezing/whistling, tightness in chest, asthma attacks or	Compared with ECRHS II, FeNO > 18.7 ppb had the best combination of sensitivity (69.2%) and specificity (71%), with a positive predictive value of 24% and a negative predictive value of 95% for the diagnosis of asthma.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
		questionnaire, N= 55	17 had rhinitis; mean age 40.6 years (SD: 1.5), 47.1% males, 5.8% current smokers and 25 were atopics; mean age 41 years (SD:1.35), 64% males, 20% current smokers.	treatment for MD-diagnosed asthma.	
		FeNO, N= 55		Measured by offline Chemiluminescent analyzer (model 280; Sievers) at a flow rate of 350 mL/sec. Order of tests, & specifics e.g. beta-agonists witheld, were not specified, but ATS guidelines referenced.	
Cordeiro, 2011[7]	Netherlands, longitudinal nonrandomized, outpatient setting, medium risk of bias.	Reference test; Clinical Diagnosis, N=114	42 in Asthma group Mean age 39 years, (range 7-83), 33% males, 93% atopic. 10% smokers. 72 non-asthmatics mean age 38 years (range 7-87), 40% males, 58% atopic. 10% smokers.	Clinical assessment of the diagnosis of asthma was based on a history of typical respiratory symptoms and an FEV_1 improvement of >12% (of the percent predicted value) and >200 mL or PC20 histamine of ≤8 mg/Ml, according to the Global Initiative for Asthma guidelines. SABA withheld 8 hours, LABA withheld 48 hours	Asthmatic patients had a higher mean FeNO level than healthy controls (44 ppb versus 17 ppb; $p < 0.001$). The ROC curve for FeNO to diagnose asthma showed area under curve (AUC) was 0.88 (CI, 0.80 to 0.95). The highest cutoff sum of sensitivity and specificity was 27 ppb. It had a sensitivity of 78%, specificity of 92%, a PPV of 86% and a NPV of 87% for a diagnosis of asthma. Diagnostic accuracy was 0.86.
		FeNO, N=114		FeNO was measured online at a constant flow rate of 50 mL/s and expressed as ppb. FeNO measurements were performed with the Niox Flex before any PFT done	
Deykin, 2002[8]	United States, Cross sectional study,outpatient setting, medium risk of bias.	Reference test; Positive bronchial challenge Positive Methacoline challenge test, N= 62	34 asthmatic patients, mean age 29.6 years (SD: 1.6), 41% males. 28 healthy individuals, mean age 27.3 years (SD: 1.3), 43% males.	Asthma diagnosed with either a 12% improvement in FEV_1 after inhalation of a β-agonist or a methacholine PC20 of ≤ 8 mg/ml.	Compared to Methacoline challenge test, Offline FeNO 30.7 ppb: sensitivity 70.6%; specificity 75% Offline FeNO 19.2 ppb: sensitivity 64.7%; specificity 67.7% Offline FeNO 13.2 ppb: sensitivity 73.5%; specificity 71.4% Offline FeNO 10.4 ppb: sensitivity 79.4%; specificity 71.4% Offline FeNO 8.7 ppb: sensitivity 66.7%; specificity 71.4%
		FeNO, N= 62		Offline: Measured at a single visit using a chemiluminescence analyzer (model 280; Sievers, Boulder, CO) within 12 hours of collections that made at 50,	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
				100, 200, 350, and 500 ml/second in triplicate. Online: Measured using a NOA 280 (Sievers) at a pressure of 10 mm Hg, the flow through the system was 43, 108, 210, and 250 ml/second.	Online FeNO 30.9 ppb: sensitivity 72.2%; specificity 70.6% Online FeNO 14.4 ppb: sensitivity 66.7%; specificity 70.6% Online FeNO 10.0 ppb: sensitivity 66.7%; specificity 70.6% Online FeNO 9.9 ppb: sensitivity 72.2%; specificity 76.5%
Dupont, 2003[9]	Belgium, Prospective cohort, outpatient setting, medium risk of bias.	Reference test; Combined (Positive bronchial challenge + Bronchodilator response) Airways hyperresponsiveness (PC20) and/or spirometry response to salbutamol, N= 240	160 Asthmatic patients; Mean Age 41 years (SD: 17), 48.1% male, 0% smoker. 80 healthy control; Mean age 43 years (SD: 14), 42.5% male, 0% smoker.	Airways hyperresponsiveness defined as histamine PC20 < 8 mg/mL. Standard spirometric methods to assess bronchodilator reversibility (FEV1 reversibility to beta-2-agonist >12%).	Compared with airways hyperresponsiveness (PC20) and/or spirometry response to salbutamol, the best FeNO cutoff associated with highest accuracy was 13 ppb with: Sensitivity: 85%. Specificity: 80%. PPV: 89.5%. NPV: 89.5%. Accuracy: 0.83. Other cutoffs results were reported in the analysis as well.
		FeNO, N= 240		Flow rate of 200 mL/s using an Eco Physics CLD 700 AL MED chemiluminescence analyzer (Eco Physics; Durnten, Switzerland) adapted for on-line recording. Patients and subjects did not consume any alcohol-containing or caffeinated beverages in the 4 h before the test, nor did they receive inhaled short-acting B2-mimetics in the 8 h prior to the measurements.	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
Florentin, 2014[10]	France, Case-control study, outpatient setting, high risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) clinical diagnosis, Spirometry, Bronchodilator reversibility or work-related specific IgE, N= 178	19 Occupational asthmatics and 159 controls mean age 25 years (SD: 2.9), 56.2% males, 49.4% smokers, 43.3% atopic.	Asthma diagnosis was based on the combination of standardized questionnaire derived from the Epidemiological study on the genetics and environment of asthma, bronchial hyper-responsiveness and atopy (EGEA) study, and undergo clinical specific IgE (sIgE) testing and lung function investigations, including carbon monoxide and spirometry measurements.	Compared to clinical diagnosis, Spirometry, Bronchodilator reversibility or work-related specific IgE; FeNO 8.5 ppb had sensitivity 78.9%; specificity 42.8%. FeNO 10.5 ppb: sensitivity 68.4%; specificity 56%. FeNO 25 ppb: sensitivity 42.1%; specificity 92.4%. FeNO 50 ppb: sensitivity 21%; specificity 98.7%. FeNO 8.5 ppb combined with positive clinical examination had sensitivity 79% and specificity 80.5% in asthma diagnosis.
		FeNO, N= 178		Measured using Niox-Mino Analyser; Aerocrine, Stockholm, Sweden.	
Fortuna, 2007[11]	Spain, Prospective study, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) clinical history and positive Methacholine challenge, N= 57	28 Asthmatic Median age 37 years, range 18-68, 10.7% smokers and 14.3% ex-smokers. 22 Control Mean age 38 years, range 18-64, 14.3% smokers and 10.7% ex-smokers.	Day 1 patient filled in clinical symptom questionnaire and underwent FeNO, spirometry with bronchodilator, & induced sputum. Methacholine challenge test was performed next day – positive if PD20 ≤16 mg/mL.	Compared with clinical history and methacholine challenge test, FeNO at 20 ppb had sensitivity 77%, specificity 64%, PPV 62% and NPV 78% in the diagnosis of asthma. Cutoff that best distinguished between asthmatics and non-asthmatics was FeNO 23 ppb

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		FeNO, N= 57		Aerocrine (NioxMinor, Solna, Sweden) following the recommendations of the ERS and ATS.	
Fukuhara, 2011[12]	Japan, Prospective study, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) Conventional criteria:, N= 61	42 asthmatics; mean age 54.8 years, range 50-59.7, 52.4% males, 7% current smokers, 21.4% former smokers and 71.4% non-smokers. 19 controls; mean age 57.4 years, range 48.5-66.2, 47.3% males, 15.8% current smokers, 21% former smokers and 66.7% non-smokers.	Asthma diagnosis was based on diagnosed by conventional criteria. It includes subjective symptoms and any two positive tests (Airway hyper-responsiveness (AHR) or Bronchodilator reversibility (BDR) or Eosinophil count in induced sputum). Positive bronchodilator reversibility is defined as an increase in FEV_1 of 200 mL and ≥ 12% from baseline after inhalation of a short-acting β-2 agonist. Positive airway hyper-responsiveness was defined as a value <12.5 units. .	Compared to conventional criteria or AHR or BDR or Eos%, FeNO 40 ppb had sensitivity 78.6% and specificity 89.5% in asthma diagnosis.
		FeNO, N= 61		FeNO cutoff levels for diagnosing asthma from 3 prior studies from same authors ~40 ppb. Measured using an online chemiluminescence analyzer (NA623N; Chest MI, Tokyo, Japan) at a constant mouth pressure of 16 cm H2O and a flow of 50 mL/sec.	
Grzelewski, 2014[13]	Poland, Retrospective, cross sectional, outpatient setting, medium risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response) clinical symptoms plus	60.3% asthmatic and 39.7% control. Mean age 10.4 year, 60.4% males.	Diagnosis of asthma was made by allergy specialists based on symptoms of asthma, findings on examination of respiratory system, & improvement in FEV1 ≥12% after administration of salbutamol.	FeNO cutoff of 15.8 ppb, clinical symptoms plus bronchodilator response, had 59% sensitivity and 46% specificity. Overall study showed more helpful data to exclude asthma in schoolchildren with allergic rhinitis or positive specific IgE:

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
		bronchodilator response, N= 3612			70%<NPV<80%
		FeNO, N= 3612		Measured by chemiluminescence analyzer (model 280i nitric oxide analyzer; Sievers, Boulder, CO) t flow rate (50 ml/ sec) As a standard procedure in Allergy outpatient clinic, sequence of tests was: FeNO, Rint, whole body plethysmography, spirometry.	
Heffler, 2006[14]	Italy, prospective study, outpatient setting, low risk of bias.	Reference test; Combined (Positive bronchial challenge + Bronchodilator response) Positive Methacoline challenge (PD20) or Bronchial reversibility, N= 48	Patients referred to Specialty Clinic with persistent rhinitis & lower airways symptoms. 18 asthmatic, mean age 42.33 years, range 17–69, 50% males, All nonsmokers, 77.8% atopic. 30 healthy subjects, mean age 38.73 years, range 11–75, 40% males, All nonsmokers, 70% atopic.	Asthma diagnosed with either a 12% improvement in FEV_1 after inhalation of a β-agonist or a methacholine PC20 of $\leq$ 8 mg/ml.	Compared with Methacholine challenge test, the cut-off point of FeNO 36 ppb was associated with the highest combination of specificity 60.0% and sensitivity (77.8%), resulting in a NPV of 81.8% and in a PPV of 54%. All other cutoffs results were reported in the analysis.
		FeNO, N= 48		Measurement after mouthwash using a chemiluminescence analyser (NiOX, Aerocrine AB, Solna, Sweden) calibrated with a certified FeNO calibration gas mixture at a flow rate of 50 ml/sec.	
Henriksen, 2000[15]	Norway, cross sectional study, outpatient setting, high risk of bias.	Reference test, Combined (Clinical Diagnosis +Positive bronchial challenge)	Suspected asthma (N=138) Mean age 16.3 years, 44% males, 21% Smokers, BMI 22.5 Kg/m^2.	Methacholine reactivity defined as >20% drop FEV1 (PD20). If baseline spiro showed obstruction, broncho-dilator response defined as >15% improvement in FEV1. A large-scale epidemiological survey (Young Helseundersùkelsen i Nord-	52% of the suspected asthmatics and 20% of the control subjects had elevated levels of FeNO (>8 ppb). 45% of the suspected asthmatics and 11% of the control subjects had elevated levels of FeNO (>11

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
		Survey and methacholine challenge test, N= 331	Control subjects (N= 193) Mean age 16 years, 46% male, 13% smokers, BMI 21.9 Kg/m^2.	Trùndelag (Health Survey in NorthTrùndelag; HUNT). It was conducted by the Norwegian State Institute of Public Health.	ppb).
		FeNO, N=331		Measured by LR 2000 NO gas analyzer (Logan Research Ltd, London, UK). The sampling flow rate was 250 mL/min at One visit.	
Ishizuka, 2011[16]	Japan. Cross sectional study, outpatient setting, high risk of bias.	Reference test; Clinical Diagnosis European Community Respiratory Health Survey (ECRHS) questionnaire, N= 584	Mean age 19.6 years; range 18-24 years, 46% males.	Japanese version of the ECRHS questionnaire.	FeNO at 38 ppb cut-off, compared with ECRHS, had sensitivity of 87% and specificity of 74%.
		FeNO, N= 584		Measured using an offline kit produced by the Center for Environmental Information Science (Tokyo, Japan) expiratory flow rate is adjusted to 50 mL/sec.	
Jerzynska, 2014[17]	Poland. Cross sectional study, outpatient setting, high risk of bias	Reference test; Combined (Clinical Diagnosis + Bronchodilator response) clinical symptoms and Spirometry, N= 1767	1053 asthmatic and 714 controls. Mean age 11.2 years, 59.3% males, 64.6% atopic.	Pulmonary function testing was done with a Master Screen unit (Erich Jaeger Gmbh-Hochberg, Germany). An improvement in the pre-bronchodilator FEV_1 > 12% after administration of salbutamol (200 ug) in all the patients considered diagnostic.	For patients with atopy and allergic rhinitis (389 patients), FeNO at 23 ppb cut-off had: sensitivity: 90% (95% CI: 68 to 98%), specificity 52% (95% CI: 42 to 61%), PPV 25% (95% CI: 16 to 37%), and NPP: 97% (95% CI: 88 to 99%).
		FeNO, N= 1767		Using a chemiluminescence analyzer (model 280i nitric oxide analyzer; Sievers, Boulder, CO, USA) provides on-line continuous measurement of	

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				NO in a single exhalation with a detection range of 0.1–500 ppb, and exhaled at a constant flow rate (50 mL/s) from total lung capacity to residual volume without breath holding.	
Katsoulis, 2013 [18]	Greece, longitudinal nonrandomized study, outpatient setting, medium risk of bias.	Reference test; Positive bronchial challenge methacholine challenge test, N =122	112 symptomatic patients, mean age of 25 years, 85% males, 30% smokers, 46% atopic.	PD20 of methacholine <800 µg was considered diagnostic for asthma.	FeNO at 32 ppb cut-off, compared with Methacholine with PD20 <800 µg had sensitivity of 47% and a specificity of 85%, AUC = 0.691. In smokers, FeNO at 11 ppb was associated with a sensitivity of 85% and a specificity of 5%, AUC = 0.625. In atopic patients: FeNO at 26 ppb was associated with a sensitivity of 55% and a specificity of 85%, AUC = 0.677.
		FeNO, N =122		Measured by (NIOX MINO, airway inflammation monitor; Aerocrine, Solna, Sweden) that provides measurements at 50 ml/sec exhalation flow rate.	
Kostikas 2008 [19]	Greece. Cross sectional study, medium risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) clinical diagnosis, bronchodilator response and bronchial challenge, N= 149	63 asthmatics mean age 21.6 years (SD: 2.7), 53.9% males, 36.5% smokers. 86 controls (57 rhinitis and 29 with non-specific symptoms) 57 with rhinitis; mean age 21.8 years (SD: 3), 33.3% smokers. 29 non-specific symptoms; mean age 22.1 years	Diagnosis of asthma made after FeNO measurements, based on evaluation by a respiratory physician blinded to FeNO results using prespecified criteria: Hx of relevant lower respiratory tract symptoms, along with 1 of: bronchodilator response (increase in FEV1 >12% and >200 mL) or positive methacholine bronchial challenge test, or clinical and spirometric response to a 4-week trial ICS.	In comparison with bronchodilator response and bronchial challenge, FeNO values >25 ppb had specificity 90% for the diagnosis of asthma in all study groups; specificity rises further to approximately > 95% for FeNO values > 30 ppb. In contrast, a cut-off point > 10 ppb presents sensitivity of 85% in the whole study group, rising to approximately 95% in nonsmokers. All cutoffs results are reported in detailed in the analysis as well.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
		FeNO, N= 149	(SD: 3.1), 37.9% smokers.	FeNO was measured once per month, using an exhaled NO (eNO) monitoring system NIOX (Aerocrine, Solna, Sweden) via chemiluminescence according to ATS guidelines at 50 mL/sec exhalation flow rate.	
Lemiere, 2010 [20]	Canada and Belgium, Cross sectional study, low risk of bias.	Reference test; Positive bronchial challenge Specific inhalation challenges (SICs) , N= 43	24 Occupational asthmatics mean age 40.5 years (SD: 10.1) 76.9% males, 38.4% current smokers, 65.4% atopic.	SIC was considered positive if a reproducible fall in FEV 1 of 20% or more occurred after exposure to the offending agent along with a characteristic pattern of an asthmatic reaction.	In comparison with SICs, 10 ppb change in FeNO between baseline and 7 hours post-exposure had sensitivity: 21% and specificity 87.5%. In comparison with SICs, 10 ppb change in FeNO between baseline and 24 hours post-exposure had sensitivity: 36.8% and specificity 81.2%.
		FeNO, N= 43	19 non-asthmatics mean age 44.8 years (SD: 10.8) 63.4% males, 26.8% current smokers, 53.8% atopic.	Canada; measured at multiple visits using offline Chemiluminescent analyzers (280i Sievers; GE; Boulder, CO). Belgium; measuredy at multiple visits using an online (NiOX; Aerocrine AB; Solna, Sweden). Sputum cell counts & FeNO were collected at end of control day and at 7 hours and 24 hours after exposure to offending agent.	
Malinovschi , 2012 [21]	Denmark, Cross sectional study, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) Methacoline challenge test	96 asthmatic patients mean age of 32.7 years, 40.6% males, 53.1% ever smoked. 186 symptomatic non-asthmatic patients mean age of 32.7 years,	All subjects were interviewed by a respiratory specialist who diagnosed asthma based on presence of compatible Sx + at least 1 of following 1) Airway hyper-responsiveness to methacholine < 8.0 µmol. 2) At least 250 ml increase in FEV1 after bronchodilator. 3) Daily use of systemic steroid, ICS, or inhaled beta2-agonist. 4) Asthma symptoms during but not	Non-smokers (N= 108): In comparison with Methacoline challenge test or asthma symptoms, FeNO at 15 ppb cut-off had a sensitivity of 77.8%, a specificity of 63.5%, PPV of 60%, NPV 80%, AUC of 0.72. Ex- Smokers (N= 62): FeNO at 22 ppb cut-off had a sensitivity of 63.2%, a specificity of 86.1%,

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
		or asthma symptoms, N=282	39.8% males, 64.1% ever smoked.	outside pollen season if patient had allergic rhinitis.	PPV of 67%, NPV 84%, AUC of 0.74. Current smokers (N= 112): FeNO at 17 ppb cut-off had a sensitivity of 56.3%, a specificity of 82.5%, PPV of 57%, NPV 82%, AUC of 0.70.
		FeNO, N=282		Measured by using an online technique at a exhalation flow-rate of 50 mL/s, based on electrochemical sensor (NIOX Mino, Aerocrine AB, Solna, Sweden) before any lung function tests.	
Martin, 2016 [22]	United Kingdom, longitudinal nonrandomized, high risk of bias.	Reference test; Combined (Clinical Diagnosis + Positive bronchial challenge) clinical diagnosis and positive bronchial challenge test, N= 74	28 asthma patients, median age 29 years; range 18-70, 39% males, 17.9% current smoker, 14.3% ex-smoker, 14.3% atopics (eczema). 46 non asthmatic, median age 22 years; range 18-73, 50% males, 10.9% current smokers, 19.6% ex-smokers.	Diagnosis was made if reversibility of ≥12% and ≥200 mL in FEV_1, after inhalation of 400 µg salbutamol, or methacholine (PC20) of ≤8 mg/mL in adult patients with respiratory symptoms suggestive of asthma who were thought to require ICS by their physician	The ROC curve to assess the utility of baseline FeNO level as a diagnostic test for asthma had an area under the curve (AUC) of 0.62 (p=0.09). However, ROC curve for baseline FeNO level as predictor of ICS response after 4 weeks had AUC of 0.89 (p<0.0001). Optimal FeNO cut-off point for predicting non-response to ICS was <27 ppb (NPV 93%) & for predicting response was >33 ppb (PPV 92%).
		FeNO, N= 74		Measured by (NIOX MINO; Aerocrine, Tolna, Sweden).	
Matsunaga, 2011 [23]	Japan, Cross sectional study, outpatient setting, high risk of bias.	Reference test; Clinical Diagnosis medical history, N= 366	142 asthmatic patients mean age of 41.5 years, 49% males, 37% current smokers.	Asthma was diagnosed based on presence of significant airway reversibility and/or airway hyper responsiveness during the 6 months follow up period. (cutoffs not specified)	FeNO at 22 ppb cut-off, compared with medical history had sensitivity 90.8%, specificity 83.9% and AUC 0.896.
		FeNO, N= 366	224 healthy controls mean age of 39.4 years, 44% males, 23% current smokers.	Measured by online electrochemical nitric oxide analyzer (NIOX MINO; Aerocrine AB, Solna, Sweden) at a constant flow rate of 50 mL/sec.	

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Menzies, 2007 [24]	Scotland, Prospective study, high risk of bias.	Reference test; clinical diagnosis, N= 151	101 asthmatic patients, mean age 48.5 years (SD: 1.29), 46.5% males. 50 healthy volunteers, mean age 35.6 years (SD: 1.70), 36% males.	Patients known to have persistent mild-to-moderate asthma from clinical trials database.	In comparison to clinical diagnosis, FeNO (MINO) at 13 ppb had sensitivity 83.2%, specificity 27%, and the AUC was 0.654. In comparison to clinical diagnosis, FeNO (NIOX) at 12.5 ppb had sensitivity 83.2%, specificity 27% and the AUC was 0.619
		FeNO (NIOX device), N= 151		Measured three times at one visi by laboratory-based analyzers (NIOX; Aerocrine AB) at a flow rate of 50 mL/sec. Average was taken for analysis.	
		FeNO (MINO device), N 101		Single measurement at one visit by portable nitric oxide analyzer (MINO; Aerocrine AB; Smidesva¨gen, Sweden) at a flow rate of 50 mL/sec.MINO measurement was always taken after NIOX.	
Miedinger, 2007 [25]	Switzerland, longitudinal nonrandomized study, medium risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response) Clinical diagnosis and Airway hyperresponsiveness (AHR), N= 101	14 asthmatics and 87 healthy controls. Mean age 41 years, range 23 to 64, All male firefighters, 33% current smokers.	Asthma was defined as respiratory symptoms and a history of wheezing not restricted to the last 12 months combined with provocative dose of methacholine causing a 20% fall in FEV1 (PD_{20}) and/or provocative dose of mannitol causing a 15% fall in FEV1 (PD_{15})	FeNO at 20 ppb vs. Clinical diagnosis and AHR: sensitivity 60%; specificity 55%. FeNO at 47 ppb vs. Clinical diagnosis and AHR: sensitivity 33%; specificity 94%. FeNO at 20 ppb vs. PD15: sensitivity 64%; specificity 59%. FeNO at 47 ppb vs. PD15: sensitivity 42%; specificity 96%.
		Reference test; Positive bronchial challenge Mannitol challenge (PD15) , N= 101		If the FEV_1 fell by 10% based on the FEV_1, the dose producing this fall was repeated. The challenge was stopped if the FEV_1 fell by 15%, or when the maximum dose had been administered.	
		FeNO, N= 101		Measured by Nitric oxide analyzer (NIOX; Aerocrine AB; Solna, Sweden)	

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				at a flow rate of 0.045 to 0.055 L/sec.	
Miedinger, 2009 [26]	Switzerland, Cross sectional study, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Positive bronchial challenge) clinical diagnosis and mannitol bronchial provocation test, N= 235	42 asthmatics. All males, Age range 18-19 years, 38% current smokers. 187 non- asthmatics All males, Age range 18-19 years, 33% current smokers.	Asthma was diagnosed by a military physician not involved in this study per the medical record, results of bronchial provocation test (methacholine and mannitol), current respiratory symptoms and use of asthma medication. All subjects administed the validated German version of a specific respiratory disease questionnaire originally used in the SAPALDIA study. Methacholine challenge was positive if FEV1 >20% decline (PD20)at dose of ≤2mg. Mannitol bronchoprovocation was positive if there was a decline in FEV1 >15% from baseline, or a 10% incremental decline between consecutive doses.	Compared to clinical diagnosis and mannitol bronchial provocation, FeNO 36.5 ppb (N=45) had sensitivity 36%, specificity 84%, PPV 33% and NPV 86%. FeNO 20 ppb: sensitivity 57%, specificity 62%, PPV 25% and NPV 67%.
		FeNO, N= 235		Performed prior to spirometry, using a device with a built-in biofeedback mechanism (NIOX MINO, Aerocrine AB, Solna, Sweden) at a flow rate of 50 mL/sec.	
Munnik, 2009 [27]	Netherlands, Cross sectional study, outpatients setting, medium risk of bias.	Reference test; Positive bronchial challenge histamine (PD20) test, N= 362	140 asthmatics Mean age 45 years (SD: 11). 222 non-asthmatic Mean age 51 years (SD: 12).	. Airway hyperresponsiveness was defined as a PC20 of <8 mg/ml.	The AUC ROC for FeNO to diagnose asthma is 0.826 (p value <0.001).

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
		FeNO, N= 362		FeNO measured prior to other maneuvers that day. Short and long acting bronchodilators held for 8 and 12 hours respectively pre-testing. Measured at one visit by ECO MEDICS CLD 88 in conjunction with DFeNOX 88 (Eco Physics, Durnten, Switzerland) (center# 1) and by Niox Mino device (Aerocrine, New Providence, United States of America) (center# 2), both using an exhalation flow of 50 ml/sec.	
Nayak, 2013 [28]	India. Cross sectional study, outpatient setting, medium risk of bias.	Reference test; Clinical Diagnosis spirometry, N= 100	55 asthmatic patients, 51% on inhalational steroids, mean age of 45.2 years; range of 12-82 years, 42% males 45 controls, mean age of 48.5 years; ranges 16-76 years, 49% males	Asthma diagnosis and categorization based on GINA 2009 guidelines – symptomatology, FEV1 and post bronchodilator reversibility. P. K. Morgan spirometry and pulmonary function tests were done by a trained technician as per ATS standard guidelines.	FeNO at 8 ppb cut-off, compared with spirometry had sensitivity of 72% and specificity of 88%. The mean FeNO levels were significantly higher in both steroid treated cases (15.7 ppb) and steroid naïve cases (41.5 ppb) as compared with controls (14.4 ppb).
		FeNO, N= 100		Three FeNO measurements were recorded for each patient using chemiluminescence NO-analyser. Repeat measurements were performed until the three values agreed to 10% of the mean. Mean value of the 3 measurements was recorded as final. FeNO level of < 8.0 ppb was taken as normal.	
Pedrosa, 2010 [29]	Spain, cross sectional study, outpatient setting, low risk of bias.	Reference test; Positive bronchial challenge Methacholine challenge (MCH), N= 114	35 asthmatics and 79 healthy controls. mean age 34 years (SD: 13) 62.6% males, 14.8% current smokers, 87% atopic	Asthma was diagnosed on the basis of consistent symptoms and a positive methacholine challenge. A positive methacholine challenge was defined as a decrease in FEV1 from a baseline of 20% or higher obtained after methacholine inhalation.	Compared to MCH, FeNO 40 ppb had sensitivity 74.3% and specificity 72.5% in asthma diagnosis.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
		FeNO, N= 114		Measured just before the methacholine challenge. Measured using a portable nitric oxide analyzer (NIOX MINOTM; Aerocrine, Solna, Sweden), at a flow rate of 50 mL/sec.	
Perez Tarazona, 2011 [30]	Spain, cross-sectional study, outpatient setting, low risk of bias.	Reference test; Clinical Diagnosis Spirometry, N=144	57 asthmatics mean age 10.4 years (SD: 2.1), 70% males, mean weight 39.4 Kg (SD: 12,7). 87 controls mean age 10.4 years (SD: 2.1), 47% males, mean weight 40.4 Kg (SD: 13,9).	Diagnosis based on clinical history consistent with asthma (history of recurrent cough, wheeze or breathing difficulties with a good response to bronchodilator treatment.) and pulmonary function testing using Portable spirometer Datospir Micro A® (Sibelmed, Barcelona)	Compared to spirometry, the best FeNO cutoff was 19 ppb to diagnose asthma with sensitivity 91.4% and specificity 87.2%. other cutoffs were reported in the analysis.
		FeNO, N=144		Measured for multiple attempts at one visit Using a chemiluminescence analyser (NiOX , Aerocrine AB, Solna, Sweden). Two values of FeNO were obtained and the average was used for the analysis.	
Pizzimenti, 2009 [31]	Italy, prospective study, outpatient clinic, medium risk of bias.	FeNO, N= 156	14 asthmatics and 142 controls. 41% males, 47.4% atopic, 9% smokers	Bronchial hyperresponsiveness (PD20 FEV-1<800 mu) in asthmatic patients.	Compared with methachoine challenge test and spirometry, FeNO cut-off value of 55 ppb had the best combination of sensitivity of 78%, and specificity of 88%, for diagnosis asthma. AUC was 0.85.
		Reference test; Combined (Clinical Diagnosis + Positive bronchial challenge) Methacoline challenge test and spirometry, N= 156		Measured by portable analyzer NIOX-MINOA (Aerocrine AB, Solna, Sweden).	

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Ramser, 2008 [32]	Switzerland, Cross sectional study, outpatient setting, low risk of bias.	Reference test; Positive bronchial challenge Exercise induced bronchoconstriction (EIB) , N= 169	84 asthmatics and 50 healthy controls. Age range 6-16 years, 57% males, 61% Atopic.	The protocol was FeNO and exercise bronchoprovocation, if exercise provocation negative or could not exercise they then had methacholine challenge. EIB was defined by a decrease in FEV_1 by ≥15% of baseline.	FeNO at 10 ppb vs. MCH: sensitivity 83%; specificity 19% FeNO at 20 ppb vs. MCH: sensitivity 61%; specificity 62% FeNO at 30 ppb vs. MCH: sensitivity 41%; specificity 74% FeNO at 40 ppb vs. MCH: sensitivity 29%; specificity 85% FeNO at 50 ppb vs. MCH: sensitivity 26%; specificity 91% FeNO at 10 ppb vs. EIB: sensitivity 86%; specificity 32% FeNO at 20 ppb vs. EIB: sensitivity 64%; specificity 66% FeNO at 30 ppb vs. EIB: sensitivity 50%; specificity 78% FeNO at 40 ppb vs. EIB: sensitivity 36%; specificity 86% FeNO at 50 ppb vs. EIB: sensitivity 32%; specificity 88%
		Reference test; Positive bronchial challenge Methacholine challenge (MCH), N= 169		MCH challenge was done according to ARS/ETS guidelines using a panel of incremental dosages of MCH, and a dose of 1.8 mg was defined as threshold of PD20 to differentiate normal airway responsiveness from bronchial hyperresponsiveness.	
		FeNO, N= 169		FeNO measured prior to other pulmonary testing. One visit measurement using an online Chemoluminescence analyzer (CLD 77 AM; 191 192 M. RAMSER ET AL. Eco Physics, Durnten, Switzerland) at a flow rate of 50 mL/sec.	
Sachs-Olsen, 2010 [33]	Norway, prospective control study, outpatient setting, low risk of bias.	Reference test; clinical diagnosis, N= 227	31 asthmatics (17 with current asthma (mean age 10.7 years (SD: 0.8) and 14 with allergic asthma (mean age 10.8 years (SD: 0.8). 196 healthy patients (mean age 10.9 years (SD: 0.7).	Gold standard was clinicaldiagnosis based on definition below. Asthma diagnosis if 2 out of 3 criteria were met; 1) Dyspnea, chest tightness and/or wheezing. 2) Doctor's diagnosis of asthma. 3) Use of asthma medication. Allergic asthma defined as asthma in the presence of allergic sensitization.	Compared to clinical diagnosis, FeNO 15.6 ppb: sensitivity 35% and specificity 94%. FeNO 16.7 ppb: sensitivity 32% and specificity 96%. FeNO 20.4 ppb: sensitivity 26% and specificity 97%.
		FeNO, N= 227		Measured online by the single breath technique, with a EcoMedics Exhalyzer CLD 88sp with DFeNOX 88 (ECO MEDICS AG, Duernten, Switzerland). NO-free air was inhaled to near total lung capacity, followed	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
				immediately by full exhalation at a constant flow of 50 ml/s, expiratory pressure was maintained between 5–20 mmHg to close the soft palate. FeNO was recorded as mean value from three (alternatively two in a few patients) successive reproducible plateaus.	
Sato, 2008[34]	Japan, longitudinal nonrandomized, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) Clinical diagnosis, airway hyper-responsivenes s or Bronchodilator reversibility, N= 71	48 asthmatics; 30 bronchial asthmatics had mean age of 55.5 years, range 48.9 to 62.5, 66.6% males and 26.6% smokers. And 18 had cough variant asthma with mean age 48.2 years, range 39.4-57.0, 38.8% males and 16.7% smokers. 23 Non asthmatics; 8 had eosinophilic bronchitis with mean age of 45.3 years, range 33.3-57.2, 50% males and 12.5% smokers. And 15 had other disorders with mean age of 55.5 years, range 47.5-63.5, 54% males and 33.3% smokers.	Spirometry measured using Chestac-11 Cyber S-type; Chest MI, Inc., Tokyo, Japan). Positive bronchodilator reversibility is defined as an increase in FEV_1 of 200 mL and ≥ 12% from baseline 20 min after inhalation of a short-acting β-2 agonist. Airway hyper-responsiveness (Methacoline challenge test) was defined as a value <12.5 units. The total cumulative dose of methacholine at the end of inhaling the highest dose was 50 units.	Compared to clinical diagnosis, airway hyper-responsiveness or bronchodilator reversibility, FeNO 38.8 ppb had sensitivity 79.2% and specificity 91.3% in diagnosing asthma.
		FeNO, N= 71		Measured before other pulmonary testing. Measured three times at a single visit with a chemiluminescence analyzer (Kimoto, Osaka, Japan) wuith exhalation constant flow of 50 mL/sec.	
Schleich, 2012[35]	Belgium, cross section study, medium risk of	Reference test; Positive bronchial	Overall mean age of 41 years, 42% males,	Methacholine challenges were performed according to a slightly adapted Cockroft's tidal breathing	FeNO at 34 ppb cut-off, compared with Methacholine challenge test had: sensitivity: 35.4%, specificity:

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
	bias.	challenge Methacholine challenge, N= 174	34% current smokers, 48% atopic.	method. Asthma was diagnosed based on airway hyper responsiveness demonstrated by inhaled concentration of Methacholine provoking a 20% fall in FEV_1 of less than 16 mg/m.	95.4%, positive predictive value: 88%, negative predictive value: 62%, AUC = 0.62.
		FeNO, N= 174		Measured by chemiluminescence (NIOX, Aerocrine, Sweden), at a flow rate of 50 ml/sec.	
Schneider, 2013 Schneider, 2014 [36, 37]	Germany. Prospective diagnostic study, outpatient setting, medium risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) Whole body plethysmography (WBP) and bronchial provocation, N= 388	154 asthmatic patients; mean age 40.5 years, 40.9% males, 48.7% ever smoked. 234 healthy; Mea age 44.6 years, 39.3% males, 42.3% ever smoked. After 1 year of follow up 81 lost to follow up, 83 had asthma; mean age of 41.9 years, 40% males, 43.3% ever smoked. 219 had no asthma; mean age of 45.5 years, 40.6% males, 48.4% ever smoked.	Spirometry were performed, patients with FEV_1 < 80% predicted received salbutamol with an additional WBP investigation 20 min later. Asthma if FEV_1/VC was $\leq$0.70, clinical symptoms and history fitted and the change in FEV_1 was $\geq$ 12% compared with baseline and $\geq$ 200 mL and lung function returned to the predicted normal range.	FeNO at 20 ppb cut-off, compared with WBP and bronchial provocation had sensitivity: 60%, specificity: 63%, PPV: 51%, NPV: 71%. FeNO at 25 ppb cut-off, compared with WBP and bronchial provocation had sensitivity: 49%, specificity: 75%, PPV: 56%, NPV: 69%. After 1 year of follow up: FeNO at 26 ppb cut-off, compared with bronchial provocation had sensitivity: 47%, specificity: 73.1%, PPV: 39.8%, NPV: 78.4, AUC: 0.603
		FeNO N= 388		FENO measured prior to other pulmonary testing. Measured by (NioxMino, Aerocrine, Solna, Sweden) at a flow rate of 50 mL/s, prior to body plethysmography and bronchial provocation.	
Schneider, 2009[38]	Germany, Prospective study, low risk of bias.	Reference test; Combined (Positive bronchial challenge + Bronchodilator response)	160 patients. mean age 43.9 years, 45% males. 75 asthmatics; Mean age 38.7 years (SD:15.1),	Patients with FEV_1 < 80% of predicted received a bronchodilation test with an additional performance of whole body plethysmography (WBP) 20 minutes after inhaling salbutamol. An incomplete bronchodilator response was stated if the bronchodilation	Compared with a 20% fall of FEV_1 after inhaling methacholine concentration $\leq$ 4 mg/ml, FeNO 12 ppb (N=34): sensitivity 90%, specificity 25%, PPV 40% and NPV 81%.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
		Bodyplethysmography and Bronchial Provocation, N= 160	41% males, 40% ever smokers. 85 controls as following; 25 COPD, 8 had an overlap of COPD and asthma, and 52 had no Obstructive airway disease; 65.8% ever smokers.	response was ≥ 12% as compared to baseline and at least 200 ml and lung volumes remained below predicted. An asthma diagnosis was made when there was a 20% fall in FEV_1 from the baseline value (PC20) after inhaling methacholine step wise until the maximum concentration (16 mg/mL)	Compared with a 20% fall in FEV_1 from the baseline value (PC20) after inhaling methacholine concentration ≤ 16 mg/ml, FeNO 46 ppb (N=30): sensitivity 32%, specificity 93%, PPV 80% and NPV 61%. FeNO 76 ppb (N= 11): sensitivity 13%, specificity 100% and PPV 100%. In non-smokers (N=110), FeNO 46 ppb had sensitivity 34% and specificity 94%. PPV increased up to 88% and NPV was 52%. FeNO 65 ppb showed specificity of 100% and PPV of 100%. Other cutoffs results are reported in detailed in the analysis as well.
		FeNO, N= 160		Measured by NioxMino® analyzer at a mouth flow rate of 50 mL/sec over ten seconds and a pressure of 10 cm H2O as per guideline recommendation.	
Sivan, 2009 [39]	Israel, Prospective study, outpatient clinic, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response) Clinical Diagnosis and bronchodilator response, N= 150	69 Asthmatics mean age 12.6 years, 58% males. 44 healthy controls, mean age 12 years, 55% males.	Asthma was diagnosed by use of conventional clinical criteria and was based on the patient's history of 2 or more clinical exacerbations of wheezing documented by a physician, dyspnea, or cough relieved by bronchodilators, documented variability in FEV_1> 15% in response to bronchodilators at any time during the follow-up period (reversibility), or documented variability in FEV_1> 15% over time with or without controller medications: inhaled corticosteroids (ICS) or montelukast.	In comparison with clinical diagnosis and bronchodilator response, FeNO at 19 ppb was the best cutoff in the diagnosis of asthma with sensitivity 86% specificity 89%, PPV 92% and NPV 80%. Other cutoffs results are reported in the analysis. Eos at 2.7% ppb was the best cutoff in asthma diagnosis with sensitivity 85% and specificity 89%.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
		FeNO, N= 150		One visit measurement using Chemiluminescence analyzer (Eco Physics CLD88, NO chemiluminescence analyzer; EcoMedics AG, Duernten, Switzerland) and the Denox 88 NO free supplier module (EcoMedics AG) with online recording, during a single breath exhalation. Test was repeated until 3 reproducible FeNO values were obtained, and the average was recorded.	FeNO at 19 ppb combined with Eos at 3% showed the best asthma diagnosis value with sensitivity 87% and specificity 89%.
Smith 2004 [40]	New Zealand, prospective study, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response) relevant symptom history, bronchodilator reversibility and bronchial hyperresponsiveness, N=47	17 asthmatics mean age 41.6 years, range 9–72, 53% males. 30 healthy controls mean age 31.8 years, range 9–64, 37% males.	Diagnosis of asthma was based on 1/:Relevant symptom history provided using American Thoracic Society criteria.and 2/Positive hypertonic saline was defined as a 15% fall in FEV1 (PD15) of less than 20 ml. and /or 3/Positive bronchial reversibility defined as an increase in FEV1 of 12% or greater from baseline 15 minutes after inhaled albuterol.	Compared with symptom history, bronchodilator reversibility and bronchial hyperresponsiveness, FeNO > 20 ppb had sensitivity 88% and specificity 79% in asthma diagnosis.
		FeNO, N=47		FENO was measured before any forced expiratory maneuvers. Measured at three visits at two exhalation flow rates (50 and 250 ml/second). FeNO levels were read at the first NO plateau for the flow rate of 50 ml/second and at the end-of exhalation carbon dioxide plateau for the 250 ml/second.	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
Thomas, 2005 [41]	Australia, cross-sectional study, high risk of bias.	Reference test; Positive bronchial challenge (Hypertonic Saline Challenge), N= 107	Mean age 14.7 years (SD: 2.3), 57.1% males.	Asthma was defined a priori as an either one symptom of asthma or a PD15 to saline which was defined as a provocative dose of 4% saline to cause a 15% fall in FEV_1 was calculated by linear interpolation (PD15).	FeNO at 7 ppb cut-off, compared with hypertonic saline challenge test at PD15 had a positive predictive value of 54%, and a negative predictive value of 83%. If more than one symptom defined a diagnosis of asthma, FeNO positive predictive value was 63%, negative predictive value was 69%, sensitivity was 47% and specificity was 93%.
		FeNO, N= 107		using a chemiluminescent technique, FeNO was measured off-line by using a 2-L gasimpermeable bag, and the samples were analyzed within 6 hours on a Dasibi oxides of nitrogen analyzer (Model 2107 Dasibi Corporation, Glendale, CA, USA)	
Travers, 2007 [42]	New Zealand, cross sectional study, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response) clinical diagnosis and bronchodilator response, N= 258	70 asthmatics and 193 healthy subjects. Mean age 56.2 years (SD: 12.9), 52.8% males. 11.9% current smokers, 42.4% Ever smokers.	Physician diagnosis of asthma and symptoms in the previous 12 months or physician diagnosis of asthma and inhaler use in the previous 12 months or an increase in FEV_1> 15% compared with baseline after bronchodilator administration or documented diurnal peak flow variation> 20% in any of the first 7 days of recordings.	Asthma not taking ICS: In comparison with clinical diagnosis and bronchodilator response, FeNO 20 ppb had sensitivity 49% and specificity 61%. FeNO 50 ppb had sensitivity 19% and specificity 96%. Moderate to severe asthma: In comparison with clinical diagnosis and bronchodilator response, FeNO 20 ppb had sensitivity 67% and specificity 61% FeNO 50 ppb had sensitivity 20% and specificity 96%
		FeNO, N= 258		FeNO measured before other pulmonary testing. Withdeld SABA for 6 hours, LABA for 36 hours, and anti-histamine use for 72 hours. FeNO measured using an online Chemoluminescence analyzer nitric oxide monitor (NIOX; Aerocrine AB, Solna, Sweden). Exhalation flow rate	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)
				50ml/sec.	
Woo, 2012 [43]	South Korea, longitudinal cohort study, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) Symtotoms , spirometry and methacholine challenge, N=245	167 asthma patients; Mean age 11.7 years, 77% atopic 67% males, 26% passive smokers. 78 healthy controls.	Asthmatic patients diagnosed if they had symptom including cough, wheezing, or shortness of breath with reversible airflow obstruction (≥12% improvement in FEV_1 in response to inhaled b2-agonist) and/or airway hyper responsiveness (methacholine PC_{20} ≤8 mg/mL).	FeNO at 22 ppb cut-off, compared with Spirometry and methacholine challenge test had sensitivity: 57%, specificity: 87%, PPV: 91%, and NPV: 38%. The diagnostic performance of FeNO using cut off of 22 ppb was better in atopic subjects versus non-atopic with a sensitivity 72.1%, Specificity 85%, PPV 91.2% and NPV 58.6%.
		FeNO, N=245		Measured by (NIOX MINO; Aerocrine AB, Solna, Sweden), Exhalation times were 10 s with a 2-min analysis period, at a constant flow rate of 50 mL/sec.	
Yao, 2011 [44]	Taiwan, cross sectional study, medium risk of bias.	Reference test; Clinical diagnosis modified ISAAC questionnaire, N=1651	70 asthmatic and 1478 controls mean age 10.3 years, 48.9% males.	Asthma was defined as ever having asthma and either the occurrence of wheeze in the last 12 months or current use of asthma medication.	Compared with modified ISAAC questionnaire, FeNO cut-off of 28 ppb had a sensitivity of 64.3%, a specificity of 69.9%, a PPV of 8.8%, NPV of 97.7% and AUC of 0.67.
		FeNO, N=1651		Using an online chemiluminescence analyzer (CLD 88sp NO analyzers, Eco Medics, Duernten, Switzerland), with a constant flow rate of 50mL/sec.	

