Respiratory Journal Club 2015

Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study

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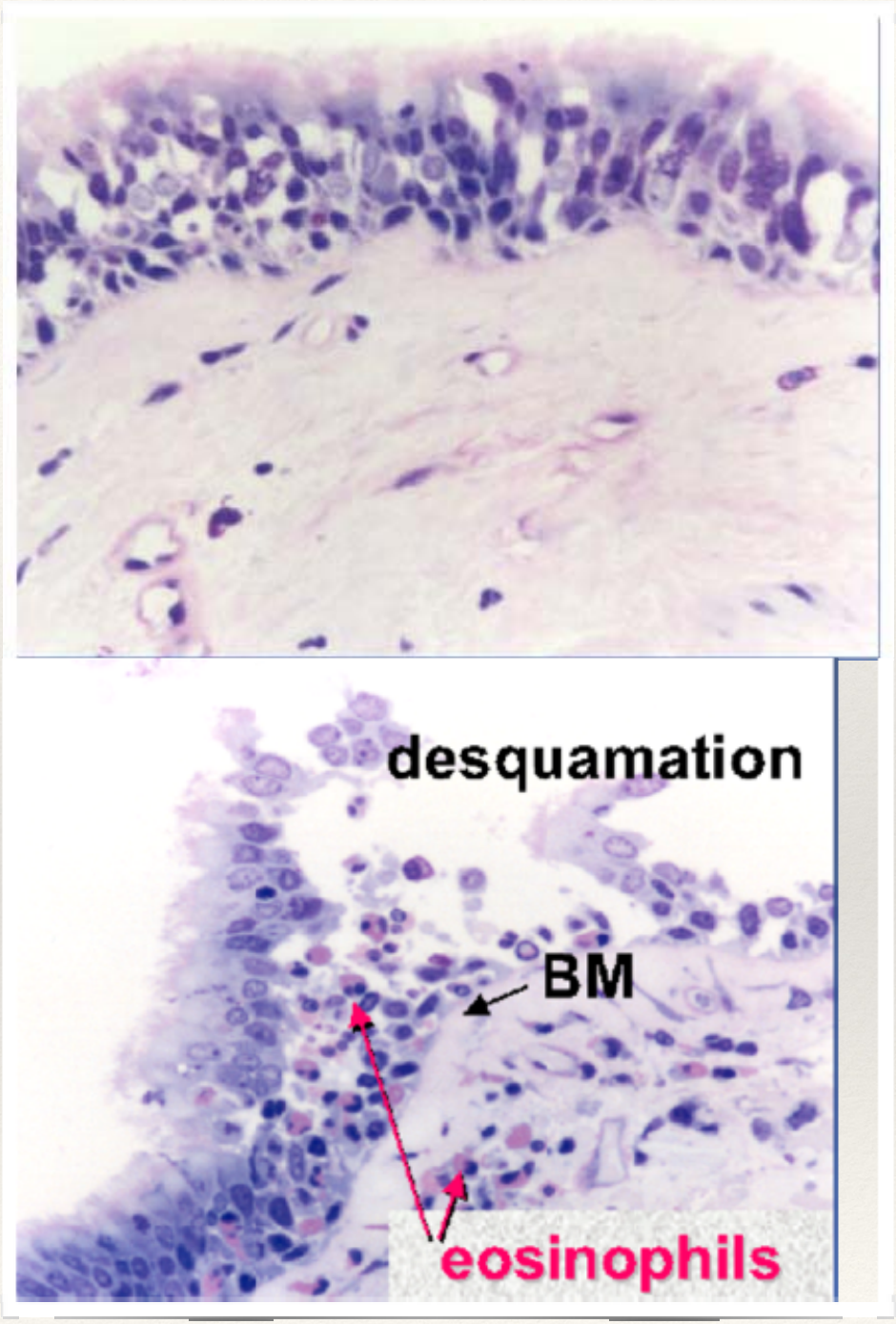
Outline of Presentation

