HOKKAIDO UNIVERSITY

HOKKAIDO UNIVERSITY
Graduate School of Medicine

Lessons from the HiCARAT study:

Hokkaido-based **I**nvestigative **C**ohort **A**nalysis for **R**efractory **A**s**t**hma

December 7th , 2019. Taiwan

Masaharu Nishimura,
Hokkaido COPD cohort study investigators

Professor emeritus, Hokkaido University
Housi General Medical Clinic and Hokkaido Institute of Respiratory diseases

COI disclosure

Masaharu Nishimura

Relevant financial relationships with a commercial interest:

Research grants from AstraZeneca, Kyorin, and MSD

Asthma

Definition

Characterized by repetitive cough, wheezing, dyspnea,

reversible airway narrowing, and airway hyperresponsiveness.

Important features for diagnosis of asthma

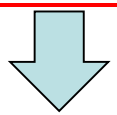
1. Paroxysmal dyspnea, wheezing, repeated cough
2. Reversible airflow limitation
3. Airway hyperresponsiveness
4. Atopy: IgE antibodies against environmental allergens
5. Airway inflammation:
   Increased eosinophils in sputum and peripheral blood
   high ECP
   Creola bodies
   increased fraction of exhaled nitric oxide (FeNO)
6. Differential diagnosis:
   Exclude diseases caused by other cardiopulmonary disorders

(Japanese Guideline for Adult Asthma 2012)

Diagnosis of COPD

1. **Postbronchodilator $FEV_1/FVC < 0.70$**

2. **Excludes other diseases characterized by airflow limitation**



- **Asthma**
- **Tuberculosis**
- **Diffuse pan bronchiolitis (DPB)**

……

(Japanese Guideline for COPD ver 4)

"Asthma syndrome"

Phenotypic categories

Atopic ——— **Non-atopic**

High IgE ——— **Low IgE**

Single allergen ——— **Multiple allergens**

Child-onset ——— **Adult/Late-onset**

Sputum

eosinophilic —— **neutrophilic** —— **paucigranulocytic**

High FeNO ——— **Low FeNO**

High periostin ——— **Low periostin**

Treatment steps for asthma

		Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Long-term management agents	ICS	Inhaled corticosteroid (low dose)	Inhaled corticosteroid (low to medium doses)	Inhaled corticosteroid (medium to high doses)	Inhaled corticosteroid (high dose)
	Basic treatment	If the above agent cannot be used, use one of the following agents. · LTRA · Theophylline sustained-release preparation (unnecessary for rare symptoms)	If the above agent is ineffective, concomitantly use one of the following agents. · LABA (a compounding agent can be used) · LTRA · Theophylline sustained-release preparation	Concomitantly use one or more of the agents below. · LABA (a compounding agent can be used) · LTRA · Theophylline sustained-release preparation	Concomitantly use multiple agents of those below. · LABA (a compounding agent can be used) · LTRA · Theophylline sustained-release preparation If poorly controlled with all of the above agents, add either or both of the agents below. · Anti-IgE antibody‡ · Oral corticosteroid§
	Additional treatment	Antiallergics other than LTRA†	Antiallergics other than LTRA†	Antiallergics other than LTRA†	Antiallergics other than LTRA†
Exacerbation treatment¶		Inhaled SABA	Inhaled SABA	Inhaled SABA	Inhaled SABA