AUC: area under the curve; BMI: body mass index; Eos: Eosinophilia count; ERS/ATS recommendation: The European Respiratory Society/ American Thoracic Society recommendation; COPD: chronic obstructive chronic disease; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; ISAAC questionnaire: International Study of Asthma and Allergies in Childhood questionnaire; MCH: Methacholine; NPV: negative predictive value; PC15: provocation concentration causing a 15% fall in FEV_1; PC20: provocation concentration causing a 20% fall in FEV_1; PD15: provocation dose causing a 15% declaine in FEV_1; PD20: provocation dose causing a 20% decline in FEV_1; PPV: positive predictive value; ROC curve: receiver operating characteristic curve; RCT; randomized clinical trial; SD: standard deviation.

Table C.2. Characteristics of the included studies in KQ 1b

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
Agache, 2012 [45]	Romania, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 46	**Non- difficult asthma group (N=22)** Mean age 7.36 years (SD: 0.67), 81% male , 86.36% atopy, 22.73% tobacco exposure, 4.55% Obesity 568.18 mcg (SD:49) beclomethasone **Difficult asthma group (N=24)** Mean age 7.71 years (SD: 0.61), 66.67% male, 91.67% atopy, 31.82% tobacco exposure 25% Obesity, 572.92 mcg (SD: 87.77) beclomethasone	FeNO measurement was done using (NIOX MINO, Aerocrine AB); exhaled NO values were corrected for height, male sex, atopy, and infection status. The patients were seen regularly at 1- to 4-month intervals for 12 months, depending on the level of asthma control achieved. ≥ 45ppb was used as cutoff for persistently high FeNO	Persistently high FeNO in difficult asthma was a significant risk factor comparing to non-difficult asthma: OR: 0.0297; 95% CI: 0.0010 to 0.8790 Asthma exacerbations, which defines as acute attack requiring oral or systemic corticosteroids, at Baseline (at least 3 moderate or severe asthma exacerbations in the previous year) was 13.64% in non-difficult asthma group and 79.17% Difficult asthma.	Baseline: Non- difficult asthma: 15.85 ppb (SD: 2.70) Difficult asthma: 26.28 ppb (SD: 4.6).	In children with uncontrolled persistent asthma on ICS, persistently high FeNO was an independent risk factor for difficult to control asthma (along with obesity and severe rhinitis)
		Spirometry, N= 46		Lung function testing was done using (spirometry; Microlab MK 8, CareFusion) after a washout period of 12 hours for LABAs and of 4 hours for SABAs; postbronchodilator FEV_1 and magnitude of the bronchodilator response were considered. The patients were seen regularly at 1- to 4-month intervals for 12 months, depending on the level of asthma control achieved.		Baseline: Non- difficult asthma: 103.53 (SD: 2.53) Difficult asthma: 91.13 (SD: 3.04).	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
Beerthuizen, 2016 [46]	Netherlands, RCT, outpatient setting, unclear risk of bias.	**Group 1**_ Standard care; ACT every 4 months (N= 89)	Mean age 10.2 years (SD: 3.2), Male 69 %, atopy 100 %.		Cost: Among healthcare cost categories, only the amount of nurse practitioners' consultations differed significantly between the strategies.	Group 1_average €86 annual expenditure (1.20 consultations per patient per year) Group 2_ €129 annual expenditure (1.79 consultations per year per patient) Group 3_ €96 (1.33 consultations per patient per year).	RCT of children with atopic asthma compared standard care vs web-based monthly monitoring ACT vs FeNO and ACT every 4 months. Web-based monitoring was preferred from a healthcare perspective, while the FeNO-based strategy was preferred from a societal perspective.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
		Group 2_ Web-based; Monthly ACT (N= 91)	Mean age 10.6 years (SD: 2.8), Male 66 %, atopy 100%.		Quality of Life (QALY) _EuroQoL-5 dimensions (EQ-5D): A 5 domains scale; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. All range from 1 to 3, where 1 represents the most favorable score: Group 2 has a statistically non-significant better utility score.	Group 1: 0.928 Group 2: 0.939 Group 3: 0.932 Group 2 vs 1: 0.011 (−0.005 to 0.027) Group 2 vs 3: 0.006 (−0.008 to 0.021) Group 3 vs 1: 0.004 (−0.018 to 0.026)	QALYs and costs were not statistically significant changes.
		Group 3_ FeNO-based; FeNO and ACT every 4 months (N= 92)	Mean age 10.3 years (SD: 2.9), Male 67 %, atopy 100 %	FeNO was measured online on the NIOX chemiluminescence analyzer or NIOX MINO (Aerocrine, Stockholm, Sweden) according to guidelines, offline,	Cost effectiveness: Assessed by cost-effectiveness acceptability curves (CEACs). From a healthcare perspective (based on healthcare costs only) at willingness-to-pay threshold of €40000/ QALY, Group 2 was the most cost-effective, followed by Group 3 and 1. From a societal perspective (including both	From a healthcare perspective, Group 1: 3%. Group 2: 77% Group 3: 20% From a societal perspective, Group 3: 83%.	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
					healthcare costs and costs due to loss of productivity) at a willingness-to-pay of about €40000/QALY, Group 3 has the highest chance of being most cost-effective.		

Berg, 2008 [47]	Sweden, Cost-effectiveness study, Unclear risk of bias	NR	NR	NR	Asthma diagnosis based on FeNO measurement results in a cost of £38 per patient compared with £26 for standard diagnostics (defined as one or more of the following: spirometry, reversibility testing, bronchial provocation and sputum eosinophil count) . In mild to severe patients, asthma management with FeNO measurement instead of standard guidelines results in cost-savings of £30 per patient and year. In a more severe population, management with FeNO measurement would save costs of £160 per patient		Economic evaluation showing that management using FeNO reduced total cost per patient per year compared to standard diagnostic test (spirometry, reversibility testing, bronchial provocation and sputum eosinophil count).
Bernstein, 2009 [48]	United States & Spain, cross-sectional, medium risk of bias.	FeNO, N=209	Overall N=100 in Uinted States and 109 in Spain. Age: median (IQR): USA: 50 years (40-60), Spain 37 years (25-49). Male: USA 45%, Spain 38%. Caucasians 79% in United States, and 100% in Spain Atopy: USA 83%, Spain	using a chemiluminescene analyzer (Niox model, Aerocrine, Inc. Solna, Sweden) with a range of detection between less than 1 to 500,000 ppb at the US site and the NioxMino analyzer (MiNo, Aerocrine AB; Smidesvagen, Sweden) at the Spain site.	There were no significant differences among FeNO means across ACT categories for patients from the US site (p=0.31). However, for the Spain site, the FeNO mean for ACT <20 (65.8)	FeNO: median (IQR): USA 28.8 (14.5 to 51.9), Spain 42.0 (26.0 to 73.0).	In adult asthmatics, FeNO was correlated negatively with ACT only in patients not on ICS. In other subgroups in the study there was no correlation.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
			62%.		was significantly higher than the means for ACT 20–24 (41.0, p<0.01) and ACT 25 (35.2, p<0.01). The FeNO mean value for the Spain site, 45.6, was significantly Higher than the USA site, 24.2 (p<0.001).		
		Spirometry, N=209		Forced spirometry at the US site was performed using a Koko spirometer, following the guidelines of the American Thoracic Society. Forced spirometry was performed at the Spanish site using a Jaeger APS pro spirometer (Erich Jaeger, Germany). FEV_1, FVC, and peak expiratory flow rate (PEFR) were recorded for each subject using Crapo spirometric reference values in US and using Castellsague reference values in Spain.	For each site, FEV_1 was positively correlated when patients were dichotomized by ICS usage Correlations was +0.39 (p<0.05) at the USA site, and +0.26 (p> 0.05) at the Spain site.	FEV_1 %, median (IQR): USA 72 (58 to 87.5), Spain 103 (89 to 116).	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
		Asthma Control Test (ACT), N=209		Patients from the US completed the English version of the ACT, whereas those from Spain completed the validated Spanish version.	For each site, ACT was positively correlated when patients were dichotomized by ICS usage Correlations was +0.40 (p<0.001) at the USA site, and +0.32 (p< 0.05) at the Spain site. Negative correlations were obtained between ACT and FeNO at the Spain site only.	ACT: median (IQR): USA 18 (13 to 22), Spain 22 (19 to 24).	
Bora, 2011 [49]	Turkey, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N= 83	Mean age 42.3 years (SD: 11.4), 15.7% male, 9% ever smokers, 23% current smokers.	Using a nitric oxide analyzer (NIOX MINO Airway Inflammation Monitor; Aerocrine AB; Solna, Sweden) at a flow rate of 0.05 liters per second at baseline and 3 months later. FeNO threshold was accepted as 20 ppb.	The proportions of patients with FeNO levels > 20 ppb were 21%, 45% and 38% in current smokers, non-smokers and ex-smokers, respectively (P =0.189)	Baseline: 15 ppb (11-26). FeNO > 20 ppb (%) Totally controlled asthma (N=8): 38 Partially controlled asthma (N=36): 53 Uncontrolled asthma (N=39): 25. At 3 months: 14 (11 to 21) FeNO > 20 ppb	In adults with asthma on ICS, FeNO did not differentiate those controlled, partially controlled or uncontrolled.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
						(%) Totally controlled asthma (N=10): 20 Partially controlled asthma (N=39): 26 Uncontrolled asthma (N=34): 38.	
		ACT score, N= 83		A 5 items patient-based questionnaire that investigates the disease control. Patients are questioned about their perception of asthma control in the previous 4 weeks. Totally controlled (ACT = 25), partially controlled (ACT = 20-24) and uncontrolled (ACT ≤ 19).		Baseline: 18.98 (SD: 4.59) At 3 months: 19.65 (SD: 4.11).	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 83		The test was repeated three times using a spirometer (Jaeger Master Screen Pneumo Spirolab II®). Measurements were according to the ATS criteria and the best values were recorded.		FEV_1 Baseline: 93.9 ± 13.7 At 3 months: 93.0 ± 15.8 (P=0.968) FEV_1/FVC Baseline: 78.2 ± 6.9 At 3 months: 77.7 ± 7.1 (P=0.387).	
		Methacholine bronchial provocation test positivity, N= 83		According to the 2-min breathing protocol as described in ATS guideline. The patients inhaled methacholine at the doses of 0.0625, 0.125, 0.250, 0.500, 1, 4, 8 and 16 mg/mL after three repetitive FEV_1 measurements. Thereafter, the pulmonary function test was repeated. The dose which caused a 20% or more decrease in baseline FEV_1 value was accepted as provocative dose (PD20). A PD20 value of < 8 mg/mL was accepted as an indicator of positive		Baseline: 59 Totally controlled asthma (N=8): 62 Partially controlled asthma (N=36): 56 Uncontrolled asthma (N=39): 62 At 3 months: 45 Totally controlled asthma (N=10): 30 Partially controlled	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
				BHR.		asthma (N=39): 54 Uncontrolled asthma (N=34): 38	
		sputum eosinophil > 3%, N= 83		After medication with a short-acting β2 agonist, sputum was induced by inhalation of 3% hypertonic saline by a nebulizer (Pari Master, Pari Respiratory Equipment Inc. Richmond, VA, USA) with an output of 0.5 ml/min saline for a maximum period of 20 minutes via a mouthpiece. The patients were encouraged to cough and expectorate sputum in a sterile petri dish 10 minutes after the onset of nebulization and every 5 minutes. Three flow-volume curves were obtained before and after each inhalation for patients with a FEV_1 value < 80%. The sputum induction was terminated when a > 15% FEV_1 decrease was observed in comparison to baseline value or when a symptom		Baseline: 23 Totally controlled asthma (N=5): 0 Partially controlled asthma (N=21): 23 Uncontrolled asthma (N=21): 29 At 3 months: 30 (P=0.791) Totally controlled asthma (N=4): 50 Partially controlled asthma (N=15): 27 Uncontrolled asthma (N=11): 27	
		sputum neutrophil, , N= 83				Baseline: 32 (11 to 50) Totally controlled	

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				occurred.		asthma: 26 (10 to 44) Partially controlled asthma: 22 (9 to 45) Uncontrolled asthma: 33 (15 to 57) At 3 months: 34 (18 to 56) (P=0.241) Totally controlled asthma: 42 (29 to 53) Partially controlled asthma: 28 (18 to 56) Uncontrolled asthma: 46 (18 to 64)	
Cano-Garcinuño, 2010 [50]	Spain, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=149	Mean age 10.1 years (SD: 2.1), Males 62.4% Weight 41.2 Kg (SD: 12.7), BMI 19.5 (SD: 3.5)	Using a portable nitric oxide analyzer (NIOX MINO, Aerocrine, Solna, Sweden), which provides FeNO measurements at a flow rate of 50 mL/s.	Lung function was associated with higher FeNO values only in children treated with ICs. Reduced FEV_1/FVC (before or after the	cough in the preceding 4 weeks was associated with a higher FeNO level: median 38.5 ppb (IQR, 19.6-64.0) vs	In children with asthma, FeNO correlated with wheezing and cough the previous 4 weeks. No other

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		Spirometry, N=149		Patients then underwent a spirometry test and a bronchodilator test by inhaling 400µg of salbutamol through a spacer chamber. We performed pulmonary function testing both before and after the salbutamol challenge and obtained the following: FEV_1, the ratio of FEV_1 to forced vital capacity (FVC) and the forced expiratory flow, mid-expiratory phase (FEF).	bronchodilator test) was the spirometric parameter most strongly related to inflammatory measurements. A low FEV_1 (baseline or after salbutamol) was independent of FeNO Level. For the whole sample, FeNO level was not related to asthma control, use of health care resources, limitation of daily activities, or clinical variables. Only cough in the preceding 4 weeks was associated with a higher FeNO.	27.5 ppb (IQR, 11.5-51.3); P=.041. FEV_1, FEF25-75, and FEV_1 values after the challenge with salbutamol were not associated with FeNO level, although patients with reduced FEV_1/FVC had higher FE NO levels, both before and after inhalation: before, median 64.0 ppb (IQR, 33.1-77.8) vs 32.5 (IQR, 16.9 56.6); P=.023; after, median 61.3 ppb (IQR, 48.0- 106.5) vs 32.8 (IQR, 17.0 57.1); P=.021.	associations were demonstrated with symptom frequency, bronchodilator use, asthma crises, hospital admissions, limitation of daily activities, or spirometry results. In patients treated with ICs, FeNO was not related to the clinical expression of asthma except for a reduced ratio of forced expiratory volume in 1 second to force vital capacity.

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Ciprandi, 2013 [51]	Italy, cross section, inpatient setting, low risk of bias.	FeNO, N= 180	Median age 13 years, Male 57.2%,	Measured by chemiluminescence analyzer (Model 280 Nitric Oxide Analyzer; Severs Instrument Inc., Boulder, CO, USA) at 50 ml/sec, at one visit, steroid prior to test was 0%.		34 ppb (range 29 to 38).	In children, FeNO was strongly related with the response to reversibility to bronchodilation testing and could predict bronchial reversibility.
		Spirometry, N= 180		Using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, UK), with optoelectronic whirl flow meter. It was performed as stated by the ATS and ERS.		FVC, FEV_1, and FEF25–75 were 92%, 81%, and 69% of predicted, respectively.	
		Bronchodilator responsiveness, N= 171		According to international guidelines and using a salbutamol metered dose of 400 mcg. Reversibility (bronchodilator responsiveness, BDR) was considered if an increase of at least 12% of FEV_1 was achieved from baseline, according to ERS/ATS guidelines.		95%	
de Bot, 2013 [52]	Netherlands, longitudinal nonrandomized, outpatient setting,	FeNO, N= 93	Mean age 11.3 years (SD: 3), 65% Male, 100% allergic rhinitis.	A single measurement of FeNO was performed at baseline and after 2 years using a hand-held portable nitric oxide analyser (NIOX MINO, Aerocrine AB, Solna,		At baseline (N=91): 36 ppb (18 to 55) At 2 years (N=77): 34 ppb (19 to	In children with allergic rhinitis and asthma, FeNO was elevated and did not correlate with

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	medium risk of bias.			Sweden) at a mouth flow rate of 50mL/s over 10 seconds.		59)	nasal or asthma symptoms
		House dust mite-specific IgE, N= 93		Serum IgE antibodies to Dermatophagoides pteronyssinus were determined at baseline and after 2 years using the CAP- Phadiatop, according to the manufacturer's instructions. Allergen-specific IgE values of >0.7kU/L (class II) were considered positive.		At baseline (N=93): 55.0 kU/L (SD: 37.2). At 2 years (N=77): 58.4 kU/L (SD: 33.8).	
		Symptoms score, N=93		Symptoms of wheezing/dyspnea and dry cough during the night were subjectively assessed according to a grading scale: 0=no complaints, 1=minor complaints, 2=moderate complaints, 3=serious complaints; the maximum score was 6:		At baseline (N=93): 0.9 (SD: 0.9) At 2 years (N=78): 0.4 (SD: 0.8).	
Delclaux, 2008 [53]	France, longitudinal nonrandomized, inpatient setting, medium risk of bias.	FeNO, N=65	Mean age 34 years (SD: 10), males 40%, weight 68 Kg (SD: 14), atopy (self-reported) 69%, current smokers 30.8%, ever smokers 7.7%.	Offline Exhaled NO Measurement, The fraction of NO, collected at a constant flow rate of 100 mL/s, was measured using a chemiluminescent analyzer (ENDONO 8000; SERES, Aix en Provence,	The severity of an asthma attack did not influence exhaled NO values on emergency department admission (p=0.27). When	FeNO Baseline: 49 (26 to 78), At 2 Hours: 45 (27 to 69) At 6 hours: 48 (25 to 66).	In adults seen in emergency department, an increase in FeNO is observed in almost all patients with

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				France).	considering the whole group, no significant modification of FeNO 0.1 was evidenced during emergency department stay (first 6 hours), whereas a highly significant decrease in FeNO 0.1 was observed after 6 to 15 days of treatment (49 [28 to 69] versus 20 [13 to 27], n=38; p<0.0001).		acute asthma. Subsequent increase within 6 hours is associated with a better degree of asthma control in the subsequent week.
		Spirometry, N=65				PEF rate (L/min%): Baseline: 295 (SD: 111), At 2 hours: 389 (SD: 104), At 6 hours: 424 (SD: 127).	
Fritsch, 2006 [54]	Austria, RCT, outpatient setting, unclear risk of bias.	Rx based on symptoms, beta-agonist use, lung function and FeNO, N=22	Mean age 11.3 years (SD:3.4), 63.6% males	FeNO was measured prior to lung function testing according to ATS recommendations at a flow rate of 50 ml/ sec with the single breath online method using the NIOX1 instrument (Aerocrine AB, Stockholm, Sweden). At each visit repeated exhalations were performed until three NO plateau values agreed at a 10% level.	Significant relationships were found between FeNO and symptoms over the last 4 weeks, as well as with BHR. There was a significant inverse relationship between FeNO and the dose of ICSs (b ¼ 8.67; P < 0.002).	FeNO cutoff of 22.9 ppb, had 80% sensitivity, and 60% specificity, and 53% PPV for predicting exacerbations. FeNO baseline 34.6 ppb (17.5 to 107.5) FEV_1 baseline 101 % pred (91.1 to 107.5)	The cut-off point of 22.9 ppb FeNO best predicted exacerbations (sensitivity of 80% and specificity of 60%) in children with mild to moderate asthma.

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		Rx based on symptoms, beta-agonist use, and lung function only, N=25	Mean age 12.1 years (SD: 2.8), 56% males	Spirometry was performed in a Jaeger Masterlab (Version 4.34, Jaeger, Wuerzburg, Germany) according to ATS recommendations. The best of three maneuvers was recorded and reference values of Zapletal were applied. FEV_1 and maximum expiratory flow at 50% of forced vital capacity (MEF50) were used for analyses.		FeNO baseline 31 ppb (20.8 to 54.8) FEV_1 baseline 93.7 % pred (83.8 to 99.6)	

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Gelb, 2006 [55]	Canada, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=44	Mean age 51 years (SD: 21), males 45.5%, current smoker 0%.	measured using a chemiluminescence analyzer (Sievers NOA 280; Ionics Instruments; Boulder, CO) at an expiratory flow rate of 100 mL/s with varying expiratory airflow resistors (Ionics; Boulder, CO). Exhaled NO was measured at three separate, constant expiratory flow rates: 100, 150, and 200 mL/s in triplicate; and the mean of three values obtained within 10% of each other was used to calculate bronchial NO maximal flow (large airway NO flux [J'awNO]) and small airway/alveolar NO (CANO) using the technique of Tsoukias and George.	If baseline FeNO was ≥28 ppb, exacerbation occurred in 13 of 17 asthmatics (76%); if baseline FeNO was < 28 ppb, exacerbation occurred only in 9 of 27 asthmatics (33%).	When FeNO ≤22 ppb (N= 19), FEV_1 2.0 L (SD: 0.6) or 69 % pred (SD: 14), FVC 3.1 L (SD: 1.1) or 89 % pred (SD: 15), FVE1/FVC 63% (SD: 10). When FeNO >22 ppb (N= 25), FEV_1 2.2 L (SD: 0.9) or 72 % pred (SD: 25), FVC 3.2 L (SD: 1.1) or 89 % pred (SD: 23), FVE1/FVC 68 % (SD: 11). Baseline FEV_1 2.1 L (SD: 0.71) or 70 % pred (SD: 20) of predicted after 180 microgram of albuterol. Healthy subjects (N= 34), FEV_1 3.0 L (SD: 0.8) or 91	In controlled asthmatics on ICS, baseline FeNO with cutoff point of 28 ppb can predict first exacerbation over a follow up of 6 months (area under the curve 0.71; sensitivity, 0.59; specificity, 0.82; positive predictive value, 0.77; negative predictive value, 0.87; LR(+), 3.3; LR(-), 0.5; relative risk for exacerbation 3.4 (95% CI, 1.3-9.1).
		Spirometry, N=44		When clinically stable for at least 6 weeks, asthmatic patients were instructed to continue all their medications, except to withhold inhaled long-acting 2-agonists for 48 h and inhaled albuterol sulfate and ipratropium	If the baseline FEV_1 in liters was ≤76% of predicted, exacerbation requiring at least one course of tapering oral or parenteral corticosteroids over		

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				bromide for 6 h prior to testing. Lung function, including lung volumes, single-breath diffusing capacity, and static lung elastic recoil pressures were measured using a pressure-compensated flow plethysmograph (Model 6200 Autobox; SensorMedics, Viasys; Yorba Linda, CA).	18 months occurred in 20 of 31 asthmatics (65%); if FEV_1 was >76% of predicted, exacerbation occurred only in 2 of 13 asthmatics (15%) [p 0.003, 2 8.84]. Using ROC plots for first asthma exacerbation, with cutoff point for FEV_1 at 76% predicted, the area under the curve was 0.67; sensitivity, 0.91; specificity, 0.50; positive predictive value, 0.65; negative predictive value, 0.85; LR(+), 1.8; and LR(-), 0.18.	% pred (SD: 12). FVC 0.07 L (SD: 1) and 96 % pred (SD: 12) FEV_1/FVC 81 % (SD: 6).	

Gill, 2005 [56]	United States, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=46	Mean age 19 years (4–54), 35 % males, 100 % atopics, 17% current smoker	Measured by the manufacturer (NIOX; Aerocrine AB, Stockholm, Sweden). Baseline FeNO measurements were recorded either before the first bronchodilator treatment was administered or at the first point in care that did not interfere with the treating physician's management and patient stabilization.	Changes in FeNO were not associated with NIH class of asthma severity hospitalization, or relapse.		FeNO measurements in ED patients with acute asthma exacerbations were poorly reproducible and did not correlate with standard measures of asthma severity.
		Spirometry, N=46		Measured using handheld spirometry (KoKo Peak Pro 6; PDS Healthcare Products, Inc., Louisville, CO) in accordance with ATS standards			
Griese, 2000 [57]	Germany, RCT, outpatient setting, low risk of bias.	FeNO, N=74	Mean age 9.7 years (4-16), 76.1 % males, 100 % atoptics.	FeNO was measured online with a chemiluminescence analyzer (Logon LR 2000, Rochester, Kent, UK) sensitive to ENO at concentrations of 1-5000 parts per billion (ppb, by volume). The response time (10-90%) was <0.65 sec.	FeNO in relation to the recommended change in inhaled therapy.	FeNO > 13ppb = Step up (24) vs No change (8) vs step down (5). FeNO < 13ppb= Step up (12) vs No change (11) vs step down (13).	FeNO values did not correlate with current disease severity in children
		Spirometry, N=74			FEV_1 in relation to the recommended change in inhaled therapy.	FEV_1< 80% pred = Step up (6) vs No change (1) vs step down (1). FEV_1> 80% pred= Step up (26) vs No change (12) vs step down (17).	

		Symptom score, N=74			Symptom score in relation to the recommended change in inhaled therapy.	Symptoms Yes = Step up (34) vs No change (15) vs step down (11). Symptoms no = Step up (2) vs No change (4) vs step down (8).	
Gruffydd-Jones, 2007 [58]	United Kingdom, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 37	Adults (n=22) median age 56.5 years (37.75-60.5), males 36.4%, ever smokers 36%. Children (n=15), median age 9 years (8-12), males 73%, ever smokers 0%.	Measurements were performed on the Niox chemiluminescence eNO analyzer (Aerocrine Ltd, Sweden) at an expiratory flow of 50ml/sec as per guideline recommendations. It was aimed to obtain three NO values that agreed within 10% of each other (as per ERS guidelines), and repeated exhalations were performed up to a maximum of 10 or when the subject tired.	There was no statistically significant difference in the coefficient of variation (CV) between children and adults (median (IQR) 35.0 (29.6 to 48.4) and 32.4 (20.9 to 51.7) respectively. A significant correlations were observed in adults between changes in lung function and changes in FeNO (a rise in FeNO was moderately correlated with a fall in % predicted FEV_1, (r= -0.33, p<0.001), and between changes in FeNO and changes in Asthma Quality of Life Questionnaire scores (a rise in FeNO was weakly correlated with worsening asthma	Adults: 31.2 ppb (11.5 to 61.9). Children: 55.3 ppb (11.6 to 102.1). FeNO was reduced significantly between the first and the last study visit in children (median change in FeNO =14.5 ppb (-41.5 to -0.2), p= 0.01) but not significantly in adults (-9.1 ppb (-28.7 to 2.7), p=0.14). FeNO was non-significantly lower at baseline in adults than children (median FeNO: 31.2 ppb (11.5 to 61.9) vs. 55.3	In adults and children seen every 2 weeks for 12 weeks, FeNO values correlated with ACQ, AQLQ and bronchodilator use.

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					related health status, r= -0.22, p=0.02).	ppb (11.6 to 102.1) ppb, p=0.38), but not at the final visit 30.7 (15.7 to 43.2) vs. 24.8 (14.7 to 55.7), p=0.60).	
		Spirometry, N=37		Spirometry: (Vitalograph) performed as per ERS guidelines.		Adults: FEV_1% (median, IQR): 86.5 (57.25 to 101.75), PEF: 435 (400 to 457). Children: FEV_1% (median, IQR): 82 (76 to 94), PEF 310 (280 to 410),	
		Asthma Control Questionnaire (ACQ), N=37		ACQ: Short-term symptomatic asthma control – the Asthma Control Questionnaire (ACQ) in adults only (this instrument has not been		Adults: 1.1 (0.4-2.3).	

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				validated in children.)			
		Asthma Mini Quality of Life Questionnaire (AQLQ), N=37		Health status: in adults – the Asthma Mini Quality of Life Questionnaire (AQLQ); and in children – the Paediatric Caregivers Quality-of-life Questionnaire (PQLQ).		Adults: 5.6 (4.1 to 6.7). Children: 6.1 (5.0 to 6.7).	
Habib, 2014 [59]	Saudi Arabia, Cross section study, outpatient setting, high risk of bias.	FeNO, N= 53	Mean age 36.1 years (SD: 14.3), 79.2% male, 43.4% ex-smokers, Weight 28.0 Kg (SD: 5.0) 60% ICS-treated, 64.8% Atopy,	According to the present recommendations of the American Thoracic Society using handheld NIOX MINO Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden). A FeNO level of >47 ppb was used to indicate inflammation and uncontrolled asthma	Mean FeNO values were significantly higher in patients with an ACT score <20 of 65.5 ppb (SD: 35.4) compared with those patients with an ACT score ≥20 of 27.4 ppb (SD: 10.5). Linear regression analysis revealed a significant negative correlation of FeNO with ACT score (r=-0.581, p<0.0001). There was no significant correlation of FeNO with age, height,	Baseline: 48.9 ppb (SD: 33.3).	In adult asthmatics, there was an inverse relationship between ACT scores and FeNO. At the international cutoff point of 20, the sensitivity was 95.2, and the specificity was 68.8. Maximum sensitivity and specificity were observed at an ACT score cut off point of 19

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					weight, asthma duration, and ventilatory function tests.		(sensitivity: 90.5 and specificity: 81.2).
		Spirometry, N= 53		Ventilatory functions were measured using an electronic spirometer (Vitalograph Co, Clare, Ireland), which was calibrated daily		FEV_1 at baseline: 83.8% pred (SD: 7.7).	
		ACT Score, N= 53		Arabic version of the ACT score questionnaire was used		Baseline: 17.6 (SD: 4.9).	
Hanson, 2013 [60]	United States, retrospective chart review, outpatient setting, high risk of bias.	FeNO, N=75	Age mean (range) 6.4 (4.75-7), 52 % males, BMI 16.9 Kg/m2 (12.2-28.4), 33% atopic dermatitis, 71% allergic rhinitis, 33% ever smokers.	Single-breath FeNO testing was performed using the NIOX MINO device, using a 10-second exhalation time and measured in parts per billion. For subjects unable to perform this maneuver, a 6- second exhalation time was used.	Regression coefficients for assessment of the overall impact of age, asthma severity, allergic rhinitis, atopic dermatitis, use of ICSs, and use of LTRAs on FeNO	Asthma severity had the greatest impact on FeNO (0.32), followed by ICS (-0.27), atopic dermatitis and age (each 0.23), allergic rhinitis (0.20), and LTRAs (-0.16).	In children age 4-7 FeNO values correlated with asthma severity, atopic dermatitis and steroids use; and marginally with allergic rhinitis (p=0.06)
		Spirometry. N=36				Mean FEV_1/FVC 91 % pred (92 to 9.2). Mean FEV_1 102 % pred (SD: 20.1).	

		Childhood Asthma Control Test (C-ACT) score, N=43		Validated Childhood Asthma Control Test (C-ACT) score (ACT score >19 indicating inadequate control).		Mean C-ACT 17.9 (SD: 5.9) range 4 to 27.	
Harkins, 2004 [61]	United States, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N=22	Age range 28-48.years, current smokers 0%.	Using off-line in 10-L Mylar bags after subjects inhaled through an NO-free filter. Content of the bags was measured for NO via chemiluminescnence.	Those with exacerbation within 2 weeks of routine appointment had a higher mean FeNO 29.67 ppb (SD: 14.48) compared with those who did not 12.92 ppb (SD: 5.17).	Patients without exacerbation: FeNO 12.92 ppb (SD: 5.17) FEV_1 1.82 L (SD: 0.99) FEV_1 53.6 % pred (SD: 23.2). Patients with exacerbation: FeNO 29.67 ppb (SD: 14.48). FEV_1 1.81 L (SD: 0.61) FEV_1 62.5 % pred (SD: 15.6).	Adult asthmatics who had an exacerbation in the previous 2 weeks had a higher mean FeNO (29.67 vs 12.92).
		Spirometry, N=22		Spirometry was obtained following ATS guidelines.			
Hayata, 2013 [62]	Japan, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 297	**Group 1: Low PEF variability (Min% Max ≥80%) (N=245):** Mean age 47.7 years (SD: 15.1), 41.6% male, 75.5% atopy, BMI 22.4 (SD: 3.7), 31.4% Ex-Smokers, 356 ug/day (SD: 133) dose of inhaled steroid.	Online electrochemical nitric oxide analyzer (NIOX MINO; Aerocrine AB, Solna, Sweden) over a week.		At baseline: Group 1: 25.3 ppb (SD: 12.8). Group 2: 51.8 ppb (SD: 22.1. FeNO for predicting Min%Max < 80%: 1.08; (95% CI: 1.05 to 1.11).	In adults asthmatics on ICS, FeNO 40 ppb yielded 75% sensitivity and 90% specificity for identifying the subjects with high variability in PEF.

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		Spirometry, N= 297	**Group 2; High PEF variability (Min% Max < 80%) (N=52):** Mean age 51.7 years (SD: 13.5), 51.9% male, 82.7% atopy, BMI 23.4 (SD: 4.1), 48.1% Ex-Smokers, 433 ug/day (SD: 225) dose of inhaled steroid.	It was measured at baseline and after a week.		FEV_1 at baseline: Group 1: 100.4% pred (SD: 12.8) Group 2: 82.8 % pred (SD: 12.3. FEV_1 for predicting Min%Max < 80%: 1.14; (95% CI: 1.05 to 1.24) FEV_1/FVC at baseline: Group 1: 78.1 % pred (SD: 9.1). Group 2: 70.3 % pred (SD: 10.6) FEV_1/FVC for predicting Min%Max < 80%: 1.03; (95% CI: 0.95 to 1.12)	
		Asthma Control Questionnaire (ACQ), N= 297		The ACQ-5 is a questionnaire that assesses asthma condition according to five items, each of which can be rated on a seven point scale.0 represents		At baseline: Group 1: 0.4 ± 0.4 Group 2: 0.9 ± 0.5 (P <0.001) OR for predicting	

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				excellent asthma control and 6 represents extremely poor control. The overall score was the mean of the five responses. It was measured at baseline and after a week.		Min%Max < 80%: 11.86; 95% CI: 3.55 to 39.61	
Hsu, 2013 [63]	Taiwan, Cross sectional, outpatient setting, high risk of bias.	FeNO, N=56	Mean age 62.3 years (SD: 16.3), 62.5% male.	Flow of 50mL/sec, using an offline and online chemiluminescence (NOA 280i; Sievers Boulder, CO) in one visit.		Online FeNO groups: Age >65 (N=29): 37.2 ppb (SD: 19.9) Age 20-65 (N=27): 39.8 ppb (SD: 33.8). Online FeNO groups: Controlled/partially: 35.1 ppb (SD: 20.4) Uncontrolled: 45.5 ppb (SD: 38.8). Offline FeNO groups: Age >65 (N=29): 19.2 ppb (SD: 9).	In elderly asthmatics, FeNO measurement was feasible and correlated with ACT

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						Age 20-65 (N=27): 20.5 ppb (SD: 13.5). Offline FeNO Group Controlled/partially: 18.1 ppb (SD: 9) Uncontrolled: 23.2 ppb (SD: 14.4).	
		Spirometry, N=56				FEV_1% pred Age >65 (N=29): 76.3% pred (SD: 21.9). Age 20-65 (N=27): 85.6 % pred (SD: 17.8). FEV_1/FVC Age >65 (N=29): 62.8 % pred (SD: 9.9) Age 20-65 (N=27): 71.4 % pred (SD: 8.6).	
		Asthma Control Test (ACT), N=56		ACT score of ≤19 was defined as poorly controlled asthma		Overall: 20.7 (SD: 4.1). Age >65 (N=29): 19.8 (SD: 4.8).	

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						Age 20-65 (N=27): 21.8 (SD: 2.8).	
Ko, 2011 [64]	China, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 379	Mean age 46.1 years (SD: 13.2), 31.7% male, 0% current smokers.	using chemiluminescence analyser (NOA280i, Sievers Instruments, Boulder, CO, USA) at a flow rate of 50 mL/sec.		Baseline: 66.9 ppb (SD: 51.9). Asthma exacerbation at 6 months prediction: AUC 0.45, (P: 0.16). Urgent health-care utilization at 6 months prediction: AUC 0.44, (P: 0.15).	In men with asthma, FeNO level at baseline did not predict healthcare utilization over 6 months
		Spirometry, N= 379		Spirometry pre- and postbronchodilator was performed using the Vitalograph (Buckingham, UK) spirometer in the sitting position, according to the ATS/ERS standards. The updated predicted spirometry values for the Hong Kong Chinese were adopted.		Baseline: Pre-bronchodilator FEV_1 (N = 339): 85.2% pred (SD: 20.5). Post-bronchodilator (N = 374) FEV_1: 90.4% pred (SD: 20.8). Asthma exacerbation at	

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						6 months prediction: Pre-bronchodilator: AUC 0.54, (P: 0.33) Post-bronchodilator: AUC 0.55, (P: 0.19). Urgent health-care utilization at 6 months prediction: Pre-bronchodilator: AUC 0.53, (P: 0.50). Post-bronchodilator: AUC 0.53, (P: 0.48).	
		ACT score, N= 379		The ACT is a five-item questionnaire to assess asthma control in the previous 4 weeks. The sum of the scores of the five questions gave the total ACT score (range 5–25). The higher the score, the better the asthma control. The ACT questionnaire was		Baseline: 20.0 (SD: 4.1). Asthma exacerbation at 6 months prediction: AUC 0.69, (P: <0.0001). Urgent health-	

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				translated into Chinese by a qualified translator and then back-translated into English by another qualified translator, and any inconsistencies found were appropriately corrected		care utilization at 6 months prediction: AUC 0.66, (P: <0.0001).	
Kostikas, 2011 [65]	Greece, Cross section study, outpatient setting, medium risk of bias.	FeNO, N= 274	Well controlled (N = 99) Mea age 51 years (SD: 18), 35% male, 31.3% current Smokers, BMI 28.5 (SD: 4.7), 67.7% ICS-treated. Partly controlled (N = 115) Mean age 51 years (SD: 17), 41% male, 28.7% current smokers, BMI 27.5 (SD: 5.1), 79.1% ICS-treated. Uncontrolled (N = 60) Mean age 46 years (SD: 15), 40% male 31.7% current smoker, BMI 28.0 (SD: 5.0), 60% ICS-treated.	using a portable NO analyzer (NIOX MINO Airway Inflammation Monitor, Aerocrine, Solna, Sweden) at a flow of 50 mL/sec.	FeNO cutoff >22 ppb provided best predictor of not well-controlled in steroid-naive non-smokers, however, FeNO cutoff >27 ppb provided best predictor of NOT well-controlled in steroid-treated non-smokers.	Well controlled: 16 (13 to 20) Partly controlled: 27 (19 to 44) Uncontrolled: 59 (23 to 111) FeNO cutoff >22 ppb provided best predictor of not well-controlled in steroid-naive non-smokers: Sensitivity: 0.87 Specificity: 0.81 PPV: 0.90 NPV: 0.76 AUC: 0.899 (0.778 to 0.967) FeNO cutoff >27 ppb	FeNO had AUC of 0.790 for the identification of not well-controlled asthma (using ACT). FeNO values >30 ppb presented positive predictive values (PPV) > 0.85 with the exception of smokers treated with inhaled corticosteroids.

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						provided best predictor of not well-controlled in steroid-treated non-smokers: Sensitivity: 0.64 Specificity: 0.94 PPV: 0.95 NPV: 0.60 AUC: 0.844 (0.775 to 0.899)	
		EBC pH, N= 274		EBC was collected using a commercially available device (EcoScreen, Viasys, Germany). Subjects rinsed their mouth with distilled water and performed tidal breathing for 15 min while wearing a nose clip. EBC pH was measured using a commercially available pH meter (Model 3510, Jenway, Essex, UK), immediately after the collection of condensate. Stable pH was achieved after deaeration of the EBC with argon (350 mL/min for 10 min).		Well controlled: 7.44 (7.34 to 7.57) Partly controlled: 7.25 (7.12 to 7.36) Uncontrolled: 7.14 (7.05 to 7.21)	

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		Asthma Control Questionnaire (ACQ) , N= 274		Juniper's Asthma Control Questionnaire (ACQ) was used.		Well controlled: 0.57 (0.29 to 0.86) Partly controlled: 1.86 (1.14 to 2.71) Uncontrolled: 3.43 (2.57 to 4.00)	
		Asthma Control Test (ACT) , N= 274				Well controlled: 23 (22 to 24) Partly controlled: 18 (17 to 19) Uncontrolled: 14 (11 to 17)	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
Kwok, 2008 [66]	United States, cross sectional, inpatient setting, high risk of bias.	FeNO, N= 90	Mean age 8.9 years (7.9-9.8), 67% male.	Chemiluminescence analyzer (NIOX MINO) through several visits in 81% of patients. The initial measurement was performed before or after the initial administration of b-adrenergic agonists, but always before the administration of corticosteroids.	There was no difference in the median FeNO concentrations among subjects with mild, moderate, or severe acute asthma exacerbations (P = 0.65)	The mean change in FeNO concentrations from the start to the end of treatment was 0.24 ppb (-1.45 to 1.94).	In children 2–18 years old seen in an urban ED for acute asthma exacerbation, measurement of FeNO was difficult for a large proportion of children and did not correlate with other measures of acute severity
Leblanc, 2013 [67]	Portugal, longitudinal non randomized, outpatient setting, medium risk of bias.	FeNO, N=185	Mean age 37.48 years (SD: 14.88), 21.6 % males	Measured by chemiluminescence analysis, using NIOX instrument (Aerocrine; Sweden). FeNO evaluation a cut-off value of 35 ppb was used (15) with higher levels reflecting a greater probability of airway eosinophilic inflammation	FeNO change with asthma severity (based on FEV_1)	The mean values of FEV_1 were 85.5% (SD of 21.6%) for patients with low probability of inflammation (FeN0<35) and 84.8% (SD of 16.0%) for those with FeN0≥35.	Among patients with partially and controlled asthma, 60% had FeNO less than 35.

		Spirometry, N=232		Spirometry values, FEV_1 and FEF25-75%, were expressed as 3-level variables: percent predicted less than 60%, between 60 and 80% and greater than 80%		Among patients with FeNO < 35 ppb, 66% had FEV_1 > 89% and 52% had asthma control test score > 19.	
		Score registration of the Asthma Control Test, N=232		Divided into 3 different groups: less or equal to 19 (uncontrolled asthma), 20 to 24 (partially controlled) and equal to 25 (well controlled asthma). A second ana lysis was performed dividing ACT™ score in 2 groups (score ≤19 and >19)			
Lex, 2007 [68]	Germany, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N=85	Mean age 11 years (5-16) male 52%.	Measured by online chemiluminescence analyzer (NOA280, Sievers Instruments, Boulder, CO), at 50 ml/sec, Steroid prior to test was 49.4%, bronchodilators withheld prior to test was 9.4%.	FeNO was significantly elevated in those with exercise induced bronchoconstriction (EIB) defined as reduction of FeV1 > 15% vs those without. The cut off level of FeNO 25 ppb resulted in the best combination of sensitivity and specificity to predict exercise c induced bronchoconstriction .	With EIB (N=12) 51.3 ppb (31.1 to 67.3) vs Without EIB (N= 73) 20.2 ppb (10.9 to 42.3). Sensitivity 100% Specificity 58% PPV 28% NPV 100% AUC 0.796	In children with atopic asthma, FeNO was significantly elevated in those with exercise induced reduction of FeV1 (> 15%) with NPP 100% and PPV 28%. NPV and PPV for reported asthma symptoms within 2 weeks preceding the

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		Spirometry, N= 85		Patients were asked to withhold ß2-agonists for at least 12 hr; inhaled steroids were not withdrawn prior to testing. After measuring specific airway resistance (sRaw,tot) by body plethysmography, baseline spirometry was performed.	FEV_1 and FVC were significantly elevated in those with exercise induced bronchoconstriction (EIB) vs those without EIB, however, FEV_1/FVC ratio was lower in patients with EIB vs without EIB.	With EIB (N=12) FEV_1% pred 95.2 (88 to 105.3) FVC % pred 86.1 (78.1 to 98.1) FEV_1/FVC % pred 116.2 (111.1 to 123) Without EIB (N= 73) FEV_1% pred 101.9 (95 to 114) FVC % pred 94.7 (85 to 105.6) FEV_1/FVC % pred 114.9 (108.1 to 263.2).	study were 96% and 26%. Thus, FeNO can be used to exclude EIB in atopic child
		Asthma symptoms in 2 weeks preceding exercise challenge, N= 38			Asthma symptoms in 2 weeks preceding exercise challenge has a higher specificity but lower sensitivity, NPV and PPV to predict exercise induced bronchoconstriction (reduction of FEV_1	sensitivity 83% specificity 62% PPV 26% NPV 96%	

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					>15%) than FeNO.		
Mahut, 2010 [69]	France, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=200	Mean age 16 years (12-38), male 52.5% current smoker 0%, atopy 82%	Measured by online chemiluminescence analyser (ENDONO 8000; SERES, at 50-250 ml/sec, Steroid use prior to test was 82.5%	FeNO did not correlate with ACQ /short-ACQ nor was influenced by severity classes.		In adults and children stable and on treatment (mostly ICS), FeNO did not correlate with ACQ or short ACQ.
		Asthma Control Diary (ACD) and Asthma Control Questionnaire (ACQ), N= 200			There was a good agreement between ACD and the weekly telephonic ACQs questionnaires when considering weekly assessments separately as well as the multiple assessments per patient.		