- Background
- Reason of study
- Study design
- Outcomes
- Conclusion
- Limitations

Pathology behind asthma

Eosinophil Airway Inflammation

- Main cause of late-phase airway inflammation
- T_h2 cells produce a cytokine environment (Il-5 and IgE antibodies) - infiltration and activation of eosinophils
- Degranulation epithelial damage and airway hyper-responsiveness



Sputum vs Blood Eosinophil Counts

Sputum eosinophil has been the current biomarker used in determining future exacerbation of asthma symptoms and disease severity

Limitations of Sputum Eosinophil:

(1) Sputum eosinophil count was only available in a limited number of GP surgeries

(2) Very small cohort studies have been done to prove the link between sputum eosinophil count and asthma exacerbations

Advantages of Blood Eosinophil:

(1) Blood eosinophil count is available to every GP doctor.

KV1

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KV1 small cohort studies were done on highly characterised patients and not reflective of patients in the general community setting

Keeran Vickneson, 24/11/2015

Design of the UK Cohort Study

Study centre

Funding by Teva Pharmaceuticals

Aims

Primary aim

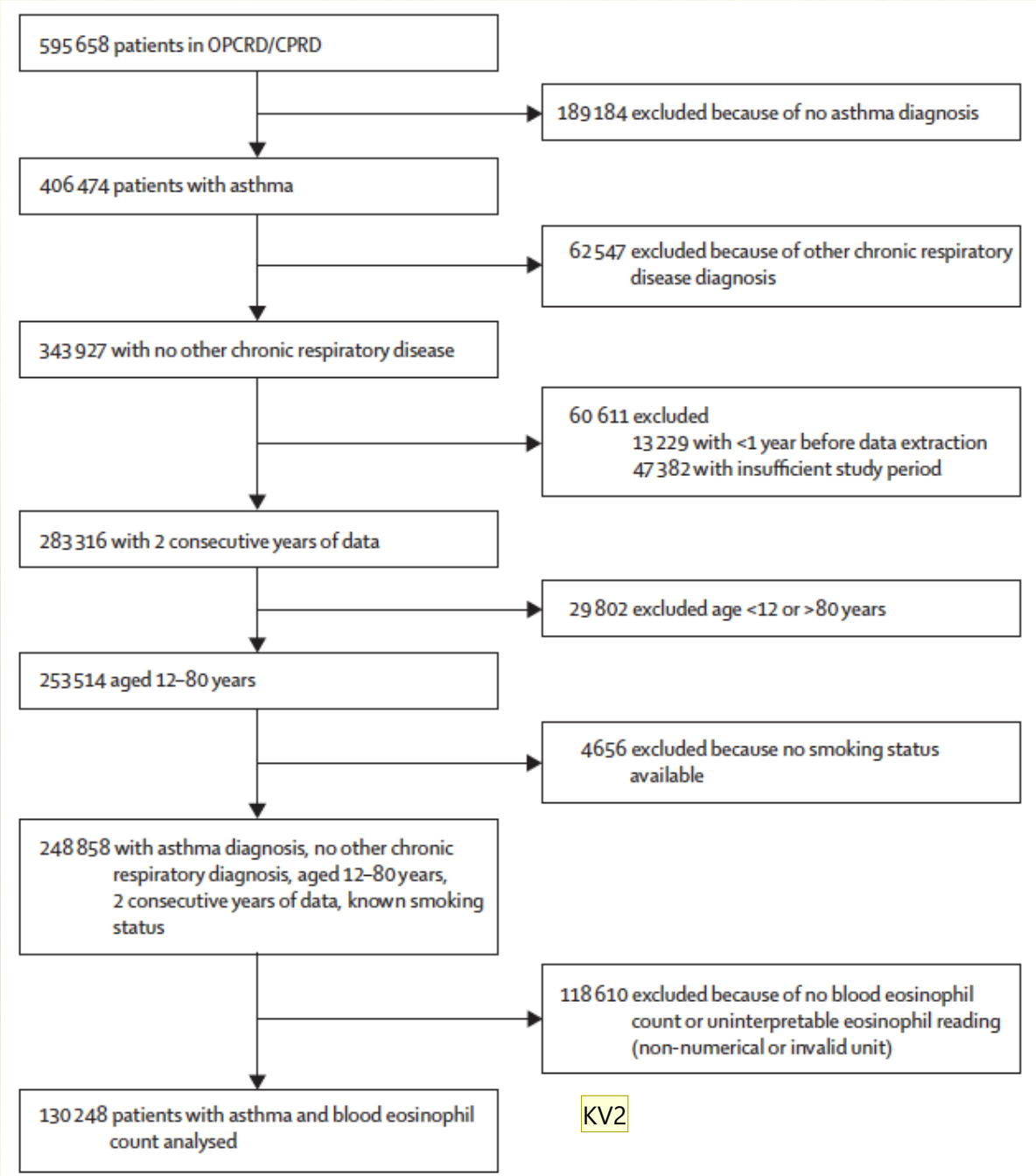
Investigating the relation between blood eosinophil count with asthma exacerbations and asthma control during the subsequent year