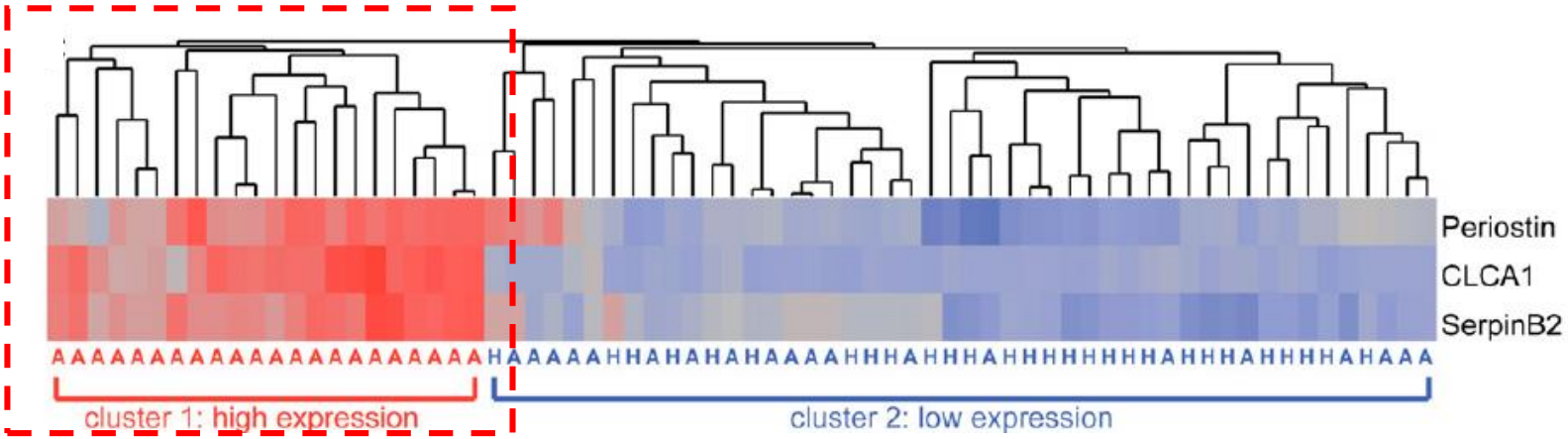
Anti-IL4,13 antibody

Anti-IL5 antibody
Anti-IL5R antibody
Anti-IL4,13 antibody

(Japanese Guideline for Adult Asthma 2012)

T-helper Type 2–driven Inflammation Defines Major Subphenotypes of Asthma

(Woodorff PG, et al. AJRCCM 2009)

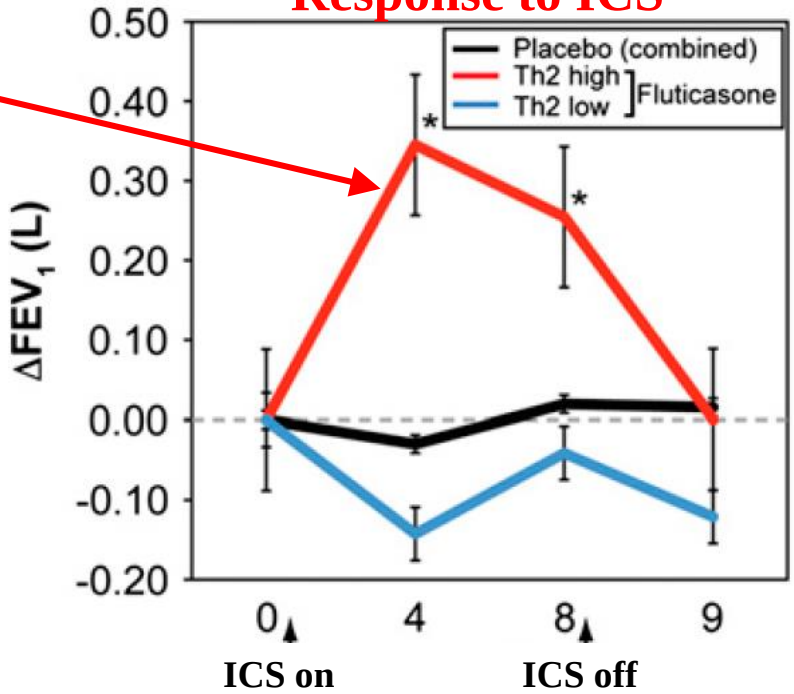


Genes induced by IL-13

Th2 high asthma

- **High eosinophils (sputum, blood)**
- **High total IgE**
- **Periostin↑ IL-13↑**

Response to ICS



Asthma: response to ICS

Non-eosinophilic cor ticosteroid unresponsive asthma

Ian D Pavord, Chris E Brightling, Gerrit Woltmann, Andrew J Wardlaw

(Pavord ID, et al. Lancet 1999)