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Martins, 2008 [70]	Portugal, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=54	mean age 7.8 years (SD: 1.1), Males 57.4%, atopy; 38.9% sensitized to at least one aeroallergen, 22.2% had positive skins prick tests for grass and/or olive tree pollen and 35.2% positive for house-dust mites.	FeNO measurement was read after the spirometry was performed, using a portable analyzer, Niox® Mino (Aerocrine, Sweden), in which the expiratory flow rate is maintained at 50 mL/s.	The correlation between FeNO and FEV_1, FEV_1/FVC and ΔFEV_1 was weak and not statistically significant (rho -0.189, -12.8 and 0.038 respectively). Comparing the	The mean FEV_1 value (a percentage of the theoretical value) was 100% (SD:14), the ΔFEV_1 (a variation percentage in relation to the base value) was	In children, FeNO levels could differentiate those who had exacerbations and needed bronchodilators in the previous 6 months.

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		Spirometry, N=54		The spirometer used was a Vitalograph® Compact (Buckingham, UK). 200µg of salbutamol were administered for the bronchodilation challenge.	children who had at least one wheezing and/or respiratory difficulty episode in the six months prior to the evaluation with those who were complaint-free during the same period, we find statistically significant differences for the ΔFEV_1 (8% median [p25-75%: 3.25-16.5%] versus 4.5% median [p25-75%: 3-7%] respectively; p=0.04). We also find statistically significant differences for the FeNO (23 ppb median [p25-75%: 12-31.75 ppb] versus12 ppb median [p25-75%: 9-21.25 ppb] respectively; p=0.02).	8.1% (SD: 7.3) and the con-centration of nitric oxide in exhaled air (FeNO) in parts per billion (ppb) was 20.8 ppb (SD: 14.7). Comparing the children who needed to use a bronchodilator in the six months prior to the evaluation with those who had no need of this medication, we find statistically significant differences for the FeNO: 27 ppb median [p25-75%: 19.75-34.25 ppb] versus 11 ppb median [p25-75%: 9-18.75 ppb] respectively; p<0.0001.	

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McCormack, 2013 [71]	United States, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 150	Mean age 11 years (5-17), 57% Male, 91% Black, 43.3% ex-smokers Weight 28.0 Kg (SD: 5.0), 60% ICS-treated, 90% Atopy.	FeNO level was measured at baseline, 3, 6, 9, and 12 months using the online Niox MINO (Aerocrine Inc) according to the ATS guidelines.	FeNO level was not a strong predictor of asthma-related health-care use in the subsequent 3 months; however, lung function was a better predictor than FeNO. ED visit in the past 12 months n: 111 patients. Acute visit in the 12 months follow period: 237 in 78 patients. ED visit in the 12 months follow period: 125 in 58 patients. Hospitalizations: 7 in 5 patients.	Baseline: 32 ppb (16-61)	In high risk children (minorities in urban areas with persistent asthma and atopy) on controller medication, FeNO every 3 months was not a significant predictor of acute visits, ED visits, unscheduled doctor visits, or hospitalization in adjusted analysis.
		Spirometry, N= 150		Spirometry was performed at baseline, 3, 6, 9, and 12 months according to ATS guidelines using a KoKo spirometer (nSpire Health Inc) and National Health and Nutrition Examination Survey reference equations for calculating % predicted values.		FEV_1 Baseline: 94.4% pred (SD: 17.7) FEV/FVC Baseline: 80.7 % pred (SD: 9.6).	
Menzies, 2008 [72]	United Kingdom, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=267	Mean age 51.6 years (SD: 1.1), 46% male, 0% ever smokers, 0% current smokers.	Online chemiluminescence analyzer (NIOX MINO) through one time visit during 3 months period.	Exacerbations experience at 3 months: 14 patients Exacerbations experience in the 12 months before the visit: 72 patients Royal College of Physicians symptom score of 0	Exacerbation group: 31.3 ppb (SD: 8.3). No exacerbation group: 28.0 ppb (SD: 1.7) (P: 0.66)	In adults with asthma, FeNO was measured and correlated with exacerbations 12 months before and 3 months after. Levels of FeNO were
		Spirometry, N= 267.		Was performed in accordance with American Thoracic		Exacerbation group: 85 % pred (SD: 5.9).	

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				Society/European Respiratory Society guidelines to determine forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC.	was identified as a significant negative predictor for exacerbations in the 12 months (P = 0.008) and 3 months (P = 0.005) before the clinic visit but not for the 3 months after the visit (P = 0.45)	No exacerbation group: 86.7% pred (SD: 1.3) (P: 0.75).	significantly lower in frequently exacerbating patients receiving higher doses of maintenance ICS compared with patients with mild disease who were corticosteroid naive. Measurement of FeNO was an insensitive method (sensitivity, 66.7%; specificity, 51.9% at a cutoff value of 20 ppb) for identifying patients who subsequently exacerbated.

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Meyts, 2003 [73]	Belgium, cross-sectional, outpatient setting, high risk of bias.	FeNO, N=73	Good asthma control (defined if both day- and night-time symptoms were absent, if the frequency of short-acting beta2-agonist use was less than four times during the past 2 weeks, and if the FEV1 of a well-per) (N= 21) median age 10.9 years, atopy 76%. Acceptable asthma control (N= 31) median age 10.9 years, atopy 83.9%. Insufficient asthma control (N= 21) median age 10.7 years, atopy 85.7%.	Exhaled air was led via a Teflon tubing system to the chemiluminiscence analyzer (Ecophysics CLD 700 AL MED, Durnten, Switzerland). Air was continuously sampled at a sampling rate of 0.700 ml/min. Response time of the analyzer was 1 sec; detection limit for NO was 1 part per billion (ppb).	Percentages of change in FEV 1 (median (quartiles)) After salbutamol administration were 2% (0-7) for group 1, 2% (2–8%) for group 2, and 8% (6–14%) for group 3. These percentages differed significantly between all three groups (P¼ 0.005), between groups 1 and 3 (P¼ 0.002), and between groups 2 and 3 (P¼ 0.006).	Good asthma control: baseline FEV_1% 101 (SD: 15), FVC% 105 (SD: 11). FeNO median 11 ppb (quartiles 9-21). Acceptable asthma control: baseline FEV_1% 94 (SD: 15), FVC% 103 (SD: 14). FeNO median 15 ppb (quartiles 11-26). Insufficient asthma control: baseline FEV_1% 91 (SD: 15), FVC% 103 (SD: 14).	In children with asthma seen in outpatient settings, FeNO differentiates those with insufficient, acceptable and good control (defined if both day- and night-time symptoms were absent, if the frequency of short-acting beta2-agonist use was less than four times during the past 2 weeks, and if the FEV1 of a well-per) (28 ppb, 15 ppb, 11ppb; p<0.01).

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 73		All subjects underwent baseline and postbronchodilator (20 min after 400 micro.g salbutamol administration with pMDI and Volumatic 1 spacer) flow-volume measurements, using the IOS digital (Jaeger, Germany).		FeNO median 28 ppb (quartiles 19-33).	
Michils, 2008 [74]	Belgium, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=341		FeNO was measured before any forced expiratory maneuvers using a daily calibrated LR 2000 chemoluminescence analyzer (Logan Research Ltd, Rochester, UK) with on-line measurement of a single exhalation at flow rate of 50 mL.s-1 (ATS/European Respiratory Society standard).	In non-severe asthma, an optimal control was documented at the first visit in 164 pairs (out of 415). Loss of optimal control at visit two is considered as a positive event. This occurred in 39 occasions. In the whole population, an	ICS naïve patients: 49.8 ppb (24 to 103.5). ICS dose ≤500 microg: 27 ppb (11.7 to 62.1), ICS >500 microg: 20.5 ppb (9 to 46.7),	In unselected population of adults with persistent asthma, FeNO correlated with ACT and need for control optimization. This correlation was reduced in those of high dose ICS.

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		Spirometry, N= 341		Spirometry was performed using a Zan 300 spirometer (Zan1, Oberthulba, Germany). Pre-bronchodilator FEV_1 was used as an index of airway caliber.	FeNO increase, 30% makes a loss of optimal control unlikely (NPV 82%). In steroid naïve patients, an initial FeNO level. 35 ppb predicts asthma control optimization in two out of three cases (PPV 68%). In ICS-treated patients, asthma control is unlikely to become optimal after treatment increase if FeNO was 35 ppb at the first visit (NPV 88%). FEV_1 never predicted optimization.	ICS naïve patients: FEV_1%: 88.9 (SD:18.5) ICS dose ≤500 microg: FEV_1%: 90.1+/-15.1, ICS >500 microg: FEV_1%: 84.1 (SD: 19)	
		Asthma Control Questionaire (ACQ), N= 341				ICS naïve patients: 2 (0 to 5.2). ICS dose ≤500 microg: 0.8 (0 to 4.8). ICS >500 microg: 1.3 (0 to 5.2).	

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Michils, 2009 [75]	Belgium, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 470	Nonsmokers (n= 411) Mean Age 41 years (SD: 16), male 47.4%, atopic 85.1%. Smokers (n=59); mean age 38 years (SD: 11), male57.6%, atopic 91.5%.	Measured by online chemoluminescence analyzer (Logan Research Ltd, Rochester, UK) at a flow rate of 50 mL/sec (American Thoracic Society (ATS)/European Respiratory Society (ERS) standard).	FeNO exhibits high operating characteristics in both nonsmoking and smoking groups. The cut-off values for decreases in FeNO which had the highest NPVs for establishing control were 30% in nonsmokers and 20% in smokers. When considering the subgroup of smoking patients treated with >500 mg equivalents BDP.day-1, FeNO was no longer significant in assessing an improvement of asthma control. As for improvement assessment, FeNO exhibited analogous operating characteristics in nonsmoking and smoking patients.	Baseline FeNO: Nonsmokers: 33.7 (14.3 to 79.2), smokers: 18.1 (6.9 to 47.5).	Correlation between FeNO and ACQ were noted in smokers and nonsmokers on ICS.
		Asthma control questionnaire (ACQ), N= 470		Asthma control was assessed using a French translation of the short version of the ACQ of Juniper et al.		ACQ score: Nonsmokers: 1.5 (0 to 5), smokers: 1.7 (0 to 5.3).	

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		Spirometry, N= 470			With a cut-off value at 30% change, a high NPV was observed in both groups. When considering the subgroup of smoking patients treated with >500 mg equivalents BDP.day-1, FeNO operating characteristics in assessing asthma control worsening are less significant.	FEV_1: Nonsmokers: 85.6 (SD: 15.7), smokers: 86.2 (SD:17.9).	
Nayak, 2013 [28]	India, Cross section study, Inpatient setting, medium	FeNO, N= 100	Asthmatics (N=55): Mean age 45.2 years (12-82), 41.8% male, 51% On inhalational steroids.	Three FeNO measurements were recorded for each subject using chemiluminescence NO-analyser and the procedure was performed as per standard	The FeNO levels were not significantly lower in steroid treated cases as compared with steroid naïve cases.	asthmatics: 16.5 ppb (SD: 10.3) Controls: 5.5 ppb (SD: 2.7).	In patients with bronchial asthma, FeNO levels significantly correlate with the severity of

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	risk of bias.		Controls (N=45): Mean age 48.5 years (16-76), 48.9% Male.	recommendation. FeNO level of < 8.0 ppb was taken as normal.		Steroid-treated cases (N=28): 15.7 ppb (SD: 9.8). Steroid-naive cases (N=27): 17.3 ppb (SD: 10.9). Correlation of FeNO with severity of asthma in steroid-treated cases: Mild asthma: 6.3 ± 2.6 Moderate asthma: 15.1 ± 9.7 Severe asthma: 18.8 ± 9.7. Correlation of FeNO with severity of asthma in steroid-naïve cases: Mild asthma: 11.9 ± 8.3 Moderate asthma: 20.7 ± 8.2 Severe asthma:	asthma and the levels reduce with steroid therapy.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
						28.9 ± 11.3	
Nittner-Marszalska, 2013 [76]	Poland, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=72	Pregnant asthmatics with a median age 29 years (18-38), 0% male, 0% current smokers, 73.6% atopy.	Flow of 50mL/sec, using an online chemoluminescence analyzer (NIOX, Aerocrine, Stockholm, Sweden), in a fasting status every month for 6 months.	No asthma exacerbation experience. It is defined as an episode of increasing asthma symptoms requiring a change of corticosteroids treatment.	31.6 ppb (7.3 to 129.8).	Pregnant asthmatics women underwent monthly FeNO and there was a weak correlation between FeNO and ACT and wide variation in FeNO values. Results were the same in atopic and non-atopic women. Levels did not significantly differ in women who lost control from values during control.
		Spirometry, N=72		Spirometry (Master Scope, Jeager, Germany) was performed according to the recommendations of the American Thoracic Society and the European Respiratory Society		FEV_1 97.1% pred (55 to 135).	
Ozier, 2011 [77]	France. longitudinal cohort study, medium risk of bias.	FeNO (EndoNO), N= 90	controlled asthma (N= 62) mean age of 38.5, 32% males, 77.4% atopic, 23% ever smoked. uncontrolled asthma (n=28):	chemiluminescence device EndoNO (SERES, France) on-line at a flow rate of 50 ml/s and a pressure of 10 cm H2O		FeNO (EndoNO) cutoff of 22 ppb (n=89) can predict the persistence of asthma control with: Sensitivity	In Adults, FeNO can predict the persistence of asthma control in controlled patients and may can be used in asthma

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			mean age of 44.8 years, 46% males, 82.1 atopic, 32% ever smoked.			77.7%, specificity 62.9%, PPV 47.7%, NPV 86.7%.	management since it can accurately be measured by means of hand-held devices.
		FeNO (MINO) , N= 90		Electrochemical device NIOX MINO (Aerocrine AB, Sweden).		FeNO (MINO) cutoff of 31 ppb (n=78) can predict the persistence of asthma control with: Sensitivity 60%, specificity 66%, PPV 45.4%, NPV 77.8%.	
		Asthma control questionnaire (ACQ) , N= 90		All clinical and the functional items were equally weighted and averaged (each quoted from 0-6).		Well controlled: 0.62 Non-well controlled 2.48	
Papakosta , 2011 [78]	Greece, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 160	Adults with newly diagnosed asthma Mean age 39.7 years (SD: 16.6), 35% male.	FeNO was measured at an expiratory flow rate of 50 ml/s by a chemiluminescence analyzer (CLD 88sp; ECO MEDICS AG, Duernten, Switzerland) according to the latest American Thoracic Society / European Respiratory		Baseline: 25.97 ppb (SD: 25.68) At 4–12 weeks after initiation of treatment: 17.0 ppb (SD: 14.77). Completely Controlled	In adults with newly diagnosed asthma, patients with uncontrolled asthma had statistically higher FeNO values than patients with

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
				Society (ATS/ERS) recommendations.		group (N=37) Baseline: 20.52 ppb (SD:24.97) At 4–12 weeks after initiation of treatment (N = 48): 19.23 ppb (SD: 18.18). Partly controlled (N=85) Baseline: 24.39 ppb (SD: 20.58) At 4–12 weeks after initiation of treatment: 15.39 ppb (SD: 12.72) Uncontrolled (N= 38) Baseline: 34.78 ppb (SD: 33.92). At 4–12 weeks after initiation of treatment (N = 13): 21.04 ppb (SD: 14.66)	partly controlled (p = .038) and completely controlled asthma (p = .016). ACT score was found to have a negative correlation with FeNO.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 160		FEV_1 was measured by an electronic spirometer (Wright Ventilometer, Clement Clarke International, London England).		Baseline: FEV_1 88.18% pred (SD: 14.17) At 4–12 weeks after initiation of treatment: FEV_1 92.63 % pred (SD: 12.34) Completely controlled (n = 37): Baseline: FEV_1 0.28 % pred (SD: 14.60) At 4–12 weeks after initiation of treatment (N = 48): FEV_1 95.07 % pred (SD: 13.01) Partly controlled (N= 85): Baseline FEV_1 88.74 % pred (SD: 13.19) At 4–12 weeks after initiation of treatment (N = 99):	

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						FEV_1 92.23 % pred (SD: 11.79) Uncontrolled (N = 38): Baseline FEV_1 84.89 % pred (SD: 15.62) At 4–12 weeks after initiation of treatment (N = 13): FEV_1 86.71 % pred (SD: 12.57).	
		Asthma Control Test (ACT) score, N= 160		The ACT questionnaires administered to the patients of this study had been formally translated into Greek. Patients were classified into three groups based on ACT scores (9): completely controlled (ACT score = 25), partly controlled (ACT score range = 20–24), and uncontrolled (ACT score range = 5–19).		Baseline: 21.27 ± 3.74 At 4–12 weeks after initiation of treatment: 23.00 ± 2.19 (P < 0.001)	
Plaza, 2013 [79]	Spain, longitudinal nonrandomized,	FeNO, N= 381	Mean age 44.3 years (SD: 14.86), 43% male, 66.4% atopy.	Flow of 50mL/sec, using a NioxMino® portable equipment (Aerocrine, Sweden)	The combination of FeNO and ACQ-7, showed 75% specificity and a	Baseline: 44.18 ppb (SD: 29.82) At 1 month:	In adults with not well controlled persistent

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	outpatient setting, low risk of bias.				85.2% positive predictive value to identify patients with not well controlled asthma. The area under the ROC curve was 0.8754 for FeNO and ACQ-7 combined, and 0.544 for sole FeNO.	26.8 ppb (SD: 20.82).	asthma and a positive bronchodilator test, adding FeNO to ACQ-7 increased the detection of not well controlled asthma following maintenance therapy adjustment by 14.8%.
		Spirometry, N= 381		Spirometry was performed according to the European Respiratory Society/American Thoracic Society guidelines using the predicted values for Mediterranean populations.		FEV_1 Baseline: 79% pred (SD: 18.8) At 1 month: 85.3% pred (SD: 16.6).	
		ACQ-7 score, N= 381		The questionnaire contains 7 items comprising 6 multiple choice test questions on the frequency of asthma symptoms and the use of rescue medication within the prior 7 days, and the FEV_1 percent of predicted value. The total ACQ-7 score, computed from its 7 items, ranges from 0 (maximum control) to 6 (minimum control), and a 0.75 point threshold was chosen to consider controlled asthma		Baseline: 2.21 (SD: 0.81) At 1 month: 1.10 (SD: 0.78).	
Quaedvlieg, 2009 [80]	Belgium, cross section, outpatient setting, low	FeNO, N= 134	Well controlled group (N=31): mean age 40 years (SD: 13), Male 52%,	measured by an online chemoluminescence analyser (NIOX, Aerocrine, Stockholm, Sweden), at one visit, at a	There is no FeNO significant difference between the three groups.	Controlled mean 47.9 ppb (11.4 to 130), borderline mean 30.6 ppb (2.8 to	In adults with asthma mostly on ICS, FeNO did not differentiate

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	risk of bias.		Ever smokers 32%, current smokers 3%, atopy 90%. Borderline group (N=32): mean age 47 years (SD: 12), Male 50%, Ever smokers 0%, current smokers 25%, atopy 69%. Uncontrolled group (N=71): mean age 42 years (SD: 12), Male 49%, Ever smokers 20%, current smokers 20%, atopy 69%.	flow rate of 50 mL/s, in accordance with the recommendations of the ATS/ERS task force. Corticosteroid use and bronchodialtors withhold prior to test in each group were 64%, 62%, 65% and 100%, 100%,100%, prospectively.		222), uncontrolled mean 50.2 ppb (4.1 to 244).	well controlled/borderline controlled/well-controlled based on ACQ.
		A bronchial responsiveness (methacholine challenge test), N= 134		Measured by a modified Cockroft's method. Inhaled tidal breathing for 2 min fourfold increasing concentrations of methacholine chloride from 0.06 to 16 mg/mL. The aerosol was generated by a jet nebulizer (Hudson, Temecula, CA, USA).	Uncontrolled asthmatics had a greater BHR to methacholine than controlled asthma.	PC20 in controlled mean 6.3 mg/ml (0.17 to 16), borderline mean 3.9 mg/ml (0.05 to 16), uncontrolled mean 1.6 mg/ml (0.06 to 16).	
		Sputum eosinophilia, N= 134		induced by inhalation of a hypertonic saline (NaCl 4.5%) combined with additional salbutamol delivered by an ultrasonic nebulizer (Ultra-Neb 2000, De Vilbiss, Somerset, PA, USA) with an output set at 0.9 mL/min. Sputum was weighed and homogenized by adding three volumes of PBS,	Uncontrolled asthmatics had a greater sputum eosinophilia than controlled and borderline asthma.	Controlled mean 0.4% (0 to 31.2), borderline mean 1.4% (0 to 26), uncontrolled 5.6% (0 to 93.4).	

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				vortexed for 30 s and centrifuged at 800 g for 10 min at 41C.			
		Spirometry, N= 134		Electronic spirometer connected in real time to a computer (Spirobank, MIR, Rome, Italy). All manoeuvres were repeated three times and the best FEV_1 value was selected by the software program (Winspiro, MIR).		FEV_1 (% pred); controlled mean 101 (SD: 11), borderline mean 88 (SD: 13), uncontrolled mean 81 (SD: 27). FEV_1/FVC (%); controlled mean 80.6 (SD: 4.5), borderline mean 76.5 (SD: 6.5), uncontrolled mean 79 (SD: 21).	
		Asthma Control Questionnaire (ACQ), N= 134		The ACQ score from the six-item Juniper ACQ questionnaire deleting the FEV_1 from the original questionnaire (0 = totally controlled and 6 = severely uncontrolled).		Controlled ACQ < 0.75, uncontrolled ACQ > 1.5, borderline ACQ 0.75-1.5.	
Raj, 2014 [81]	India, longitudinal cohort study, outpatient setting, medium	FeNO, N= 243	mean age of 8.3 years, 76% males, 100% atopic (positive to at least one allergen).	measurement was done using NIOX MINO (Aerocrine AB, Solna, Sweden), 81% were on inhaled steroids,	Pulmonary score did not correlate with acute exacerbation FeNO (r=0.1, Spearman correlation, P=0.29).	Baseline (n=185) Median 15 ppb (9-26) Personal best (n=218) Median 8 ppb	In children with acute exacerbation of asthma, FeNO during exacerbation was not higher

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	risk of bias.				FeNO cutoff = 20 ppb during exacerbation had a sensitivity of 44%, specificity of 68.7%, AUC of 0.59.	(5-12) During exacerbation (n=143) Median 17.7 ppb (12-25.3).	than that during follow up but was significantly higher than personal best. FeNO during acute exacerbation did not correlate with the severity of acute exacerbation and could not diagnose or predict exacerbation.
		Spirometry, N= 243		Spirometry was done using portable spirometer (Superspiro MK2, Micro Medical Ltd, UK)			
		Pulmonary score, N= 243		Each parameter is rated on a 0-3 scale, with a maximum total score of 9. Mild, moderate, and severe acute exacerbations were defined as pulmonary score of 0-3, 4- 6, and 7-9, respectively.			
Ricciardolo, 2016 [82]	Italy, cross sectional, outpatient setting, high risk of bias.	FeNO, N=363	Mean age 46.28 years (SD: 17.11), 41.3 % males, BMI 25.31 kg/m^2 (SD: 5.18), 81.3% atopic (allergy).	Measured with a chemiluminescence analyser(Eco Medics CLD88 sp, Duernten, Switzerland) beforespirometry; the detection limit of the apparatus was 1-5parts per billion (ppb), as required by ATS guidelines	Compared to controlled and partly controlled asthmatic, poorly controlled asthmatics showed the highest FeNO values ($p < 0.001$), with a probability almost four times greater to have pathological values	Poorly controlled asthmatic median: 42.90 ppb, 25th-75th:19.63 to 77.15). (OR: 3.71, 95%CI: (1.74 to 7.89); p = 0.002)	FeNO assessment in clinical practice may be a useful tool for monitoring asthmatics as it is associated with several clinical factors, including asthma

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		Spirometry, N=363		Spirometry was performed using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, England, ---predictive values ECCS 1993), with optoelectronic whirl flowmeter.	compared to controlled asthmatic patients (p = 0.002).		control.
Robroeks, 2007 [83]	Netherlands, cross sectional study, outpatient clinic, high risk of bias.	FeNO, N= 64	mean age 10.7 years (SD: 0.4), mean weight 38 Kg (SD: 2).	Measured at one visit using offline chemoluminescence analyzer nitric oxide monitor (NIOX; Aerocrine AB, Solna, Sweden) at an exhalation flow rate of 50 ml/sec.	Compared to FEV_1, FeNO, IFN-g and IL-4 were significant indicators of an asthma diagnosis, with odds ratios ranging from 1.03 for FeNO to 5.21 for IL-4 in EBC.	FeNO at 30ppb: OR: 3.32; 95% CI: 1.05 to 10.5. FeNO at 20 ppb: OR: 2.26; 95%CI: 0.92 to 5.55.	FeNO, 8-isoprostane, IFN-gamma and IL-4 were significant indicators of asthma control with a sensitivity of 82%, specificity of 80%, and area under the curve was 0.761.
		exhaled breath condensate (EBC), N= 64		The acidity of EBC was immediately measured in non-deaerated samples (Radiometer, type PHM201, Zoetermeer, the Netherlands) and EBC was rapidly frozen at 80 1C using dry ice, and was stored at 80 1C until analysis. Then, cytokines (IFN-g, TNF-a, IL-2, -4, -5, -10) were assayed with flow cytometry (CBA, BD Biosciences, San Diego, CA, USA).			

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Rosias, 2004 [84]	Netherlands, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N=23	Mean age 10.6 years (SD: 2.8), weight 35.4 Kg (SD: 12.3).	FeNO was measured by means of NIOX (Aerocrine, Solna, Sweden) according to the criteria of the American Thoracic Society. At a constant flow rate at 50 ml/sec, guided by a balloon meter. The mean FeNO value of three consecutive measurements was used for analysis.	The correlate ons found between FeNO and preFEV_1 (r ¼ 0.59, P< 0.05), and FeNO and ACQ score (r¼ 0.48, P¼ 0.06).	FeNO median 23.1 (SD: 5). FEV_1% pred; Pre-FEV_1: 96.4% (SD:16.2), Post-FEV_1: 103.2% (SD: 16.7).	In children with mild to moderate persistent asthma on ICS, FeNO weakly correlated with asthma control questionnaire (p=0.06).
		Spirometry, N= 23					
Sato, 2009 [85]	Japan, cross sectional, inpatient setting, medium risk of bias.	FeNO, N=78	Non-exacerbation group (N=62): mean age 60.4 years (SD: 14.1), male 43.5%, atopic% 54.8, BMI 21.7 (SD: 8.6), current smoker 12.9%, ever smoker 19.4%. Exacerbation group (N=16):	Using an online collection apparatus using chemiluminescence (280A Sievers Nitric Oxide Analyzer, Boulder, CO, USA) according to the ATS (American Thoracic Society) guidelines.	The area under the curve (AUC) of the cut-off points of the second node, as the combination of the ACT score ≤23 and the percentage of predicted FEV_1 ≤91.8% (AUC 0.678, 95% CI	FeNO: non-exacerbation group: 42.8 (SD: 30.6), exacerbation group: 47.1 (SD: 40.2).	In adults with mild to moderate asthma, clinically stable for 3 months on ICS, FeNO did not accurately predict future exacerbations over a year

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		Spirometry, N=78	mean age 64.6 years (SD: 7.2), male 37.5%, atopic% 56.3, BMI 21.9 (SD: 7.8), current smoker 6.3%, ever smoker 18.8%.	When clinically stable for at least 2 months, asthmatic patients were instructed to continue all their medications, except to withhold inhaled long-acting ß2-agonists for 24 hours and inhaled albuterol sulfate for 6 hours before testing. Spirometry was performed	0.513 to 0.833) are the most predictive factors in comparison with those of the first node, as the ACT score ≤23 (AUC 0.613, 95% CI 0.453 to 0.773), or those of the third node, as the combination of the ACT score ≤23, and the percentage of predicted ≤91.8% and FeNO≥36.7 ppb (AUC 0.625, 95% CI 0.453 to 0.797).	Baseline FEV_1% Non-exacerbation group: 92.7 (SD: 15.8), exacerbation group: 83.3 (SD: 17).	(AUC 0.501 (0.341–0.661), sensitivity 0.44, specificity 0.57.
		ACT, N=78		using a CHESTAC-8800 (CHEST, Tokyo, Japan).		ACT score: non-exacerbation group: 23.6 (SD: 2.2), exacerbation group: 23.4 (SD: 1.8).	
Shirai, 2008 [86]	Japan, cross sectional, outpatient setting, high risk of bias.	FeNO, N= 105 Classified by 5-item ACT questionnaire score. (Totally controlled =25, well controlled = 20-24, uncontrolle	Total controlled (N=45) Median age 54 years (35-62), male 42.2%, ever smoker 24.4%, current smoker 8.9%. Well controlled (N=28) Median age 57 years (43-67), male 32.1%, ever smoker 23.1%, current smoker 14.3%.	Measured by online nitric oxide analyzer (Sievers NOA 280i; Sievers, Boulder, Colorado) at 50 ml/sec.	FeNO were significantly lower in the totally controlled asthma group than in the uncontrolled asthma group. ACT score was negatively correlated with FeNO, however, it was a weak correlation (r= -0.310).	Total controlled Median 53 (44.5 to 64.5). Well controlled Median 61.9 (33.5 to 105.6). Uncontrolled Median 72.1 (45.9 to 142.8).	In adults with asthma on ICS for 3 months, ACT ability to differentiate controlled from uncontrolled was improved with FeNO

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		d= 5-19).	Uncontrolled (N=32) Median age 49 years (36-62), male 32%, ever smoker 37.5%, current smoker 12.5%.				
		Spirometry, N= 105			No significant differences were seen in %FEV_1 and FEV_1/ FVC between three groups. ACT score was positively correlated with %FEV_1 but not with FEV_1/FVC, however, it was a weak correlation FEV_1% pred (r 0.219).	FEV_1 % pred Total controlled median 93.4 (84.5 to 105.4). Well controlled median 87.9 (76.0 to 94.3). Uncontrolled median 86.4 (71.8 to 95.9). FEV_1/FVC Total controlled median 78.0 (66.9 to 84.9). Well controlled median 73.4 (66.4 to 80.6). Uncontrolled median 73.2 (62.9 to 84.5).	

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Szefler, 2008 [87]	United States, RCT, outpatient setting, low risk of bias.	FeNO monitoring, N= 276. (guideline-based care and FeNO)	Mean age 14.4 years (SD: 2.1), 52.9% males, Race: Black 66%, Hispanic 22%, other or mixed 11%.	Measured by a rapid-response chemiluminescent analyzer (flow rate 50 mL/s; NIOX System, Aerocrine, Sweden) according to the guidelines of the American Thoracic Society.	Maximum days with symptoms, which was our primary endpoint, did not differ between treatment groups over the study period (p=0·78). Control levels did not differ between groups. lung function, fraction of exhaled NO, and adherence did not differ between groups during the study; however, despite the level of control achieved, fraction of exhaled NO was less than 20 ppb in only 190 (35·6%) of 534 participants on at least 80% of visits during the treatment period.	306/534 patients (57·3%) had their asthma under good control (control level=1) for at least 80% of visits. In 122/534 patients (22·8%), asthma control was at level 3 or 4 for at least 20% of visits. (22·1% of FeNO monitoring Group and 23·6% of control group).	Patients aged 12–20 years with persistent asthma randomized to guideline based treatment vs treatment modified by FeNO (for 46weeks). Both groups had similar days with symptoms, and exacerbation rate. FeNO group had higher ICS doses.
		Control (guideline based care only), N=270	Mean age 14.4 years (SD: 2.1), 52.6% males, Race: Black 61%, Hispanic 23%, other or mixed 16%.				
van der Valk, 2012 [88]	Netherlands, Switzerland and Italy, longitudinal nonrandomized,	FeNO, N=27	Moderate exacerbations (N=18): Mean age 11.7 years (SD: 2.5), 44.4% male, Weight 43.8 Kg (SD: 11.8).	Fractional exhaled nitric oxide was measured daily using a handheld airway inflammation monitor (NIOX MINO, Aerocrine, Solna, Sweden), along with daily symptom scores		Moderate exacerbations (N=18): 21 ppb (14 to 32). Severe exacerbations	In Children with asthma receiving daily measurements of FeNO, slope and trends can

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	outpatient setting, medium risk of bias.		Severe exacerbations (N=9): Mean age 10.1 years (SD: 2.1), 22.2% male, Weight 37.6 Kg (SD: 11.1).	for 30 weeks at home		(N=9): 19 ppb (10 to 40).	predict exacerbations
		Spirometry N=27				Moderate exacerbations (N=18): FEV_1 86.7% pred (SD: 16.6) Severe exacerbations (N=9): FEV_1 78.7% pred (SD: 24.3).	
van Vliet, 2015 [89]	The Netherlands, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N =96	Age mean (range) 10 (6-17), 52 % males, 76 % atoptic asthma	FeNO was measured online using a NIOX analyzer (Aerocrine, Solna, Sweden) according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria. A standard flow rate of 50 ± 5 ml/sec was required for a correct maneuver.	Performance of, FeNO in prediction of asthma exacerbation	Estimate (95% CI) -0.011 (−0.029 to 0.007)	In asthmatic children on ICS, FeNO measured every 2 months did not predict exacerbations even when combined with inflammatory

		ACQ Questionnaire, N=96		The ACQ was used to assess asthma control at the clinical visits. The cut-off points used for level of asthma control were: ACQ ≥ 0.75 (controlled asthma); 0.75< ACQ ≤1.5 (partly controlled); and ACQ >1.5 (uncontrolled asthma).	Performance of asthma clinical characteristics (ACQ score) in prediction of asthma exacerbation	Estimate (95% CI) 0.082 (- 0.424 to 0.589)	markers and clinical characteristics.
		spirometry, N=96		Performed by means of the ZAN 100 spirometer, according to ATS/ERS standards (nSpire Health GmbH, Oberthulba, Germany). Recorded parameters included: FEV_1, forced vital capacity (FVC) and maximum expiratory flow at 50% of FVC (MEF50)	Performance of (Bronchodilator response, delta FEV_1 % predicted value) in prediction of asthma exacerbation	Estimate (95% CI) −0.047 (−0.104 to 0.011)	
Visitsunthorn, 2014 [90]	Thailand, Cross-sectional study, outpatient setting, high risk of bias.	FeNO, N=114	Mean age 12.3 years (SD: 3.5), 61.4% males, BMI 20.21 (SD: 4.65), atopy 100%.	Measured by means of an electrochemical technique (ECO medics, CLD 88 sp, chemiluminescence NO-analyzer with optional ultrasonic flow meter). Carried out according to the manufacturer's and American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations, requires a single-breath on-line measurement with the mouthpiece in place.	The FeNO levels and log FeNO in patients with different asthma control status	uncontrolled group FeNO 39.15 ppb (2.40 to 192.30), partly controlled group FeNO 24.90 ppb (2.20 to 85.70) controlled group FeNO 19.20 ppb (5.10 to 108.90). The mean+ SD of Log FeNO in controlled group 1.295+0.31, partly controlled group 1.298+0.41 uncontrolled group 1.417+0.49	In children with asthma (mostly mild persistent), FeNO levels differentiated controlled, partly controlled and uncontrolled in those not on ICS (trend was not statistically significant in those on ICS)
		Spirometry, N= 114		Spirometry was performed using the standard method.			

Voorend-van Bergen, 2015 [91]	The Netherlands, RCT, outpatient setting, high risk of bias.	FeNO, N= 266	FeNO Group (n=92) Mean age 10.3 years (SD: 2.9), 67 % males, 100 % atoptic. Web based mointoringgroup (n =91) Mean age 10.6 years (SD: 2.8), 66 % males, 100 % atoptic. Standard care Group (n=89) Mean age 10.2 years (SD: 3.2), 69 % males, 100 % atoptic.	FeNO was measured online on the NIOX chemiluminescence analyzer or NIOX MINO (Aerocrine, Stockholm, Sweden) according to guidelines, offline, Assessed using an electronic spirometer (Masterscreen, Jaeger, Würzburg, Germany) and expressed as percentage predicted or z-score according to= GLI2012	Mean difference was higher in web group than other groups.	FeNO change from baseline over time expressed as ratio of geometric means; FeNO group 1.40 Web group 1.64 Standard care group 1.18	RCT of children with atopic asthma compared web-based monthly monitoring ACT vs FeNO and ACT every 4 months vs standard care. There was no statistically significant difference in terms of ACT or asthma free days. Lower ICS use was in the web based approach. QALYs and costs were not statistically significant
		Spirometry, N= 229			FEV_1 % pred mean difference was higher in standard care group than other groups.	FeNO group 0.16 Web group -0.10 Standard care group 0.26	
		Asthma Control Test, N= 269		Used the Dutch, translated and linguistically validated version of the ACT (MAPI-research institute, Lyon, France) in children from the age of 12 years, and the C-ACT for children aged 4–11 years	Mean difference was higher in web group than other groups.	FeNO group 0.12 Web group 1.73 Standard care group 0.37	
Warke, 2004 [92]	Ireland, cross sectional, outpatient setting, high risk of bias.	FeNO, N=133	Median age 9.9 years (range 5-14), 53.3% male.	Measured by online chemiluminescence analyzer (NOATM 280, Sievers Instruments Inc., Boulder, Colorado). The flow rate was 50 ml/s and this corresponded to a mouth pressure of 17 cm	FeNO levels (median [IQR] ppb) were significantly elevated in children who had recent symptoms compared with those without	Recent symptoms (n = 101) 14.6 ppb [6.5 to 45.3]) vs those without recent symptoms (n=32) 6.0 ppb	In children, FeNO levels differed significantly between the controlled and uncontrolled asthmatics and

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
				H2O.	recent symptoms. The difference between medians was 8.6 ppb (95% CI for the difference 1.8 to 13.9, p = 0.004). However, there was a significant difference in FeNO levels between the controlled and uncontrolled group (difference between medians 17.9 ppb [95% CI for difference 0.1 to 22.8], p=0.03).	[3.2 to 17.4].	between the three treatment decision subgroups (up, down, or unchanged).
		Spirometry, N=133		Performing a forced expiratory maneuver (MicroLab 3300 spirometer, Micro Medical Ltd., Gillingham, UK).			
Yamashita, 2015 [93]	Japan. longitudinal cohort study, outpatient setting, high risk of bias.	FeNO, N=37	uncontrolled asthma (N= 18) mean age of 49.2, 33.4% males, 16.6% current smokers. controlled asthma (N= 19) mean age of 52.2, 23.3% males, 5.3% current smokers.	NIOX MINO© (Aerocrine AB, Solna, Sweden), at a constant flow rate of 50 mL/s.	Using a FeNO cut-off level of 34 ppb yielded a sensitivity of 76.5% and specificity of 73.7% for the achievement of full asthma control. AUC = 0.86.	uncontrolled 60.7ppb (SD35). controlled: 24.9 ppb (SD 14.5)	Using a FeNO cut-off level of 34 ppb yielded a sensitivity of 76.5% and specificity of 73.7% for the achievement of full asthma control.
		Gold standard, N=37		A positive indication of airway reversibility after inhalation of a short-acting β2 agonist, response to a provocative concentration of methacholine, or sputum eosinophil counts >3% or FeNO levels >22 parts per billion (ppb). Mild			

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
				asthma was defined as a forced expiratory volume within 1 s (FEV_1.0 predicted) of >80% at the first diagnosis of asthma.			
Yang, 2015 [94]	Korea, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N=145	Mean age 10.58 years (SD: 2.60), males 71%, BMI 19.15 (SD: 3.75), atopy 100%	FeNO was measured by an NO analyzer with electrochemical sensors (NIOX MINO; Aerocrine AB, Solna, Sweden), according to the ERS/ATS guidelines. Constant flow rate of 50 mL/s. FeNO was measured twice and a third measurement was performed if there is a more than 10% difference between first 2 measurements.	H-FeNO (mean (95% CI, ppb) (No loss of asthma control vs loss of asthma control) R21FeNO (%) mean (95% CI) (No loss of asthma control vs loss of asthma control)	32.98 (29.70 to 36.63) vs 59.82 (55.60 to 64.35) 22.80 (16.41 to 29.19) vs 58.10 (53.45 to 62.75)	In patients aged 8-16 years with atopic asthma serially monitored over 2 years, loss of asthma control was predicted by the highest FeNO of serial measurements and the rate of FeNO > 21 ppb.
		Spirometry, N=145		Lung function tests were performed with spirometer (Vmax SensorMedics, Yorba Linda, CA, USA) in accordance with ERS/ATS recommendations	L-%FEV_1 mean (95% CI) (No loss of asthma control vs loss of asthma control) L-FEV_1/FVC (%) mean (95% CI) (No loss of asthma control vs loss of asthma control)	84.40 (80.34 to 88.46) vs 78.03 (75.41 to 80.64) 79.63 (77.12 to 82.13) vs 74.16 (72.32 to 76.00)	
Yavuz, 2012 [95]	Turkey, longitudinal	FeNO, N= 76	Mean age 8.7 years (SD: 1.4),	Using an online NIOX-MINO; Aerocrine,	A C-ACT score of 22 or less had 69%	**Baseline:** Well controlled	In children, multivariate

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
	nonrandomized, outpatient setting, low risk of bias.		61.8% male.	Stockholm, Sweden at a flow of 50mL/sec. The mean value of three consecutive measurements was used for analysis. Bronchodilators withheld prior to FeNO test in 39.5 %.	sensitivity and 77% specificity in determining not well-controlled asthma, whereas a FeNO value of 19 ppb or higher had 61% sensitivity and 59% specificity in patients who completed 3 visits.	asthma (N=40): 16 ppb (13–22) Not well controlled asthma (N=36): 20 ppb (13–28). **At 1 month:** Well controlled asthma (N=45): 18 ppb (12 to 26.5). Not well controlled asthma (N=19): 23 ppb (16 to 31). **At 2 months:** Well controlled asthma (N=39): 16 ppb (13 to 26) Not well controlled asthma (N=12): 21.5 ppb (14 to 69).	analysis revealed that a C-ACT score of 22 or less (odds ratio, 8.75; 95% CI, 4.35–17.59) and a FeNO of 19 ppb or greater (odds ratio, 2.60; 95% CI, 1.07–6.29; P .03) were significant indicators for not well-controlled asthma.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 76		Spirometry tests used ZAN100 spirometry system (nSpire Health, Longmont, Colorado)		**Baseline:** Well controlled asthma (N=40): FEV_1 96% pred (89 to 103) FEV_1/FVC 90% pred (84 to 94) Not well controlled asthma (N=36): FEV_1 84% pred (75 to 94) FEV_1/FVC 85% pred (80 to 94). **At 1 month:** Well controlled asthma (N=45): FEV_1 97% pred (89 to 102) FEV_1/FVC 91% pred (85 to 95). Not well controlled asthma (N=19): FEV_1 84% pred (74 to 94). FEV_1/FVC 87% pred (80 to 94). **At 2 months:** Well controlled asthma (N=39): FEV_1 93% pred (86 to 105) FEV_1/FVC 89% pred (83 to 94). Not well controlled	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
		Childhood Asthma Control Test (C-ACT), N= 76		The official Turkish version of the C-ACT questionnaire was administered. Children and parents answered their respective parts of the test separately, and the sum of their scores was used for analysis. Absolute values for the C-ACT scores are demonstrated, and changes in C-ACT scores are expressed as a percentage of the initial value.		**Baseline:** Well controlled asthma (N=40): 24 (21 to 26) Not well controlled asthma (N=36): 19 (17 to 21) **At 1 month:** Well controlled asthma (N=45): 25 (23 to 26) Not well controlled asthma (N=19): 20 (16 to 23) **At 2 months:** Well controlled asthma (N=39): 24 (22 to 26) Not well controlled asthma (N=12): 23 (21 to 25).	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
Zeiger, 2006 [96]	United States, RCT with cross-over, outpatient setting, unclear risk of bias.	FeNO, N= 99	Range age (6-13) years, Male 59%.	Measured by (78% online) NIOX Aerocrine AB – chemiluminescence,	FeNO decreased after 16 weeks of fluticasone propionate (FB) 100 mg BID, and montelukast (MT) 5-10 mg once a day but the decrease was greater after fluticasone. Change in FeNO correlated with improvements in asthma control days (ASDs) in fluticasone but not with montelukast.	Baseline 39.5 ppb (34.2 to 44.7) FP 20.6 ppb (15.0 to 26.2) MT 30.9 ppb (25.5 to 36.2) FP-MT mean difference -10.3 ppb (-16.9 to -3.7). FeNO vs ACDs FP -0.21 (-0.33 to -0.08) MT -0.04 (0.17 to 0.09)	Change in FeNO level significantly predicted asthma control days in children treated with fluticasone (but not montelukast)
		Spirometry, N= 126			Fluticasone (FB) led to significant improvements in prebronchodilator FEV/FVC while montelukast (MT) associated with a significant but small decrease. However, greater improvements in prebronchodilator FEV_1/FVC occurred after fluticasone (FB) than after montelukast (MT).	FEV_1/FVC % baseline 126 80.1 (79.1 to 81.1) FP 82.2 (80.9 to 83.6) MT 79.0 (77.6 to 80.5) FP-MT mean difference 3.2 (2.3 to 4.1)	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
		Asthma control questionnaire , N= 127			Compared with baseline, both fluticasone (FB) and montelukast (MT) treatments were associated with significant improvements in ACQ scores, but better control was achieved with fluticasone.	Baseline 0.96 (0.89 to 1.03) FP mean 0.59 (0.50 to 0.69) MT mean 0.76(0.66 to 0.87) FP- MT mean difference -0.17(-0.27 to -0.07)	
Zeiger, 2011 [97]	United States, Cross section study, outpatient setting, medium	FeNO, N= 325	Group 1; 1st quartile of FeNO (7-19 ppb): (N=88) Mean age 37.2 years (SD: 14.5), 25% Male, 59.1% Allergic rhinitis 30.7% Atopic dermatitis	FeNO measurements were done using the NIOX MINO® handheld device (Aerocrine AB, Solna, Sweden)		Group 1: 15 ppb (7 to 19) Group 2: 25 ppb (20 to 28) Group 3: 37 ppb (29 to 47) Group 4: 72 ppb (48 to 215)	In atopic 12- to 56-year-old persistent asthmatics on ICS, higher FeNO levels significantly correlated with

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
	risk of bias.	Spirometry, , N= 325	BMI 28.6 (SD: 7.9). Group 2; 2nd quartile of FeNO (20- 28 ppb): (N=77) Mean age 37.7 years (SD: 14.4), 41.6% male, 55.8% Allergic rhinitis, 27.3% Atopic dermatitis, BMI 28.2 (SD: 6.6). Group 3; 3rd quartile of FeNO (29- 47 ppb): (N=79) Mean age 36.4 years (SD: 14.8), 51.6% male, 60.8% Allergic rhinitis, 26.6% Atopic dermatitis, BMI 28.6 (SD: 6.5). Group 4; 4th quartile of FeNO (48- 215 ppb): (N=81) Mean age 31.4 years (SD: 14.8), 42% male 59.3% Allergic rhinitis, 32.1% Atopic dermatitis, BMI 27.6 (SD: 6.5).	Spirometry captured FEV_1, FEV_1% predicted, and FEV_1/FVC using the KOKO electronic Pneumotach spirometer (Ferraris Respiratory, Louisville, CO, USA) by ATS standards and over-reading for quality assurance. Age, gender, and ethnicity appropriate prediction equations were used to calculate the percent of predicted FEV_1.		FEV_1 Group 1: 89.4% pred (SD: 14.0) Group 2: 87.1 % pred (SD:14.1) Group 3: 84.8 % pred (SD:13.9) Group 4: 83.8 % pred (SD:16.8) FEV_1/FVC Group 1: 0.80 % pred (SD:0.08) Group 2: 0.77 % pred (SD:0.09) Group 3: 0.77 % pred (SD:0.08) Group 4: 0.74 % pred (SD:0.09)	more SABA dispensing and oral steroids courses in the past year, lower FEV (1) % predicted levels, but not ACT score.
		Asthma Control Test (ACT) score, N= 325		>19 controlled, 16–19 not well controlled, and <16 very poorly controlled		Asthma control test: 3-level categories (%) **Group 1:** controlled: 61.4 not well controlled: 18.2 very poorly controlled: 20.5 **Group 2:** controlled: 57.1 not well controlled: 20.8	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
						very poorly controlled: 22.1 **Group 3:** controlled: 75.9 not well controlled: 15.2 very poorly controlled: 8.9 **Group 4**: controlled: 48.1 not well controlled: 28.4 very poorly controlled: 23.5 Emergency department/urgent care (%) Group 1: 33 Group 2: 28.6 Group 3: 22.8 Group 4: 38.3 Hospitalization (%) Group 1: 2.3 Group 2: 7.8 Group 3: 0 Group 4: 11.1	

ACT: asthma control test; ACQ: Asthma control questionnaire; AUC: area under the curve; BHR: Bronchial Hyperreactivity; BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; EBC: Exhaled breath condensate; ED: emergency department; ERS/ATS recommendation: The European Respiratory Society/ American Thoracic Society recommendation; FEF: forced expiratory flow; FEF25–75: forced expiratory flow at 25–75% of forced vital capacity; Eos: Eosinophilia count; FeNO: fraction exhaled nitric oxide; FEV1: forced expiratory volume in the first second; FEV1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; IFN: Interferon; IgE: Immunoglobulin E; IL: Interleukin; IQR: interquartile range; LR: likelihood ratio; LTRA: Leukotriene receptor antagonist; NPV: negative predictive value; NR: Non-Reported; OR: odds ratio; PC15: provocation concentration causing a 15% fall in FEV1; PC20: provocation concentration

causing a 20% fall in FEV1; PD15: provocation dose causing a 15% decline in FEV1; PD20: provocation dose causing a 20% decline in FEV1; PEF: he peak expiratory flow; PH: potential hydrogen; pMDI: pressurized Metered-Dose Inhaler; PPV: positive predictive value; R: correlation coeffieient; RCT: randomized clinical trial; ROC curve: receiver operating characteristic curve; SD: standard deviation; QALYs: Quality-Adjusted Life-Year.