Secondary aim

Identification of potential relations between demographic and clinical characteristics and prospective risk of raised eosinophil counts

Study type

Historical cohort study (one of the largest studies conducted)



Cohort study data was obtained from the OPRCD and CPRD databases - 248858 patients met study eligibility criteria but only 130248 (52%) had a recorded blood eosinophil count

Inclusion criteria:

- Asthma diagnosis
- Recorded blood eosinophil count
- 1 year of continuous records (before and after their their most recent blood eosinophil count
- Aged between 12-80
- Presence of smoking status

Exclusion criteria:

- Diagnosed with other chronic respiratory diseases
- Eosinophil count >5000 per μL (avoidance of extreme outliers

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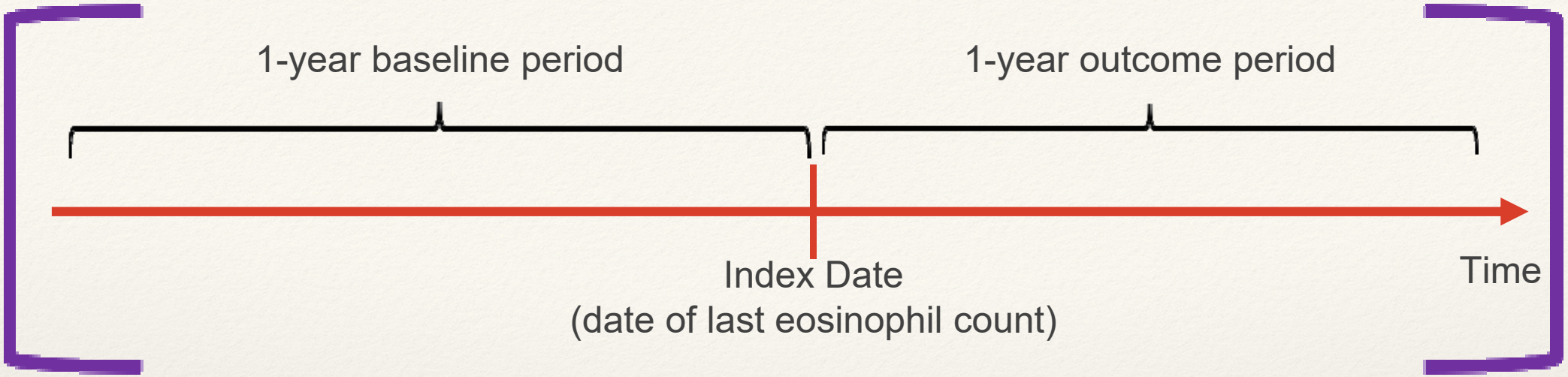
KV2 patient data was cross-referenced to avoid duplication of individual studied

Keeran Vickneson, 22/11/2015



Patients were divided into two cohorts

- Blood eosinophil count of 400 cells per µL or less
- Blood eosinophil count of >400 cells per µL

Categorical Variables were measured using the chi-squared test (patient demographics, comorbidities, severe exacerbations, acute respiratory events, asthma control, etc.)