Sputum eo<3% **Sputum eo≥3%**

	Eos <3%	Eos ⩾3%
Number	9	14
Age (years)	53	45
Male	5	11
Atopy	2	8
Current smoker	3	1
ΔFEV, (mL)	100 (−193 to 394)	142 (−5 to 289)
ΔSymptom VAS (mm)	−0·7 (15·4 to −16·8)	−24·4 (−12·5 to −36·3)
ΔPEF amplitude % mean	−3·2 (4·3 to −10·7)	−7·0 (−2·5 to −11·6)
ΔPC_{20} (doubling doses)	0 (−1·2 to 1·2)	2·1 (1·3 to 3·0)
Decrease sputum eos (fold)	1·6 (0·98 to 2·7)	7·1 (3·7 to 13·5)

Patient details with mean (95% CI) change in measures after treatment with budesonide in those stratified according to sputum eosinophil (eos) count

To evaluate the effect of smoking on asthma phenotypes···

Asthmatic subjects

Smokers **vs.** **Non-smokers**

Decline in Lung Function in the Busselton Health Study

The Effects of Asthma and Cigarette Smoking

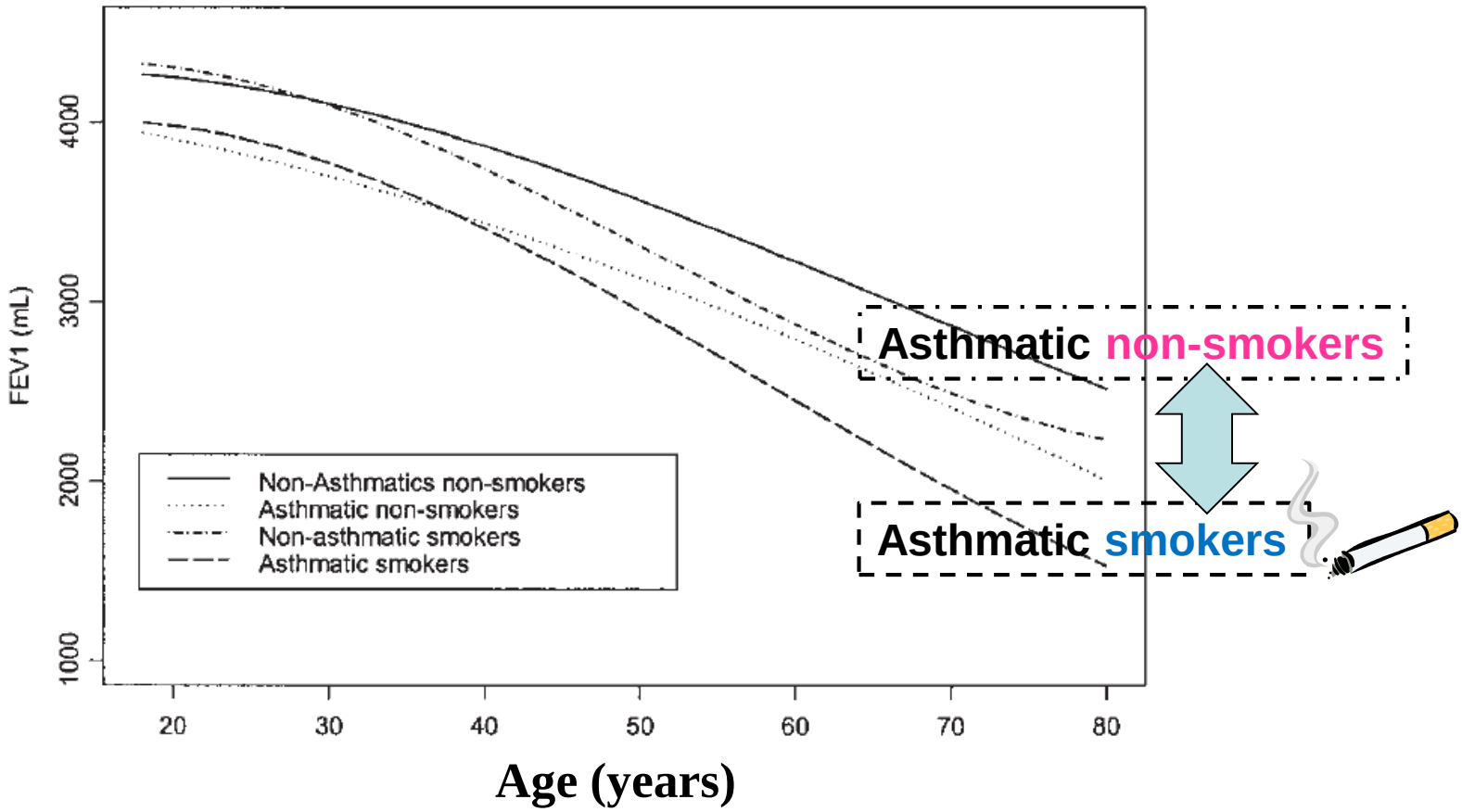
(AL James et al. AJRCCM 2005)