Table C.3. Characteristics of the included studies in KQ 1b (Adherence)

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
Beck-Ripp, 2002 [98]	Germany, RCT, outpatient setting, high risk of bias.	FeNO, N= 31	Mean age 10.5 years (SD: 0.5), 51% male	Measured by on-line chemiluminescence analysis in the LR 2000 NO analyser (Logan Research, Rochester, Kent, UK).	Correlation between the reduction of FeNO and the compliance, with inhaled budesonide during the 4-week run-in period. Compliance calculated as (Pulmicort Turbohaler doses taken for each steroid treatment course / doses prescribed) x 100 (%).	A positive correlation was established between the patients' compliance to take their prescribed inhaled steroid medication and the reduction of FeNO. With a better compliance with budesonide a greater reduction of FeNO during the run-in period was observed (p<0.01, r=0.59).	FeNO values were associated with compliance to therapy in children.
		Spirometry, N= 31		Spirometry was performed in a Jager MasterLab (Jager, Wurzburg, Germany) and the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and mean maximal expiratory flow (MMEF) were measured according to the recommendations of the American Thoracic Society (ATS).			
Vijverberg, 2012 [99]	Netherlands, cross sectional, inpatient setting, medium risk of bias.	FeNO, N= 601	Mean age 9 years (SD: 2.2), 62.9% male, 80.1% atopy, 12.9% tobacco exposure, 88.5% were on ICS.	Online hand-held electrochemical analyzer (NIOX Mino; Aerocrine, Solna, Sweden) with an expiration time of 6 s. FeNO was dichotomized using a cutoff value of 25 ppb.	There was a very weak correlation between FeNO levels and total ACQ score (R= 0.13, p< 0.01). FeNO >25 ppb was associated with lower medication adherence rates (OR: 0.4; 95% CI 0.3 to 0.6), fewer antibiotic courses in the past year (OR: 0.6; 95% CI: 0.4 to	FeNO median 13 ppb (7-27), >25 ppb in 26.8% and <5 ppb in 6% patients.	In children with asthma (mostly on ICS), high FeNO was associated with low adherence based on parental reported Medication Adherence Report Scale (OR: 0.4; 95% CI: 0.3–0.6)
		Asthma Control Questionnaire (ACQ), N=601		Asthma control was assessed using the 6-item version of the ACQ (symptoms plus rescue medication use). An ACQ score < 0.75 was considered 'well-controlled asthma', a score ≥0.75		Well controlled in 56.2% patients.	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Disease activities and asthma outcomes	Test findings (mean, SD)	Conclusions
				was considered 'not well-controlled asthma'	0.9), fewer leukotriene antagonists use in the past year (OR: 0.4; 95% CI: 0.2 to 0.9), and fewer visits to a Pulmonary pediatrician (OR: 0.6; 95% CI: 0.4 to 0.9).		

ACQ: Asthma control questionnaire; CI: confidence interval; ERS/ATS recommendation: The European Respiratory Society/ American Thoracic Society recommendation; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; ICS: inhaled corticosteroid; OR: odds ratio; R= correlation; SD: standard deviation.

Table C.4. Characteristics of the included studies in KQ 1c (Algorithm using FeNO to guide drug therapy for RCTs)

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of FeNO administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Calhoun, 2012 [100]	United States, RCT with cross-over, outpatient setting, unclear risk of bias.	FeNO, N =324	Group 1: Physician Assessment based adjustment (PABA), (N=114) Mean age 34.2 years (SD: 11.9), 36.8% male, BMI 28.2 Kg/m2 (SD: 7.9), 85.1% atopic. Group 2: Biomarker -based adjustment (BBA), (N = 115) Mean age 34.8 years (SD: 11.3), 28.7% male, BMI 29 Kg/m2 (SD: 7.3), 86.1% atopic. Group 3: Symptom based adjustment (SBA), (N = 113) Mean age 36 years (SD: 12.2), 26.5% male, BMI 27.1 Kg/m2 (SD: 6.2), 82.3% atopic.	Every 6 weeks for 9 months.	Inhaled corticosteroid therapy adjusted based on FeNO or day-to-day symptoms.	Asthma exacerbation (including multiple episodes) rates did not differ among the treatment groups 0.23 (97.5% CI, 0.10 to 0.37) events/person-year for PABA vs 0.21 (97.5% CI, 0.10 to 0.32) for BBA and 0.12 (97.5% CI, 0.03 to 0.21) for SBA. The hazard ratio was PABA vs BBA 1.1 (97.5% CI, 0.4 to 2.8), PABA vs SBA 2.0 (97.5% CI, 0.8 to 5.4), BBA vs SBA 1.9 (97.5% CI, 0.7 to 4.9).	At 12 weeks: Group 1 (N=108): 21.38 (0.62) Group 2 (N=114): 18.88 (0.66) Group 3 (N=110): 20.78 (0.54)	In adults with mild to moderate asthma controlled by low-dose ICS, FeNO based or symptom-based or physician assessment-based adjustment of ICS had similar treatment failure.
		Sputum eosinophils, N =324					At 6 weeks: Group 1 (N=79): 0.40 (0 to 1.20) Group 2 (N=67): 0.20 (0 to 0.80) Group 3 (N=76): 0.40 (0 to 1.40)	
		Blood eosinophils /mm3, N =324					At 4 weeks: Group 1 (N=111): 132.0 (100.0 to 222.0) Group 2 (N=108): 178.5 (100.0 to 300.0) Group 3 (N=108): 169.0 (100.0 to 224.0)	
		Asthma Control Questionnaire, N =324		Scores on the Asthma Control Questionnaire range from 0 to 6, with a higher score indicating worse asthma control; the minimal clinically			At 12 weeks: Group 1: 0.72 (SD: 0.50) Group 2: 0.79 (SD: 0.54) Group 3: 0.73 (SD: 0.49)	

Author , Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of FeNO administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
				important difference (MID) is 0.5				
		Asthma Quality of Life Questionnaire , N =324		Scores on the Asthma Quality of Life Questionnaire range from 1 to 7, with a higher score indicating a better quality of life; the MID is 0.5			At 6 weeks: Group 1 (N=112): 6.27 (SD: 0.76) Group 2 (N=115): 6.16 (SD: 0.77) Group 3 (N=113): 6.25 (SD: 0.72)	
		Asthma Symptom Utility Index , N =324		Scores on the Asthma Symptom Utility Index range from 0 to 1, with a higher score indicating better asthma control; the MID is Unclear, but a difference of 0.3 is suggested to distinguish between mild to moderate and moderate to severe asthma.			At 12 weeks: Group 1: 0.90 (SD: 0.10) Group 2: 0.88 (SD: 0.12) Group 3: 0.90 (SD: 0.10)	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of FeNO administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
De Jongste, 2009 [101]	Europe, RCT, outpatient setting, high risk of bias.	FeNO, N=151	FeNO group (adjust for FeNO and symptoms) (N= 77): Mean age 11.6 years (SD: 2.6), 59.7% 46 males, weight 43.4 Kg (SD: 12.5), Race 91% were white, 100% atopic.	Measured by (NIOX MINO; Aerocrine, Solna, Sweden). Measurements were performed daily. Measurement time was recorded by the device for later review.	30 weeks of ICS which doses were adjusted every 3 weeks on the basis of either FeNO and symptom	There were 372 ICS dose changes in the FeNO group, as compared with 174 in the symptom group. At the end of the study, the	Baseline FeNO: FeNO group: 27.5 ppb (15 to 54), symptom group: 32 ppb (15 to 59).	Children with atopic asthma were monitored daily for symptoms (vs symptoms and FeNO) over 30 weeks and ICS doses

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of FeNO administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N=151	Symptom group (adjusted only for symptoms) (N=74): age 11.8 years (SD: 4.3), 73% males, weight 42.2 Kg (SD: 14.5), race 88% were white, 100% atopic.	All children recorded asthma symptoms in a palmtop electronic diary (PalmOne Tungsten W PDA equipped with TrialMax software; CRF Inc., Helsinki, Finland).	scores, or symptom scores alone.	FeNO group used 200 (0 to 500) mg, and the symptom group 200 (100 to 500) mg, of budesonide equivalent per day (P<0.0001 for both changes from baseline). The time course of ICS dose changes, and the change from baseline, did not differ significantly between groups (P = 0.76 at the end of the study for the changes from baseline). The ICS dose distribution at the end was similar in both groups. ICS could be stopped in 16 children in the FeNO group, and in 12 in the symptom group (P = 0.98).	Baseline FEV_1%: FeNO group: 55% pred (SD: 15) Symptom group: 55% pred (SD: 12). Baseline reversibility of FEV_1%: FeNO group: +7 % pred (SD: 11), symptom group: +6 % pred (SD: 7).	were adjusted by phone every 3 weeks. Both groups had similar outcomes in terms of symptoms and exacerbations.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of FeNO administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Hashimoto, 2011 [102]	Netherlands, RCT, outpatient setting, high risk of bias.	FeNO, N= 51	Group 1: Internet-based management group (N=51) Mean age 48.5 years (SD: 12.4), 45% male, 41.2% current smokers BMI 28.3 Kg/m2 (SD: 5.4), 45% atopic	Online hand-held NO analyser (Niox Mino; Aerocrine AB, Solna, Sweden) before medicine intake on a daily basis for 6 months. In group 2 the test was done on a monthly basis	36 months of daily oral prednison 10 mg/day (5-15).	ACQ and FeNO contributed to the decisions of the computer algorithm in 84% and 16% cases, respectively.	Baseline: Group 1: 38 ppb (18 to 81) Group 2: 34 ppb (13 to 75)	In adults with prednisone-dependent asthma, an internet-based management tool including home monitoring of symptoms, lung function and FeNO in severe asthma is superior to conventional treatment in reducing total corticosteroid consumption without compromising asthma control or asthma-related quality of life.
		Spirometry, N= 51	Group 2: Conventional management group (N=38) mean age 52.4 years (SD: 11.7), 47% male, 44.7% current smokers, BMI 30 Kg/m2 (SD: 8.8), 50% atopic.	Lung function was done hand-held spirometer (Piko-1; Ferraris Respiratory, Hertford, UK). In group 2 the test was done on a monthly basis			FEV_1 baseline Group 1: 76.3 % (SD: 24.7) Group 2: 71.3 % (SD:21) FVC baseline Group 1: 113 % (SD:11.1) Group 2: 94 % (SD:15.5) FEV_1/FVC baseline Group 1: 0.63 % (SD:0.18) Group 2: 0.69 % (SD:0.49)	
		Juniper Asthma control questionnaires (ACQ) score, N= 51		Asthma control questionnaires (ACQ) were completed weekly. In group 2 the test was done on a monthly basis			Mean difference Group 1: 0.26 (SD: 0.09) Group 2: 0.12 (SD:0.12)	
		Juniper		Asthma-related			Mean difference	

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		Asthma-related quality of life questionnaires (AQLQ) score, N= 51		quality of life questionnaires (AQLQ) were completed at baseline and every 3 months thereafter. In group 2 the test was done on a monthly basis			Group 1: -0.03 (SD:0.10) Group 2: 0.14 (SD:0.13)	
Honkoop, 2015 [103]	Netherlands, RCT, outpatient setting, high risk of bias.	FeNO, N=611	Partly Controlled group (PCa) (N= 219): Mean age 38.9 years (SD: 9.3), 31.6 % males, BMI 26.8 Kg/m2 (SD: 5.9), 13% current smoker. Controlled group (Ca) (N= 203) Mean age 39.9 years (SD: 9.8), 34.2 % males, BMI 26.0 kg/m^2 (SD: 4.9), 16% current smoker. FeNO controlled group (FCa) (N= 189) Mean age 39.5 years (SD: 9), 27.7 % males, BMI 26.1 kg/m^2 (SD: 5.1), 14% current smoker	Measured by NIOX MINO (Electro-chemical), at an exhalation flow rate 50 ml/sec.	Treatment decisions were based on a dedicated algorithm for each strategy. Medication classified as an asthma treatment step ranging from 0 (only short-acting b-agonists) to 5 (oral prednisone) based on the US National Asthma Education and	Quality of life using EuroQol classification system (EQ-5D) (95% CI)	PCa group 0.89 (0.88 to 0.90) Ca group 0.91 (0.90 to 0.91) FCa group 0.90 (0.89 to 0.90)	Adults randomized to an algorithm that uses FeNO + asthma controlled questionnaire to adjust treatment had better symptom control, lower medication use and was cost-effective, compared with strategies using only the questionnaire. Quality of life and exacerbations were similar.
						Intervention costs (dollars)	PCa group $ 0. Ca group $ 0. FCa group $ 105.	
						Asthma-related visits (dollars, 95% CI)	PCa group $ 269 (234 to 304) Ca group $ 281 (257 to 308) FCa group $ 224 (205 to 242)	

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					Prevention Program guideline.	Asthma medication (dollars, 95% CI)	PCa group $ 452 (427 to 479) Ca group $ 551 (526 to 588) FCa group $ 456 (429 to 482)	
Malerba, 2015 [104]	Italy, RCT, outpatient setting, unclear risk of bias.	FeNO, N= 28	Group A: treatment according to FeNO and sputum eosinophils (N= 14) mean age age 45.2 years (SD: 31.2), 36 % males, 21% ever smoker. Group B: treatment according to clinical score (N= 14) Mean age 46.7 years (SD: 30.1), 43 % males, 29% ever smoker.	measured with a high-resolution chemiluminescence NO analyzer (Ecomedics AG CLD88; Ecomedics; Durnten, Switzerland). Measurements were carried out according to the ATS guidelines using a standardized method for the single-breath online measurement of FeNO in adults.	24 months of adjusted inhaled corticosteroids (ICS) treatment.	Compared with baseline, mean FeNO at 24 months were reduced in both groups but were lower in the group A.	Group A At baseline 56.2 (SD: 33.8) At 12 month 22.6 (SD: 10.5) At 24 month 18.2 (SD: 5.3) Group B At baseline 48.3 (SD: 19.7) At 12 month 51.6 (SD: 41) At 24 month 39.8 (SD: 29.4)	Adults with eosinophilic asthma randomized to treatment based on FeNO and sputum eosinophils had lower mean symptom score and exacerbations without increase in ICS treatment.
		Symptom score, N= 28				Compared with baseline, mean symptom scores at 24 months were reduced in both groups	Group A At baseline 28.7 (SD: 7.3) At 12 month 9.1 (SD: 1.8) At 24 month 8.1 (SD: 1)	

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						but were lower in the group A.	Group B At baseline 27.8 (SD: 6.7) At 12 month) 13.4 (SD: 3.4) At 24 month) 11 (SD: 2.6)	
		Spirometry, N= 28				Compared with baseline, mean FEV_1 % pred at 24 months were increased in both groups but were higher in the group A.	Group A FEV_1 at baseline 99.3% (SD: 19.7). FEV_1 at 12 month 104.4% (SD: 11.8) FEV_1 at 24 month 107.6% (SD: 12.1) Group B FEV_1 at baseline 96.2% (SD: 10.6). FEV_1 at 12 month 102% (SD: 12.4). FEV_1 at 24 month 100.5% (SD: 11.6)	
Peirsman, 2014 [105]	Belgium, RCT, outpatient setting, high risk of bias.	FeNO, N= 99	Clinical group (N=50) Mean age 10.7 years (SD: 2.1), 66 % males, 19.5% tobacco exposure.	Measured by NIOX MINO (Electro-chemical), at an exhalation flow rate of 50 ml/sec.	In the clinical group, asthma control and treatment	Number of asthma exacerbations over 1 year, count	Clinical group 35/ 1 year FeNO group 18/ 1 year	Children randomized to a FeNO based algorithm (lowering

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			FeNO group (N=49) Mean age 10.6 years (SD: 2.2), 67 % males, 11.6% tobacco exposure.		adjustments during each visit were determined by the reporting of symptoms. In the FeNO group, FeNO measurements were primarily used to adjust the treatment.	Percentage of Symptom-free days, median (interquartile range)	Clinical group 79.6% (51.7 to 94.0) FeNO group 83.7% (27.1 to 91.9)	FeNO below 20 ppb) had fewer exacerbations than a comparison group in which treatment was adjusted based on clinical and spirometry parameters based on the GINA guidelines. FeNO did not improve symptom free days and was associated with an increased leukotriene receptor antagonist use and higher inhaled corticosteroid doses.
						Number of children with >1 hospital admission, count/total (%)	Clinical group 2.3% FeNO group 2.3%	

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Petsky, 2015 [106]	Australia, RCT, outpatient setting, low risk of bias.	FeNO, N= 63	Group 1: Treatment strategy based on FeNO levels, adjusted for atopy (N=31): Median age 10.17 years (range 6.56 to12.69), 58.1% male, 74% atopic. Group 2; The symptoms-based management (N=32): Median age 10.08 years (range 6.25 to 12.44), 40.6% male, 87.1% atopic.	Measured with a chemiluminescence analyser (Sievers NOA 280i, Colorado, USA) with children exhaling at 0.05 L/sec for >4 sec in order to obtain a stable NO value for >2 sec. Patients were followed up for 12-months, with monthly visits for the first 4 months and every 2 months thereafter. At each visit patients assessed with FeNO first, then spirometry before and after 400 mg inhaled salbutamol.	Fluticasone and Budesonide (different doses based on specific hierarchy). The difference between final and baseline dose: Group 1: 0 (-175, 100) Group 2: -200 (-300, 100) (P= 0.139). The cumulative dose per child-year: Group 1: 168,000 (93000, 210000) Group 2: 105000 (73500, 156000) (P= 0.016).	FeNO values not significantly different between the groups at the end of, or at any time point of the study.	Baseline: Group 1: 24.00 (10.92 to 48.45) Group 2: 25.60 (13.40 to 53.70) ≥1 exacerbation over the study period Group 1: 6 Group 2: 15 ≥2 exacerbations per year: Group 1: 3 Group 2: 5	Taking atopy into account when using FeNO to tailor asthma medications is likely beneficial in reducing the number of children with severe exacerbations at the expense of increased ICS use. The strategy is unlikely beneficial for improving asthma control.
		Spirometry, N= 63		Spirometry was performed using ATS criteria and % predicted based on local age and sex matched reference values in Hong Kong and Eigen from Australian data (Hibbert (children ≥8 years) in Brisbane.		FEV_1 % predicted values not significantly different between the groups at the end of, or at any time point of the study.	FEV_1 Baseline: Pre-bronchodilation: Group 1: 92.10 (85.20 to 102.90) Group 2: 88.00 (83.65 to 104.15) Post-bronchodilation Group 1: 97.30 (88.90 to	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of FeNO administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
							101.35) Group 2: 91.50 (82.30 to 105.4)	
		Asthma symptom score, N= 63		The asthma scores were quantified by entering the numerical answer into a spreadsheet and average obtained for the previous month.			Baseline: Group 1: 3.0 (0 to 13.38) Group 2: 6.75 (1.13 to 23.0) At 12 months: Group 1: 0 (0 to 8.75) Group 2: 0 (0 to 17.25)	
Pijnenburg, 2005[107]	Netherlands, RCT, outpatient setting, high risk of bias.	FeNO, N=85	FeNO Group (treatment were made on both FeNO and symptoms) (N= 39) mean age 11.9 years (SD: 2.9), 64.1% males, Weight 43.2 kg (SD: 15.0) Symptom Group (treatment were made only on symptoms) (n=46) Mean age 11.9 years (SD: 2.9) 65.2% males, Weight 48.5 kg (SD: 18.8).	FeNO was measured online according to guidelines from the European Respiratory.	Inhaled corticosteroids (≥400 or ≤400 mg budesonide or equivalent daily dose).	No FeNO significant change was found Within the FeNO group adjusted for baseline, whereas in the symptom group, there was a significant increase in FeNO. However, at all-time points, FeNO correlated strongly with later FeNO values in the same	FeNO group Ratio of geometric means 1.32 (95% CI, 1.04 to 1.68). Symptom group From 30.8 to 36.7 ppb.	In children with asthma, 1 year of steroid titration based on FeNO did not result in higher steroid doses but did improve airway hyper-responsiveness and inflammation
		Spirometry, N= 85		Measured by Masterscreen electronic spirometer (Jaeger, Wurzburg, Germany).				

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of FeNO administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
						subjects (all p< 0.001).		
Pike, 2013 [108]	United Kingdom, RCT with cross-over, outpatient setting, low risk of bias.	FeNO, N= 90	Group 1: FeNO-driven therapy (N=44) Mean age 10.51 years (SD: 2.62), 47.7% male, 9.1% tobacco exposure 81.1% atopic. Group 2: Standard management (N=46) Mean age 11.42 years (SD: 2.69), 65.2% male, 13% tobacco exposure, 88.4% atopic.	Using an online chemiluminescence portable monitor (NIOX MINO; Aerocrine, Solna, Sweden) through several visits (two times monthly) during 12 months period.	Inhaled corticosteroid dose (400–800 mcg/day or >800 mcg/day beclomethasone equivalent) according to symptoms control. Median initial corticosteroid	Neither group experienced a significant change in FeNO during follow-up.	FeNO changes Group1 3.1 ppb (-5.5 to 11.6) Group2 3.3 ppb (-8.5 to 15.1) Median number of exacerbations: Group 1: 3 (range 1–5). Group 2: 2 (range 1–4). Percentage of patients with exacerbation: Group 1: 84.1%.	Children with moderate to severe asthma randomized to FeNO-driven therapy (adjustment of ICS and LABA) or to a standard management group (driven by conventional markers of asthma control). No difference

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		Spirometry, N= 90			dose: Group 1: 750 ug (400 to 1000) Group 2: 800 ug (400 to 1000) Median final corticosteroid dose: Group 1: 800 ug (400 to 1000) Group 2: 500 ug (400 to 1000)	There is no significant change different in FEV_1, FVC or FEF 25–75% during follow-up between groups.	Group 2: 82.6%. Of these, severe exacerbation ≥ 8 hours admission: Group 1: 11.4%. Group 2: 6.5%.	was found between the two groups in either change in corticosteroid dose or exacerbation frequency. Results were similar in atopic asthmatics.
Powell, 2011 [109]	Australia RCT, outpatient setting, low risk of bias.	FeNO, N= 220	Group 1; FeNO-guided asthma management (N=111) All pregnant women, mean age 28.1 years (range 27.12–29.09), 37.9% ex-smoker, BMI 27.9 Kg/m2 (range 24.1–32.4), 41.4% were on ICS,	using an online chemiluminescence ECOMEDICS, Duernten, Switzerland at a flow rate of 50 mL/sec, monthly visit for 5 months.	Inhaled corticosteroid titrate based on FeNO levels. Median Beclomethasone	ER/labor ward visit: Group 1: 0.04 (0.001 to 0.07) Group 2: 0.02 (-0.01 to 0.04) Hospital	FeNO at baseline: Group 1: 13.9 (6.6 to 32.0) Group 2: 13.1 (7.5 to 24.0) FeNO at the end of the study: Group 1:	Pregnant, non-smoking women with asthma were randomly assigned before 22 weeks' gestation to treatment

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			75.2% atopic Group 2; Clinical guideline algorithm (N=109) All pregnant women, mean age 28.8 years (range 27.72–29.84), 40.2% ex-smoker, BMI 28.7 Kg/m2 (range 24.1–32.8), 43.1% were on ICS, 76.2% atopic,		dipropionate equivalent ICS dose (µg per day) Baseline: Group 1: 800 (400–1600) Group 2: 800 (400–1600) At 23 weeks: Group 1: 200 (0 to 400) Group 2: 0 (0 to 800)	admission: Group 1: 0 (0 to 0) Group 2: 0.03 (-0.004 to 0.06) Unplanned or unscheduled doctors visit: Group 1: 0.26 (0.16 to 0.36) Group 2: 0.56 (0.40 to 0.72)	10.55 (5.95 to 19.3) Group 2: 11(5.9 to 21.4)	adjustment at monthly visits by an algorithm using clinical symptoms or FeNO to uptitrated (FeNO >29 ppb) or down titrate (FeNO <16 ppb) ICS. The exacerbation rate was lower in the FeNO group (incidence rate ratio 0.496, 95% CI 0.325-0.755, NNT=6). Quality of life and neonatal hospitalizations were also better with FeNO approach.
		Spirometry, N= 220					FEV_1% at baseline Group 1: 95.10 % (92.76 to 97.44) Group 2: 96.12 % (93.49 to 98.73) FEV_1 at the end of the study: Group 1: 96.4 % (94.31 to 98.46) Group 2: 94.4 % (91.84 to 96.96)	
		Asthma Quality of Life Questionnai (AQLQ-M), N= 220		Asthma Quality of Life Questionnaire_ Marks; Good=0, poor=10.			AQLQ Group 1: 0.75 (0.38 to 1.25) AQLQ Group 2: 0.81 (0.38 to 1.63)	

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Shaw, 2007 [110]	United Kingdom, RCT, outpatient setting, low risk of bias.	FeNO, N= 118	FeNO group: therapy based on FeNO (N=58) Median age 50 years (20-75), 69% male, BMI 27.5 Kg/m2 (SD: 5.02), 22% ever smokers, Oral steroid courses in last yr/patient (mean ± SD): 1.2 ± 2.0 62% atopic Symptom group: therapy based on British Thoracic Society guidelines (N=60) Median age 52 years (24-81), 67% male, BMI 28.1 Kg/m2 (SD: 5.43), 25% ever smokers, 70% atopic	using a Niox chemiluminescence analyser (Aerocrine, Stockholm, Sweden), at a flow of 50 mL/sec, through several visits (every 2-4 weeks) during 12 months period.	Corticosteroid therapy in stepwise reduction fashion.	The total amount of inhaled corticosteroid used during the study was 11% greater (95% CI, 15 to 37%; p 0.40) in the FeNO group compared with the control group.	Exacerbations Group 1: 12 patients Group 2: 19 patients	Adults with a primary care diagnosis of asthma were randomized to corticosteroid therapy based on either FeNO measurements or British Thoracic Society guidelines. There was no significant difference in exacerbations. The final daily dose of ICS was lower in the FeNO group (557 vs. 895 g; mean difference, 338 g; 95% CI, 640 to 37; p 0.028).
Smith, 2005 [111]	New Zealand, RCT, unclear risk of bias.	FeNO, N= 94	Overall mean age 45 years (12 to 73). FeNO group (N=46) and Control group (N= 48).	Measured with 15 ppb used as the cutoff point for controlled vs uncontrolled, at 250 ml/sec.	12 months of upward adjusted daily dose of Fluticasone 292 to 370 µg (FeNO group) and 567 to 641	No significant differences between groups.	FeNO group Baseline 8.2 (7 to 9.5) 12 months 8.6 (7.5 to 9.9). Control group Baseline 6.5 (5.2 to 1.8) 12 months	In adults, With the use of FeNO measurements, maintenance doses of inhaled corticosteroids may be

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					µg (control group).		7.6 (6.4 to 9.1).	significantly reduced without compromising asthma control.
		Clinical outcomes, (exacerbation), N= 94				A non-significant reduction in the FeNO group compared with control.	FeNO group 0.49 episode per patient per year (0.20 to 0.78). Control group 0.90 episode per patient per year (0.31 to 1.49).	
		spirometry, N= 94		According to the American Thoracic Society criteria.		No significant differences in FEV_1% pred in the two groups.	FeNO group FEV_1% pred Baseline 85.2 (79.4 to 91). 12 months 86.1 (80.6 to 91.6). Control group Fev1% pred Baseline 83.8 (77.5 to 90.1). 12 months 82.3 (75.8 to 88.8).	

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		Sputum eosinophilia, N= 94				No significant differences in sputum eosinophils. At 12 months, 65.8% in the FeNO group and 65.9 % in the control group had sputum eosinophil counts of < 3%.	FeNO group Baseline 2.5 (1.7 to 3.7). 12 months 1.1 (0.7 to 1.8). Control group Baseline 1.7 (1 to 2.8). 12 months 1.2 (0.7 to 2).	
Syk, 2013 [112]	Sweden, RCT, outpatient setting, high risk of bias.	FeNO, N= 181	Group 1: FeNO guided treatment (N= 93) Mean age 40.9 years (SD: 11.8), 51.6% male, 0% current smoker, BMI 27.0 Kg/m2 (SD: 5.08), 100% atopic. Group 2: Usual care (N=88) Mean age 41.1 years (SD: 12.9), 52.3% male, 0% current smoker, BMI 26.1 Kg/m2 (SD: 4.79), 100% atopic.	using an online Chemiluminescence NIOX MINO; Aerocrine AB, Solna, Sweden) at a flow rate of 50 mL/sec, Cutoff levels were based on data that showed that most healthy subjects had FeNO levels below 20 ppb and on the suggestion that levels above approximately 25 ppb are associated with eosinophilic inflammation.	Median Budesonide equivalent ICS dose (ug/d) Baseline: Group 1: 400 (400-800) Group 2: 400 (400-800) At 1 year: Group 1: 0 (-400 to 400) Group 2: 0 (-200 to 200)	Exacerbations after 1 year: Moderate (≥1 event) Group1: 8.6% Group2: 22.7% Severe (≥1 event) Group 1: 8.6% Group 2: 6.8% Any (≥1 event) Group1: 16.1% Group2: 28.4%	FeNO Change after 1 year Group 1 (N=87): -2.57 (SD: 20.94) Group 2 (N=78): -1.46 (SD: 23.86)	Primary care adult patients randomized to an algorithm that adjusts ICS and leukotriene receptor antagonists based on FeNO had lower exacerbation rate and improved symptom control without increasing overall inhaled

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of FeNO administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 181				No. of exacerbations / patient/y (95% CI): Group 1: 0.22 (0.14 to 0.34) Group 2: 0.41 (0.29 to 0.58)	FEV_1 % pred change after 1 year: Group 1 (N=88): -0.034 (SD: 0.28) Group 2 (N=78): -0.006 (SD: 0.28) FVC % pred change after 1 year: Group 1 (N=88): -0.084 (SD: 0.35) Group 2 (N=78): -0.019 (SD: 0.29) FEV_1/FVC % Change after 1 year: Group 1 (N=88): 0.009 (SD: 0.057) Group 2 (N=78): 0.002 (SD: 0.054)	corticosteroid use (compared with control group)
		Asthma Control Questionnaire score, N= 181		Juniper 6-item Asthma Control Questionnaire			Change after 1 year: Group 1 (N=81): -0.17 (-0.67 to 0.17) Group 2 (N=74): 0 (-0.33 to 0.50)	
		Mini Asthma Quality of Life Questionnaire, N= 181		Juniper Mini Asthma Quality of Life Questionnaire			Change after 1 year: Group 1 (N=80): 0.23 (0.07 to 0.73)	

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							Group 2 (N=77): 0.07 (-0.20 to 0.80).	
		Gothenburg Quality of Life Instrument, N=181		Generic quality of life.			Change after 1 year: Group 1 (N=85): 0.06 (-0.22 to 0.28) Group 2 (N=78): 0 (-0.39 to 0.39).	
Verini, 2010 [113]	Italy, RCT, high risk of bias.	FeNO, N= 32 (therapy was assessed by FeNO measurements and GINA guidelines)	Mean age 10.7 years (SD: 2.4), 56.2% male.	Measeured by online chemiluminescence assay (Ecomedics CLD 88), according to ATS-ERS, at 50 ml/sec.	12 months of inhaled corticosteroid (N= 20), antileukotrienes (N= 8) or none (N= 5).	Asthma Severity score (ASS) and Asthma Exacerbation Frequency (AEF) significantly decreased at 6 months, however, there was no increase in Asthma therapy score (ATS) over time.	**ASS mean** baseline 1.09 (SD: 0.81) 6 month 0.56 (SD: 75) 12 months 0.75 (SD: 0.95) **AFE mean** baseline 1.96 (SD: 1.18) 6 month 1 .01 (SD: 0.96) 12 months 0.83 (SD: 0.98) **AST mean** baseline 1.5 (SD: 0.7) 6 month 1.43 (SD: 0.7) 12 months 1 .53 (SD: 0.6).	In children with allergic asthma, a strategy of FeNO monitoring (vs GINA based management) reduced asthma severity score and asthma exacerbation score.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of FeNO administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		GINA, N= 32 (therapy was assessed based on symptoms, short acting β2-agonist use, and lung function, according to GINA guidelines).	Mean age 11.3 years (SD: 2.1), 56.2% male		12 months of inhaled corticosteroid (N= 15), antileukotrienes (N= 3) or none (N= 4).	No difference was detected in ASS and AFE in the corresponding times. However, asthma therapy score (ATS) was significantly step up at 6 month.	**ASS mean** Baseline 1.09 (SD: 0.77) 6 month 0.93 (SD: 0.61) 12 month 0.92 (SD:0.82) **AFE mean** baseline 2.01 (SD: 1.17) 6 month 1.78 (SD: 1.29) 12 months 1.85 (SD: 1.34) **AST mean** baseline 1.03 (SD: 0.9) 6 month 1.62 (SD: 0.6) 12 months 1.4 (SD: 0.7).	

ACQ: Asthma control quiestionaire; BMI: body mass index; CI: confidence interval; FEF25–75: forced expiratory flow at 25–75% of forced vital capacity; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted, FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: Long acting Beta-agonist; PEF: peak expiratory flow; RCT: randomized clinical trial; SD: standard deviation.

Table C.5. Characteristics of the included studies in KQ 1c (Algorithm using FeNO to guide drug therapy NON-RCTs)

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Griese, 2000 [57]	Germany, prospective nonrandomized, outpatient setting, low risk of bias.	FeNO, N=74	Mean age 9.7 years (range 4-16), 76.1 % males, 100 % atoptic.	FeNO was measured online with a chemiluminescence analyzer (Logon LR 2000, Rochester, Kent, UK) sensitive to ENO at concentrations of 1-5000 parts per billion (ppb, by volume). The response time (10-90%) was <0.65 sec.	Step wise approach system.	FeNO in relation to the recommended change in inhaled therapy.	FeNO > 13ppb = Step up (24) vs No change (8) vs step down (5). FeNO < 13ppb= Step up (12) vs No change (11) vs step down (13).	In children, FeNO values above 13 ppb weakly correlated with the changes in asthma therapy and had modest sensitivity of 0.67 and a specificity of 0.65 to predict a step up in therapy.
		Spirometry, N=74				FEV_1 in relation to the recommended change in inhaled therapy.	FEV_1< 80% pred = Step up (6) vs No change (1) vs step down (1). FEV_1> 80% pred= Step up (26) vs No change (12) vs step down (17).	
		Symptom score, N=74				Symptom score in relation to the recommended change in inhaled therapy.	Symptoms Yes = Step up (34) vs No change (15) vs step down (11). Symptoms no = Step up (2) vs No change (4) vs step down (8).	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Laforce, 2014 [114]	United States, observational, outpatient setting, high risk of bias.	FeNO, N =50	Mean age 35.1 years (SD: 15.81), 40 % male, BMI 27.4 kg/m^2 (SD: 6.2), 30% ex-smoker,	Measurement was obtained (NIOX MINO, Aerocrine AB, Solna, Sweden)	94% were on short acting B-agonists, 40% on long acting B-agonists combined with anti-inflammatory medication, and 16% on leukotriene receptor antagonists.	Asthma medication changes based on FeNO results.	No medication change (64%), added medication or increased medication dose (20%), and Subtracted medication or decreased medication dose (16%).	Treatment decisions made in a single office visit based on a single FeNO test in 50 asthmatics led to change in therapy (augmentation in 20% and reduction in 16%) and were estimated to reduce cost by $629 per patient per year.
		Asthma control test (ACT) scores, N =50				FeNO values by ACT scores	ACT scores ≤19= FeNO 40.3 ppb (SD: 50.84). ACT scores ≥19= FeNO 26.1 ppb (SD: 21.96).	
		Spirometry, N = 50				FeNO values by FEV_1	≤80% Predicted= FeNO 41.1 ppb (SD: 46.92). >80% Predicted= FeNO 41.1 ppb (SD: 46.92).	
Malerba, 2008 [115]	Italy, longitudinal nonrandomized study, medium risk of bias.	FeNO, N= 14	Mean age 43.9 years (SD: 10.1), 43% male, Weight 67.2 Kg (SD: 10.8), 43% ever smokers, 0% current smokers 100% Eosinophilic phenotype.	Online chemiluminescence nitric oxide analyzer (Ecomedics AG CLD88; Ecomedics. Durnten, Switzerland), at a flow of 50 mL/sec, through several visits during 12 months period, 4	12 months of Inhaled corticosteroids in a stepwise fashion according to FeNO and sputum eosinophilia values.	There is a significant positive correlation between FeNO and sputum Eosinophilia (r= 0.49, P < 0.01 at baseline; r= 0.53, P < 0.01 at 3 months;	Baseline: 57 ppb (SD: 33) At 3 months: 26 ppb (SD: 16) At 6 months: 17 ppb (SD: 8) At 12 months: 22 ppb (SD: 10)	Adults with mild-moderate persistent asthma treated based on FeNO and sputum eosinophils had fewer symptoms and exacerbations compared

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
				weeks washout.		r= 0.28, P < 0.01 at 6 months). Also, there is a significant positive correlation between FeNO and sputum eosinophilia mean difference at 6 months (r = 0.41, P < 0.01) but not at 3 months (r = 0.06, P = 0.39). Mean number of exacerbations was significantly lower		with the previous year in which they were treated conventionally
		Spirometry, N= 14		Spirometry and maximal fill flow-volume curve were obtained using a pneumotachograph with volume integrator (CAD/ Net system 1070; Medical Graphics Corporation; St. Paul, MN). Static lung volumes were measured by means of the multibreath nitrogen washout method.			FEV_1 baseline: 99% pred (SD: 20) At 3 months: 101% pred (SD:17) At 6 months: 103 % pred (SD:15) At 12 months: 105 % pred (SD:12) FEV_1/FVC Baseline: 91 % pred (SD:11) At 3 months: 91 % pred (SD:10) At 6 months: 93 % pred (SD:10) At 12 months: 95 % pred (SD:7)	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Sputum eosinophilia (sEOS), N =14		Subjects were pretreated with inhaled salbutamol (200 ug by metered-dose inhaler), and 10 min later hypertonic (4.5%) sterile saline nebulized solution was inhaled for three periods of 5 min at most by means of an ultrasonic nebulizer (Ultraneb 2000; DeVilbiss; Somerset, PA). The subjects were instructed to cough sputum into containers. If any symptom occurred, nebulization was discontinued. The cutoff for an abnormal result was defined when sEos count was > 3% as percentage cells.		compared to baseline (3 vs 9 exacerbations, P < 0.001).	Count at Baseline: 27% (SD: 27) At 3 months: 13% (SD: 15) At 6 months: 4% (SD: 3) At 12 months: 3% (SD: 3)	
Malerba, 2012 [116]	Italy, longitudinal nonrandomized, inpatient	FeNO, N= 14	Mean age 44.9 years, 42.9% male 42.9% ex-smokers, Mean weight 67.2 Kg, 64.3% atopic	Using an online high-resolution chemiluminescence nitric oxide analyzer	Median beclomethasone equivalent: At baseline:	No changes were observed in the frequency of clinical	FeNO (ppb) at Baseline: 20.7 At 6 months: 26.1 At 12 months:	Titration of ICS based on FeNO and sputum eosinophils in

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
	setting			(Ecomedics AG CLD88; Ecomedics; Dumten, Switzerland). Values of FeNO included from 4 to 20 ppb were considered within normal limits.	500 ug At 6 months: 750 ug At 12 months: 500 ug.	asthma exacerbations (3, 4 and 3 exacerbations at baseline, 6 month, and 12 month visit, respectively).	19.8	adults with mild-to-moderate persistent asthma was associated with reduction in symptom scores and ICS dosage.
		Spirometry, N= 14		Spirometry and maximal full flow-volume curve were obtained using a pneumotachograph with volume integrator (CAD/ Net system 1070; Medical Graphics Corporation, St. Paul, MN, USA).			FEV_1 % pred at baseline: 99.5 At 6 months: 98 At 12 months: 100 FEV_1/FVC % pred at baseline: 94 At 6 months: 92 At 12 months: 93	
		Methacholine challenge test (PD20), N= 14		The methacholine challenge was performed as a dose-response curve by increasing (doubling) doses of methacholine chlorohydrate (starting with 12.5 ug) every 3 min. The test was stopped when the highest dose (1.600 ug) was			PD20 (ug) at baseline: 714.5 At 6 months: 995.8 At 12 months: 877	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
				tolerated, or if a fall> 20% in forced expiratory volume in the first second FEV_1 from baseline (saline solution) was induced after methacholine inhalation. A methacholine challenge result was considered positive if the PD20 was < 1.600 ug.				
		Sputum Eosinophilia count (sEos), N= 14		After baseline spirometry measurements, subjects were pretreated with inhaled salbutamol (200 ug by metered-dose inhaler), and 10 min later hypertonic (4.5%) sterile saline nebulized solution was inhaled for three periods for a maximum of 5 min by means of an ultrasonic nebulizer (Ultraneb 2000; DeVilbiss; Somerset, PA,			sEos count (%) at baseline: 2.7 At 6 months: 3.6 At 12 months: 1.9	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
				USA). The cut-off for an abnormal result was defined when sEos count was> 3% as percentage cells.				
		symptom score, N =14		Obtained from diary cards. Mean daily symptom scores (dyspnea, wheezing, cough, daytime and nighttime awakenings, each scored 0 to 3.			Mean score at baseline: 10 At 6 months: 8.5 At 12 months: 8	
Wan, 2014 [117]	Taiwan, Cross section study, high risk of bias.	FeNO, N= 140	mean age 6 years, 56.6% males, 100% were on ICS.	Measured by (MINO device) once every three months for one year.	ICS (Flixotide 50 g; 2 puffs) with or without Singulair (5 mg orally per day).	FeNO levels decreased in 86.4% patients and increased in 13.6% patients, which were correlated with the changing of C-CAT (≥20 ppb, ≤19 ppb).	Baseline 32.31 ppb (SD: 13)	In Children with Asthma who received ICS, FeNO can be used to detect response to treatment.
		International Study of Asthma and Allergies in Childhood questionnaire (ISAAC) , N= 140					Baseline 18.13 (SD: 2.10).	