Variables measured on the interval or ratio scale were compared with a t test or a Mann-Whitney U test

Baseline

	Total (n=130 248)	Blood eosinophil cohort		p value*
		≤400 cells per µL (n=109 319)	>400 cells per µL (n=20 929)	
Peripheral blood eosinophil count (cells per µL)	200 (120–340)	200 (100–300)	580 (500–700)	
Sex, male	42 067 (32·3%)	33 895 (31·0%)	8172 (39·0%)	<0·0001
Age (years)	49 (36–63)	50 (37–63)	45 (31–61)	<0·0001†
BMI (kg/m²)‡	27 (24–32)	28 (24–32)	27 (23–31)	<0·0001†
Smoking status				<0·0001
Non-smokers	72 552 (55·7%)	59 966 (54·9%)	12 586 (60·1%)	
Current smokers	24 443 (18·8%)	20 998 (19·2%)	3445 (16·5%)	
Ex-smokers	33 253 (25·5%)	28 355 (25·9%)	4898 (23·4%)	
Percent predicted FEV_1 or PEF‡	84 (71–96)	84 (71–96)	83 (70–96)	<0·0001†
Comorbid rhinitis				<0·0001
None	79 457 (61·0%)	68 426 (62·6%)	11 031 (52·7%)	
Allergic	37 548 (28·8%)	30 775 (28·2%)	6773 (32·4%)	
Non-allergic	7659 (5·9%)	6424 (5·9%)	1235 (5·9%)	
Nasal polyps	5584 (4·3%)	3694 (3·4%)	1890 (9·0%)	
Comorbid eczema	42 065 (32·3%)	34 136 (31·2%)	7929 (37·9%)	<0·0001
Comorbid diabetes	25 859 (19·9%)	21 933 (20·1%)	3926 (18·8%)	<0·0001
Charlson comorbidity index				<0·0001
0	95 709 (73·5%)	80 541 (73·7%)	15 168 (72·5%)	
1–4	28 310 (21·7%)	23 390 (21·4%)	4920 (23·5%)	
≥5	6229 (4·8%)	5388 (4·9%)	841 (4·0%)	
Mean baseline blood eosinophil count >400 cells per µL	24 429 (18·8%)	7809 (7·1%)	16 620 (79·4%)	<0·0001
BTS therapy steps§				<0·0001
No therapy	13 488 (10·4%)	11 714 (10·7%)	1774 (8·5%)	
1	14 563 (11·2%)	12 220 (11·2%)	2343 (11·2%)	
2	41 978 (32·2%)	35 498 (32·5%)	6480 (31·0%)	
3	29 868 (22·9%)	24 966 (22·8%)	4902 (23·4%)	
4	29 218 (22·4%)	23 980 (21·9%)	5238 (25·0%)	
5	1133 (0·9%)	941 (0·9%)	192 (0·9%)	
Asthma therapy				<0·0001
None	13 492 (10·4%)	11 716 (10·7%)	1776 (8·5%)	
SABA ± SAMA	14 579 (11·2%)	12 230 (11·2%)	2349 (11·2%)	
LABA ± LAMA	588 (0·5%)	509 (0·5%)	79 (0·4%)	
LTRA ± LABA ± LAMA	360 (0·3%)	309 (0·3%)	51 (0·2%)	
ICS	50 485 (38·8%)	42 786 (39·1%)	7699 (36·8%)	
ICS+LABA ± LAMA	44 439 (34·1%)	36 698 (33·6%)	7741 (37·0%)	
ICS+LTRA ± LABA ± LAMA	6252 (4·8%)	5024 (4·6%)	1228 (5·9%)	
Other	53 (0·0%)	47 (0·0%)	6 (0·0%)	
Daily dose of ICS (µg/day)	219 (55–575)	219 (55–548)	241 (55–592)	0·66
Severe exacerbations¶				<0·0001
0	105 283 (80·8%)	89 114 (81·5%)	16 169 (77·3%)	
1	15 962 (12·3%)	13 108 (12·0%)	2854 (13·6%)	
2–3	6438 (4·9%)	5095 (4·7%)	1343 (6·4%)	
≥4	2565 (2·0%)	2002 (1·8%)	563 (2·7%)	
Acute respiratory events¶				<0·0001
0	93 221 (71·6%)	78 886 (72·2%)	14 335 (68·5%)	
1	23 359 (17·9%)	19 408 (17·8%)	3951 (18·9%)	
2–3	10 354 (7·9%)	8432 (7·7%)	1922 (9·2%)	
≥4	3314 (2·5%)	2593 (2·4%)	721 (3·4%)	