N = 9317 adult

Asthmatic subjects

Smokers **vs.** **Non-smokers**

FEV1 (mL)



Age (years)

Effect of smoking on (airway) inflammation *(Matsumoto H, et al.. Allergol Int 2013)*

Smokers **vs.** **Non-smokers**

Table 1 Inflammation in smoking asthmatics

Authors, Published year	Subjects, Smoking status, Condition of treatment	Pack-years	Age, Mean (range) or mean ± SD	Samples	Effects of smoking
Boulet LP, 2006[7]	22 current smokers 27 never-smokers No use of ICS	14.0 ± 7.6 0 ± 0	31 (20-44) 29 (20-42)	Induced sputum	Neutrophil counts ↑ Eosinophil counts →
Chalmers GW, 2001[8]	31 current smokers 36 never-smokers No use of ICS	21.0 ± 16.6 0 ± 0	36.3 ± 10.6 36.0 ± 8.9	Induced sputum	Neutrophils ↑ (both counts and proportions) Eosinophils ↓ (both counts and proportions)
St-Laurent J, 2008[9]	12 current smokers 12 never-smokers No use of ICS	16.7 ± 2.2 0 ± 0	32.7 ± 2.3 25.8 ± 2.3	Bronchial biopsies	Neutrophil elastase, IFN-γ, and IL-8 ↑
Broekema M, 2009[10]	35 current smokers 46 ex-smokers 66 never-smokers 44% used ICS	3 (0-64) 15 (0.4-47) 0 (0-0)	50 (21-64) 52 (25-68) 47 (19-71)	Bronchial biopsies and induced sputum	Neutrophils → in biopsies (current and ex) Eosinophils ↓ in biopsies (current and ex) Sputum neutrophil counts ↓ (current) Sputum neutrophil counts → (ex) Sputum eosinophil counts → (current and ex)
Sunyer J, 2003[11]	301 current smokers 406 ex-smokers, 713 never-smokers		34.5 ± 9.5	Blood	Eosinophil proportions ↓
Nagasaki T, 2013[91]	46 current smokers 65 ex-smokers 196 never-smokers No use of ICS	30 ± 19 27 ± 22 0 ± 0	47 ± 13 61 ± 15 49 ± 20	Blood	Neutrophil counts ↑ Eosinophil counts ↑

Animal model

- **Smoking inhibits eosinophlic airway inflammation.**

(Thatcher TH, et al. Am J Physiol Lung Cell Mol Physiol 2008)

(Botelho FM, et al. Am J Respir Cell Mol Biol 2011)

(Melgert BN, et al. Am. J. Respir. Cell Mol Biol 2004)

- **Smoking enhances eosinophlic airway inflammation.**

(Moerloose KB et al. AJRCCM 2005)

(Nakamura Y et al. JACI 2008)

(Van Hove CL, et al. Respir Res 2008)

Effect of smoking on (airway) inflammation *(Matsumoto H, et al.. Allergol Int 2013)*

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Smoking

- **Neutrophilic inflammation**
- **Eosinophilic inflammation**

↑↓→???

Hokkaido-based **I**nvestigative **C**ohort **A**nalysis for **R**efractory **A**s**t**hma (Hi-CARAT)

(NO. UMIN 000003254)

- Patients diagnosed with severe asthma by respiratory physicians based on the ATS criteria of severe/refractory asthma *(AJRCCM 2000)* were enrolled at Hokkaido University Hospital and 29 affiliated hospitals and clinics between February 2010 and September 2012.

- We attempted to recruit patients with severe asthma, including smokers.

Additional criteria for patients

When patients were well-controlled under the current medications (not fulfilled any of minor characteristics 2, 4, and 5 at the entry), these subjects were confirmed that they experienced episodic deterioration of symptoms, urgent care visits, and rescue use of short-acting bronchodilators when current medication was reduced within one year.