ACT: Asthma control test; FEF25–75: forced expiratory flow at 25–75% of forced vital capacity; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; PD20: provocation dose causing a 20% decline in FEV_1; PEF: he peak expiratory flow; R: correlation coefficient; SD: standard deviation.

Table C.6. Characteristics of the included studies in KQ 1c (Drug selection)

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Ciolkowski, 2016 [118]	Poland, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=86	Mean age 14 years (SD: 5), 73.3% male, 4 % Eosinophilic phenotype, 97.6% atopic.	Three measurement by online electrochemical-based Medisoft HypAir FE (NO) device (Medisoft SA, Belgium), at 50 ml/sec, steroid prior to test was 100%.	12 months of montelukast switched form patients daily low-dose ICS.	FeNO increased significantly more in patients last visit prior to exacerbation (N= 22) than final values of patients who completed the study (N= 64). However, an increased risk of exacerbations was noted among patients with FeNO> 20 ppb.	26 ppb (SD: 15) to 39 ppb (SD: 31) vs 18.5 (SD: 12) to 24.5 ppb (SD: 15). FeNO > 20 ppb (RR 3.7, 95% CI: 1.3 to 10.7, p=0.01).	In children with mild asthma on low dose ICS who were switched to montelukast, FeNO >20 ppb predicts exacerbations, however, the strongest factors that predict exacerbation was Eosinophilia.
		Spirometry, N= 86		Using (Easy One - Medizin Technik Schweiz) according to the ATS/ERS guidelines, with at least three correct forced exhalations. The dose-response slope (DRS) was calculated as the ratio of reduction of FEV_1 (% of		DRS increased in patients last visit prior to exacerbation (N= 22) and decreased in patients who completed the study (N= 64). An increased risk of exacerbations	0.55 (SD: 53) to 2.06 (SD: 3.46) vs 0.22 (SD: 0.29) to 0.29 (SD: 0.38). DRS > 0.25 (RR 9.5, 95% CI: 2.8 to 31.6, p <0.01.	

				initial value) by volume of the sodium chloride inhaled (mL)		was noted among patients with DRS > 0.25.		
		Asthma control test (version for adults and older children), N= 86				The median ACT score at the last visit prior to exacerbation (n= 22) remained in the range of good asthma control but was slightly lower than final values of patients who completed the study (N= 64).	23.5 (SD: 3) vs 25 (SD: 1).	
		Sputum eosinophilia, N= 72		An 8 cycles of inhalation of 4.5% sodium chloride: 30 s, 30 s, 1 min, 2 min, and then four times for 4 min. Then, sputum was assessed macroscopically for plugs at the time of collection. An adequate specimen was defined as one producing countable cytospin slides for an estimation via differential cell count, with minimal squamous contamination		Sputum eosinophilia increased significantly more in patients last visit prior to exacerbation (N= 22) than final values of patients who completed the study (N= 64). An increased risk of exacerbations was noted among patients with initial Eos% > 2.5%.	5.8% (SD: 4.6) to 7.3 (SD: 5) vs 0.7% (SD: 2) to 2% (SD: 3.5). Eos> 2.5%; RR 36.6, 95% CI: 7.1 to 189.3, p < 0.001.	

				<50% and pulmonary macrophages present. A differential cell count was obtained from 200 cells on May-Grunwald-Giemsa stained slides.				
Cowan, 2015 [119]	New Zealand and United States, non-randomized trial, outpatient setting, low risk of bias.	FeNO, N=46	Mean age 39.8 years (SD: 2), 63 % males, Weight 78.5 Kg (SD: 2.5), 80.4% atopic.	Measured with a chemiluminescence analyzer (NiOX MINO; Aerocrine, Stockholm, Sweden) before any forced expiratory maneuvers according to current guidelines at an exhaled flow rate of 50 mL/sec.	500 mg of fluticasone (Flixotide; GlaxoSmithKline, Greenford, United Kingdom) twice daily by means of inhalation through a spacer for a period of 28 or more days.	Asthmatic patients with baseline FeNO values of 35 ppm or greater had 10.5-fold greater likelihood of response to inhaled steroids, as measured by improvement in clinical outcomes,	By 2 clinical outcomes improvements: OR, 3.43; 95% CI, 0.93 to 413.54; P 0.004. By 3 clinical outcomes improvement: OR, 10.50; 95% CI, 1.73 to 203.7; P 0.014.	In steroid-naive adults with asthma FeNO predicted clinical responsiveness to ICS. The combination of FeNO values and urinary BrTyr levels had the best prediction power
		Urinary bromotyrosine test (BrTyr), N = 46		BrTyr levels were assayed by using stable isotope dilution HPLC with online electrospray ionization tandem mass spectrometry.		Asthmatic patients with baseline urinary BrTyr level of 0.45 ng/mg of creatinine or greater were 6.22	By 2 clinical outcomes improvement: OR 6.22; 95% CI, 1.22 to 47.94; P 0.31. By 3 clinical outcomes improvement: OR 1.5; 95% CI, 0.3 to 7.3; P 0.619.	
Mahut, 2011 [120]	France, Cross section study,	FeNO, N= 169	Mean age 10.5 years (SD: 2.6), 61% male, 21 paternal and	Exhaled NO was measured online, using the Nitric Oxide Analyzer	Bronchodilator (salbutamol)	The multivariate analysis demonstrated	Correlation with bronchodilator response: r = 0.26, p =	In children, FeNO identified ICS dependent

	outpatient setting, medium risk of bias.		maternal tobacco exposure, BMI 18.0 Kg/m2 (SD: 3.5), 84% Atopic. 48% were on Beta-agonist on demand, 52% were on ICS different doses, and 43% on LABA.	(NIOX; Aerocrine AB; Solna, Sweden: measurement at a constant 50 mL/sec expiratory flow rate: FeNO.	400 µg and ICS dose > 200 µg/day.	that log FeNO correlated with bronchodilator response and ICS dose > 200 ug/day.	0.011. with ICS dose > 200 µg/d response: r = -0.17, p =0.019.	asthma phenotype
		Spirometry, N= 169		Spirometry and plethysmographic measurement of specific airway resistance and thoracic gas volume were performed according to international guidelines.			FEV_1 Pre-bronchodilator: 97 % pred (SD: 13). Post-bronchodilator: 107 % pred (SD: 12). FVC Pre-bronchodilator: 105 % pred (SD: 13). Post-bronchodilator: 108 % pred (SD: 12). FEV_1/FVC Pre-bronchodilator: 78 % pred (SD: 8). Post-bronchodilator: 84 % pred (SD: 6).	

Martin, 2016 [22]	United Kingdom, longitudinal nonrandomized study, low risk of bias.	FeNO, N=28	Mean age 29 years (range18-70), 39%, 17.9% current smoker, 14.3% ex-smoker, 14.3% atopic (eczema).	Measured by (NIOX MINO; Aerocrine, Tolna, Sweden)	12 week beclomethasone dipropionate (200 µg PID) via a metered dose inhaler.	FeNO ROC curve as a predictor of ICS response after 4 and 12 weeks had an AUC= 0.89 (p<0.0001) and AUC=0.86 (p<0.0001), respectively. FeNO < 27 ppb predicts non-responce.	AUC= 0.89 (p<0.0001) at 4 weeks and AUC=0.86 (p<0.0001) at 12 weeks.	In adult asthmatics, FeNO reliably predicts those who responds to ICS (Auc 0.89 and 0.86 at 4 and 12 weeks; respectively; level <27ppb predicts non-response).
		Blood eosinophilia, N=28				Blood eosinophil count did not perform as well as predictors of ICS response.	AUC= 0.67.	
		spirometry, N=28				FeV1 did not perform as well as predictors of ICS response.	AUC= 0.85.	
		Methacholine challenge test, N=28				PC20 did not perform as well as predictors of ICS response.	AUC= 0.32.	
Smith, 2005 [121]	New Zealand, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 52	Mean age 40.5 years (14-71), Male 24%, current smokers 6%, ever smokers 19%.	measured using a chemiluminescence analyzer (NiOX; Aerocrine, Stockholm, Sweden) at an exhaled flow rate of 50 ml/ sec.	4 weeks of inhaled fluticasone (250 g/ puff, 1 puff twice daily via matching	FeNO >47 ppb predicted treatment response in the two response endpoint (increase in	FeNO >47 ppb predicted treatment response When endpoint is increase in FEV_1 >12%: Sensitivity: 67%	FeNO > 47 ppb predicted steroid response in patients with undiagnosed respiratory symptoms.

					inhaler).	FEV_1 and increase in mean morning peak flows) better than lung function (FEV_1 < 80% predicted) and methacholine challenge test (PD20 < 8 u/mol).	Specificity: 78% PPV: 47% NPV: 89% When endpoint is increase in mean morning peak flow >15%: Sensitivity: 82% Specificity: 81% PPV: 53% NPV: 94%	Response defined as an increase in FEV_1 of 12% or greater or an increase in mean morning peak flow of 15% or greater after fluticasone, 500 g/day for 4 weeks.
		Spirometry, N= 52					FEV_1 < 80% predicted treatment response When endpoint is increase in FEV_1 >12%: Sensitivity: 17% Specificity: 88% PPV: 29% NPV: 78% When endpoint is increase in mean morning peak flow >15%: Sensitivity: 36% Specificity: 93% PPV: 57% NPV: 84%	
		Methacholine challenge test (PD20), N= 52		Measured using standard protocols.			PD20 < 8 u/mol predicted when endpoint is increase in FEV_1 >12%: Sensitivity: 58% Specificity: 69% PPV: 37% NPV: 84% When endpoint is increase in mean morning peak	

							flow >15%) Sensitivity: 55% Specificity: 68% PPV: 32% NPV: 84%	

AUC: area under the curve; CI: confidence interval; Eos: Eosinophilia count; ERS/ATS recommendation: The European Respiratory Society/ American Thoracic Society recommendation; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: long acting beta agonist; NPV: negative predictive value; OR: odds ratio; PC20: provocation concentration causing a 20% fall in FEV_1; PD20: provocation dose causing a 20% decline in FEV_1; PPV: positive predictive value; R= correlation; RCT: randomized clinical trial; SD: standard deviation.

Table C.7. Characteristics of the included studies in KQ 1d FeNO response to administration of Leukotriene receptor antagonists (LTRA)

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Bisgaard, 1999 [122]	Denmark, RCT with cross-over, outpatient setting, unclear risk of bias.	FeNO, N= 26	Mean age 12 years (6-15).	Measured by online Aerocrine NO system, at 110 ml/sec, two times per visit, steroid use prior to test was 42.3%	2 weeks of 5 mg montelukast once daily or placebo, then cross over for 2 weeks additional of 200 mg budesonide.	FeNO was significantly reduced with montelukast and budesonide Compared with placebo. This effect was independent of concurrent steroid treatment.	Montelukast mean difference from placebo 7.3 ppb (1.4 to 13.1). Budesonide mean difference from placebo 15.7 ppb (9.5 to 22.0).	FeNO was significantly reduced by 20% after 2-wk treatment with montelukast and budesonide. This effect was independent of concurrent steroid treatment.
		Spirometry, N= 24				Spirometry exhibited a tendency to improve after montelukast and after budesonide as compared with the placebo treatment period, but this was not statistically significant	FEV_1 Montelukast mean difference from placebo 0.132 L (-0.022 to 0.286) FEV_1 Budesonide mean difference from placebo 0.116 L (-0.045	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
							to 0.277).	
Bratton, 1999 [123]	United States, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=24	Mean age 9.3 years (SD: 1.6), 67 % males.	using a chemiluminescent analyzer (Model 280 NOA, Sievers Instruments, Inc., Boulder CO).	Montelukast sodium (5 mg chewable tablet) administered once daily at bedtime, and after a 2-week posttreatment washout period.	Change of FeNO after montelukast sodium treatment	Mean difference from baseline 24 ppb (P < 0.01)	In 12 children with chronic asthma, FeNO concentrations decreased after 4 week treatment with montelukast sodium, which again rose after treatment was withdrawn.
		Spirometery, N=24				Change of FEV_1 (% predicted) after montelukast sodium treatment.	FEV_1 at baseline 81 % pred (SD: 4) After Montelukast 85 % pred (SD: 4).	
Montuschi, 2007 [124]	Italy, RCT, outpatient setting, low risk of bias.	FeNO, N= 26	Montelukast group (N= 14) Mean age 10.8 years (SD: 0.5), 78.5% male Placebo group (N= 12) Mean age 10.5 years (SD: 0.6), 83% male	Measured by online NIOX system (Aerocrine; Stockholm, Sweden), at 50 ml/sec.	1 month of montelukast 5mg/day or placebo then 2 weeks treatment withdrawal.	Montelukast showed a significant reduce in FeNO, however, it was increased 2 weeks after withdrawal. No changes were seen in placebo group.	Montelukast group Week 1: 45.5 ppb Week 5: 37.9 ppb Week 7: 52.2 ppb Placebo group Week 1: 37.5 ppb Week 5: 46.3 ppb Week 7: 40.6 ppb	Montelukast reduced FeNO concentrations in children with asthma, and withdrawal can result in increased FeNO values and worsening of Spirometry.

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 26		Spirometry (Pony FX; Cosmed; Rome, Italy), and the best of three consecutive maneuvers were chosen.		Montelukast had no effect on Spirometry test results in asthmatic children, however, test results were lower than baseline after the 2 week treatment withdrawal. Placebo treatment and its withdrawal had no effect on Spirometry tests.	Montelukast group FEV_1 % pred Week 1: 93.1 (SD: 3.1) Week 5: 92.9 (SD: 3.0) Week 7: 90.7 (SD: 2.8) FEV_1/FVC Week 1: 96.7 (SD: 2.2) Week 5: 95.9 (SD: 3.0) Week 7: 94.7 (SD: 3.0) Placebo group FEV_1 % pred Week 1: 94.3 (SD: 2.4) Week 5: 95.7 (SD: 2.9) Week 7: 90.6 (SD: 3.1). FEV_1/FVC Week 1: 99.2 (SD: 2.4) Week 5: 99.8 (SD: 2.8) Week 7: 96.4 (SD: 2.8).	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Ohkura, 2009 [125]	Japan, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 20	Mean age 68.1 years (SD: 12), 75% male.	Measured by online chemiluminescence at a flow rate of 0.05 L/sec. Steroid prior to test was 100%.	1 month of Pranlukast 450 mg/day added to ICS+LABA (salmeterol 100 µg/day), then 1 month of washout period (only ICS+LABA (salmeterol 100 µg/day).	FeNO decreased significantly after adding pranlukast. FeNO after wash-out period was also lower than baseline.	Baseline 26.6 ppb (SD: 1.1). Pranlukast + ICS+ LABA 18.3 ppb (SD: 1.9). ICS+LABA 21.1 ppb (SD: 1.1).	Pranlukast added to ICS and inhaled LABA reduced FeNO.
		Spirometry, N= 20				FEV_1 increased significantly after pranlukast was added and decreased significantly after wash-out period.	Baseline 2.08 L (SD: 0.12). Pranlukast + ICS+ LABA 2.14 L (SD: 0.56). ICS+LABA 2.08 L (SD: 0.58).	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Sandrini, 2003 [126]	Canada, RCT with crossover, outpatient setting, unclear risk of bias.	FeNO, N=20	mean age 34.8 years (SD: 12.6), 25% males, 5% smoker. 12 received placebo and 8 received Montelukast.	Performed according to ATS recommendations, using an expiratory flow rate of 0.046 L/s.20The exhaled breath condensate was collected using a commercial apparatus (Cryocond; Boehringer Ingelheim; Burlington, ON, Canada) that cools and freezes the exhaled air to −30°C while patients breathe at tidal volume, wearing nose clips, for 5 min. Frozen samples were stored at −70°C. H2O2 was measured as described previously.	Two 2-week treatment periods with Montelukast (10 mg daily) or matching placebo, with each treatment being followed by 1 week of washout. The tablets were taken in the evening, and visit 2 was considered to be the initial day of the first treatment arm.	Montelukast resulted in a significant reduction of FeNO from day 1 of treatment to day 14, however, FeNO remained lower in comparison to baseline during the washout period. The maximal effect was observed on day 7. Montelukast median difference from baseline at day 7 was −11.3 ppb (25th to 75th percentile, −16.8 to −4.6), and the median difference for placebo was 1.5 (25th to 75th percentile, −1 to 9.9).	FeNO in Montelukast group (N= 8): 52.5 (38 to 102). Placebo group (N=12): 44 (28 to 95).	Montelukast r educed FeNO in adults with mild asthma in an RCT, reduction was noted as early as day 1 with a maximum effect on day 7.

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N=20		Spirometry was performed after ENO measurement and breath condensate collection using ATS standards.			FEV_1 % in Montelukast(N=8) : 88% (range 83 to 95) Placebo group (N=12): 91% (range 83 to 98)	

ATS standards: American Thorcic Society standards; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: long acting beta agonist; RCT: randomized clinical trial; SD: standard deviation.

Table C.8. Characteristics of the included studies in KQ 1d FeNO response to administration of Omalizumab

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Silkoff, 2004 [127]	United States, RCT, outpatient setting, low risk of bias.	FeNO, N=29	Mean age 9.6 years (SD: 1.4), 70 % males, Weight 37.9 Kg (SD: 13.8).	Measured by using a standardized single breath method, which conformed to American Thoracic Society recommendations for FeNO measurement	52 weeks Omalizumab (N= 18) vs placebo (N= 11). The dose of omalizumab was based on each patient's serum total IgE level and body weight at baseline to provide a dose of at least 0.016 mg/kg per IU/mL of IgE per 4-week period.	During the first 12 week of the study where steroid doses were reduced, the variability of adjusted FeNO in the placebo group was greater than that of the omalizumab group at most visits, with a significant difference between groups for AUC of adjusted FeNO. However, Omalizumab reduced FeNO after 52 weeks as reported.	AUC for adjusted FeNO Omalizumab 0.88 (SD: 0.69) vs placebo 1.65 (SD: 1.06). Omalizumab Baseline 41.9 (SD: 29.0) At 52 weeks 18.0 (SD: 21.8)	Omalizumab reduced FeNO in children
Tajiri, 2014 [128]	Japan, prospective observational study, outpatient setting, medium risk of bias.	FeNO, N =31	Mean age 55 years (SD: 16), 32.3% males, BMI 25.0 kg/m^2 (SD: 5.3), 42% ever smoker.	Using a chemiluminescence analyzer (NOA 280; Sievers, Boulder, Colorado). Fractional eNO (FeNO) levels were determined at 3 expiratory flows of 50 (FeNO50), 100, and 200 mL/sec.	48 weeks Omalizumab treatment.	FeNO changes from baseline to 48 weeks of treatment	Baseline 50.2 (SD: 60.1) At 48 weeks 31.4 (SD:28.4)	Omalizumab reduced exacerbations and symptoms and FeNO in 31 adults asthmatics.
		Spirometry, N =31		Chestac-8800 (Chest, Tokyo, Japan).		FEV_1 (L) changes from baseline to 48 weeks of	Baseline 2.17 (SD: 0.53 At 48 weeks	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
						treatment	2.24 (SD:0.55	
		Asthma Quality of Life Questionnaire (AQLQ), N =31				AQLQ Changes from baseline vs 48 weeks	1.36	
		Asthma Control Questionnaire (ACQ), N =31				ACQ Changes from baseline vs 48 weeks	-1.11	

AUC: area under the curve; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; RCT: randomized controlled trial; SD: standard deviation

Table C.9. Characteristics of the included studies in KQ 1d FeNO response to administration of Cortisone

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Baraldi, 1997 [129]	Italy, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=16	Mean age 9.3 years, range 6-13, 50 males, Weight 37.1 Kg (SD: 2.9).	measured with a chemilumescence analyzer (CLD 700 AJ-Med, Ecophysics, CH, Switzerland) sensitive to NO concentrations from 1 to 1000 ppb. Flow used was 0.7 L/min. NO reached a steady plateau during oral breathing after 1-2 min without further fluctuations.	5 days of oral corticosteroid therapy (prednisone 1 mg/kg per day orally).	5 days oral corticosteroid resulted in FeNO mean decrease by 46% (SD: 4%) $p < 0.001$) accompanied by a significant improvement in FEV_1 ($p < 0.001$).	Baseline: 31.3 ppb (SD: 4.2) After prednisone: 16.5 (SD: 2.3)	FeNO values significantly decrease after 5 days of oral prednisone given for acute exacerbation of asthma
		Spirometry, N =16		Pulmonary function parameters were measured by means of a 10 L bell spirometer Biomedin, Padua, Italy), and the best of three maneuvers was expressed as a percentage of predicted values according to Polgar and Promadhat.			FEV_1 at baseline: 62.4 % (SD: 4.4). After prednisone: 90.7 % (SD: 4.3).	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Beck-Ripp, 2002 [98]	Germany, RCT, outpatient setting, high risk of bias.	FeNO, N=31	Mean age 10.5 years (SD: 0.5), 51% males.	Measured by on-line chemiluminescence analysis in the LR 2000 NO analyser (Logan Research, Rochester, Kent, UK), however, FeNO measurement was done before spirometry.	4 weeks of two doses of inhaled budesonide, twice daily with additional inhaled b2-agonists (salbutamol 200 mg or terbutaline 500 mg) as needed vs treatment with only inhaled b2-agonists as needed	FeNO was significantly reduced after 4 weeks of combined inhaled budesonide and beta-agonist, however, FeNO was significantly increased again back to initial values when inhaled beta-agonits was used alone.	Baseline 14.8 ppb (SD: 1.9) budesonide and beta- agonist 7.6 ppb (SD: 0.8) inhaled b2-agonits 14 ppb (SD: 1.2)	FeNO values were lower in ICS users among asthmatic children
		Spirometery, N=31		Spirometry was performed in a Jager MasterLab (Jager, Wurzburg, Germany) and the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and mean maximal expiratory flow (MMEF) were measured according to the recommendations of the American Thoracic Society (ATS).		The initial 4-week inhaled budesonide treatment resulted in an increase in the FEV_1. When inhaled beta-agonits used alone, mean FEV_1 was reduced, but only changes in the later were significant.	Baseline FEV_1 83.1% (SD: 2.0) budesonide and beta- agonist 93.4% (SD: 2.4) inhaled b2-agonits 88.2 % (SD: 3.3)	
Bulac, 2015 [130]	Turkey, longitudinal nonrandomized,	FeNO, N=95	Mean age 42.6 years (SD: 12.3), 15.8 % males, Weight 72.5 K (SD: 11.8),	Performed with a NIOX MINO device according to the suggested method.	Group 1 (N=30) Budesonide/ formoterol 320/9 ug dry	Changes observed in FeNO (ppb) values (pre vs post).	Group 1 14.17 (SD: 4.78) vs 13.97 (SD:4.53) Group 2	3-weeks of beclometasone dipropionate/formoterol-HFA added to patients with

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
	outpatient setting, low risk of bias.		8.4% ex-smoker.		powder inhaler (DPI). <u>Group 2 (N=30)</u> Fluticasone/ salmeterol 500/50 ug DPI according to The combination they used. <u>Group 3 (N=35)</u> Random selection from previous two groups, and beclometasone dipropionate/ formoterol hydrofluoroalkane (HFA) 100/6 ug pMDI was prescribed.		15.57 (SD:5.08) vs 15.11 (SD:5.62) Group 3 15.17 (SD:4.83) vs 12.93 (SD:5.05)	previously controlled asthma reduced FeNO
		Spirometry, N= 95				Changes observed in FEV_1 (% pred) values (pre vs post).	Group 1 86.63 (SD:11.51) vs 89.97 (SD:12.63) Group 2 86.94 (SD:11.38) vs 87.43 (SD:10.9) Group 3 85.7 (SD:9.17) vs 90.2 (SD:12.2)	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Byrnes, 1997 131	United Kingdom, cross sectional and longitudinal, outpatients setting, medium risk of bias.	FeNO, N=31	Mean age 11 years, range 7-16. 45.2% male, 48.4% were on bronchodilators, and 51.6% on inhaled corticosteroids.	Measured by the chemiluminescence method sensitive to 2,000 4,000 ppb, per volume of NO, using an analyzer (Dasibi Environmental Corp.) with a 95% response time of 6.4 seconds. One set of measurements was performed by direct exhalation into the NO analyzer with a total flow of 440 ml/min with continuous recordings of NO in ppb, carbon dioxide in volume percent, and mouth pressure standardized to 4 mmHg.	6 months cross-sectional study subgrouped to bronchodilators alone (N=15), and inhaled corticosteroids regularly (N=16). Then, 2 weeks longitudinal study of patients never treated with steroids before (N=6), they were studies before and after starting inhaled corticosteroids.	Cross section FeNO was significantly higher in bronchodilator therapy group than in inhaled corticosteroids group. Longitudinal In asthmatics who never been treated with steroid, mean FeNO fell after 2 weeks of inhaled corticosteroid treatment.	Cross section Bronchodilators group: 126.1 (77.1), range (14.4-361.1). Inhaled corticosteroids group: 48.7 ppb (SD 43.3) Longitudinal FeNO median from 124.5 ppb to 48.6 ppb.	FeNO values were lower in ICS users.
		Spirometry, N=31				FEV_1 and FVC were significantly higher in Inhaled corticosteroids therapy group than in Bronchodilators group.	Cross section Bronchodilators group: FVC 92% (SD 14.5). FEV_1 78% (SD 10.4). Inhaled corticosteroids group: FVC 98% (SD 18.5) FEV_1 86%	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
							(SD 17.5).	
Dupont, 1998 [132]	Belgium Cross-section study, outpatient setting, high risk of bias.	FeNO, N=99	Asthmatics subdivided according to their PC20 histamine and current steroid treatment. Group 1; (No steroids for 3 month and negative histamine test) (N=56): Mean age 40 years (SD: 17), 0% smoker 60.7% atopic. Group 2; (No steroids and positive histamine test) (N=18): Mean age 42 years (SD: 18), 0% smoker, 5.6% atopic. Group 3; (Steroids and negative histamine test) (N=25): Mean age 39 years (SD: 18), 0% smoker, 60% atopic	Flow of 20 mL/sec, using an online Ecophysics CLD 700 AL MED (Dürnten, Switzerland) chemiluminescence analyzer adapted for online recording. Three reproducible recordings (15% variation) were made in one visit at 2-min intervals, and the highest of three readings was used for analysis.	Inhaled steroids (between 500 and 1000 mg beclomethasone dipropionate or equivalent for at least 6 weeks) (%): Group 1: 0 Group 2: 0 Group 3: 100 Group 4: 0		Group 1: 21 ppb (SD: 11). Group 2: 11 ppb (SD: 3). Group 3: 13 ppb (SD: 5).	FeNO correlated with airway hyperresponsiveness in steroid-naïve mild asthmatics, but not in steroid using asthmatics
		Spirometry, N=99		Spirometry was done according to American Thoracic Society (ATS) guidelines.			FEV_1 % pred Group 1: 102 (SD: 12). Group 2: 107 (SD: 12). Group 3: 108 (SD: 13). FVC % pred Group 1: 107 (SD: 12). Group 2: 107 (SD: 13). Group 3: 109 (SD: 13).	
		Airway hyperresponsi		Measured as the dose of histamine that produced			Group 1: 1.8 (SD: 2.2)	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		veness, N=99		a 20% decrease in FEV_1 (PC20histamine). Normal bronchial responsiveness (positive test) was considered when (PC20 histamine ≥ 8 mg/ml).			Group 2: > 8 Group 3: 2.0 (SD:2.2)	
Ehrs, 2010 [133]	Sweden, RCT, outpatient setting, low risk of bias.	FeNO, N=70	Corticosteroid group (N=36); mean age 38 years (18-61), 36% male, 61% ever-smoker, 33% current smokers, 67.6% atopic. Placebo group (N=34); mean age 39 years (20-63), 35% male, 44% ever-smoker, 18% current smokers, 67.6% atopic.	Measured by online chemiluminescence (NIOX®, Aerocrine, Stockholm, Sweden), at 50 ml/sec, at several visits.	A three month of Inhaled fluticasone (250 mg twice daily) or placebo.	A 3 months Fluticasone significantly reduced FeNO, as opposed to placebo.	Fluticasone; 19.3 ppb (13.3 to 39.5) vs 13.9 ppb (8.1 to 18.7). Placebo; 20.7 ppb (12.8 to 36.5) vs 23.0 ppb (10.5 to 35.7).	In steroid free mild asthmatic adults, ICS reduced FeNO and altered bronchial responsiveness but did not change quality of life.
		Spirometry, N=70		measured using a MicroLab 3300 Spirometer (Micro Medical Ltd, Rochester, Kent, UK) according to the standards of the American Thoracic Society. Spirometry was measured before and 20 min after inhalation of the bronchodilators. Significant reversibility was defined as an FEV_1 increase 10% of the pre-inhalation value.		Fluticasone slightly increased FEV_1 while placebo decreased it. However, fluticasone increased FVC but less than placebo does. Alongside, salbutamol and ipratropium bromide further increased FEV_1 and FVC in both groups before and after 3 month fluticasone and placebo.	FEV_1 after Fluticasone (2.8%) vs placebo (-0.8%). FVC after Fluticasone (0.8%) vs placebo (1.1%).	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Asthma Quality of Life Questionnaire, N=70		A 32 items questionnaire has four domains: activity limitations, symptoms, emotional functions and influence of environmental stimuli. The minimal important difference (MID) indicates the smallest difference in the score of a domain that the patient perceives as beneficial. In the AQLQ, the definition of MID is 0.5.		The mean overall score was increased in both groups. However, there were no significant differences between the fluticasone and placebo group with regard to change in quality of life.	Fluticasone; from 5.62 to 6.0 vs Placebo from 5.74 to 6.0.	
		A bronchial responsiveness (methacholine challenge test), N=70		Inhalation of the diluent followed by doubling concentrations of methacholine starting at 0.5 mg/mL. The challenge was stopped at an FEV_1 decrease (measured with a wedge spirometer; Vitalograph®, Maids Moreton, Buckingham, UK) of 20% compared with the value obtained after inhalation of the diluent or after inhalation of the highest methacholine concentration (32 mg/mL).		Fluticasone increased median methacholine responsiveness (PD20) more than placebo does.	Fluticasone; from 0.18 mg (0.07 to 0.57) to 0.42 mg (0.16 to 0.80) Vs Placebo; from 0.22 mg (0.10 to 0.50) to 0.25 mg (0.14 to 0.52).	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Erin, 2008 [134]	United Kingdom, RCT with cross-over, high risk of bias.	FeNO, N= 21	Mean age 26 years (19-39), 48% male, 38% ever smoker.	Measured by chemiluminescence analyzer (Logan Research Limited; Rochester, UK) at 50 ml/sec	A 7-day of ciclesonide 320 ug in the morning and placebo in the evening, ciclesonide 640 ug bid, and placebo.	Compared with placebo, ciclesonide 320 ILg qd improved median exhaled NO levels after 3 and 7 days. Similarly, ciclesonide 640 ILg bid improved median exhaled NO levels after 3 and 7 days. No Significant differences in FeNO were detected between patients treated with ciclesonide 320 ILg qd and 640 ILg bid.	ciclesonide 320 ug qd median difference Day 3: -17.7 ppb. Day 7: -22.6 ppb. ciclesonide 640 ug bid Day 3: -15.4 ppb. Day 7: -20.7 ppb.	FeNO values were lower in ICS users.
		Airway responsiveness (measured as the provocative concentration of adenosine monophosphate (AMP) producing a 20% reduction in FEV_1 (PC20), N= 21				Ciclesonide 320 ug qd and 640 ug bid produced Significantly greater improvements in PC20 compared with placebo on days 1, 3, and 7. There were no significant differences between ciclesonide doses for PC20 on days 1, 3, or 7.	Ciclesonide 320 ug qd mean difference Day 1: 1.59. Day 3: 1.78. Day 7: 2.13. Ciclesonide 640 ug bid mean difference Day 1: 1.23. Day 3: 1.51. Day 7: 2.20.	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 21				Ciclesonide 640 ug bid achieved Significantly greater improvements in FEV_1 compared with placebo after 3 and 7 days. Ciclesonide 320ug qd produced significantly greater improvements in FEV_1 compared with placebo after 7 days.		
		Sputum eosinophils, N= 21				Sputum eosinophils decreased after 7 days of ciclesonide treatment. Although not statistically Significant, this decrease was more pronounced with ciclesonide 640 ILg bid.		
Gelb, 2008 [135]	United States, longitudinal nonrandomized, outpatient	FeNO, N=30	Mean age 43 years (SD: 9) 20 % males, 0% smokers.	Measured using a Sievers NOAi 280 chemiluminescene analyzer (Ionics Instruments, USA) at three separate constant expiratory flow rates: 100	12 weeks as following; Visit 1: Patients were on fluticasone 250 µg/salmeterol	FeNO were significantly higher when taking S alone compared with the three other regimens.	visit1: 16 (9 to 21). visit2: 14 (9 to 21) visit3: 15 (9 to 27) visit4: 19	In nonsmoking with mild to moderate asthma on ICS, addition of montelukast did not further reduce FeNO

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
	setting, high risk of bias.			mL/s, 150 mL/s and 200 mL/s, in triplicate. The mean of three values (that were required to be within 10% of each other to be acceptable) was reported.	50 µg (F/S) twice a day for longer than a year. visit 2: After four weeks of F/S plus montelukast 10 mg (M). visit 3: After four weeks of S plus M. visit 4: After Four weeks of S only.		(10 to 32).	
		Spirometry, N=30				There were no statistical differences for spirometry in asthmatic patients during visits 1 to 4.	FEV_1 (% pred) visit1: 86 (SD:17) visit2: 86 (SD:19) visit3: 83 (SD:17) visit4 : 84 (SD:19) FEV_1/FVC (%) visit1: 77 (SD:10) visit2: 78 (SD:9) visit3: 77 (SD:10) visit4: 77 (SD:10)	
Hozawa, 2014 [136]	Japan, RCT, outpatient setting, high risk of bias.	FeNO, N=30	SMART group (N= 15) (budesonide/formoterol (BUD/FM; Symbicort) for maintenance and reliever therapy): Mean age 41.9 years (SD: 8.7), 40 % males, BMI 21.2 kg/m^2 (SD: 1.8). FP/SM group (N= 15) (fluticasone propionate/salme	Measured using a NIOX MINO® (Aerocrine, Stockholm, Sweden) before any forced expiratory maneuvers. Two readings were obtained and the mean value was used for the analysis.	SMART group (N= 15) 8 weeks of twice-daily budesonide/formoterol (BUD/FM) 160/4.5 mg plus as-needed BUD/FM. FP/SM group (N= 15) 8 weeks of one inhalation twice daily	FeNO values decreased significantly from baseline at 8 weeks in SMART group more than FP/SM group.	FeNO mean difference SMART group -13.13 ppb. FP/SM group -8.20 ppb.	When stepping up from ICS therapy, budesonide/formoterol for maintenance and reliever therapy (SMART) reduced FeNO compared with a fixed dose of maintenance therapy with fluticasone propionate/salmeterol.

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
			terol): mean age 41.3 years (SD: 9.9), 40% males, BMI 21.1 kg/m^2 (SD: 2).		fluticasone propionate/salmeterol (FP/SM) 250/50 mg plus as-needed procaterol.			
		Asthma Control Questionnaire (ACQ), N=30		Asthma Control Questionnaire (ACQ5; five-item Japanese version)		ACQ5 mean score reduced in SMART group more than FP/SM group.	SMART group Baseline 1.25 (SD:0.28) At 4 weeks 0.76 (SD: 0.23) At 8 week 0.33 (SD: 0.18). FP/SM group, baseline 1.24 (SD:0.24) At 4 weeks 1.07 (SD: 0.28) At 8 week 0.69 (SD: 0.36)	
		spirometry, N=30		measured by Spiro Sift SP370HYPER (Fukuda Denshi Co., Ltd., Tokyo, Japan).		FEV_1 improved in SMART group more than FP/SM group.	SMART group FEV_1% pred Baseline 92.4 (SD:7.2) At 4 weeks 94.2 (SD: 6.7) At 8 week 100 (SD: 7.5). FP/SM group FEV_1% pred Baseline	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
							91.9 (SD:8.9) At 4 weeks 95.9 (SD: 9.8) At 8 week 97.6 (SD: 9.2)	
Kermode, 2011[137]	Australia, longitudinal nonrandomized, medium risk of bias.	FeNO, N= 19	Mean age 36.4 years (range 20-62), 47.4% male, 0% current smokers.	Measured by an offline technique at 200 ml/s according to American Thoracic Society guidelines, at one visit, steroid prior to test was 0%.	12 weeks of treatment with fluticasone proprionate/salmeterol xinafoate 250/25 ug MDI 2 puffs bd via spacer.	The treatment reduced FeNO by 46%.	From 13.1 ppb (10.3 to 16.6) to 7.1 ppb (6.2 to 8.1).	In adults with asthma taking ICS for 12 weeks, FeNO significantly was reduced.
		Asthma Control Questionnaire (ACQ), N=19				There was a significant improvement in ACQ after treatment.	From 1.3 (1.0 to 1.6) to 0.7 (0.4 to 1.0).	
		Spirometry, N=19		Calculated by referencing the maximal inhalations to plethysmographic TLC using a Medisoft BodyBox 5500 (Medisoft Corporation, Sorrines, Belgium).		The treatment showed a significant improvement in FEV_1, FVC and the FEV_1/FVC ratio.	FEV_1: from 74.9% pred (67.2 to 82.6) to 85.0% pred (77.8 to 92.3). FVC: from 95.3% pred (88.3 to 102.3) to 100.3% pred (93.7 to 107.0). FEV_1/FVC: from 0.6 (0.6 to 0.7) to 0.7 (0.6 to 0.7).	
Kharitonov, 1996	United Kinkdom,	FeNO, N=11	Mean age 32 years (SD: 0.9),	Measured using a chemiluminescence	3 weeks Budesonide	FeNO was significantly	Budesonide Baseline	FeNO values were lower in ICS users

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
[138]	RCT with cross over, outpatient setting, unclear risk of bias.		72% males, BMI 25 kg/m^2 (SD: 5.3), 42% ever smoker.	analyzer (Dasibi Environmental Corp., Glendale, CA) sensitive to NO from 2 to 4,000 parts per billion (ppb, by volume), adapted for on-line recording of NO concentration.	(800 Mg) twice daily vs placebo	reduced after 1 week of budesonide, with further reductions at 2 and 3 wk. There were no significant FeNO changes in patients taking placebo.	203 ppb (SD: 29) at 1 week 143 ppb (SD: 27) at 3 week 120 ppb (SD: 26) <u>Placebo</u> Baseline 169 ppb (SD: 290) at 1 week 184 ppb (SD: 22) at 3 week 184 ppb (SD: 16)	
		Spirometry, N= 11		Measured with a dry spirometer (Vitalograph, Buckingham, UK). The best value of three maneuvers was expressed as a percentage of the predicted value.		There was no significant change in FEV_1 after budesonide or placebo.	Budesonide baseline FEV1 92% pred (SD:3.3) at 1 week FEV1 97% pred (SD:3.8) at 3 week FEV1 99% pred (SD:5.2) Placebo baseline FEV1 94% pred (SD:4.3) at 1 week FEV1 94% pred (SD:3.9) at 3 week FEV1 95% pred (SD:4.2)	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Kharitonov, 2002 [139]	United Kingdom, RCT, outpatient setting, low risk of bias.	FeNO, N=28	Mean age 28 years (25-30), 57% male, 0% current smokers.	A 4 week Measurement by online LR2000 analyzer (Logan Research Ltd, Rochester, Kent, UK), at several visits, corticosteroid and bronchodilators prior to test were 0%.	Inhaled 100 mg/day or 400 mg/day budesonide or placebo once daily for 3 weeks followed by 1 week off treatment.	A significant dose-dependent reduction was faster in 400 mg/day budesonide than 100 mg/day and placebo.	<u>At 3-5 days</u> 400 mg/day -2.06 (SD: 0.37) ppb/day vs 100 mg/day –0.51 (SD: 0.35) ppb/day vs placebo –0.89 (SD: 0.87) ppb/day. <u>At 3 weeks</u> 400 mg/day –0.90 (SD: 0.13) ppb/day vs 100 mg/day –0.54 (SD: 0.08) ppb/day.	There is a dose-dependent onset and cessation of FeNO of inhaled corticosteroids in patients with mild asthma. However, a significant reduction in exhaled nitrite/nitrate and S-nitrosothiols after budesonide treatment was not dose-dependent. There was no significant change in exhaled CO or 8-isoprostanes in breath condensate.
						Recovery of FeNO was faster in 400 mg/day budesonide than100 mg/day.	400 mg/day 1.89 (SD: 1.43) ppb/day) vs 100 mg/day 0.49 (SD: 0.34) ppb/day.	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Exhaled breath condensate, N=28		Nitrite (NO2) and nitrate (NO3) measured using a fluorimeter, Nitrosothiols were assessed using the Oxonon nitrosothiol detection kit (Alexis Biochemicals, Nottingham, UK), and 8-isoprostane by a specific enzyme immunoassay (EIA) kit (Cayman Chemical, Ann Arbor, USA).	Inhaled 100 mg/day or 400 mg/day budesonide or placebo once daily for 3 weeks followed by 1 week off treatment.	A non-dose dependent reduction was faster following 3-5 days of 400 mg/day budesonide than 100 mg/day, however, 100 mg/day showed a further reduction in 3 weeks than 400 mg/day.	At 3-5 days 400 mg/day –4.82 (SD: 0.99) mM/day vs 100 mg/day –3.55 (SD: 1.14) mM/day) vs placebo 0.95 (SD: 0.80) mM/day. At 3 weeks 100 mg/day –1.73 (SD: 0.44) mM/day vs 400 mg/day –0.82 (SD: 0.12) mM/day.	
						Recovery of NO2/NO3 was faster in 400 mg/day than 100 mg/day and placebo.	400 mg/day 4.03 (SD: 2.07) mM/day vs 100 mg/day 1.70 (SD: 1.79) mM/day vs Placebo –4.93 (SD: 1.39) mM/day.	
		Spirometry, N=28		Dry spirometer (Vitalograph-S, Vitalograph Ltd, Buckingham, UK). The highest of the three morning and evening PEF measurements was determined and recorded daily on the diary cards		FEV_1 and PEF did not change significantly in any of the patient groups.		