(Table 1 continues on next page)

	Total (n=130 248)	Blood eosinophil cohort		p value*
		≤400 cells per µL (n=109 319)	>400 cells per µL (n=20 929)	
(Continued from previous page)				
Risk-domain asthma control, uncontrolled	38 960 (29·9%)	32 075 (29·3%)	6885 (32·9%)	<0·0001
Overall asthma control, uncontrolled	77 255 (59·3%)	63 966 (58·5%)	13 289 (63·5%)	<0·0001
Courses of acute OCS**				<0·0001
0	105 696 (81·1%)	89 453 (81·8%)	16 243 (77·6%)	
1	14 191 (10·9%)	11 589 (10·6%)	2602 (12·4%)	
≥2	10 361 (8·0%)	8277 (7·6%)	2084 (10·0%)	
Courses of antibiotics for LRTI				0·129
0	109 448 (84·0%)	91 955 (84·1%)	17 493 (83·6%)	
1	15 491 (11·9%)	12 918 (11·8%)	2573 (12·3%)	
≥2	5309 (4·1%)	4446 (4·1%)	863 (4·1%)	

Outcomes

16% of patients had raised blood eosinophil count (>400 cells per µL)

Incidence rate
(when compared to <400 cells per µL)

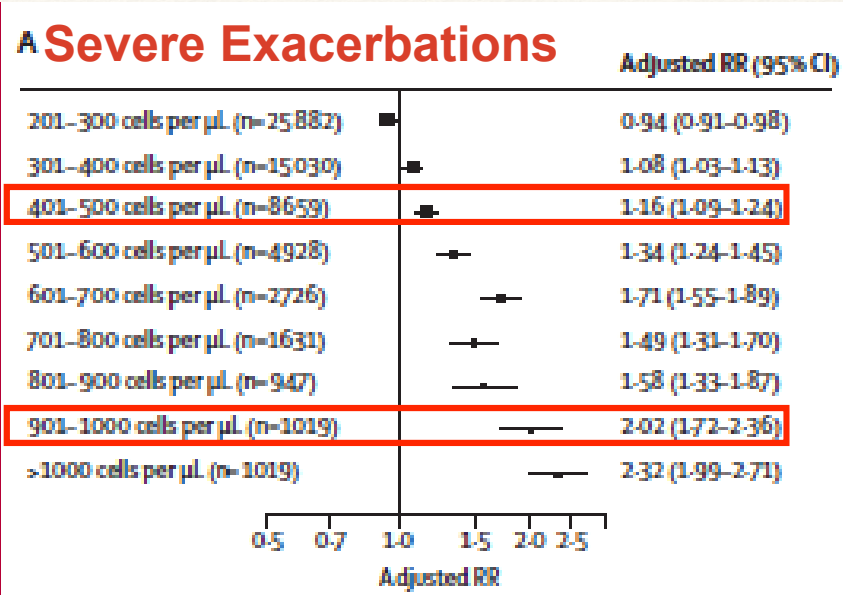
- 42% higher rate of getting severe asthma exacerbations
- 28% higher rate of getting acute respiratory events