(Kimura H, et al. Ann Am Thorac Soc. 2017)

(Konno S, at al. Ann Am Thorac Soc 2018)

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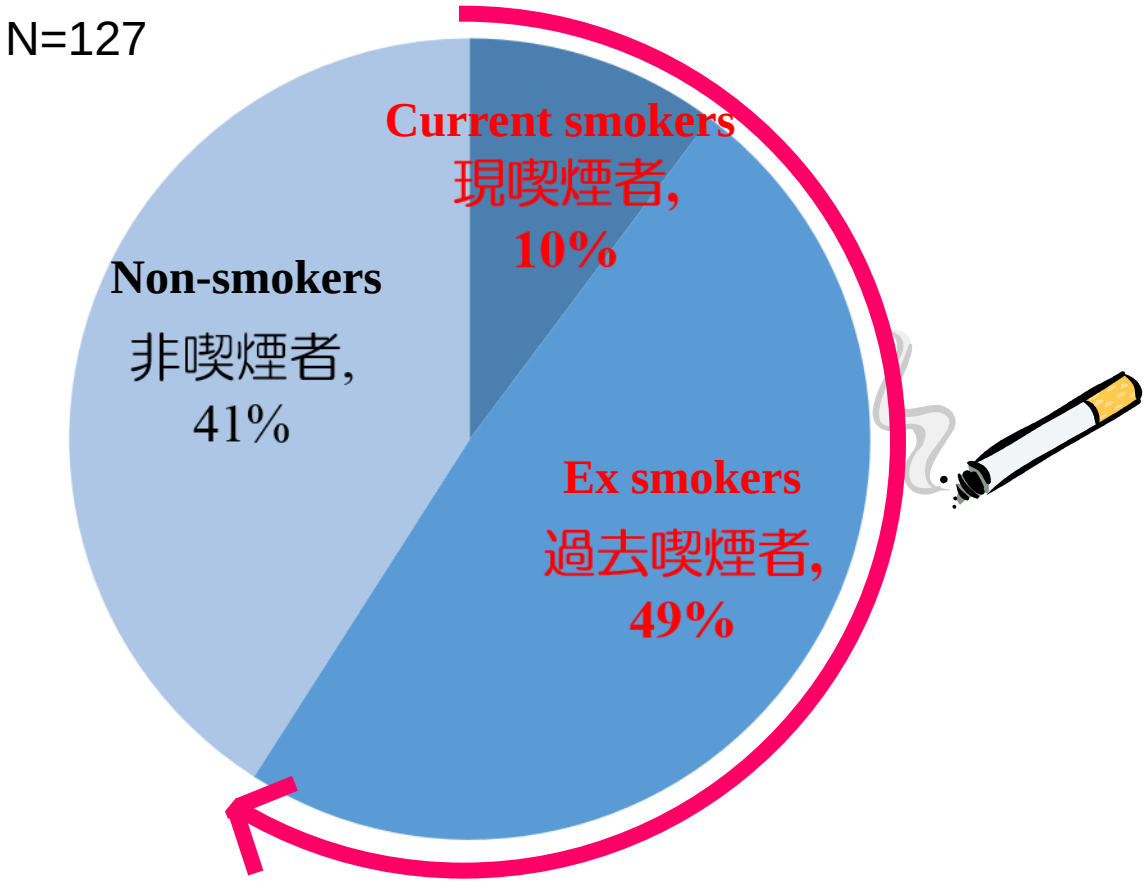
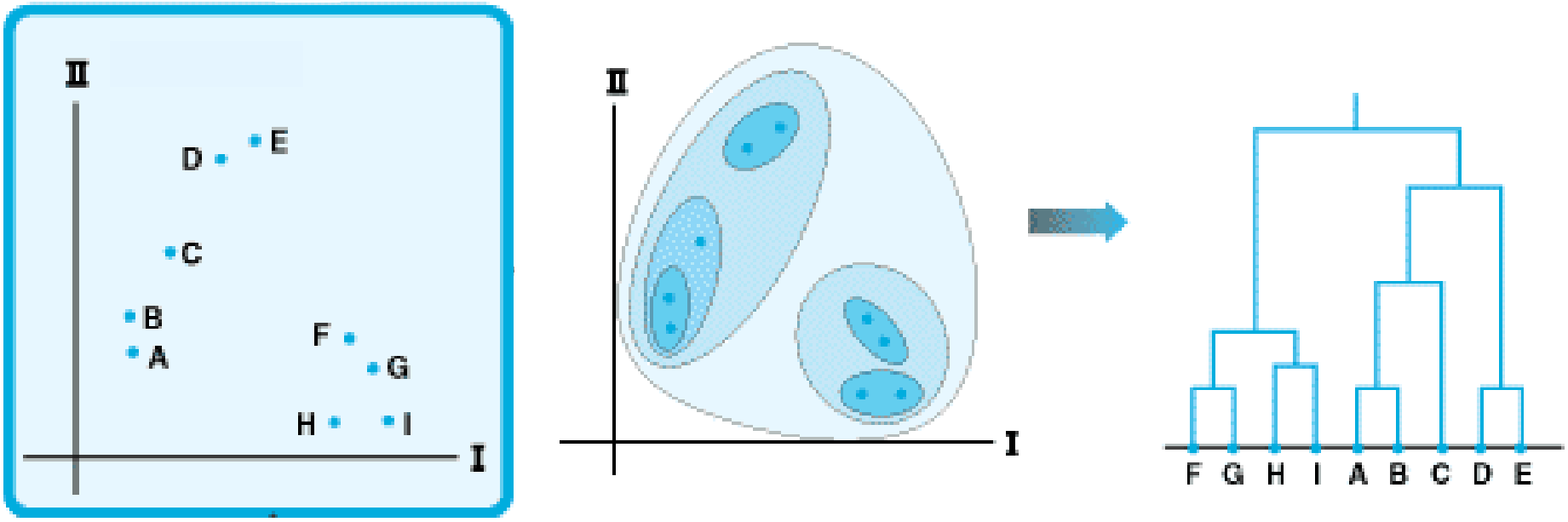
Smoking Rate (HiCARAT)