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
				by the patients.				
		Symptoms score N=28		Daytime and night time symptom scores. Scale point from no symptoms to severe, the scores were recorded daily by each patient.		A significant dose-dependent difference was seen in the reduction of symptom scores between the groups and from placebo.	400 mg/day -0.1 (SD: 0.05) units/day) vs 100 mg/day 0.11 (SD: 0.05) units/day vs Placebo 0.28 (SD: 0.14) units/day.	
		carbon monoxide, N=28		Simultaneously with FeNO by LR2000 analyser (Logan Research Ltd, Rochester, Kent, UK).		There was no effect of either treatment or placebo CO, either during the onset or cessation of their action.		
Nolte, 2013 [140]	United States, RTC, unclear risk of bias.	FeNO, N= 93	Group1 (N= 20); MF/F-MDI 100/ 10 mg Mean age 34.3 years (SD: 10.5), 35% male, BMI 25.3 Kg/m2 (SD: 5.6), 75% atopic (seasonal allergy rhinitis).	Measured online, using the Nitric Oxide Analyzer (NIOX; Aerocrine AB; Solna, Sweden), at 0.05 L/s.	Two weeks of twice a day of the following combination of mometasone/ furoate (MF) or formoterol (F); Group1 MF/F-MDI	All active treatments demonstrated significant reductions in FeNO compared with placebo. Escalating MF/F doses significantly reduced FeNO in a dose-dependent manner.	Mean difference from baseline Group 1: -35.3 Group 2: -45.4 Group 3: -61.4 Group 4: -46.1 Group 5: -51.3 Group 6: 0.1	In adults with allergic asthma, FeNO levels changed in a dose dependent manner with a combined ICS/LABA.

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Sputum eosinophilis, N= 93	Group2 (N= 17); MF/F-MDI 200/10 mg, Mean age 43 years (SD: 14.9), 41% male, BMI 25 Kg/m2 (SD: 4), 76% atopic (seasonal allergy rhinitis). Group3 (N= 12); MF/F-MDI 400/10 mg Mean age 39.8 years (SD: 15.2), 67% male, BMI 25.6 Kg/m2 (SD: 3.6), 67% atopic (seasonal allergy rhinitis). Group4 (N= 16); MF-MDI 200 mg Mean age 32.6 years (SD: 13.2), 62% male, BMI 24.9 Kg/m2 (SD: 5), 81% atopic (seasonal allergy rhinitis). Group5 (N= 15);	conducted according to ERS recommendations: after inhalation of 1 mg terbutaline, sputum was induced by inhalation of hypertonic saline in increasing concentrations (3%, 4% and 5%) for 3 time periods each of 7 min (total duration, 21 min). Sputum plugs were selected and processed, cytospins were prepared using standard methods, and a differential cell count was performed.	100/ 10 mg (N= 20) Group2 MF/F-MDI 200/10 mg, (N= 17) Group3 MF/F-MDI 400/10 mg, (N= 12) Group4 MF-MDI 200 mg, (N= 16) Group5 MF-DPI 200 mg, (N= 15) Group6 Placebo, (N= 15)	With the exception of the MF/F 100/10 mg group, all active treatment groups demonstrated higher sputum eosinophil fold reductions from baseline compared with placebo. Escalating MF/F doses significantly reduced sputum eosinophil levels in a dose-dependent manner.	Mean difference from baseline Group 1: 21.1 Group 2: -35.3 Group 3: -75.4 Group 4: -33.7 Group 5: -55.3 Group 6: 71.7	
		Spirometry, N= 93		PEF was recorded using an electronic diary (e-diary) that included a mouthpiece to capture peak flow.		Mean percentage changes from baseline in AM PEF observed for all active treatment groups were significantly superior compared with placebo. MF/F 400/10 mg was significantly superior to all other treatment groups. However, changes increased in a dose-response manner across	AM PEF mean difference from baseline Group 1: 10.3 Group 2: 12.1 Group 3: 16.6 Group 4: 7.7 Group 5: 6.8 Group 6: -1.7	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
			MF-DPI 200 mg Mean age 32 years (SD: 10.4), 60% male, BMI 25.1 Kg/m2 (SD: 4.3), 93% atopic (seasonal allergy rhinitis). <u>Group6</u> (N= 15); Placebo Mean age 42.2 years (SD: 15.1), male 38%, BMI 25.5 Kg/m2 (SD: 5.3), 77% atopic (seasonal allergy rhinitis).			escalating doses of MF/F.		
		Mannitol challenge test, N= 93				All active treatments afforded more protection against bronchial hyperresponsiveness compared with placebo. There was no observed MF/F dose response, and only the MF/F 100/10 mg treatment group achieved a statistically significant difference versus placebo	Mean difference from baseline Group 1: 0.7 (SD: 31.5) Group 2: 1.1 (SD: 62.2) Group 3: 1.1 (SD: 34) Group 4: 1.1 (SD:17.9) Group 5: 0.7 (SD: 18.3) Group 6: -0.2 (SD: -9)	
Profita, 2013 [141]	France/Italy, RCT, outpatient setting, unclear risk of bias.	FeNO, N=40	<u>nBDP group</u> (nebulized beclomethasone di propionate): mean age 11.1 years (range 10.1-12.1), 70% males, BMI 13.7 kg/m^2 (range 12.7-14.7) <u>Placebo group:</u> Mean age 13.1 years (range 9.6-	Nasal and oral FeNO were determined by chemiluminescence (N10x, Acrocrine, Solna, Sweden) following ATS/ERS recommendations.	4 weeks of nebulized beclomethasone di propionate (nBDP) (daily dose of 800 µg administered twice daily) or placebo with a face mask.	Change of nasal and oral FeNO level before treatment and difference after 4 weeks in each group.	Nasal FeNO mean difference <u>nBDP group</u> -9.3, 95% CI -212.1 to 193.6. <u>Placebo group:</u> -149.8, 95% CI -343 to 44.309. Oral FeNO mean difference <u>nBDP group</u> -29.5, 95% CI -41.6 to -17.5.	In children with allergic asthma and rhinitis, nebulized beclomethasone dipropionate for 4 weeks significantly reduces FeNO.

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
			11.2), 70% males, BMI 14.3 kg/m^2 (range 9.6-11.2).				Placebo group: -1.2, 95% CI -9.7 to 7.4.	
		Spirometry, N = 40		Measured following ATS/ERS recommendations		Change of FEV_1 % level before treatment and difference after 4 weeks in each group	nBDP group 3.86% pred, 95 CI -2.02 to 9.73. Placebo group: -2.52% pred, 95% CI -4.80 to -0.23.	
Silkoff, 2001[142]	Canada, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=15	Age range 17-40 years, 53.3% males.	Subjects inhaled medical-grade compressed air (Praxair) that contained 2 ppb NO and then exhaled via a high expiratory resistance while targeting a mouth pressure of 20 mm Hg. This produced an expiratory flow rate of 45 mL/s (including analyzer sampling rate). Exhalations were repeated until three plateau Feno values varied by 5%. The mean of the three replicate Feno values was used in all analyses.	Four 1-week periods (periods 1 to 4), the following were administered twice daily via metered dose inhaler: period 1, placebo; period 2, 100 g/d of iBDP; Period 3, 400 g/d of iBDP; Period 4, 800 g/d of iBDP.	There was a progressive fall in FeNO as the dose of iBDP was increased, and all doses of iBDP were associated with a significant change in Feno from baseline and placebo values, even after correcting for multiple comparisons.	Baseline: 103.5 (78.5 to 136.7) Period 1: 96.0 (67.9 to 135.6) Period 2: 59.0 (41.3 to 84.2) Period 3: 45.2 (35.7 to 57.2) Period 4: 37.4 (29.1 to 48.0).	In adults with non-steroid treated asthma, FeNO levels changed in a dose dependent manner with ICS.

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N=15		Performed according to American Thoracic Society guidelines using a dry rolling seal spirometer (model 130; P.K. Morgan; Gilling- ham, Kent, UK) and an XY recorder (model 7045A; Hewlett Packard; Palo Alto, CA).		No significant differences were seen for FEV_1 between any of the doses of iBDP. For FVC, there were no significant differences between any of the treatment levels, compared with baseline or placebo.	Baseline FEV_1: 3.01 L (SD: 0.73) Period 1: 3.00 L (SD: 0.84) Period 2: 3.29 L (SD: 0.71) Period 3: 3.36 L (SD: 0.73) Period 4: 3.41 L (SD: 0.80) Baseline FVC: 4.49 L (SD: 0.97 Period 1: 4.42 L (SD: 0.93) Period 2: 4.61 L (SD: 0.84) Period 3: 4.54 L (SD: 0.84) Period 4: 4.60 L (SD: 0.80)	
		Methacholine challengetest (PC20), N= 15		Methacholine challenge was performed with a tidal breathing pattern using a hand-held nebulizer according to American Thoracic Society guidelines.		No significant differences were seen for PC20 between 100 g/d and 400 g/d, between 100 g/d and 800 g/d, or between 400 g/d and 800 g/d of iBDP.	Baseline 0.01 mg/mL (0.00 to 0.19) Period 1: 0.02 (0.00 to 0.52) Period 2: 0.09 (0.00 to 3.22) Period 3: 0.31 (0.00 to 20.2) Period 4: 0.48 (0.01 to 28.1).	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Smith, 2015 [143]	Canada, cross sectional, inpatient setting, medium risk of bias.	FeNO, N= 183	Mean age 12.8 years (SD: 2.76), 57.4% males, 29.5% Parental smoking, mean weight 53.1 Kg (SD: 23.3), 33.3% atopic (eczema).	Measured using asthma inflammation monitor (NIOX MINO, Aerocrine, Sweden).	Different doses of Fluticasone (36.1%), or ciclesonide (27.3%), or Beclomethasone dipropionate (hydrofluoroalkane or chlorofluorocarbon propellant), or Budesonide.	FeNO varied according to ICS type. Mean-adjusted FeNO was lowest in fluticasone users compared with no ICS. However, There was no statistically significant difference in adjusted FeNO between ciclesonide, beclomethasone or budesonide vs no ICS.	*Mean difference fluticasone vs no ICS; 18.6 ppb, 95% CI: (1.0 to 36.2), P=0.03. *Mean difference ciclesonide vs no ICS; 5.9 ppb, 95% CI: -(9.0 to 20.8), P>0.99. *Mean difference beclomethasone vs no ICS; 6.6 ppb, 95% CI: -(10.3 to 23.5) *Mean difference budesonide vs no ICS; 17.6 ppb, 95% CI: (-5.0 to 40.2)	In children with asthma, FeNO was reduced by ICS with variation according to ICS type, suggesting a difference in relative efficacy between ICS beyond their dose equivalents.
		Spirometry, N= 183		Measured using a spirometer (Koko, PDS Instrumentation, USA).		Increased FeNO was associated with percent change in both FEV_1 and FEF 25-75 adjusted for allergic rhinitis, parental smoking and ICS type	*Coefficient FEV_1 and FeNO; 0.08, 95% CI: (0.04 to 0.12), P< 0.001. *Coefficient FEFF25-75 and FeNO; 0.13, 95% CI: (0.01 to 0.24), P=0.03.	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Spallarossa, 2001 [144]	Italy, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N=39	Mean age 11.9 years (SD: 0.6), 69% males, 100% atopic.	Online chemiluminescence analyzer (Logan LR 2000 System, Kent, UK), at 50 ml/sec, at several visits (0, 10, 40 days).	Low doses of inhaled steroids for 10–40 days.	A significant reduction in FeNO levels after low dose of inhaled steroid. However, follow up 16 patients showed that the improvement in FeNO were statistically significant after 10 days and remained stable after 40 days of treatment.	FeNO before vs after therapy 30.8 ppb (SD:3.04) vs 14.0 ppb (SD: 1.4). <u>At 10 days:</u> 14.7 ppb (SD: 2.3) <u>At 40 days:</u> 11.9 ppb (SD: 1.8).	In steroid-naive atopic children with mild intermittent asthma, ICS significantly lowered FeNO values at 10 days without further reduction at 40 days
		Spirometry, N=39		Measured by spirometry (Med Graphics, Pulmonary Function System 1070 series 2, Med Graphics Corp., St. Paul, MN). On each occasion, three forced expiratory maneuvers were obtained and the best values were retained.		A significant improvement of FEV_1, FVC and FEEF 25-75% after low dose of inhaled steroid. However, follow up 16 patients showed a significant improvement in FEV_1 and in FEF25–75% values after 10 days and remained stable after 40 days of treatment.	FEV_1 before vs after therapy 92.05 % (SD: 1.5) vs 103.1% (SD: 1.7). FVC before vs after therapy 99.8 % (SD: 2.3) vs 106.9 % (SD: 2.7). FEF25–75% before vs after therapy 80.9 % (SD: 3.5) vs 96.23 % (SD: 2.9).	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
							At 10 days; FEV_1 97.9% pred (SD: 2.6) and FEEF 25-75% 86.6% pred (SD: 4.3) At 40 days; FEV_1 95.7% pred (SD: 3.2) and PEEF 25-75% 81.2 % pred (SD: 4.7)).	
Verini, 2007 [145]	Italy, RCT with cross-over, outpatient setting, unclear risk of bias.	FeNO, N= 12	Mean age 9.5 years (SD: 3).	Measured by chemiluminescence analyzer CLD77 Echo Physics, at 5-6 L/minute.	4 weeks of inhaled fluticasone propionate 100 mg BID with either montelukast 5mg once a day or salmeterol 50 µm BID.	Additional treatment with montelukast reduced FeNO significantly (p< 0.01), however, no significant differences was observed when salmeterol was added.	Baseline 14 ppb (SD: 6.3) Montelukast 8.5 (SD: 5.0) vs salmeterol 10.7 (SD: 5.5).	In children on ICS, adding salmeterol did not change FeNO but adding montelukast does

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 12		evaluated by a pneumotachograph with an open-circuit nitrogen washout method (VMAX 22L; Sensor Medics, Yorba Linda, CA).		Additional treatment with montelukast showed no change from baseline for FEV_1 and FVC. The addition of salmeterol to FP induced a non-significant increase in both FEV_1 and FVC.	FEV_1 baseline 102.3% (SD: 21.1) Montelukast 101.6% (SD: 18.6) salmeterol 108.0% (SD: 13.5). FVC baseline 97.2% (SD: 17.4) Montelukast 97.5% (SD: 11.7) salmeterol 103.5% (SD: 11.3).	
Zeiger, 2006 [96]	United States, RCT with cross-over, outpatient setting, unclear risk of bias.	FeNO, N= 99	Range age (6-13) years, 59% male.	Measured by (78% online) NIOX Aerocrine AB – chemiluminescence,	16 weeks of fluticasone propionate (FB) 100 mg BID, and montelukast (MT) 5-10 mg once a day	Mean FeNO (ppb) decreased after fluticasone propionate (FB), and montelukast (MT) but the decrease was greater after fluticasone. FeNO correlated with improvements in asthma control days (ASDs) in fluticasone but not with montelukast.	Baseline 39.5 (34.2 to 44.7). FP 20.6 (15.0 to 26.2). MT 30.9 (25.5 to 36.2). FP-MT mean difference -10.3 (-16.9 to -3.7). FeNO vs ACDs FP -0.21 (-0.33 to -0.08). MT -0.04 (0.17 to 0.09).	In an RCT of children with asthma, FeNO was significantly reduced from baseline by both fluticasone and montelukast; however, the reduction was significantly more with fluticasone

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 126				Fluticasone (FB) led to significant improvements in prebronchodilator FEV/FVC (% pred) while montelukast (MT) associated with a significant but small decrease. However, greater improvements in prebronchodilator FEV_1/FVC occurred after fluticasone (FB) than after montelukast (MT).	FEV_1/FVC % Baseline 80.1 (79.1 to 81.1) FP 82.2 (80.9 to 83.6) MT 79.0 (77.6 to 80.5) FP-MT mean difference 3.2 (2.3 to 4.1)	
		Asthma control questionnaire, N= 127				Compared with baseline, both fluticasone (FB) and montelukast (MT) treatments were associated with significant improvements in mean ACQ scores, but better control was achieved with fluticasone.	Baseline 0.96 (0.89-1.03) FP 0.59 (0.50 to 0.69) MT 0.76 (0.66 to 0.87) FP- MT mean difference -0.17(-0.27 to -0.07)	

AST/ERS recommendation: American Thoracic Society/ European Respiratory Society/ recommendation; AUC: area under the curve; BMI: body mass index; CI: confidene interval; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: Long acting Beta-agonist; PC20: provocation concentration causing a 20% fall in FEV_1; PD20: provocation dose causing a 20% decline in FEV_1; PEF: he peak expiratory flow; RCT: randomized clinical trial; SD: standard deviation.

Table C.10. Characteristics of the included studies in KQ 1d FeNO response to administration of LABA

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Fuglsang, 1998 [146]	Denmark, RCT with crossover, outpatient setting, low risk of bias.	FeNO, N= 22	Mean age 11.6 years (7-15).	Measured by online chemiluminescence-model LR200, Logan Research, at 5-6 L/min	3 weeks of inhaled 50 µg salmeterol BID, placebo or inhaled 200 µg budesonide BID.	There was no statistically significant difference in FeNO after salmeterol and placebo treatment, however, budesonide significantly decreased to normal level.	Endpoint FeNO salmeterol: 12.7. Placebo: 10.7. Budesonide: 5.2.	FeNO levels were unaffected by salmeterol treatment for 3 weeks but were significantly reduced during budesonide therapy.
		Spirometry, N= 22				The terbutaline dose–response curve appeared flatter after the salmeterol period than after the placebo period for both FEV_1 and FEF25-75.	FEV_1 (% pred) mean difference Placebo 18% Salmeterol 2% FEF25-75% mean difference Placebo 41% Salmeterol 4%.	
Yates, 1997 [147]	United Kingdom, RCT with cross-over, outpatient, low risk of bias.	FeNO, N= 20	Talking ICS (N= 10); mean age 30.1 years (21-39), 70% male, 90% atopic. Placebo (N= 10); mean age 29.6 years (22-63),	using an online chemiluminescence analyser (Dasibi Environmental Corporation Model, Glendale, CA, USA), at 1 L/min.	One week of nebulized salbutamol (5 mg), added to inhaled glucocorticosteroids (ICS) or placebo.	Salbutamol added to inhaled ICS result in significant increase in FeNO comparted when added to placebo where shows no difference.	Talking ICS 124 ppb (SEM: 38) to 165 ppb (SEM: 85). Placebo 205 ppb (SEM: 37) to 204 ppb (SEM: 44)	Single high dose salbutamol did not increase exhaled nitric oxide in asthmatics not taking inhaled glucocorticosteroids.

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry. N= 20	60% male, 80% atopic.	Using a dry wedge spirometer (Vitalograph, Buckingham, UK).		Salbutamol showed an improvement in FEV_1 (5 pred) when added to inhaled ICS or placebo.	Talking ICS 91 (SD: 6) to 98 (SD: 5). Placebo 94 (SD: 5) to 104 (SD: 5)	

FeNO: fraction exhaled nitric oxide; FEF25–75: forced expiratory flow at 25–75% of forced vital capacity; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; RCT: randomized clinical trial; SD: standard deviation; SEM: standard error of the mean.

Table C.11. Characteristics of the included studies in KQ 1d for FeNO use for ICS reduction or withdrawal

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Cabral, 2009 [148]	Brazil, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 32	Mean age 10.3 years (SD: 2.2). 65.6% males. Moderate asthma: n=18, 12 males, age (mean +/-SD) 9.4 +/-1.9. Severe asthma n=14, 9 males, age 11.4+/-2.1.	FeNO was then measured using an off-line single-breath exhalation technique by chemiluminescence using a fast-responding analyzer (NOA 280; Sievers Instruments Inc, Boulder, Colorado). The analyzer was calibrated with a certified 47-ppb NO source (White Martins, Brazil) and 0 NO filter (Sievers Instruments Inc) before each measurement.	2 month run-in period, ICS were adjusted to equivalent doses of fluticasone administered with a metered-dose inhaler. During tapering, the dose of ICS was reduced by 25% every 2 weeks as long as the child remained stable. If the patient did not remain stable, the	FeNO level was not associated with future risk for asthma exacerbations in any of our regression models. The only factor that was associated with subsequent exacerbations in these models was an indicator of baseline severity (severe vs moderate). Even after further adjustment for exacerbations, children with severe asthma had a 2.7-fold	Baseline Moderate asthma (N=18): 29 ppb (SD: 13) severe asthma (N=14) 50 ppb (SD: 20)	In children with moderate-to severe asthma undergoing ICS reduction, FeNO measured biweekly and expressed as a continuous variable or dichotomized, was not associated with future risk for exacerbations

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 32		We performed spirometry using a spirometer that features a brass pneumotach and combines a portable unit with a computer system (KoKo spirometer; PDS Inc, Ferraris Cardio-pulmonary Systems Group, Louisville, Colorado). Children were asked to refrain from using their reliever medications for at least 4 hours before testing if possible.	ICS dose was either maintained or increased according to physician discretion; oral corticosteroids were given as needed for exacerbations.	(95% CI, 1.1 to 6.6) increased odds of having an exacerbation in the following 2 weeks when compared with children with moderate asthma.	FEV_1% pred Baseline Moderate asthma: 94.2 (SD: 16.2). Severe asthma: 50 (SD: 20).	
Hojo, 2013 [149]	Japan longitudinal nonrandomized outpatient setting, low risk of bias.	FeNO, N= 51	Global Initiative for Asthma (GINA) step1 group: (N=27) Mean age 50.2 years (SD: 8.8), 44% male, 8% ever smokers BMI 23.7 Kg/m2 (SD: 2.8), 56% atopic. Global Initiative for Asthma (GINA) step2 group: (N=24) Mean age 48.9	Online NIOX-MINO (Aerocrine Ltd., Solna, Sweden) every 8 weeks for 48 weeks.	GINA step1 group: Budesonide 400 µg and salmeterol 100 µg. GINA step2 group: Salmeterol/ fluticasone 250 at 2 puffs.	Moderate or more severe exacerbations of asthma were experienced by 6 patients (22%) in the step1 group, but only 3 in step2 group.	Baseline: step1 group 44.5 (SD: 28.7) step2 group 48.8 (SD: 31.1) At 8 weeks: step1 group 39.4 (SD: 25.5) step2 group No change At 24 weeks: step1 group: No change step2 group: 39.6 (SD: 23.6)	In adults with moderate asthma treated with either budesonide 400 µg and salmeterol 100 µg or salmeterol/ fluticasone 250 at 2 puffs, step down from medium to low dose was safely

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 51	years (SD: 11.3), 46% male, 5% ever smokers BMI 22.9 Kg/m2 (SD: 1.9), 76% atopic.	Spirometry was measured every 8 weeks.			FEV_1% pred at baseline: step1 group 72.6 (SD: 9.7) step2 group 76.5 (SD: 16.2) At 48 weeks: step1 group: 76.4 (SD: 13.5) step2 group: 79.4 (SD: 12.4)	performed using a combined FeNO and ACT approach at 8 week intervals
		Asthma control test (ACT), N= 51		ACT was measured every 8 weeks			Baseline Step1 group: 23.1 (SD: 1.4) Step2 group: 22.2 (SD:1.6)	
Jones, 2001 [150]	New Zealand, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=77	Mean age 42.9 years (range 18-74), 38.9% male, 15.6% ex-smokers, 0% current smoker.	Measured by calibrated chemiluminescence analyzer with online measurement of single exhalations according to a standard protocol, with the exception of flow rate (250 ml/s)	Corticosteroid treatment was stopped following a 2- to 4-wk run-in during which the maintenance dose remained unchanged.	The loss of control group (LOC) (N=60) experienced a 2.16-fold increase in FeNO between first and last visit, which was significantly greater than the 1.44-fold increase for the no LOC	Loss of control mean difference: 2.16 (1.88 to 2.48). No loss of control mean difference: 1.44 (1.13 to 1.82)	In adults, both single measurements and changes of FeNO (10 ppb, 15 ppb, or an increase of > 60% over baseline) had positive

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N=77		Spirometry was measured using a rolling seal spirometer.		group (p< 0.01). There were also significant differences between LOC and no LOC groups for the decrease in FEV, (p<0.01), the increase in sputum eosinophils (p= 0.04).	Loss of control FEV_1 mean difference -11.9 (-15.2 to -8.7). No loss of control FEV_1 mean difference -1.1 (-3.3 to 1.2).	predictive values that ranged from 80 to 90% for predicting and diagnosing loss of asthma control after ICS withdrawal.
		Sputum eosinophils, N=77					Loss of control mean difference 14.3 (8.0 to 20.6). No loss of control mean difference 3.3 (-1.5 to 8.0)	
Liu, 2010 [151]	United States, longitudeinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 21	Mean age 29.7 years (18-40), 14% male, 0% current smoker.	Measured by online NIOX (Aerocrine), flow rate per referenced guidelines, steroid priot to test was 100%,	6 months of stepwise fluticasone weaned from 220 ug twice daily to 220 ug once daily.	There is a linear increase pattern for FeNO associated with dose titration. However, FeNO was not a significant time-dependent predictor for the exacerbation.		Adults with moderate persistent asthma undergoing withdrawal of ICS had significant but heterogeneous rise in FeNO.
		Exhaled breath condensate (EBC), N= 21				For EBC pH, no significant trend was observed during titration, however, the fall in EBC pH was	Mean difference EBC PH in exacerbation vs non exacerbation: -0.58 (SD: 0.7) vs	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
						greater in the 6 subjects who had an exacerbation than in the 7 who did not.	0.16 (SD: 0.13).	
		Spirometry, N= 21				There is a significant linear decrease pattern for FEV_1 during dose titration. However, FEV_1 was not significant time-dependent predictor for the exacerbation.		
Obase, 2013 [152]	Japan, RCT, unclear risk of bias.	FeNO, N= 29	Step-down group (N= 15) Mean age 46.5 years. Continued group (N= 14) Mean age 45.3 years	Flow of 50 mL/sec, using an online nitric oxide analyzer (NOA 280i; Sievers Instruments, Inc., Boulder, CO) in one visit several times.	Budesonide/ formoterol Step-down group: Baseline 538 mcg/day (424–653) At 8 weeks 331 mcg/day (285–376) Continued group: Baseline 500 mcg/day (385–615) At 8 weeks 500 mcg/day (385–615)		Step-down group: Baseline 51.0 (38.5 to 63.4) At 8 weeks: 65.7 (36.0 to 95.4) Continued group: Baseline 50.9 (33.9 to 67.9) At 8 weeks: 45.0 (25.9 to 64.1)	Adults newly diagnosed asthma received budesonide/ formoterol for 8 weeks or more then randomized to continue or step-down group. In both groups, pulmonary function indicators and symptoms did not change. FeNO level
		Spirometry, N= 29		Dry spirometer (CHESTAC-33; CHEST MI, Tokyo, Japan), which meets the 1994 American Thoracic			FEV_1Step-down group: Baseline 98.8 (84.2 to113.3)	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
				Society (ATS) recommendations for diagnostic spirometry			At 8 weeks: 105.2 (94.9 to 115.5) Continued group: Baseline 94.0 (80.6 to 107.3) At 8 weeks: 92.0 (76.8 to 107.3)	decreased significantly in the dosage-continued group (from 50.9ppb to 45.0ppb), and increased significantly in the step-down group (from 51.0ppb to 65.7ppb).
		Asthma control test (ACT) , N= 29		In general, patients with a score below 0.75 have adequately controlled asthma; those with a score above 1.0 do not have well-controlled asthma. On the seven-point scale of the ACQ, a change of 0.5 in the score is the smallest that can be considered clinically important. In this study, we set a score of 0.5 or less as confirmation of adequate asthma control by ICS/LABA at baseline and after 8 weeks of treatment.			Step-down group: Baseline 24.3 (23.6 to 25.0) At 8 weeks: 22.9 (20.2 to 25.6) Continued group: Baseline 23.8 (22.8 to 24.8) At 8 weeks: 24.0 (22.4 to 25.6)	
		Asthma Control Questionnaire (ACQ) , N= 29		Patients with a score below 0.75 have adequately controlled asthma; those with a score above 1.0 do not have well-controlled			Step-down group: Baseline 0.04 (-0.02 to 0.10) At 8 weeks:	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
				asthma. On the seven-point scale of the ACQ, a change of 0.5 in the score is the smallest that can be considered clinically important. In this study, the score set of 0.5 or less as confirmation of adequate asthma control by ICS/LABA at second entry and 8 weeks after randomization.			0.31 (-0.07 to 0.68) Continued group: Baseline 0.13 (0.03 to 0.22) At 8 weeks: 0.25 (-0.05 to 0.55)	
		Asthma Quality of Life Questionnaire (AQLQ) , N= 29		The questionnaire consists of 32 questions within four domains: symptoms, activity limitation, emotional function and environmental stimuli.			Step-down group: Baseline 6.66 (6.43 to 6.88) At 8 weeks: 6.34 (5.84 to 6.85) Continued group: Baseline 6.76 (6.56 to 6.96) At 8 weeks: 6.57 (6.16 to 6.99)	
Pijnenburg, 2005[153]	Netherlands, longitudinal nonrandomized, low risk of bias.	FeNO, N=37	Group1 (without relapse) (N=28): mean age 12.2 years (range 7.3-16.9), 75% atopic, Daily dose of ICS 400 (100-400),	FeNO was measured online with an expiratory flow of 50 ml/s according to ATS and ERS guidelines. NO was continuously sampled with a sampling flow of 175 ml/min and analyzed	Baseline FeNO was measured at t = 22 and t = 0 weeks. FeNO was monitored 2, 4, 12, and 24	Two and four weeks after withdrawal of steroids geometric mean FeNO in children who were about to relapse was higher than in	<u>Group1</u> Baseline: 10.5 (7.3 to 14.2). At 2 weeks 15.7 ppb At 4 weeks 15.9 ppb	In children, FeNO measurements 2 and 4 weeks after discontinuation of ICS predicted

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
			mean weight 10.2 Kg (range 7.3-14.2). Group2 (With relapse) (N=9): Mean age 12.3 years (range 10.0-15.8), 88% atopic, daily dose of ICS 200 (100-400), mean weight 14.8 Kg (range 8.5-25.8).	by a chemiluminescence analyzer (Sievers 280 NOA, Boulder, CO, USA). The analyzer was calibrated weekly using 0 and 115 ppb NO certified gases (BOC, Herenthout, Belgium).	weeks after withdrawal of ICS.	those who did not relapse: at 2 weeks (ratio 2.3; 95% CI 1.2 to 4.1; p = 0.01) and at 4 weeks (ratio 2.6; 95% CI 1.3 to 5.1).	Group2 Baseline: 14.8 (8.5 to 25.8). At 2 weeks 35.3 ppb At 4 weeks 40.8 ppb	those who relapsed. Value of 49 ppb at 4 weeks after discontinuation had the best sensitivity (71%) and specificity (93%) for asthma relapse.
		Spirometry, N=37		Flow-volume curves were obtained with a dry rolling seal spirometer (Jaeger, Wurzburg, Germany) according to ATS guidelines. After maximal inspiration, three reproducible loops with a maximum variability in FVC of 10% were obtained. FVC and FEV_1 are expressed as percentage predicted.	Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) before and after bronchodilation were measured at t = 22, 12 and 24 weeks. At t = 0 weeks, treatment with ICS was discontinued in patients with low symptom scores (below 14).		Group1 Baseline FEV_1% 100 (73-134) FVC% 106 (80 to 139). Post-bronchodilation: FEV_1% 106 (80 to 139), Post-bronchodilation: FVC% 103 (66-127). Group2 Baseline: FEV_1% 99 (88 to 109), FVC% 105 (87 to 118). Post-bronchodilation: FEV_1% 107 (91 to 119), Post-bronchodilation: FVC% 105 (78 to 118).	

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
Prieto, 2003 [154]	Spain, longitudinal non randomized, outpatient setting, high risk of bias.	FeNO, N=37	Mean age 32.2 years, (range 28.7–35.6), 30 % males, 27% ex-smoker, 81% atopic.	Measured on-line by the restricted breath analysis according to the recommendations of the American Thoracic Society using a chemiluminescence analyzer (NiOx; Aerocrine; Solna, Sweden)	2-week run-in of beclomethasone dipropionate, 500 to 1,000 ug or equivalent daily. Then, 12 weeks with ICS at half the previous dose.	FeNO changes from the run-in period to the visit performed 2 weeks after the reduction of ICS.	FeNO ≥ 10 ppb OR 1.89, 95% CI (0.36 to 9.97).	In adults with asthma on high dose ICS that was reduced by 50%, FeNO values at baseline >15 ppb perdict reduction failure.
		Spirometry, N =37		Measured using a calibrated pneumotachograph (Jaeger MasterScope; Erich Jaeger GmbH; Wurzburg, Germany) according to standardized guidelines.				
Tsurikisawa, 2012 [155]	Japan, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 90	Exacerbation-free group (N=50); Mean age 49.1 years (SD:14.6), 34% male, 28% ever smoker, 74% atopic. Exacerbation group (N=40);	Mesured by online (80%) NO chemiluminescence analyzer (NOA model 280A, Sievers Instruments) at 70 ml/sec, steroid prior to test was 100%.	12 months of the daily inhaled corticosteroid dose that reduced by half.	FeNO was lower in exacerbation-free compared with exacerbation group after treatment. However, FeNO was a more significant predictor of success in ICS reduction than FEV_1 (p = 0.028).	Exacerbation-free group 25.6 ppb (SD: 12) Exacerbation group 43.4 ppb (SD: 27.3). 0.961, 95% CI (0.93 to 0.99).	In adult patients with moderate or severe asthma but no clinical symptoms of asthma for at least 6 months in whom ICS doses reduced by

Author, Year	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Medication (frequency, dose, duration, etc.)	Asthma outcomes	Test findings (mean, SD)	Conclusions
		Spirometry, N= 90	Mean age 50.9 years (SD:15.9), 37.5% male, 30% ever smoker, 60% atopic.	Measured by spirometer (Auto Spiro AS-303, Minato Medical Science, Osaka, Japan) after each inhalation.		FEV_1 was higher in exacerbation-free group before and after treatment compared with exacerbation group, however, FEV_1 was a less predictor of success in ICS reduction than FeNO (p = 0.03).	Exacerbation-free group 85.9 % pred (SD: 20.9) to 91.1 % pred (SD: 15.1) Exacerbation group 79.6 % pred (SD: 21.3) to 84.1 % pred (SD: 16.7). 1.1, 95% CI (1.0-1.2)	half, FeNO was a statistically independent predictor of success.

AST: American Thoracic Society;BMI: body mass index; CI: confidence interval; EBC: Exhaled breath condensate; ERS: European Respiratory Society; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; OR: odds ratio; PH: potential hydrogen; RCT: randomized clinical trial; SD: standard deviation.

Table C.12. Characteristics of the included studies in KQ 1e

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)	Conclusion
Balinotti, 2013 [156]	Argentina, cross section study, outpatient setting, low risk of bias.	FeNO, N=52	Positive API (N= 31) Mean age 19.8 months (SD: 11), 71% males, mean weight 12.2 Kg (SD: 2). FeNO= 13.5 ppb, 70.9% atopic (eczema+ allergic rhinitis). Negative API (N= 21) Mean age 15.6 months (SD: 8), 62% male, mean weight 10 Kg (SD: 3). FeNO= 5.6 ppb, 0% atopic (eczema+ allergic rhinitis).	Measured by Chemiluminescence Ecomedics CLD 88 Analyzer (Duernten Switzerland, online with tidal breathing manover, one visit several times, at flow rate 50 ml/sec.	FeNO > 8 ppb predict positive asthma predictive index (API) with a sensitivity of 74%, specificity of 76%, PPV of 82% and NPV of 66.6%.	In children < 3 years, FeNO was higher in those with positive (compared with negative) Asthma Predictive Index
		Asthma predictive index (API), N= 52		API was positive if meet 1 major (Parent with asthma or eczema diagnosis) or 2 minor criteria (allergic rhinitis diagnosis, wheeze unrelated to cold, peripheral eosinophilia >4%).		
Bloemen, 2010 [157]	Belgium, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N= 39	53.9% male, Median BMI 16.1 Kg/m2, range 14.6–17.5.	FeNO was measured online using a rapid response chemiluminescence analyser (CLD88sp; EcoMedics, Duernten, Switzerland)	Meadian FeNO 3.1 ppb, range 1.3 to 13.2 FeNO in mAPI positive: 3.6 (1.6 to 4.3). FeNO mAPI negative: 2.9 (2.1 to 5.1). No significant differences were found in FeNO based on mAPI groups, although values were slightly increased in the mAPI-positive group (3.6 ppb) compared with those in the mAPI-negative group (2.9 ppb). However, FeNO values were borderline not significantly increased in the wheezing group (p=0.06), and significantly increased in skin prick tests-positive children, especially for respiratory allergens (p=0.04).	It is possible to apply non-invasive markers (in urine, exhaled nitric oxide (FeNO) and exhaled breath condensate (EBC)) in 3-year-old children, and evaluated the biomarkers in relation to health outcomes and potential modifiers.

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)	Conclusion
		modified Asthma Predictive Index (mAPI), N=134	Mean age 3.1 years, 53% male, Median BMI 15.7 Kg/m2, range 14.5–16.7.	Symptoms of wheeze were assessed by International Study of Asthma and Allergies in Childhood core questions (Pearce et al. 1993). Based on the longitudinal questionnaire, children were classified into a mAPI-positive and a mAPI-negative group (Guilbert et al. 2004). The mAPI is based on four or more episodes of wheezing in the first 3 years of life, of which one is diagnosed by a physician, and at least one of the major criteria (parental history of asthma, atopic dermatitis and allergic sensitivity sitization to at least one aeroallergen) or at least two of the minor criteria (allergic sensitivity sitization to milk, egg or peanuts, wheezing unrelated to colds and blood eosinophils above 4%). The test is categorized as positive/negative.	mAPI were positive in: 10% of total population (N=134) and 13% of children who underwent FeNO test (N= 39).	FeNO was correlated with respiratory allergy, and was borderline significantly correlated with wheezing, but not with the asthma predictive index (mAPI).
Castro-Rodriguez, 2013 [158]	Chile/ Spain, cross section study, low risk of	FeNO, N= 27	Positive API (N=18) Mean age 13.5 months (SD: 6.3), 75% males. FeNO= 12.3 ppb. Negative API (N=9) Mean	Measured by ChemiluminescenceCLD 88 sp; Eco Physics AG, Duernten, Switzerland, Online with multiple breaths asleep post prandial, at 40-60 ml/sec.	In infants (mean age 12 months), FeNO was correlated with Asthma Predictive Index (OR = 1.12, 95% CI: 0.99 to 1.27).	In infants (mean age 12 months), FeNO was correlated with Asthma Predictive Index

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)	Conclusion
	bias.	Asthma predictive index (API), N= 27	age 11 months (SD: 8), 54.6% males. FeNO= 4.1 ppb.	Defined using the stringent index, which requires recurrent episodes of wheezing (3 episodes/ year) during the first 3 years of age and one of two major criteria (physician-diagnosed eczema or parental asthma) or two of three minor criteria (physician-diagnosis allergic rhinitis, wheezing without colds, or peripheral eosinophilia 4%).		(OR = 1.12, 95% CI: 0.99–1.27).
Caudri, 2010 [159]	Netherlands, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 306	Mean age 4 years, 53% male.	FeNO was measured offline according to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines using exhaled air samples and an ambient air sample were collected in Mylar balloons, and analysed using a chemoluminescence analyser (Sievers NOA 280B, Boulder, Colorado, USA).	A higher FeNO at 4 years were associated with more wheezing and asthma at 8 years; OR 1.6 (95% CI, 1.1 to 2.2).	In pre-school children, with symptoms suggestive of asthma, FeNO measures could predict later asthma symptoms up to the age of 8 years.
		Interrupter resistance (RINT), N= 482		Rint was measured in kPa/l with MicroRint (MicroMedical, Rochester, Kent, UK) during expiration, with occlusion of the airway at peak expiratory flow. Median values for at least five acceptable measurements were calculated.	RINT was significantly associated with wheezing at age 6, but not at 7 and 8 years, OR at 8 years is 1.1 (95% CI 0.7 to 1.6).	
Chang, 2015 [160]	United States, longitudinal	FeNO, N=116	Mean age 10.66 months (SD: 4.6), 47.5% males, 50% atopic (allergy	Infants; measured online at a constant expiratory flow from raised lung volume. In 5 years old; measured online with a	Subjects with asthma at 5 years of age had significantly higher FeNO at study entry as infants prior to any wheezing (FeNO difference: 3.5 ppb,	Infants with eczema (mean age 11 months) and high FeNO

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)	Conclusion
	nonrandomized, low risk of bias.		sensitivity sitization) 50%.	Niox eNO analyzer (Aerocrine, Solna, Sweden).	95% CI 0.12 to 6.84; p=0.04), as well as a significantly higher FeNO as 5-year-olds compared with subjects without asthma (FeNO difference: 10.8 ppb, 95% CI 1.53 to 19.99; p=0.02). Higher FeNO at study entry was significantly associated with a greater risk of asthma at 5 years of age; each 1 ppb increase in FeNO at entry was associated with an increased risk of asthma at 5 years of age (OR 1.13, 95% CI 1.01 to 1.26; p=0.04).	had greater risk of developing asthma at 5 years of age (for each 1 ppb, OR 1.13, 95% CI 1.01–1.26).
		Spirometry, N=116		FEF were obtained using the raised volume technique. FVC and FEF25–75% were expressed as z-scores using normative data from our laboratory.		
		Airway reactivity, N=116		In infants, airway reactivity to increasing concentrations of inhaled methacholine was assessed using FEF and quantified by PC30. In 5-year-olds, airway reactivity was assessed using IOS with increasing inhaled MCh using a five-breath technique according the ATS guidelines.		
		Allergen sensitivity sitization, N=116		Allergen sensitivity sitize considered when the specific IgE level was >0.35 IU/mL.		
Elliot, 2013 [161]	United States, longitudinal nonrandomized, outpatient setting, high risk of bias.	Single breath (SB)-FeNO, N=45	67% males, 27% tobacco exposed 36% atopic.	At least three flow-regulated SB-FeNO measurements by Sievers NOA 280 chemiluminescence analyser (GE Analytical Instruments, at several visits, flow rate 50 mL/sec, 2x per month, Alcohol 0%, Mouthwash 0%.	SB-FeNO > 30 ppb predicts wheezing after the age of 3 years with 77% sensitivity, 94% specificity, 95% PPV, and 73% NPV. SB-FeNO>30 ppb predict exacerbation of wheezing between 2.5-3 years with 84% sensitivity, 78% specificity, 76% PPV, and 86% NPV.	In wheezy infants/toddlers, single breath-FeNO was superior to tidal-FeNO, bronchodilator responsiveness, and the API in predicting future exacerbations and persistence of wheezing at
		Tidal-breathing mixed expired FeNO, N=45		30 seconds of quiet regular breathing with a full facemask following five breaths to washout circuit dead space measured by Sievers NOA 280	Tidal-FeNO > 62 ppb predicts wheezing after the age of 3 years with 48% sensitivity, 56% specificity, 61% PPV and 43% NPV. Tidal-FeNO>62 ppb predict	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)	Conclusion
				chemiluminescence analyser (GE Analytical Instruments; Boulder, CO, USA).	exacerbation of wheezing between 2.5-3 years with 53% sensitivity, 61% specificity, 52% PPV, 60% NPV 60.	age 3 years.
		Bronchodilator responsiveness (BDR), N=45		Was defined as ≥ 12% improvement in FEV0.5, or ≥ 25% improvement in FEF25–75.	BDR predict wheezing after the age of 3 years with 32% sensitivity, 91% specificity, 85% PPV and 43% NPV. BDR predict exacerbation of wheezing between 2.5-3 years with 38% sensitivity, 88% specificity, 71% PPV and 65% NPV.	
		The Castro-Rodriquez Asthma Predictive Index (API), N=45		Defined as meeting 1 major, or 2 minor criteria. Major Criteria included a history of parental physician-diagnosed asthma or a history of physician-diagnosed eczema in the subject. Minor Criteria included a history of physician-diagnosed allergic rhinitis or a history of wheezing apart from colds.	API predicts wheezing after the age of 3 years with 46% sensitivity, 63% specificity, 67% PPV and 42% NPV. ABI predicts exacerbation of wheezing between 2.5-3 years with 47% sensitivity, 61% specificity, 50% PPV 50%, and 58% NPV.	
Klaassen sitivity , 2012 [162]	Netherlands, longitudinal nonrandomized, low risk of bias.	FeNO, N=170	Mean age 3.3 years (SD: 0.6), 54.1% males, 30% tobacco exposure, 26% atopic.	Measured by offlien monitoring system (NIOX, Aerocrine, Solna, Sweden), 18% corticosteroid and 40% bronchodilators use prior to FeNO test.	Odds ratio for FeNO and FeNO change after 8 weeks of inhaled corticosteroids to predicted asthma after the age of 6 years are 1.02 (0.98 to 1.05) and 1.01 (0.99 to 1.04); respectively.	In children age 2-4 with recurrent wheeze, neither FeNO nor FeNO change after 8 weeks of inhaled corticosteroids predicted asthma at the age 6 years. Odds ratios were 1.02 (0.98–1.05) and
		Clinical assessment, N=170		Two paediatric pulmonologists made the diagnosis based on symptoms, lung function (reversibility to a β2- agonist and bronchial hyperresponsiveness), and medication use.		