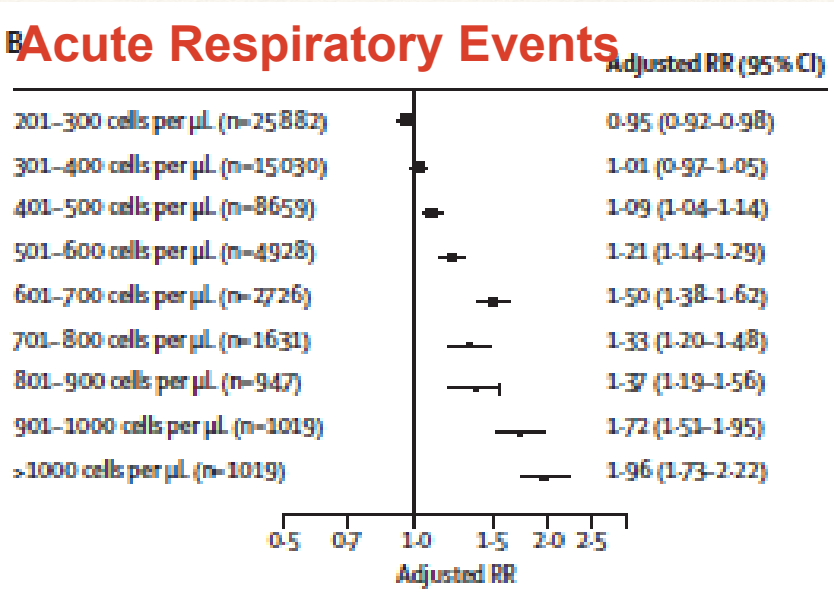
Outcome	Blood eosinophil cohort	
	≤400 cells per µL (n=109 319)	>400 cells per µL (n=20 929)
Severe exacerbation		
0	90 290 (82·6%)	16 338 (78·1%)
1	12 437 (11·4%)	2762 (13·2%)
2–3	4669 (4·3%)	1305 (6·2%)
≥4	1923 (1·8%)	524 (2·5%)
Acute respiratory event		
0	81 114 (74·2%)	14 771 (70·6%)
1	18 306 (16·7%)	3734 (17·8%)
2–3	7456 (6·8%)	1787 (8·5%)
≥4	2443 (2·2%)	637 (3·0%)
Risk-domain asthma control	78 976 (72·2%)	14 369 (68·7%)
Overall asthma control	46 953 (43·0%)	7785 (37·2%)

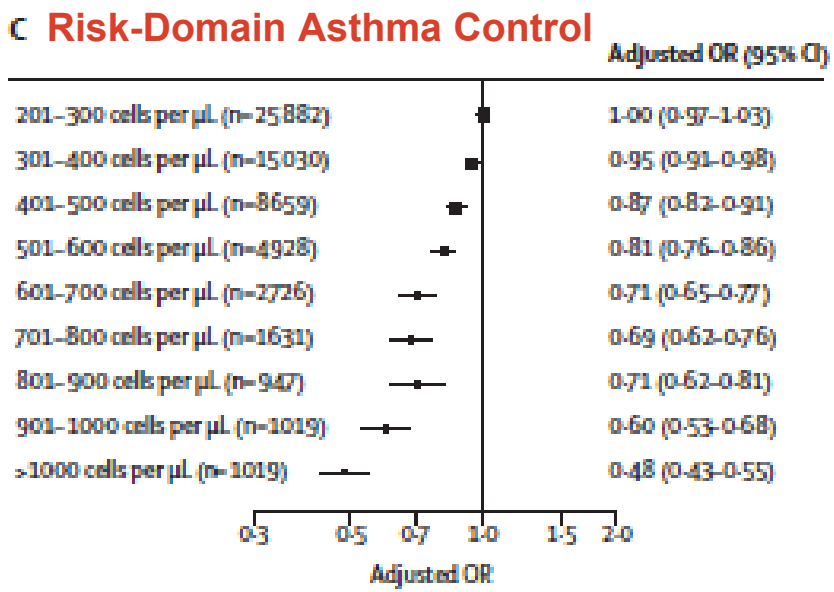
Data are n (%).