(NO. UMIN 000003254)



Cluster analysis

- An “data-dependent classification approach,”
  in which subjects are grouped on the basis of multiple similarities



What's the aim of “Cluster analysis”?

- **A process of knowledge discovery**
- **A process of development of novel hypotheses**

via classification of subjects into a limited number of clusters
on the basis of our existing knowledge and an *a priori* hypothesis.

Premature hypothesis

Cluster analysis

Strong hypothesis

A significant step toward a stronger hypothesis from our premature hypothesis

What's the aim of cluster analysis?

Inconclusive results regarding the effect of smoking on (airway) inflammation in asthma

via classification of subjects into a limited number of clusters on the basis of our initial knowledge or *a priori* hypothesis.

Premature hypothesis

- **The effects of smoking on inflammation in asthma varies.**
- **Smoking does not affect all asthmatic subjects in the same way.**

Cluster analysis

Strong hypothesis

A significant step toward a stronger hypothesis from our premature hypothesis

Measurements

The following clinical parameters were evaluated in all subjects during a 2-day stay at Hokkaido University Hospital.

- **Questionnaires** (onset age, AQLQ, smoking habit・・・・)
- **Anthropometric measurements**
- **Pulmonary function tests**

  (including BDR; salbutamol and oxitropium bromide)

- **CT imaging (Chest, Sinus, Abdominal fat)**
- **Measurement of biomarkers**
  - ・peripheral eo count ・Total serum IgE ・allergen specific IgE
  - ・sputum analysis (cell differentiation)
  - ・FeNO
  - ・Cytokines/Chemokines (sputum supernatant)

Selection of clinical variables for cluster analysis

Smoking ・Smoking status (current or ex/never) ・Pack-yrs

Obesity ・Body mass index (BMI)