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)	Conclusion
						1.01 (0.99–1.04); respectively.
Prado, 2011 [163]	Spain, cross section study, medium risk of bias.	FeNO, N=38	Mean age 10.9 months (SD: 5), 59.4% males, Eos >4% in 34.4%, 34.37% atopic (eczema).	Measured by Chemiluminescent CLD88 sp (Eco Physics AG), once in 6 months, at one visit several times, online with multiple respirations during post prandial sleep, at 40-60 ml/sec	Patients with +ve API had significantly higher values of FeNO; 16.31 ppb (SD: 9.36) vs 4.43 ppb (SD: 3.13). High FeNO was also associated with high total IgE; 75.9 (SD: 22.2) vs 6.24 (SD: 8.17) (p < 0,001). There was no significant association between eczema and elevated FeNO, or peripheral eosinophilia >400 Eos/mcL and FeNO.	In children age 2-24 months, post-prandial multiple breaths online FeNO was significantly higher in patients with higher Asthma Predictive Index.
		Asthma predictive index (API), N=38		API was positive if they had more than three episodes of wheezing or obstructive bronchitis a year during the first three years of life, while meeting 1 major criterion (parent with asthma, atopic dermatitis diagnosis and/or allergic sensitivity sitization to one or more pneumoallergens) or 2 minor criteria (milk, egg or nut food allergy, wheezing unassociated with colds in the first three years of life and/or eosinophilia in peripheral blood ≥ 4%).		
van Wonderen, 2009 [164]	Netherlands, longitudinal nonrandomized, Inpatient	FeNO, N= 131	Age range; 1-5 years, 56% male.	FeNO is measured in the hospital or general practice at age 5 using an offline technique. Exhaled air is collected in a NO-impermeable Mylar balloon (ABC balloons, Zeist, The Netherlands). All	Ongoing cohort study (The AiRway Complaints and Asthma Development, ARCADE).	

Author, Year (ref)	Study country, study design, study settings, risk of bias	FeNO and comparisons	Patient characteristics (age, gender, race, BMI/weight, tobacco use, asthma phenotype, atopy, etc)	Ways of administration (frequency, use of alcohol/mouthwash, beta-agonists prior to test)	Test findings (mean, SD)	Conclusion
	and outpatient setting, low risk of bias.			balloons are analyzed in a NO-analyzer (Aerocrine AB; Sweden) within a time period of 6–8 hours after taking the samples.		

ATS: American Thoracic Society; API: Asthma predictive index; BDR: Bronchodilator responsiveness; BMI: body mass index; EBC: exhaled breath condensate; Eos: eosinophils; FEF25–75: forced expiratory flow at 25–75% of forced vital capacity; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value; RINT: Interrupter respiratory resistance measurement; SD: standard deviation.

Appendix D. Figures

Figure D.1 Pooled sensitivity, specificity and HSROC curve for diagnosis of asthma when FeNO cutoff <=20 ppb

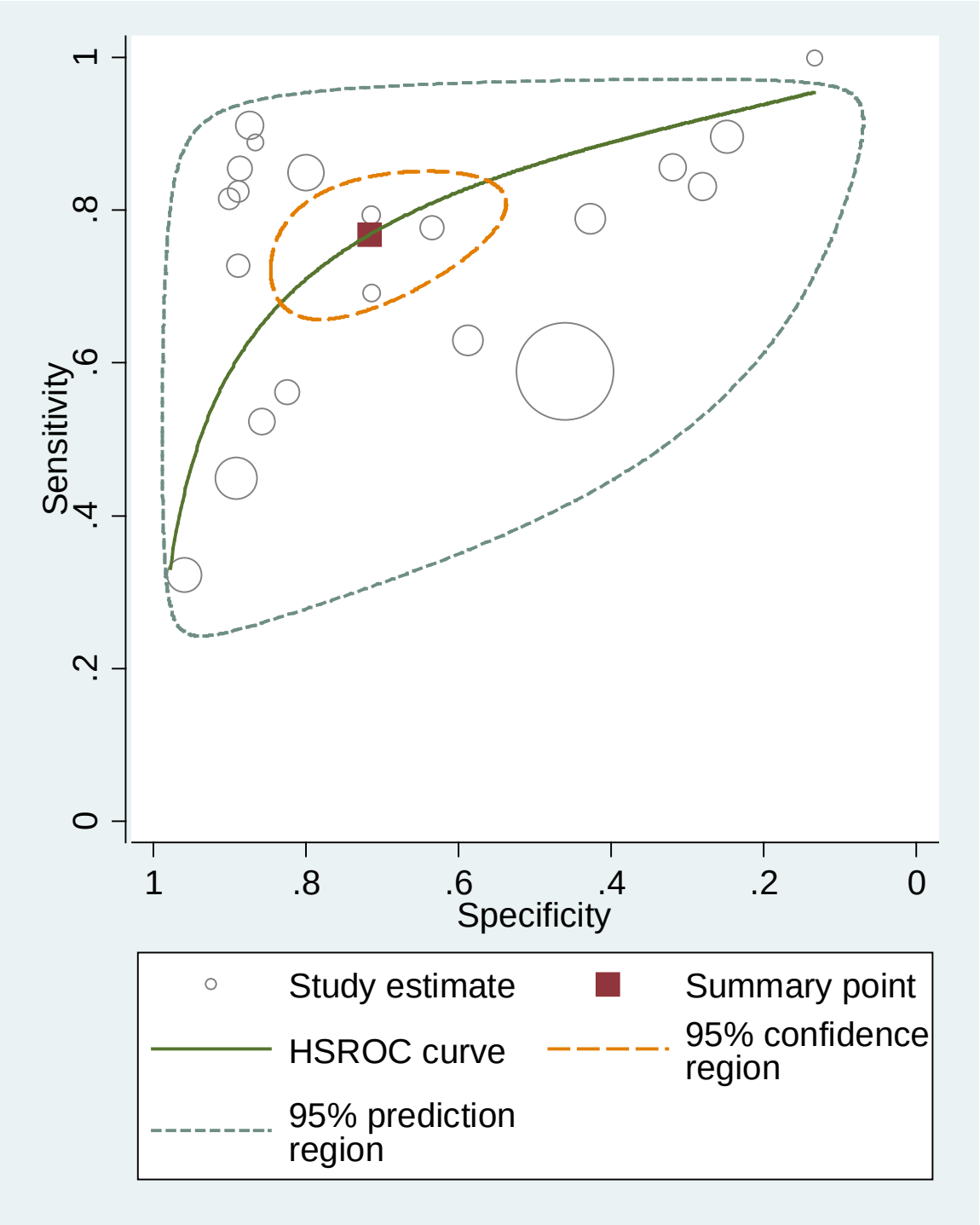


Figure D.2 Pooled sensitivity, specificity and HSROC curve for diagnosis of asthma when FeNO cutoff between 20 and 30 ppb

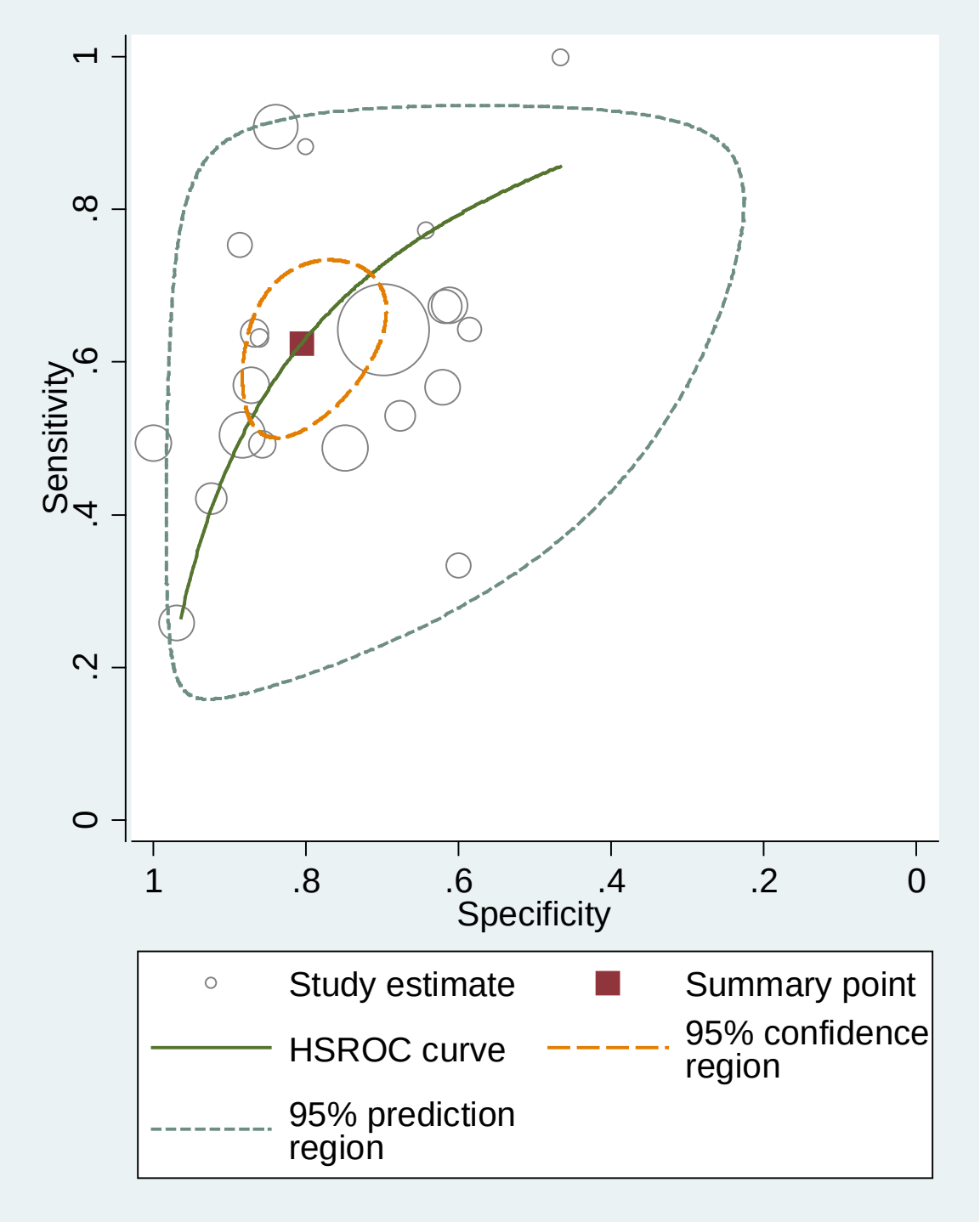


Figure D.3 Pooled sensitivity, specificity and HSROC curve for diagnosis of asthma when FeNO cutoff between 30 and 40 ppb

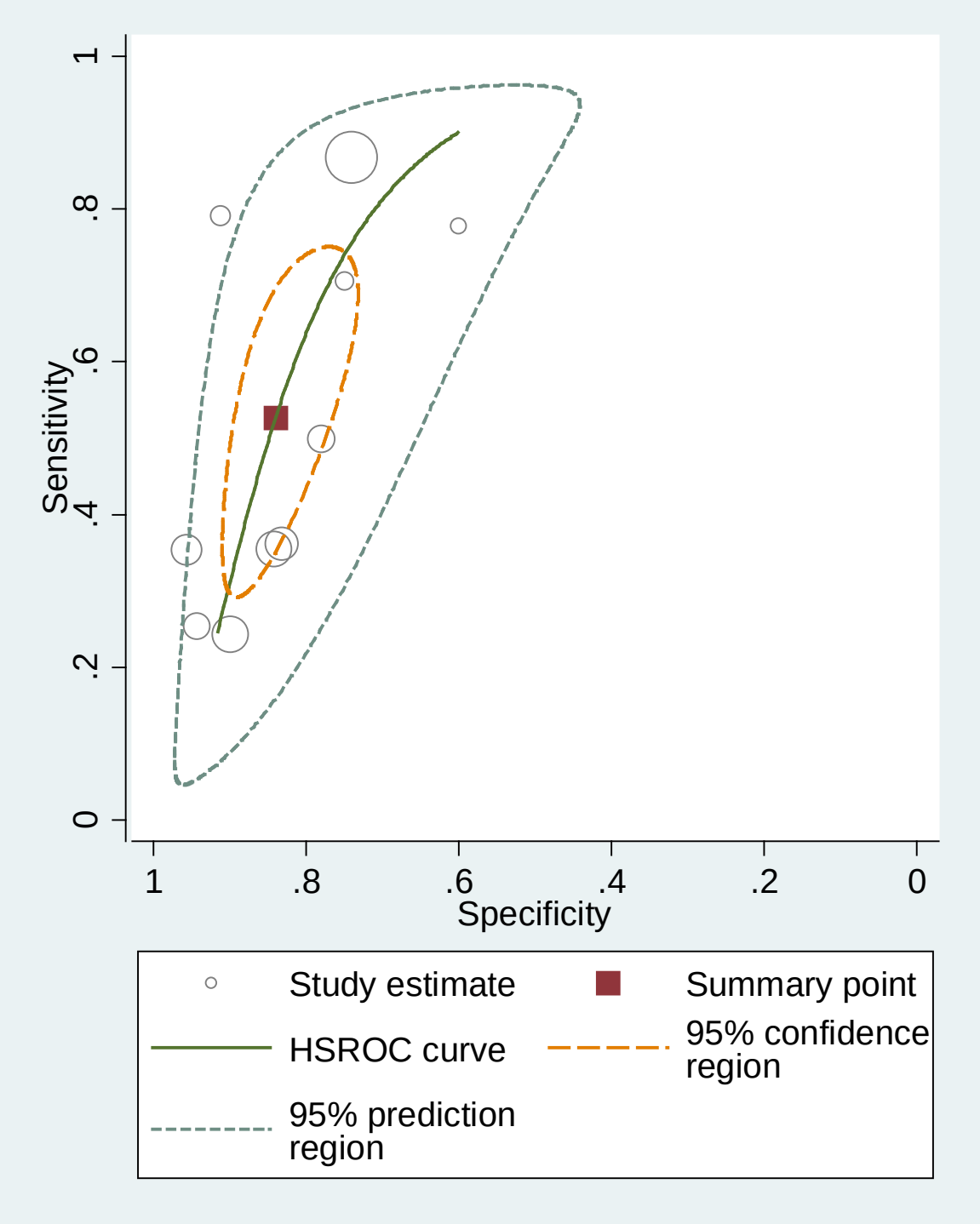


Figure D.4 Pooled sensitivity, specificity and HSROC curve for diagnosis of asthma when FeNO cutoff larger than 40 ppb

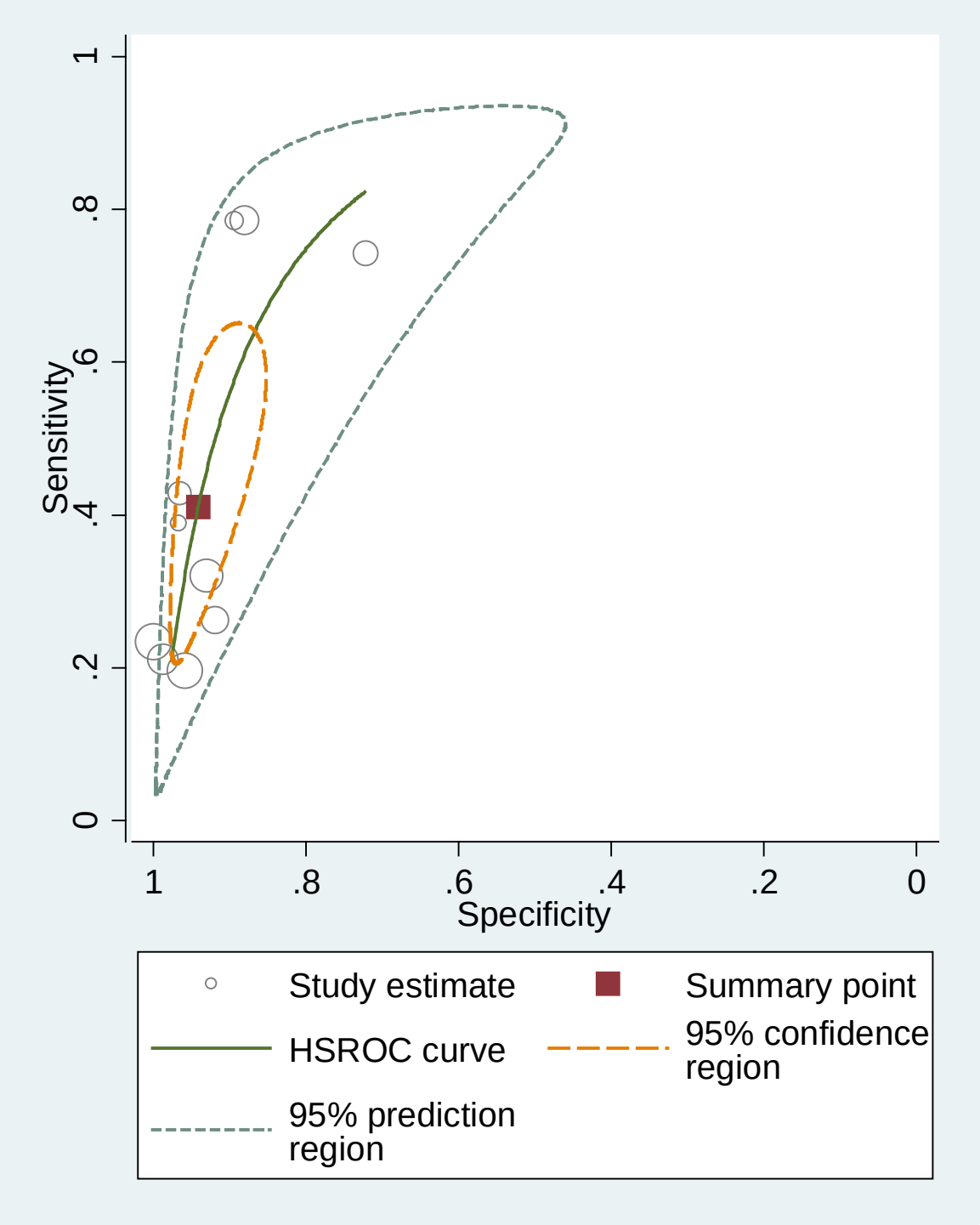
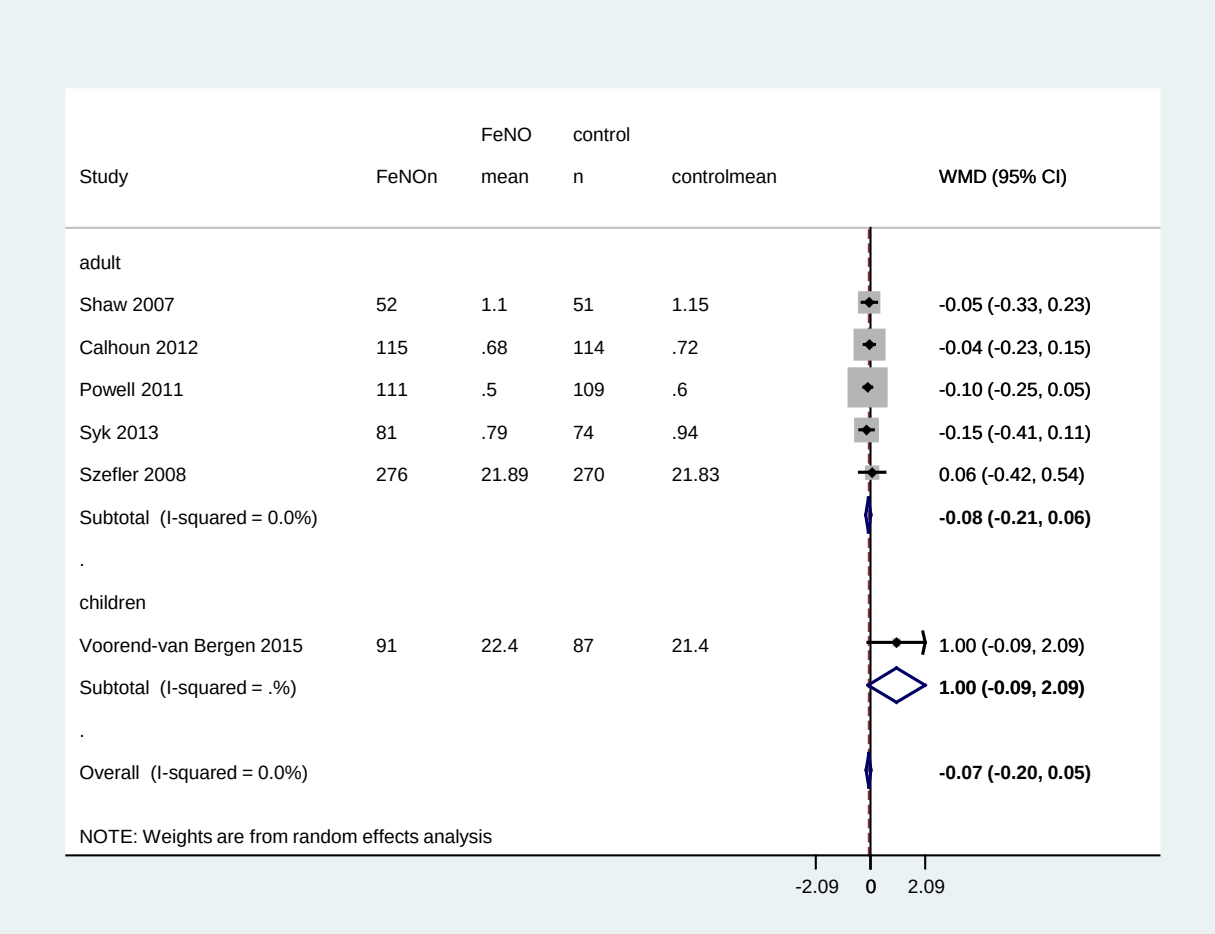
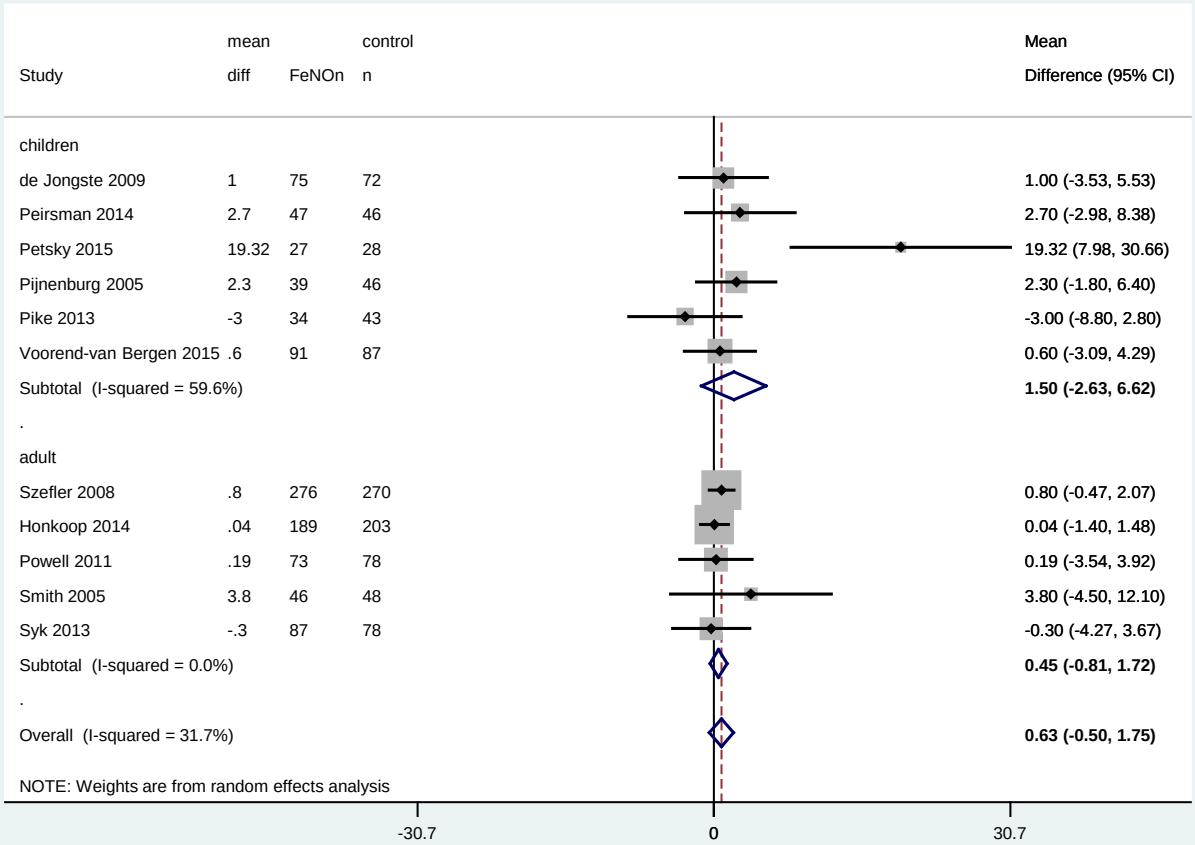


Figure D.5 Asthma Control Test



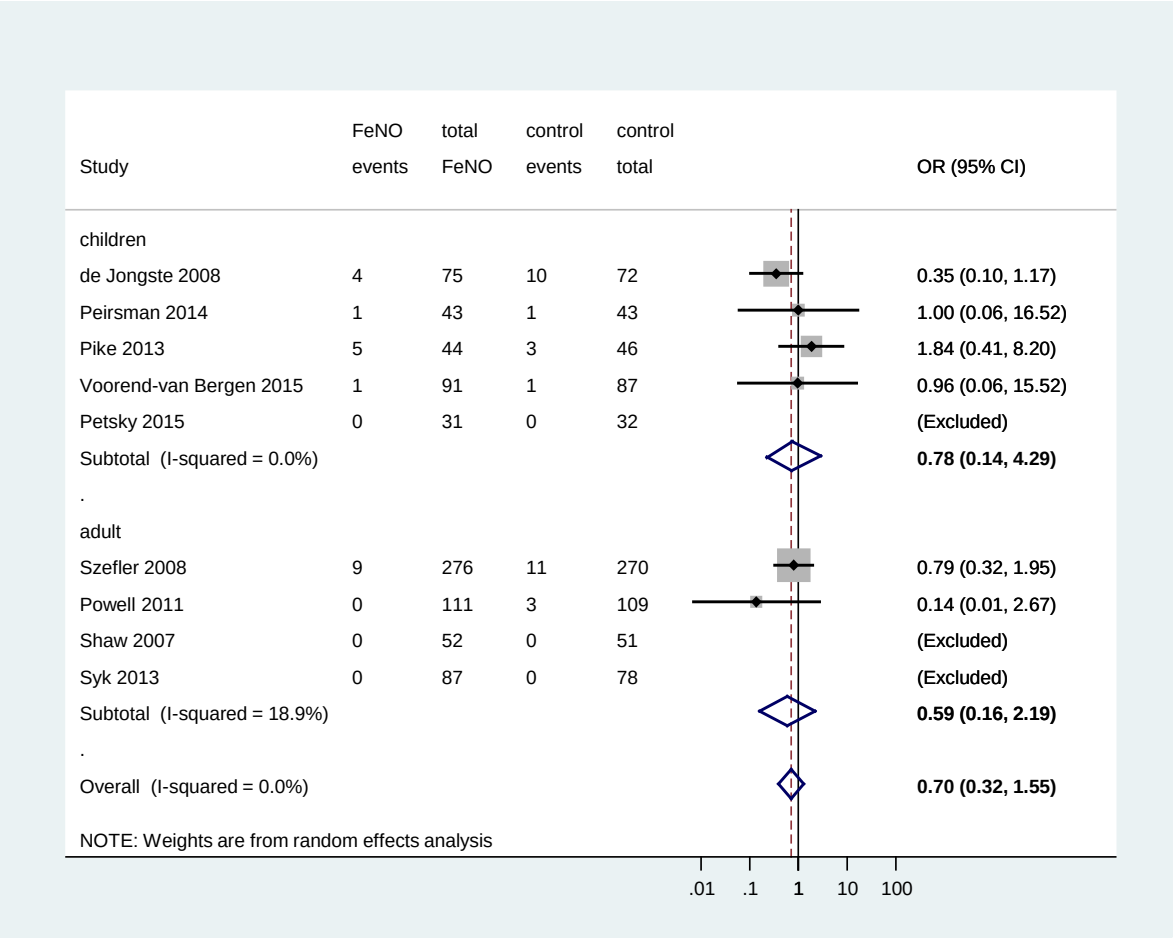
Some estimates were extracted from 2 Cochrane systematic reviews because data were not reported in published trial reports.

Figure D.6 FEV_1%



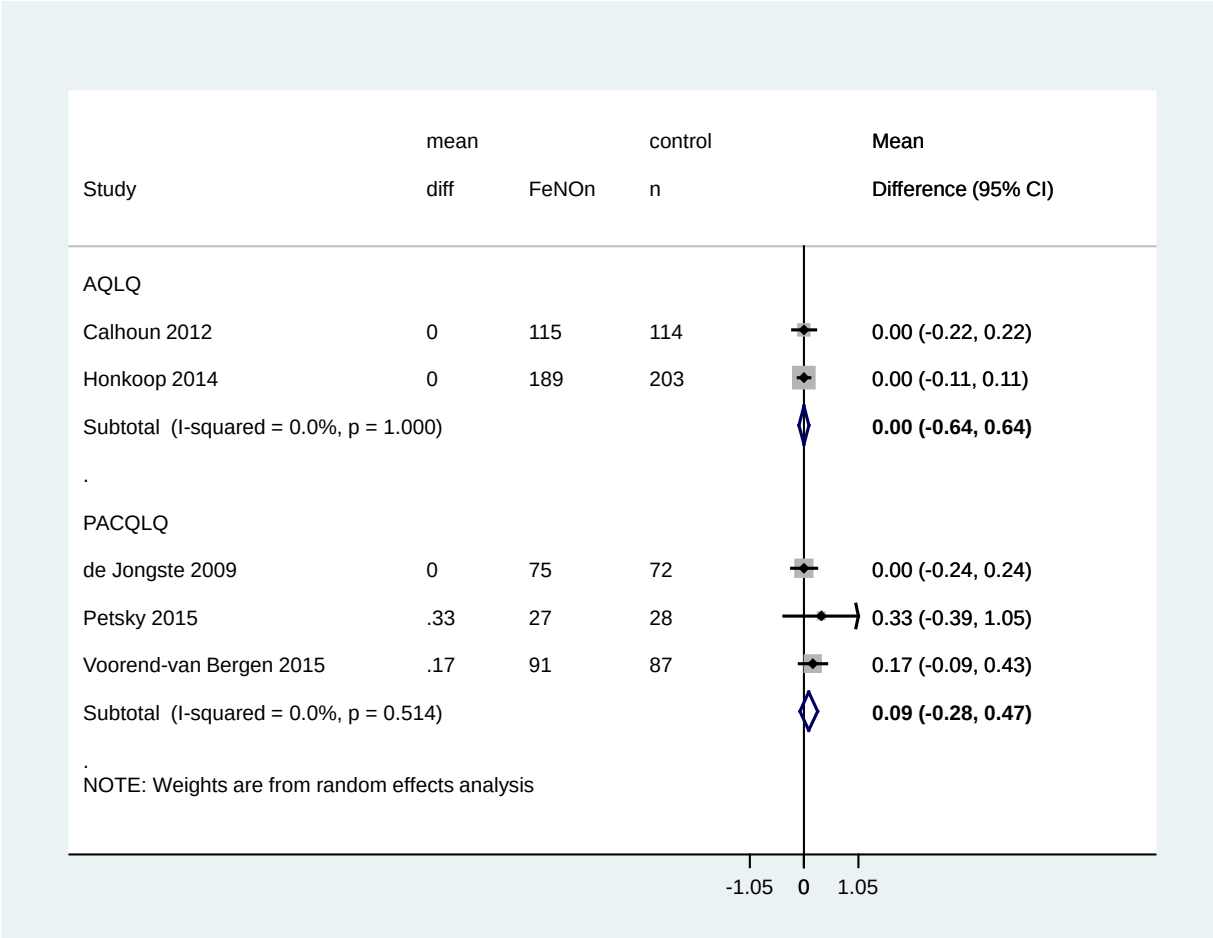
Some estimates were extracted from 2 Cochrane systematic reviews because data were not reported in published trial reports.

Figure D.7 Hospitalizations



Some estimates were extracted from 2 Cochrane systematic reviews because data were not reported in published trial reports.

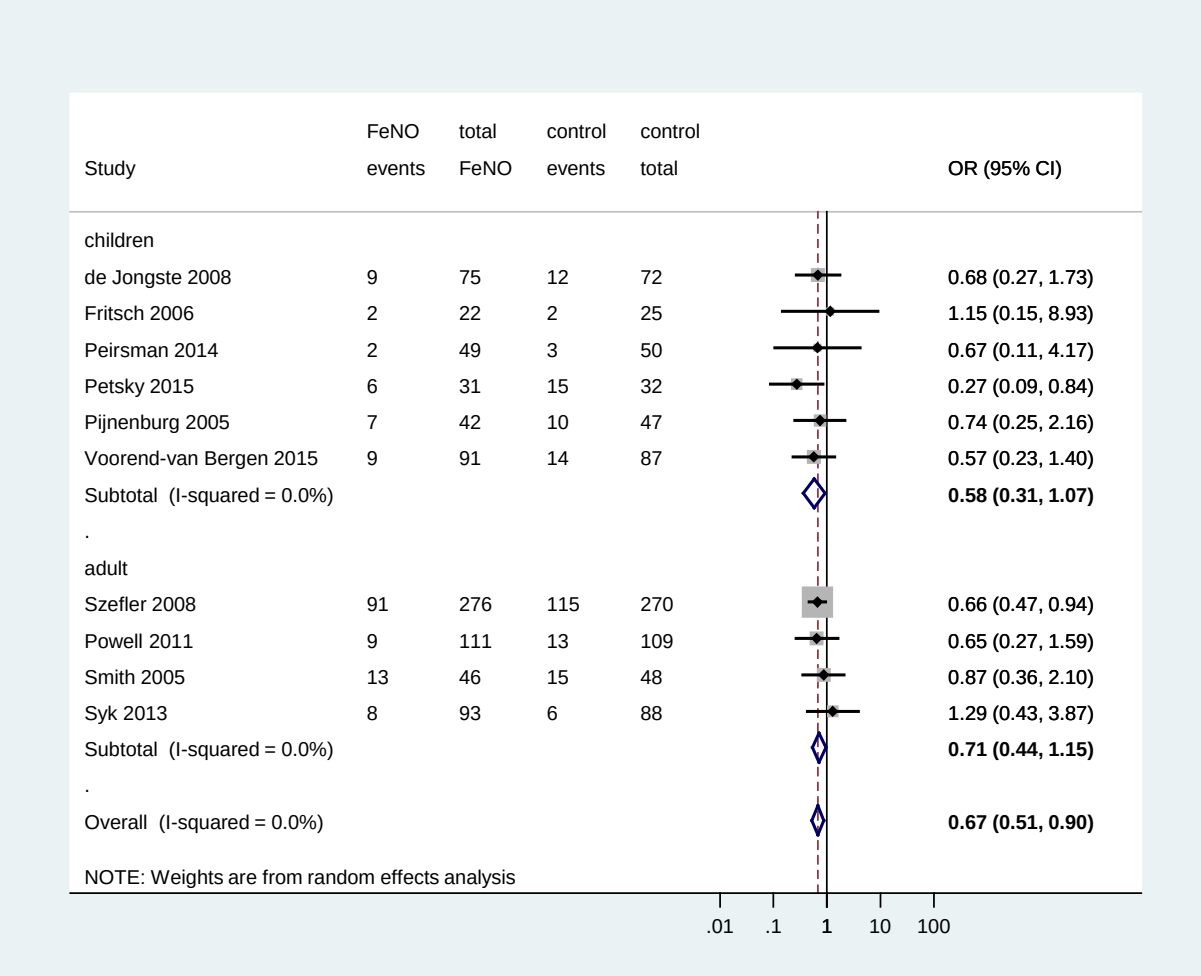
Figure D.8 Quality of life



AQLQ: Asthma Quality of Life Questionnaire; PACQLQS: Pediatric Asthma Caregiver Quality of Life Questionnaire with Standardized activities.

Some estimates were extracted from 2 Cochrane systematic reviews because data were not reported in published trial reports.

Figure D.9. Exacerbations requiring steroids



Some estimates were extracted from 2 Cochrane systematic reviews because data were not reported in published trial reports.

Figure D.10. Funnel plot for FeNO cutoffs <20 ppb

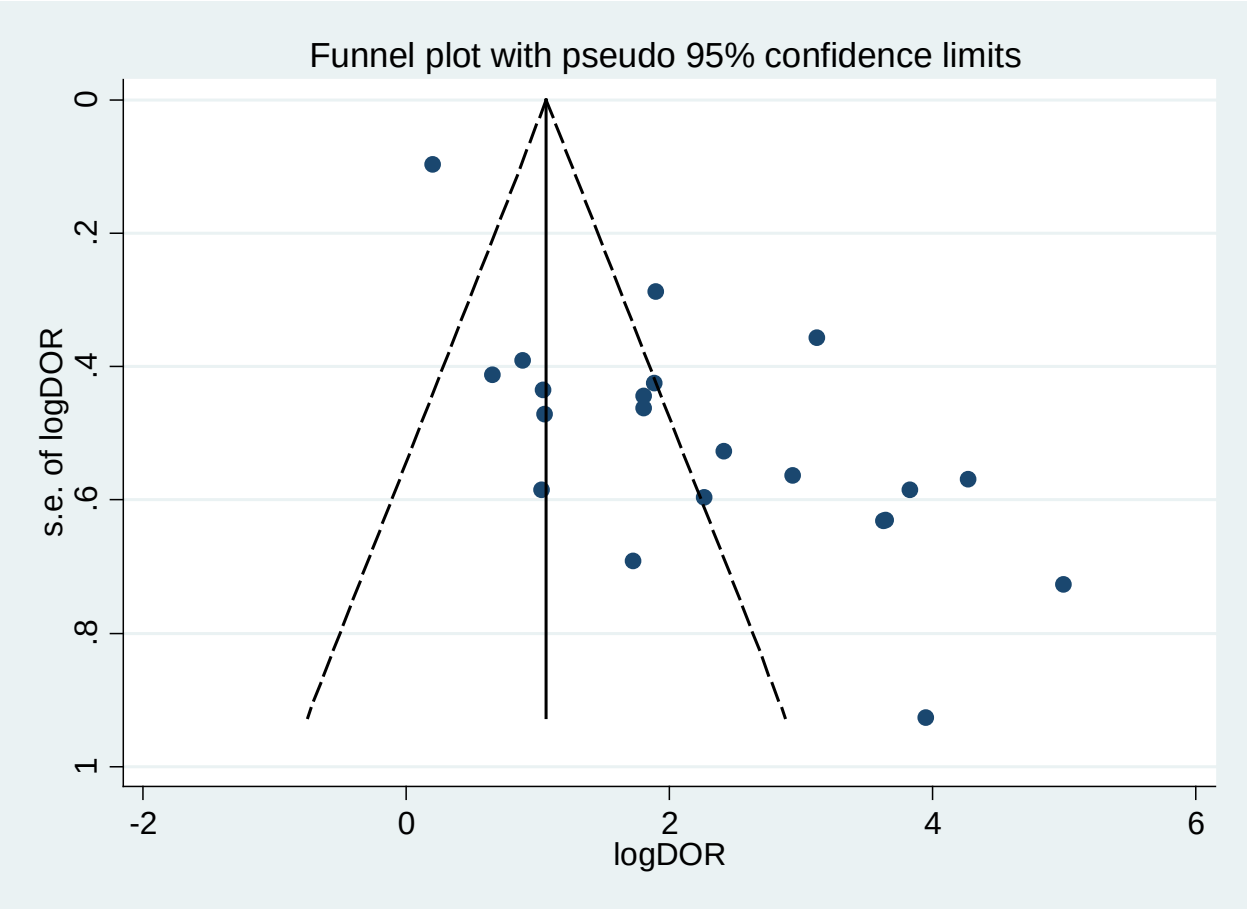
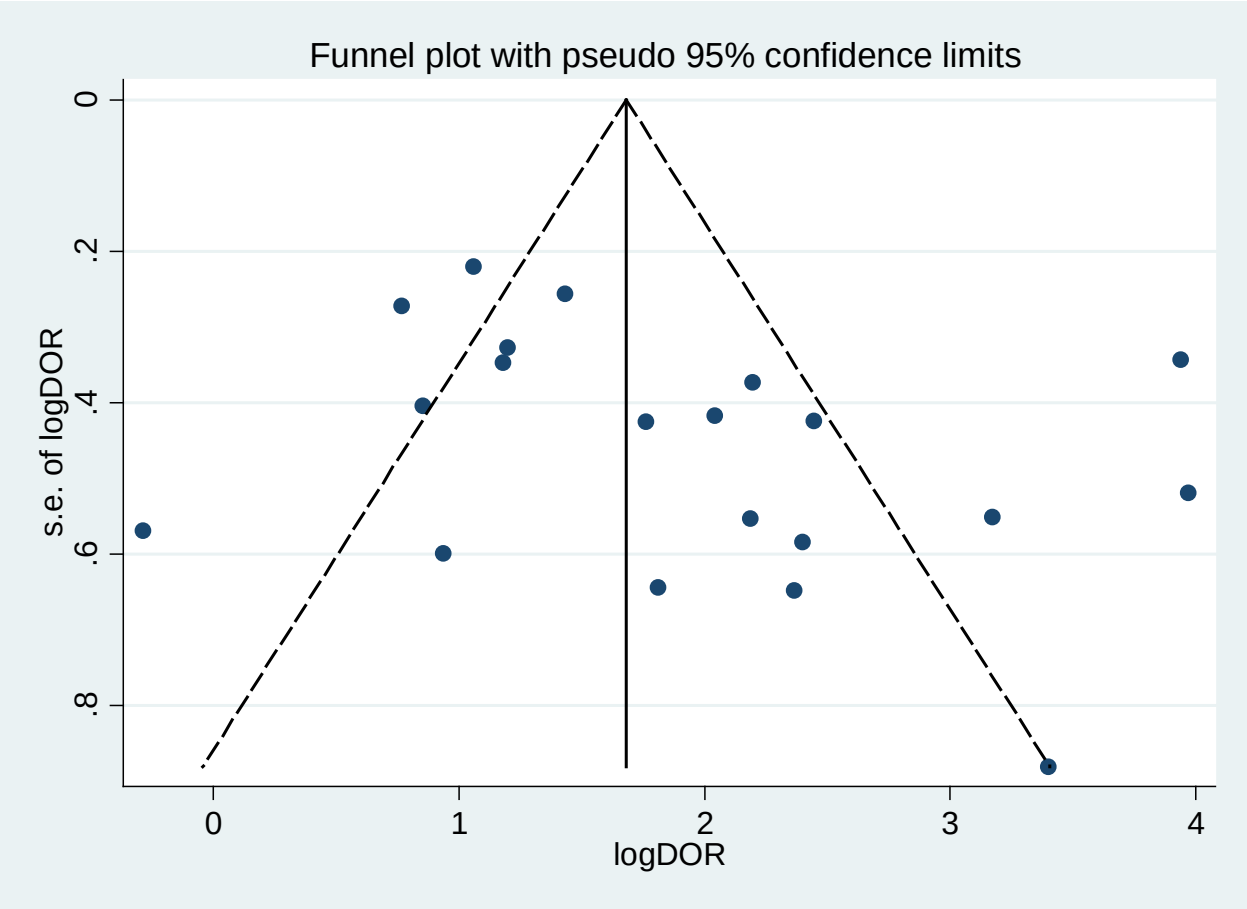


Figure D.11 Funnel plot for FeNO cutoffs 20-30 ppb



Appendix E. Subgroup Analyses

KQ 1.a: What is the diagnostic accuracy of FeNO measurement(s) for making the diagnosis of asthma in individuals ages 5 and older?