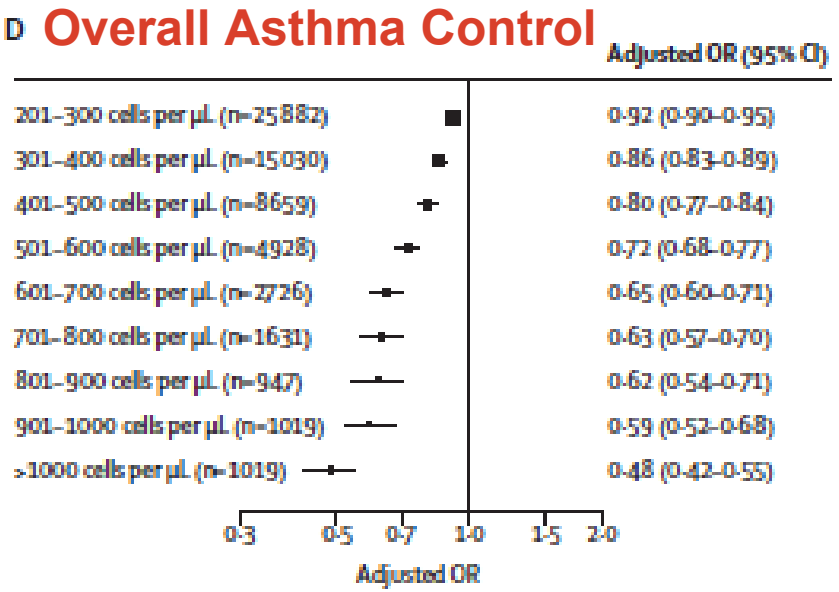
Odds ratio
(when compared to <400 cells per µL)

- 22% lower chance of achieving risk-domain asthma control
- 26% lower chance of achieving overall asthma control









Comparison between blood eosinophil count and risk of severe exacerbations

401-500 cells per µL had a 16% higher chance
901-1000 cells per µL has a 102% higher chance