Inflammation

・Peripheral eosinophil count ・FeNO

Pulmonary function

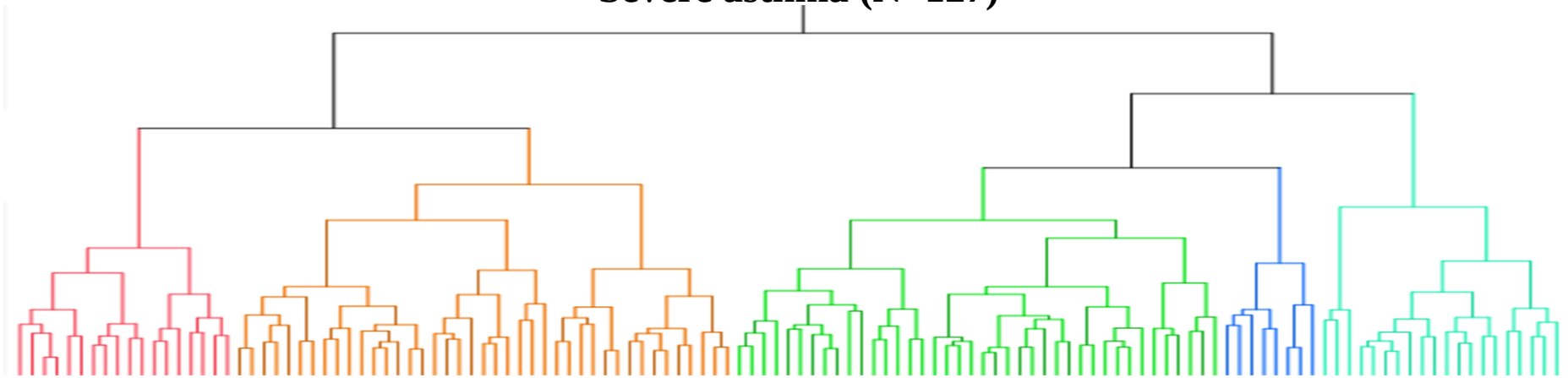
・%FEV_1 (max value) ・FEV_1/FVC ・%DL_{CO}/V_A

IgE ・Total serum IgE ・Atopic status (specific IgE)

Others ・Gender ・Age ・Onset age

Hierarchical clustering (Ward's method)

Severe asthma (N=127)