Table E.1. Subgroup analysis (reference group: healthy versus symptomatic individuals without asthma)

FeNO CutOff	Subgroup	Number of included studies	Conclusion
<20 ppb	Healthy	13 studies	Sensitivity 0.82; 95% CI (0.72 to 0.90) Sensitivity 0.78; 95% CI (0.62 to 0.88) DOR 16.45; 95% CI (7.85 to 34.49) LR+ 3.71; 95% CI (2.14 to 6.43) LR- 0.23; 95% CI (0.14 to 0.36)
	Symptomatic no asthma	9 studies	Sensitivity 0.73; 95% CI (0.60 to 0.83) Specificity 0.62; 95% CI (0.45 to 0.77) DOR 4.42; 95% CI (2.33 to 8.35) LR+ 1.92; 95% CI (1.32 to 2.78) LR- 0.43; 95% CI (0.30 to 0.63)
20-30 ppb	Healthy	10 studies	Sensitivity 0.67; 95% CI (0.52 to 0.79) Sensitivity 0.77; 95% CI (0.64 to 0.86) DOR 6.82; 95% CI (2.87 to 16.17) LR+ 2.92; 95% CI (1.74 to 4.88) LR- 0.43; 95% CI (0.28 to 0.66)
	Symptomatic no asthma	13 studies	Sensitivity 0.57; 95% CI (0.47 to 0.67) Specificity 0.84; 95% CI (0.76 to 0.90) DOR 7.30; 95% CI (4.57 to 11.66) LR+ 3.68; 95% CI (2.51 to 5.39) LR- 0.50; 95% CI (0.41 to 0.62)
30-40 ppb	Healthy	NA	NA
	Symptomatic no asthma	6 studies	Sensitivity 0.57; 95% CI (0.32 to 0.79) Specificity 0.87; 95% CI (0.76 to 0.93) DOR 8.89; 95% CI (4.65 to 17.01) LR+ 4.38; 95% CI (2.96 to 6.50) LR- 0.49; 95% CI (0.29 to 0.84)
>=40	Healthy	NA	NA
	Symptomatic no asthma	NA	NA

CI: confidence interval; DOR: diagnostic odds ratio; FeNO: fraction exhaled nitric oxide; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NA: not available; ppb: parts per billion

Table E.2. Subgroup analysis based on risk of bias

FeNO CutOff	Subgroup	Number of included studies	Conclusion
<20 ppb	Low risk of bias	11 studies	Sensitivity 0.80; 95% CI (0.67 to 0.88) Specificity 0.69; 95% CI (0.48 to 0.84) DOR 8.81; 95% CI (4.27 to 18.20) LR+ 2.57; 95% CI (1.50 to 4.45) LR- 0.29; 95% CI (0.19 to 0.45)
	Moderate risk of bias	6 studies	Sensitivity 0.74; 95% CI (0.62 to 0.84) Specificity 0.78; 95% CI (0.64 to 0.88) DOR 10.33; 95% CI (3.68 to 29.02) LR+ 3.4; 95% CI (1.85 to 6.27) LR- 0.33; 95% CI (0.20 to 0.54)
	High risk of bias	5 studies	Sensitivity 0.84; 95% CI (0.60 to 0.95) Sensitivity 0.68; 95% CI (0.41 to 0.86) DOR 11.29; 95% CI (2.75 to 46.30) LR+ 2.63; 95% CI (1.28 to 5.41) LR- 0.23; 95% CI (0.09 to 0.64)
20-30 ppb	Low risk of bias	13 studies	Sensitivity 0.68; 95% CI (0.56 to 0.78) Sensitivity 0.78; 95% CI (0.67 to 0.85) DOR 7.29; 95% CI (4.12 to 12.91) LR+ 3.03; 95% CI (2.09 to 4.40) LR- 0.42; 95% CI (0.30 to 0.57)
	Moderate risk of bias	6 studies	Sensitivity 0.53; 95% CI (0.43 to 0.62) Specificity 0.84; 95% CI (0.61 to 0.94) DOR 5.77; 95% CI (1.65 to 20.21) LR+ 3.26; 95% CI (1.18 to 8.99) LR- 0.56; 95% CI (0.43 to 0.75)
	High risk of bias	NA	NA
30-40 ppb	Low risk of bias	5 studies	Sensitivity 0.57; 95% CI (0.37 to 0.74) Sensitivity 0.79; 95% CI (0.72 to 0.85) DOR 5.02; 95% CI (2.66 to 9.44) LR+ 2.75; 95% CI (2.05 to 3.67) LR- 0.55; 95% CI (0.37 to 0.81)
	Moderate risk of bias	4 studies	Sensitivity 0.37; 95% CI (0.21 to 0.57) Specificity 0.91; 95% CI (0.82 to 0.95) DOR 5.83; 95% CI (3.28 to 10.37) LR+ 4.04; 95% CI (2.52 to 6.46) LR- 0.69; 95% CI (0.54 to 0.89)
	High risk of bias	NA	NA
>=40 ppb	Low risk of bias	7 studies	Sensitivity 0.41; 95% CI (0.24 to 0.59) Specificity 0.92; 95% CI (0.85 to 0.96) DOR 8.3; 95% CI (5.38 to 12.79) LR+ 5.33; 95% CI (3.59 to 7.91) LR- 0.64; 95% CI (0.50 to 0.83)
	Moderate risk of bias	NA	NA
	High risk of bias	NA	NA

CI: confidence interval; DOR: diagnostic odds ratio; FeNO: fraction exhaled nitric oxide; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NA: not available; ppb: parts per billion.

Table E.3. Subgroup analysis based on smoking status

Subgroup	Number of included studies	Conclusion
Non smokers	17 studies	Sensitivity 0.70; 95% CI (0.61 to 0.78) Sensitivity 0.80; 95% CI (0.74 to 0.85) DOR 9.49; 95% CI (5.62 to 16.01) LR+ 3.51; 95% CI (2.62 to 4.70) LR- 0.37; 95% CI (0.27 to 0.50)
Current Smokers	1 study	Sensitivity 0.63 Specificity 0.86 DOR 10.64 LR+ 4.50 LR- 0.43
Ex-smokers	1 study	Sensitivity 0.56 Specificity 0.83 DOR 6.07 LR+ 3.29 LR- 0.53
Smokers	1 study	Sensitivity 0.29 Specificity 0.86 DOR 2.53 LR+ 2.07 LR- 0.83

CI: confidence interval; DOR: diagnostic odds ratio; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

Table E.4. Subgroup analysis based on age

FeNO CutOff	Subgroup	Number of included studies	Conclusion
<20	18 years or older	12 studies	Sensitivity 0.80; 95% CI (0.72 to 0.86) Sensitivity 0.64; 95% CI (0.46 to 0.79) DOR 7.28; 95% CI (4.04 to 13.11) LR+ 2.25; 95% CI (1.47 to 3.44) LR- 0.31; 95% CI (0.23 to 0.41)
	Younger than 18 years	6 studies	Sensitivity 0.78; 95% CI (0.59 to 0.90) Sensitivity 0.79; 95% CI (0.55 to 0.92) DOR 13.44; 95% CI (3.56 to 50.71) LR+ 3.76; 95% CI (1.53 to 9.26) LR- 0.28; 95% CI (0.14 to 0.56)
20-30	18 years or older	6 studies	Sensitivity 0.69; 95% CI (0.57 to 0.79) Sensitivity 0.78; 95% CI (0.66 to 0.86) DOR 7.70; 95% CI (4.12 to 14.40) LR+ 3.10; 95% CI (2.02 to 4.74) LR- 0.40; 95% CI (0.29 to 0.56)
	Younger than 18 years	6 studies	Sensitivity 0.61; 95% CI (0.44 to 0.76) Sensitivity 0.89; 95% CI (0.80 to 0.94) DOR 12.13; 95% CI (5.98 to 24.63) LR+ 5.34; 95% CI (3.12 to 9.14) LR- 0.44; 95% CI (0.30 to 0.65)
30-40	18 years or older	9 studies	Sensitivity 0.53; 95% CI (0.35 to 0.70) Sensitivity 0.85; 95% CI (0.77 to 0.90) DOR 6.27; 95% CI (3.70 to 10.64) LR+ 3.46; 95% CI (2.57 to 4.66) LR- 0.55; 95% CI (0.39 to 0.78)
	Younger than 18 years	NA	NA
>=40	18 years or older	7 studies	Sensitivity 0.41; 95% CI (0.24 to 0.62) Sensitivity 0.93; 95% CI (0.86 to 0.97) DOR 9.84; 95% CI (5.46 to 17.75) LR+ 6.18; 95% CI (3.64 to 10.47) LR- 0.63; 95% CI (0.47 to 0.85)
	Younger than 18 years	NA	NA

CI: confidence interval; DOR: diagnostic odds ratio; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NA: not available.

Appendix F. Sensitivity Analysis

KQ 1.a: What is the diagnostic accuracy of FeNO measurement(s) for making the diagnosis of asthma in individuals ages 5 and older?

Table F.1. Including only studies with ICS naiive or atopy

FeNO CutOff	Number of included studies	Conclusion
Not taking ICS	13 studies	Sensitivity 0.57; 95% CI (0.46 to 0.67) Specificity 0.85; 95% CI (0.78 to 0.91) DOR 7.76; 95% CI (4.94 to 12.18) LR+ 3.91; 95% CI (2.73 to 5.61) LR- 0.504; 95% CI (0.41 to 0.62)
<20	6 studies	Sensitivity 0.79; 95% CI (0.67 to 0.87) Specificity 0.77; 95% CI (0.56 to 0.90) DOR 12.25; 95% CI (5.73 to 26.21) LR+ 3.400; 95% CI (1.75 to 6.61) LR- 0.28; 95% CI (0.19 to 0.40)
20-30	8 studies	Sensitivity 0.59; 95% CI (0.45 to 0.71) Specificity 0.84; 95% CI (0.69 to 0.9227861) DOR 7.245765; 95% CI (2.70 to 19.44) LR+ 3.60; 95% CI (1.73 to 7.47) LR- 0.50; 95% CI (0.35 to 0.70)
30-40	6 studies	Sensitivity 0.37; 95% CI (0.26 to 0.49) Specificity 0.88; 95% CI (0.81 to 0.93) DOR 4.16; 95% CI (2.71 to 6.39) LR+ 3.01; 95% CI (2.11 to 4.28) LR- 0.72; 95% CI (0.62 to 0.84)
Atopic	4 studies	Sensitivity 0.63; 95% CI (0.43 to 0.80) Specificity 0.79; 95% CI (0.65 to 0.89) DOR 6.67; 95% CI (1.59 to 27.95) LR+ 3.07; 95% CI (1.35 to 6.97) LR- 0.46; 95% CI (0.24 to 0.87)

CI: confidence interval; DOR: diagnostic odds ratio; FeNO: fraction exhaled nitric oxide; ICS: inhaled corticosteroid; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

Appendix G. Risk of Bias

Table G.1. Risk of Bias (QUADAS-2) for studies answering KQ 1a

Author, Year (ref)	Consecutive or random sample of patients	Case-control design avoided	Inappropriate exclusions avoided	Concerns regarding applicability	The index test results interpreted	The threshold pre-specified	Concern about the index test	The reference standard correctly classify the target condition	The reference standard results appropriately interpreted	Concern that the target condition	An appropriate interval between index test(s) and reference standard	All patients received a reference standard	Patients received the same reference standard	All patients included in the analysis	Overall RoB
Arora, 2006 [1]	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Avital, 2001 [2]	High	Low	Unclear	High	Low	High	Low	Low	Low	Low	Unclear	Low	Low	Low	Medium
Backer, 2014 [3]	Low	Low	Medium	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Medium
Berkman, 2005 [4]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Berlyne, 2000 [5]	High	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High
Bommarito, 2007 [6]	High	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low
Cordeiro, 2011 [7]	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Medium	Medium
Deykin, 2002 [8]	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low	Medium
Dupont, 2003 [9]	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low	Low	Medium
Florentin 2014 [10]	High	High	Low	Medium	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	High
Fortuna, 2007 [11]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Fukuhara, 2011 [12]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

Author, Year (ref)	Consecutive or random sample of patients	Case-control design avoided	Inappropriate exclusions avoided	Concerns regarding applicability	The index test results interpreted	The threshold pre-specified	Concern about the index test	The reference standard correctly classify the target condition	The reference standard results appropriately interpreted	Concern that the target condition	An appropriate interval between index test(s) and reference standard	All patients received a reference standard	Patients received the same reference standard	All patients included in the analysis	Overall RoB
Grzelewski, 2014 [12]	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Medium
Heffler, 2006 [14]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Henriksen, 2000 [15]	High	Low	Low	Low	Low	Low	Low	High	Low	High	Low	Low	Low	High	High
Ishizuka, 2011 [16]	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	High
Jerzynska, 2014 [17]	High	Low	Low	Low	Low	Low	Low	High	High	High	High	High	Low	High	High
Katsoulis, 2013 [18]	Low	Low	Low	Unclear	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	High	Medium
Kostikas, 2008 [19]	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Medium
Lemiere, 2010 [20]	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low	Low
Malinovschi, 2012 [21]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Martin, 2016 [22]	Unclear	Low	Low	Low	Low	High	High	Low	Low	Low	Low	Low	Low	High	High
Matsunaga, 2011 [23]	Unclear	Low	Low	Low	Low	Low	Low	High	High	High	Low	Low	Low	Low	High
Menzies, 2007 [24]	High	Low	Unclear	Low	Unclear	Unclear	Low	High	Low	High	Unclear	High	High	Low	High

Author, Year (ref)	Consecutive or random sample of patients	Case-control design avoided	Inappropriate exclusions avoided	Concerns regarding applicability	The index test results interpreted	The threshold pre-specified	Concern about the index test	The reference standard correctly classify the target condition	The reference standard results appropriately interpreted	Concern that the target condition	An appropriate interval between index test(s) and reference standard	All patients received a reference standard	Patients received the same reference standard	All patients included in the analysis	Overall RoB
Miedinger, 2007 [25]	High	Low	High	High	Low	Unclear	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Medium
Miedinger, 2009 [26]	Unclear	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Low
Munnik, 2009 [27]	High	Low	High	Low	Low	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low	Medium
Nayak, 2013 [28]	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Medium
Pedrosa, 2010 [29]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	Low
Perez Tarazona, 2011 [30]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Pizzimenti, 2009 [31]	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Unclear	Medium
Ramser, 2008 [32]	Low	Low	Unclear	Low	Low	Unclear	Low	High	Low	High	Unclear	Low	Low	Low	Low
Sachs-Olsen, 2010 [33]	Unclear	Low	Unclear	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low
Sato, 2008 [34]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Schleich, 2012 [35]	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Medium
Schneider, 2009 [38]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Schneid	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

Author, Year (ref)	Consecutive or random sample of patients	Case-control design avoided	Inappropriate exclusions avoided	Concerns regarding applicability	The index test results interpreted	The threshold pre-specified	Concern about the index test	The reference standard correctly classify the target condition	The reference standard results appropriately interpreted	Concern that the target condition	An appropriate interval between index test(s) and reference standard	All patients received a reference standard	Patients received the same reference standard	All patients included in the analysis	Overall RoB
er, 2012 Schneider, 2014[36, 37]															
Sivan, 2009 [39]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Smith, 2004 [40]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Medium	Low
Thomas, 2005 [41]	High	Low	Low	Low	Medium	Low	Low	High	High	High	Low	Low	Low	High	High
Traves, 2007 [42]	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Woo, 2012 [43]	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Yao, 2011 [44]	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low	Medium

Table G.2. Risk of Bias for RCTs (Cochrane ROB tool) for studies answering KQ 1b

Author, Year (ref)	Sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall RoB
	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	
Beck-Ripp, 2002 [98]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Beerthuizen, 2016 [46]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Fritsch, 2006 [54]	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear
Powell, 2011 [109]	Low	Low	Low	Low	Low	Low	Low	Low
Szefler, 2008 [87]	Low	Low	Low	Low	Low	Low	Low	Low
Voorend-van Bergen, 2015 [91]	Low	High	Low	High	Low	Low	Low	High
Zeiger, 2006 [96]	Low	Unclear	Low	Low	Low	Low	Unclear	Unclear

Table G.3. Risk of Bias for observational studies (Newcastle-Ottawa Quality Assessment Scale) for studies answering KQ 1b

Author, Year (ref)	Representativeness of the study population	Ascertainment of exposure	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Overall RoB
Agache, 2012 [45]	Low	Low	Low	Low	Low	High	Low
Bernstein, 2009 [48]	Unclear	Unclear	Low	Low	Low	Low	Medium
Berg, 2008 [47]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bora, 2011 [49]	High	High	High	Low	Low	Low	High
Cano-Garcinuño, 2010 [50]	Low	Low	Unclear	Low	Unclear	Low	Low
Ciprandi, 2013 [51]	Low	Low	Low	Low	Unclear	Low	Low
de Bot, 2013 [52]	Low	Low	Unclear	Low	High	Low	Medium
Delclaux, 2008 [53]	Low	Low	Low	Low	Unclear	High	Medium
Gelb, 2006 [55]	Low	Low	Low	Low	Low	Low	Low
Gill, 2005 [56]	High	Low	High	Low	Low	Low	High
Griese, 2000 [57]	Low	Low	Low	Low	Low	Low	Low
Gruffydd-Jones, 2007 [58]	Low	Low	Low	Low	Low	Low	Low
Habib, 2014 [59]	High	High	High	High	High	High	High
Hanson, 2013 [60]	Low	High	High	Low	High	High	High
Harkins, 2004 [61]	Low	Low	High	Low	Medium	Low	Medium
Hayata, 2013 [62]	Unclear	Low	High	Low	High	Low	Medium
Hsu, 2013 [63]	Unclear	Unclear	Low	Low	Unclear	Unclear	High
Ko, 2011 [64]	Unclear	Low	Low	Low	Low	Low	Low
Kostikas, 2011 [65]	Medium	Low	Medium	Low	Unclear	Low	Medium
Kwok, 2008 [66]	Unclear	Low	Unclear	Low	High	Low	High
Leblanc, 2013 [67]	Unclear	Low	High	Low	Low	Low	Medium
Lex, 2007 [68]	Low	Low	Unclear	Low	Unclear	Unclear	Medium
Mahut, 2010 [69]	Low	Low	Unclear	Low	Unclear	Low	Low
Malerba, 2012 [116]	Low	Low	Unclear	Low	Low	Low	Low
Martins, 2008 [70]	High	High	High	High	Low	High	High
McCormack, 2013 [71]	Low	Low	Low	Low	Low	Low	Low
Menzies, 2008 [72]	Unclear	Low	Low	Low	Low	Low	Low
Meyts, 2003 [73]	High	Low	High	High	Low	Low	High
Michils, 2008 [74]	Low	Low	Unclear	Low	Low	Low	Low
Michils, 2009 [75]	Low	Unclear	Low	Unclear	Low	Unclear	Medium
Nayak, 2013 [28]	Unclear	Low	Low	Low	High	Unclear	Medium
Nittner-Marszalska, 2013 [76]	Unclear	Low	Low	Low	Low	Low	Low
Ozier, 2011 [77]	Low	Low	Low	Medium	Low	Low	Medium
Papakosta, 2011 [78]	Low	Low	Unclear	Low	Low	Unclear	Medium

Plaza, 2013 [79]	Low	Low	Unclear	Low	Low	Low	Low
Quaedvlieg, 2009 [80]	Low	Low	Low	Low	Unclear	Low	Low
Raj, 2014 [81]	Low	Unclear	Unclear	Low	Unclear	Unclear	Medium
Ricciardolo, 2016 [82]	Low	High	Unclear	Low	Unclear	High	High
Robroeks, 2007 [83]	High	High	High	Low	High	High	High
Rosias, 2004 [84]	Low	Low	Unclear	Low	Unclear	Low	Medium
Sato, 2009 [85]	Unclear	Unclear	Low	Unclear	Low	Unclear	Medium
Shirai, 2008 [86]	Medium	Medium	Low	Low	High	Low	High
van der Valk, 2012 [88]	High	Unclear	Unclear	Low	Low	Low	Medium
van Vliet, 2015 [89]	Unclear	Low	Unclear	Low	Low	Low	Low
Vijverberg, 2012 [99]	Low	Low	Low	Low	High	Low	Medium
Visitsunthorn, 2013 [90]	High	High	Low	High	High	High	High
Warke, 2004 [92]	High	Low	Unclear	Low	Low	Unclear	High
Yamashita, 2015 [93]	Low	Low	Medium	Low	Low	High	High
Yang, 2015 [94]	High	Low	Unclear	Low	Low	Low	Medium
Yavuz, 2012 [95]	Low	Low	Low	Low	Low	High	Low
Zeiger, 2011 [97]	Low	Unclear	Low	Low	Unclear	Low	Medium

Table G.4. Risk of Bias for RCTs (Cochrane ROB tool) for studies answering KQ 1c

Author, Year (ref)	Sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall RoB
	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	
Calhoun, 2012 [100]	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear
De Jongste, 2009 [101]	Low	Unclear	High	Unclear	Low	Low	Low	High
Hashimoto, 2011 [102]	Low	Unclear	High	High	Low	Low	Low	High
Honkoop, 2015 [103]	Low	Low	High	High	Low	Low	Low	High
Malerba, 2015 [104]	High	High	Low	High	Low	Low	Low	Unclear
Peirsman, 2014 [105]	High	High	Low	High	Low	Low	Low	High
Petsky, 2015 [106]	Low	Low	Low	Low	Low	Low	Low	Low
Pijnenburg, 2005[107]	High	High	High	High	Low	Low	Low	High
Pike, 2013 [108]	Low	Low	Low	Low	Low	Low	Low	Low
Powell, 2011 [109]	Low	Low	Low	Low	Low	Low	Low	Low
Shaw, 2007 [110]	Low	Low	Low	High	Low	Low	Low	Low
Smith, 2005[111]	Low	Unclear	Low	High	Low	Low	Low	Unclear
Syk, 2013 [112]	Low	Low	High	High	Low	Low	Low	High
Verini, 2010 [113]	Low	Unclear	High	Unclear	Low	Low	Low	High

Table G.5. Risk of Bias for observational studies (Newcastle-Ottawa Quality Assessment Scale) for studies answering KQ 1c

Author, Year (ref)	Representativeness of the study population	Ascertainment of exposure	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Overall RoB
	High/Medium/Low/Unclear	High/Medium/Low/Unclear	High/Medium/Low/Unclear	High/Medium/Low/Unclear	High/Medium/Low/Unclear	High/Medium/Low/Unclear	High/Medium/Low
Ciolkowski, 2016 [118]	High	High	High	Low	Low	Low	High
Cowan, 2015 [119]	Low	Low	Low	Low	Unclear	Low	Low
Griese, 2000 [57]	Low	Low	Low	Low	Low	Low	Low
Laforce, 2014 [114]	High	High	Low	Low	Unclear	Unclear	High
Mahut, 2011 [120]	Unclear	Low	Low	Low	High	Low	Medium
Malerba, 2008 [115]	Unclear	Low	Unclear	Low	Low	Low	Medium
Malerba, 2012 [116]	Low	Low	Unclear	Low	Low	Low	Low
Martin, 2016 [22]	Low	Low	High	Low	Low	Low	Low
Smith, 2005 [121]	Low	Low	Low	Low	Low	Low	Low
Wan, 2014 [117]	High	Low	High	Low	Low	Low	High

Table G.6. Risk of Bias for RCTs (Cochrane ROB tool) for studies answering KQ 1d

Author, Year (ref)	Sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall RoB
	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	
Beck-Ripp, 2002 [98]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Bisgaard, 1999 [122]	Low	Unclear	Low	Low	Unclear	Low	Low	Unclear
Ehrs, 2010 [133]	Low	Unclear	Low	Low	Low	Low	Low	Low
Erin, 2008 [134]	Low	Low	Low	Low	High	Low	High	High
Fuglsang, 1998 [146]	Low	Unclear	Low	Low	Low	Low	Low	Low
Hozawa, 2014 [136]	Low	Unclear	Low	High	Low	Low	High	High
Kharitonov, 1996 [138]	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear
Kharitonov, 2002 [139]	Low	Unclear	Low	Low	Low	Low	Low	Low
Montuschi, 2007 [124]	Low	Unclear	Low	Low	Low	Low	Low	Low
Nolte, 2013[140]	Low	Unclear	Low	Low	Low	Low	Unclear	Unclear
Obase, 2013 [152]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Profita, 2013 [141]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear
Sandrini, 2003 [126]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Silkoff, 2004 [127]	Low	Low	Low	Low	Low	Low	Unclear	Low
Verini, 2007 [145]	Low	Unclear	High	Low	Low	Low	Low	Unclear
Yates, 1997 [147]	Low	Unclear	Low	Low	Low	Low	Low	Low
Zeiger, 2006 [96]	Low	Unclear	Low	Low	Low	Low	Unclear	Unclear

Table G.7. Risk of Bias for for observational studies (Newcastle-Ottawa Quality Assessment Scale) for studies answering KQ 1d

Author, Year (ref)	Representativeness of the study population	Ascertainment of exposure	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Overall RoB
Baraldi, 1997 [129]	Low	Low	Unclear	Low	High	Low	High
Bratton, 1999 [123]	Low	Low	Low	Low	High	High	High
Bulac, 2015 [130]	Low	Low	Low	Low	Low	Low	Low
Byrnes, 1997 [131]	Medium	Low	Unclear	Low	Medium	Unclear	Medium
Cabral, 2009 [148]	Low	Low	Unclear	Low	Low	High	Medium
Dupont, 1998 [132]	Medium	Low	Unclear	Low	High	High	High
Gelb, 2008 [135]	Unclear	Low	High	Low	Unclear	Low	High
Hojo, 2013 [149]	Unclear	Low	Low	Low	Low	Low	Low
Jones, 2001 [150]	Low	Low	Low	Low	Low	Low	Low
Kermode, 2011 [137]	Low	Low	High	Low	Low	Low	Medium
Liu, 2010 [151]	Low	Low	Unclear	Low	Low	High	Medium
Ohkura, 2009 [125]	Low	Low	Unclear	Low	Low	Low	Low
Pijnenburg, 2005 [153]	Low	Low	Low	Low	Low	Low	Low
Prieto, 2003 [154]	High	Low	Low	Low	Low	Low	High
Silkoff, 2001 [142]	Unclear	Low	Low	Low	High	Unclear	High
Smith, 2015 [143]	Unclear	Unclear	High	Low	Low	Low	Medium
Spallarossa, 2001 [144]	Low	Low	Low	Low	Unclear	High/	Medium
Tajiri, 2014 [128]	Low	Low	Unclear	Low	High	Low	Medium
Tsurikisawa, 2012 [155]	Low	Low	Low	Low	Low	Low	Low

Table G.8. Risk of Bias for observational studies (Newcastle-Ottawa Quality Assessment Scale) for studies answering KQ 1e

Author, Year (ref)	Representativeness of the study population	Ascertainment of exposure	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Overall RoB
Balinotti, 2013 [156]	Low	Low	Low	Low	Low	Low	Low
Bloemen, 2010 [157]	High	High	Low	Low	High	Low	High
Castro-Rodriguez, 2013 [158]	Low	Low	Low	Low	Low	Low	Low
Caudri, 2010 [159]	Low	Low	Low	Low	Low	Low	Low
Chang, 2015 [160]	Low	Low	Low	Low	Low	Low	Low
Elliot, 2013 [161]	Unclear	Unclear	Unclear	Low	Low	High	High
Klaassen, 2012 [162]	Low	Low	Unclear	Low	Low	Low	Low
Prado, 2011 [163]	Low	Unclear	High	Low	Unclear	Unclear	Medium
van Wonderen, 2009 [164]	Low	Low	Unclear	Low	Low	Low	Low

Appendix H. Assessment of the Strength of Evidence

Table H. 1. Assessment of the Strength of Evidence KQ1a

FeNO CutOff [1]	Reference test	Study design and sample size	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
<20 ppb	Clinical Diagnosis	8 observational studies[4, 6, 15, 23, 24, 28, 30, 33] (1,199 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
	Positive bronchial challenge	5 observational studies [1, 2, 4, 8, 32] (320 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
	Combination of clinical diagnosis, bronchial challenge, and/or Bronchodilator response	9 observational studies [5, 9, 10, 13, 14, 19, 21, 38, 39] (2,683Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
	Overall (all available studies regardless of reference test)	21 observational studies [1, 2, 4-6, 8-10, 13-15, 19, 21, 23, 24, 28, 30, 32, 33, 38, 39] (4,129 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
20-30 ppb	Clinical Diagnosis	5 observational studies [7, 23, 33, 38, 44] (2,637 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
	Combination of clinical diagnosis, bronchial challenge/ Bronchodilator response	15 observational studies [9-11, 14, 17, 19, 21, 25, 26, 36-40, 42, 43] (2,327Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
	Overall (all available studies regardless of reference test)	22 observational studies [1, 3, 7, 9-11, 14, 17, 19, 21, 23, 25, 26, 30, 33, 36-40, 42-44] (5,189 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
30-40 ppb	Overall (all available studies regardless of reference test)	10 observational studies [8, 9, 14, 16, 19, 26, 32, 34, 35, 38] (1,753 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
>=40 ppb	Combination of clinical diagnosis,	8 observational studies [10, 12, 14, 25, 31, 38,	Medium	Consistent	Direct	Precise	Undetected	Moderate

FeNO CutOff[1]	Reference test	Study design and sample size	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
	bronchial challenge/ Bronchodilator response	[42, 43] (1,142 Patients)						
	Overall (all available studies regardless of reference test)	10 observational studies [10, 12, 14, 25, 29, 31, 32, 42, 43, 165] (1,368 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate

Table H. 2. Assessment of the Strength of Evidence KQ1b. Narrative Evaluation.

Question	Study design and sample size	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Can FeNO levels predict the current control of asthma or the risk of future exacerbations?	19 observational studies in adults [48, 49, 55, 59, 61-65, 72, 74-76, 78-80, 85, 86, 97] (4,146 Patients) 21 observational in children [45, 46, 50-52, 54, 57, 60, 68, 70, 71, 73, 84, 88-92, 94-96, 99] (3,926 Patients)	Low	Consistent	Direct	Precise	Undetected	Low (Observational studies)
Can FeNO be used to monitor asthma status during acute exacerbations?	4 observational studies [53, 56, 66, 81] (1,013 patients)	Low	Consistent	Direct	Precise	Undetected	Low (Observational studies)
Can FeNO be used to monitor adherence to asthma medications?	3 observational studies [87, 98, 99] (1,035 patients)	Low	Consistent	Direct	Precise	Undetected	Low (Observational studies)

Table H. 3. Assessment of the Strength of Evidence KQ1c.

Outcome	Study design and sample size	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
Adults							
Exacerbations[1]	6 RCTs[87, 103, 109-112] (1,536 patients)	Low[1]	Consistent	Direct	Precise	Undetected	High
Exacerbations requiring systemic steroids	4 RCTs[87, 109, 111, 112] (1,041 patients)	Low	Consistent	Direct	Imprecise[2]	Undetected	Moderate (Imprecision)
Hospitalizations	4 RCTs[87, 109, 110, 112] (1,034 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)
Quality of life	2 RCTs[100, 103] (621 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)
FEV_1 % predicted	5 RCTs[87, 103, 109, 111, 112] (1,348 patients)	Low	Consistent	Indirect	Severely Imprecise	Undetected	Insufficient (Severe imprecision and indirectness)
Asthma control test	5 RCTs[87, 100, 109, 110, 112] (1,523 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)
Children							
Exacerbations[1]	7 RCTs[54, 91, 101, 105-108] (733 patients)	Low[1]	Consistent	Direct	Precise	Undetected	High
Exacerbations requiring systemic steroids	6 RCTs[54, 91, 101, 105-107] (733 patients)	Low	Consistent	Direct	Imprecise[2]	Undetected	Moderate (Imprecision)
Hospitalizations	(623 patients) 5 RCTs[91, 101, 105, 106, 108] (564 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)
Quality of life	3 RCTs[91, 101, 106] (380 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)
FEV_1 % predicted	5 RCTs[91, 101, 105-108] (635 patients)	Low	Inconsistent	Indirect	Severely Imprecise	Undetected	Insufficient (Severe imprecision, indirectness and inconsistency)

Asthma control test	1 RCT[91] (178 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)

[1] Six trials were unblinded (3 in adults and 3 in children). Therefore, it is also reasonable to reduce the strength of evidence due to study limitations making it moderate. We did not rate down because results were consistent in blinded vs unblinded trials.

[2]The pooled effect of adults and children is precise, suggesting that the outcome in either subgroup (adults or children) is underpowered and the apparent imprecision is just due to small sample size. The effect size in children becomes statistically significant using the DerSimonian-Laird method.

Table H. 4. Assessment of the Strength of Evidence KQ1e. Narrative Evaluation.

Question	Study design and sample size	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of evidence
FeNO testing done at age 0-4 years for the prediction of a future diagnosis of asthma.	3 observational studies[159, 160, 162] (346 patients)	Low	Inconsistent[1]	Direct	Precise	Undetected	Insufficient (inconsistency)
The association between FeNO testing done at age 0-4 years with the Asthma Predictive Index	5 observational studies[156-158, 161, 163] (959 patients)	Low	Consistent	Direct	Precise	Undetected	Low (Observational studies)
The association between FeNO testing done at age 0-4 years with wheezing	7 observational studies[166-172] (1,126 patients)	Low	Consistent	Direct	Precise	Undetected	Low (Observational studies)

[1] Studies were showing opposing and inconsistent conclusions

Appendix I. Additional Tables

Table I.1. Studies correlating FeNO performed in early childhood to current wheezing (excluded from this systematic review)

Author	Year of publication	Conclusions
Sayao [166]	2016	In children (age 3-5 years), FeNO at 6ppb and 10ppb diagnoses wheezers from non-wheezers and from non-current wheezers; respectively
Malmberg [167]	2003	In children (age 3.8–7.5 years) with probable asthma, FeNO was higher than control children
Oh [168]	2013	In children age 4-6, FeNO was higher in persistent wheezers than transient wheezers and non-wheezers. Among persistent wheezers, FeNO was higher in those with atopy and airway hyperresponsiveness.
Wildhaber [172]	1999	In healthy infants 3-24 months, single breath FeNO was higher in wheezy infants and those with a family history of atopy
Latzin [170]	2006	FeNO measured after birth was associated with increased risk of subsequent respiratory symptoms and in infants of smoking mothers
Ratjen [169]	2000	Reduced airway NO concentrations in infants with virus-associated acute wheezy bronchitis
Franklin [171]	2004	In infants (5-100 weeks), no significant difference in FeNO found between healthy and wheezy ones, but those with doctor-diagnosed eczema had significantly raised levels

Table I.2. FeNO based algorithms used in randomized trials

Author, Year (ref)	intervention
Calhoun, 2012 [100]	Asthmatics had their inhaled corticosteroids adjusted (inhaled beclomethasone or equivalent dose) adjustedevery 6 weeks for each group; Physician Assessment based adjustment (PABA) group; based on National Heart, Lung and Blood Institute guidelines. Biomarker - based adjustment (BBA) group; using FeNO measurement as following; If FeNO < 22 ppb, step down one level of therapy, 22-35 ppb, maintaine current level, > 36 ppb, step up one level. Symptom based adjustment (SBA) group; clinical symptoms promoting albuterol rescue use. After randomization, all outcomes were measured at 2, 4, 6, 12, 18, 24, 30, and 36 weeks visit. Primary outcomes: time to first treatment failure, hospitalizations, urgent care visits and other adverse events. Secondary outcomes: spirometry, albuterol reversibility, methacholine responsiveness, sputum eosinophils, daytime and nighttime symptom and rescue beta-agonist diaries, Asthma Control Questionnaire, Asthma Symptom Utility Index, and AQLQ.
De Jongste, 2009 [101]	Participants were seen after randomization at 3, 12, 21, and 30 weeks. Assessments included FeNO. Spirometry before and after salbutamol, and recording of adverse events. PACQLQS was administered at the first and last visits. All parents were phoned every 3 weeks between visits, and medication (inhaled budesonide or equivalent ICS doses) was adapted as following; FeNO group: according to geometric mean FeNO over the preceding 3 weeks and cumulative symptom scores. If FeNO > 20-25 ppb, increase ICS. If FeNO < 20-25 ppb, then decrease ICS if symptoms score < 60 cumulative in 3 weeks or no change in ICS doses if symptoms score > 60 cumulative in 3 weeks. Symptom group: adjusted only for symptoms.
Hashimoto, 2011 [102]	Monthly clinic visit for 6 months. FeNO were measured on a daily basis before medicine intake. ACT and spirometry were completed weekly. AQLQ was completed at baseline and every 3 months afterward. Internet strategy group: oral prednisone or equivalent oral steroid dose was adjusted based on the 3 components: electronic diary, monitoring support by nurses, and algorithm (which includes ACQ and daily FeNO measurement). If FeNO increase by > 10 ppb, step up ICS. If FeNO decrease by > 10 ppb, step down ICS. Conventional strategy group: steroids were down-titrated based on GINA guidelines at monthly visits.
Honkoop, 2015 [103]	Participants were seen every 3 months over the course of 1 year. At each visit, a patient's asthma control status was classified based on the ACQ score as controlled (ACQ score < 0.75), partially controlled (ACQ score > 0.75) or uncontrolled (ACQ score> 1.5). Additionally in the FeNO controlled (FCa) strategy as 3 subcategories of FeNO: low/absence of airway inflammation for values < 25 ppb, intermediate at 26 to 50 ppb, and high/presence of airway inflammation > 50 ppb. Treatment (inhaled beclomethasone or equivalent ICS doses) decisions were based on a dedicated algorithm for each strategy. If FeNO low, step down ICS, if FeNO intermediate, no change in ICS doses, if FeNO high, step up ICS.
Malerba, 2015 [104]	Patients attended five visits after recruitment; 3, 6, 12, 18 and 24 months. At each visit, patients underwent clinical evaluation, lung function tests, sputum induction, and FeNO measurements were carried out according to the ATS guidelines. In group A, treatment (inaheld beclomethasone or ICS equivalent doses) was based on FeNO as following: if FeNO < 10ppb, step down therapy, if FeNO 11-20 ppb, no change in ICS dose, and if FeNO > 20 pbb, step up therapy. Also, sputum eosinophil values, symptoms and bronchodilator use were considered. In group B, treatment was prescribed according to the clinical symptoms score.
Peirsman, 2014 [105]	All patients attended five visits; one every 3 months over a year. Clinical group, at each visit, asthma control and treatment (LTRA, LABA, and inhaled budesonide or equivalent ICS doses) adjustments were determined by the reporting of symptoms, the need for rescue treatment during the two preceding weeks and spirometry, based on the GINA guidelines. FeNO group, FeNO measurements were primarily used to adjust the treatment. If FeNO < 20 ppb and controlled, add LTRA, decrease ICS stop LABA. If FeNO < 20

Author, Year (ref)	intervention
	ppb and uncontrolled, add LTRA, consider decrease ICS and stop LABA. if FeNO > 20 ppb regardless of symptoms, then increase ICS, add LTRA and stop LABA.
Petsky, 2015 [106]	Monthly visits for the first 4 months and every 2 months thereafter over a year. At each visit, patients assessed with FeNO first, then spirometry before and after 400 mg inhaled salbutamol. Group 1: treatment strategy was based on FeNO levels, adjusted for atopy. If FeNO was elevated (FeNO > 10 ppb in children with no positive skin prick test (SPT), >12 ppb in children with one positive SPT, and >20 ppb in children with 2 or more positive SPT), then therapy was stepped up. If FeNO was low for two consecutive visits, medications were stepped down. Group 2: symptoms-based management.
Pijnenburg, 2005 [108]	Participants were seen for a year, at five visits with 3-month intervals. At each visit, FeNO was measured and the ICS dose was then adapted to FeNO and/or symptom scores recorded during the previous 2 weeks. At visits 1 and 5, pulmonary function tests and bronchoprovocation tests with methacholine were performed. FeNO Group: treatment (inhaled budesonide or equivalent ICS doses) was made on both FeNO and symptoms. If FeNO > 30 ppb regardless of symptoms, increase ICS dose, if FeNO < 30 ppb and symptoms > 14, then continue with ICS dose, if FeNO < 30 ppb and symptoms < 14, then decrease ICS dose. Symptom Group: treatment was made only on symptoms.
Pike, 2013 [108]	Participants were assessed 2 monthly for 12 months. At each visit, a single measure of FeNO and FEV_1 were taken according to ATS/ERS guidelines. Finally, an assessing clinician assessed treatment adherence by direct questioning, recorded exacerbations and administered a questionnaire reviewing symptoms and reliever use over the preceding 2 months. Group 1: therapy (LTRA, LABA and inhaled beclomethasone or equivalent doses of budesonide or fluticasone) adjusted by FeNO measurements. If asthma poor controlled; FeNO > 25 ppb, increase ICS or add LTRA, FeNO <25 ppb, increase LABA. If asthma well controlled; FeNO > 25 ppb, increase ICS or add add LTRA, FeNO 15-25 ppb, continue current treatment, FeNO < 15 ppb, reduce ICS and LABA. Group 2: standard management
Powell, 2011 [109]	Women were reviewed monthly at the antenatal clinic until delivery. At each visit, clinical symptoms, ACQ score, present treatment, FeNO, and FEV_1 were measured. ACQ score, FeNO concentration, and treatment (inhaled budesonide or equivalent ICS doses) were sent by facsimile to the algorithm keeper for treatment changes recommendation. FeNO group: they used a sequential process, first, the FeNO concentration to adjust inhaled corticosteroids dose and second, the ACQ score to adjust the dose of long acting β2 agonist. Clinical group: they were based on asthma control using Juniper ACQ with cutoff points defined as: well controlled asthma (ACQ score < 0.75), partially controlled (ACQ score 0.75-1.50) and uncontrolled (ACQ score > 1.5).
Shaw, 2007 [110]	Participants were seen monthly for the first 4 months and every 2 months thereafter. At each visit, FeNO, FEV_1 and Juniper asthma control questionnaire were taken. At the 6- and 12-month visit, induced sputum and methacholine challenge testing were also performed. FeNO group: when FeNO > 26 ppb, ICS ICS (daily beclomethasone diproprionate (BDP) or equivalent ICS doses) was increased. If < 16 ppb, or < 26 ppb on 2 separate occasions, treatment was decreased Control group: when JACS > 1.57, treatment was doubled. If JACS < 1.57 for 2 consecutive months, the treatment was halved
Smith, 2005[111]	A 12 months phase where patients were evaluated on six occasions at intervals of two months. At each visit, FeNO were measured. If the FeNO > 15 ppb or if the asthma was uncontrolled, treatment (inhaled fluticasone) was increased by one step. If the FeNO level < 15 ppb or if the asthma was controlled for two consecutive visits, the dose was titrated back down one step. However, treatment was not decreased below the optimal dose or to placebo.
Syk, 2013 [112]	Participants were seen after baseline at 2, 4, 8, and 12 month. At each visit, FeNO, ACT, and registration of exacerbations were taken. mAQLQ and GQLI were taken at baseline, month 4, and month 12.

Author, Year (ref)	intervention
	FeNO group: treatment (inhaled budesonide or equivalent ICS dose) was adjusted according to a FeNO algorithm and 6 fixed treatment steps. Control group: treatment was adjusted according to usual care including patient-reported symptoms, SABA use, physical examination, and lung functions results.
Verini, 2010 [113]	ASS, AEf, ATS, and immunoallergological and functional data were evaluated at the start of the study, 6 months, and 1 year later. FeNO group: therapy consisted of ICS, LABA and LTRA was assessed by FeNO measurements (as the mean of three readings represent the value for each measurement, FeNO > 12 ppb were considered as an indication to increase the number of drugs, whereas < 12 ppb lead to a reduction or to a maintenance in the amount of drugs) and GINA guidelines. GINA group: therapy was assessed based on symptoms, short acting β2-agonist use, and lung function, according to GINA guidelines.

ACQ score: Asthma Control Questionnaire score; ACT score: asthma control test; AEf: Asthma Exacerbation frequency; AQLQ: Asthma Quality of Life Questionnaire; ASS: Asthma Severity score; ATS guidelines: American Thoracic Society guidelines; ATS/ERS guidelines: The American Thoracic Society/ European Respiratory Society guidelines; ATS: Asthma Therapy score; FeNO: Fractional exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; GINA guidelines: Global Initiative for Asthma guidelines; GQLI: Gothenburg Quality of Life Instrument; ICS: Inhaled corticosteroid; LABA: Long-acting beta-2-agonists; LTRA: Leukotriene receptor antagonist; mAQLQ: Mini Asthma Quality of Life Questionnaire; PACQLQS: Pediatric Asthma Caregiver Quality of Life Questionnaire with Standardized activities; SABA: Short-acting beta-2 agonist.

Appendix J. References

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