compared against

<200 cells per µL

Added value of the study

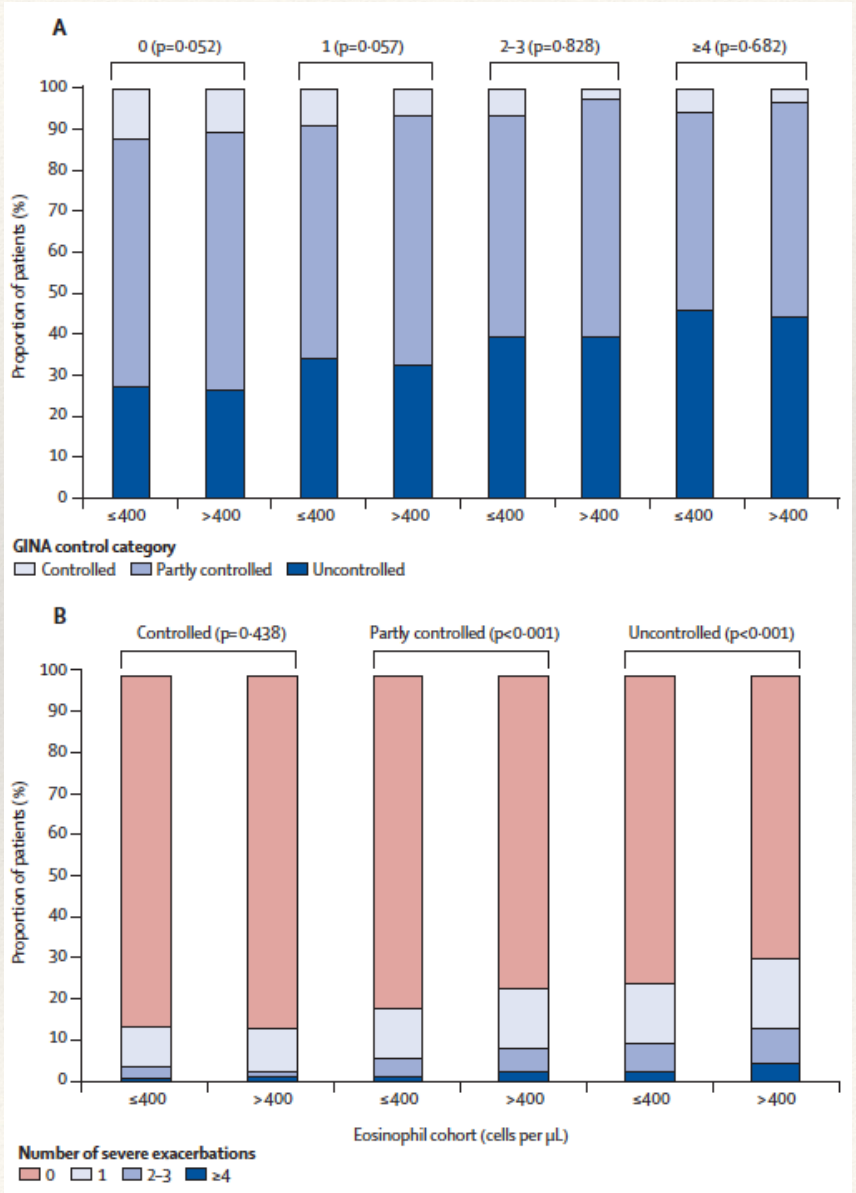
	Total (n=13 552)*	Blood eosinophil cohort		p value†
		≤400 cells per µL (n=11 355)	>400 cells per µL (n=2197)	
Controlled	1481 (10·9%)	1282 (11·3%)	199 (9·1%)	0·005
Partly controlled	8128 (60·0%)	6763 (59·6%)	1365 (62·1%)	
Uncontrolled	3943 (29·1%)	3310 (29·2%)	633 (28·8%)	

Data are n (%). GINA=Global Initiative for Asthma.[23] *GINA control data were available for 13 552 (10·4%) of the overall patient population of 130 248. †χ^2.

Table 4: **GINA current clinical control by blood eosinophil cohort**

13552 patients from both cohorts had completed an OPCRD asthma questionnaire (able to compare GINA current clinical control with the eosinophil cohorts

- Eosinophilia was associated with increased risk of exacerbations within GINA partly controlled and controlled categories
- Dissociation between symptoms and risk of exacerbations for patients with severe asthma



Slide 10

KV3 Blood eosinophil count was more strongly associated with risk of exacerbations than frequency of daily symptoms

Using current symptom control may not be sufficient to assess current asthma control - other predictors of risk need to be used

Keeran Vickneson, 24/11/2015

Conclusion

- Eosinophilia is a good biomarker for future asthma exacerbations or poor asthma control regardless of current symptoms
- Identification of asthmatic patients with milder clinical phenotype
- Prescription of greater doses of inhaled corticosteroid or prescription of mepolizumab and reslizumab (monoclonal antibodies directed against IL-5 - inhibit eosinophilic airway inflammation)

Limitations

- Observation studies can only show association and not causation
- Analysis was based on a single blood eosinophil count per patient
- Type of medication taken before the blood eosinophil measurement (oral prednisolone??)
- Funding from Teva Pharmaceuticals - coincidence of paper publication with end-stage clinical trials of reflizumab

KV4

Slide 12

KV4 Cannot assume that a raised blood eosinophil count causes increased exacerbations - its more of a biomarker for asthma

Restrictions of available data - know whether they are smokers, ex-smokers or non-smokers (no idea on pack years)

Most of the patients were on inhaled asthma therapy - treatment with ICS could alter blood eosinophil counts

Keeran Vickneson, 24/11/2015

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Questions

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