preserved %FEV1

Low %FEV1

Early-onset

Late-onset

Cluster 1
Atopic
Eosinophilic
High IgE

Cluster 2
Less Eosinophilic
Low IgE
Low LMS

Low FEV1/FVC

Cluster 3
Eosinophilic
High IgE
High LMS

Cluster 4
Less Eosinophilic
Low IgE
Low LMS

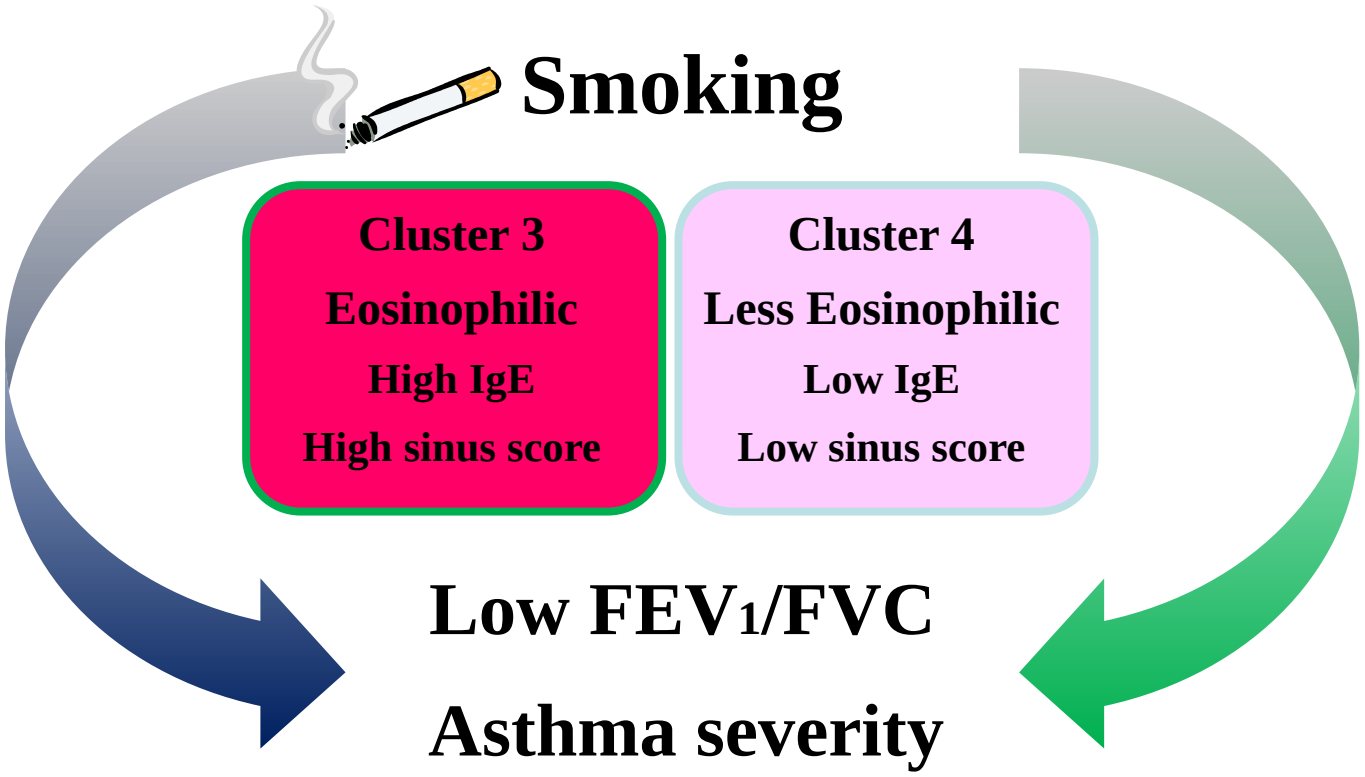
Smoking-related

High BMI

Cluster 5
Eosinophilic
Female
High LMS

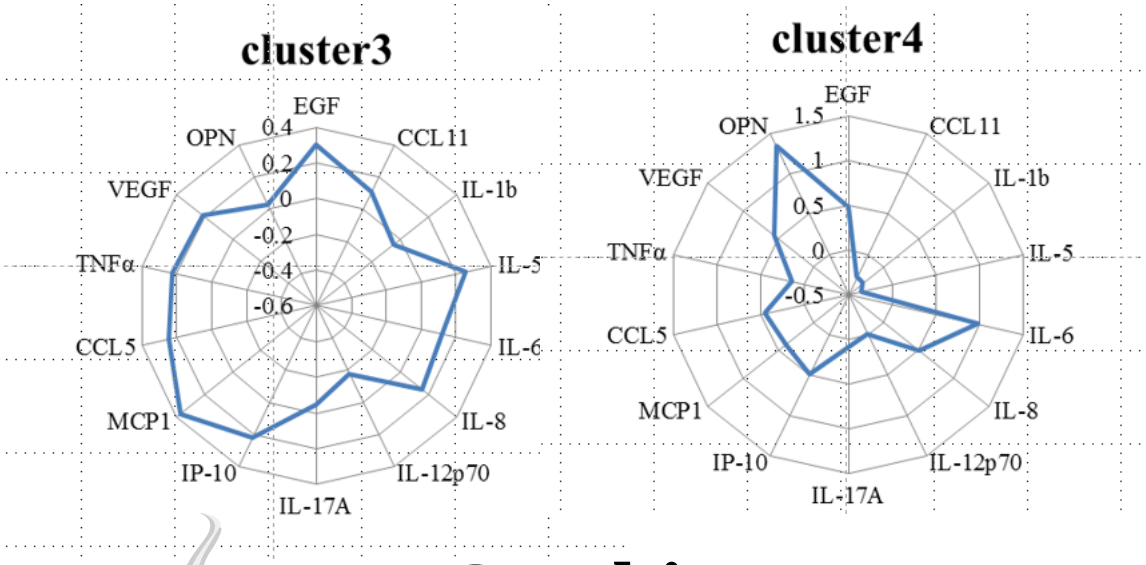
Eosinophilic

(Konno S, et al. Ann Am Thorac Soc 2018)



(Konno S, et al. Ann Am Thorac Soc 2018)

Sputum supernatant



Smoking

IL-5

Cluster 3
Eosinophilic
High IgE
High sinus score

Cluster 4
Less Eosinophilic
Low IgE
Low sinus score

IL-6

OPN

Low FEV_1/FVC
Asthma severity

(Konno S, et al. Ann Am Thorac Soc 2018)

Decline in Lung Function in the Busselton Health Study

The Effects of Asthma and Cigarette Smoking

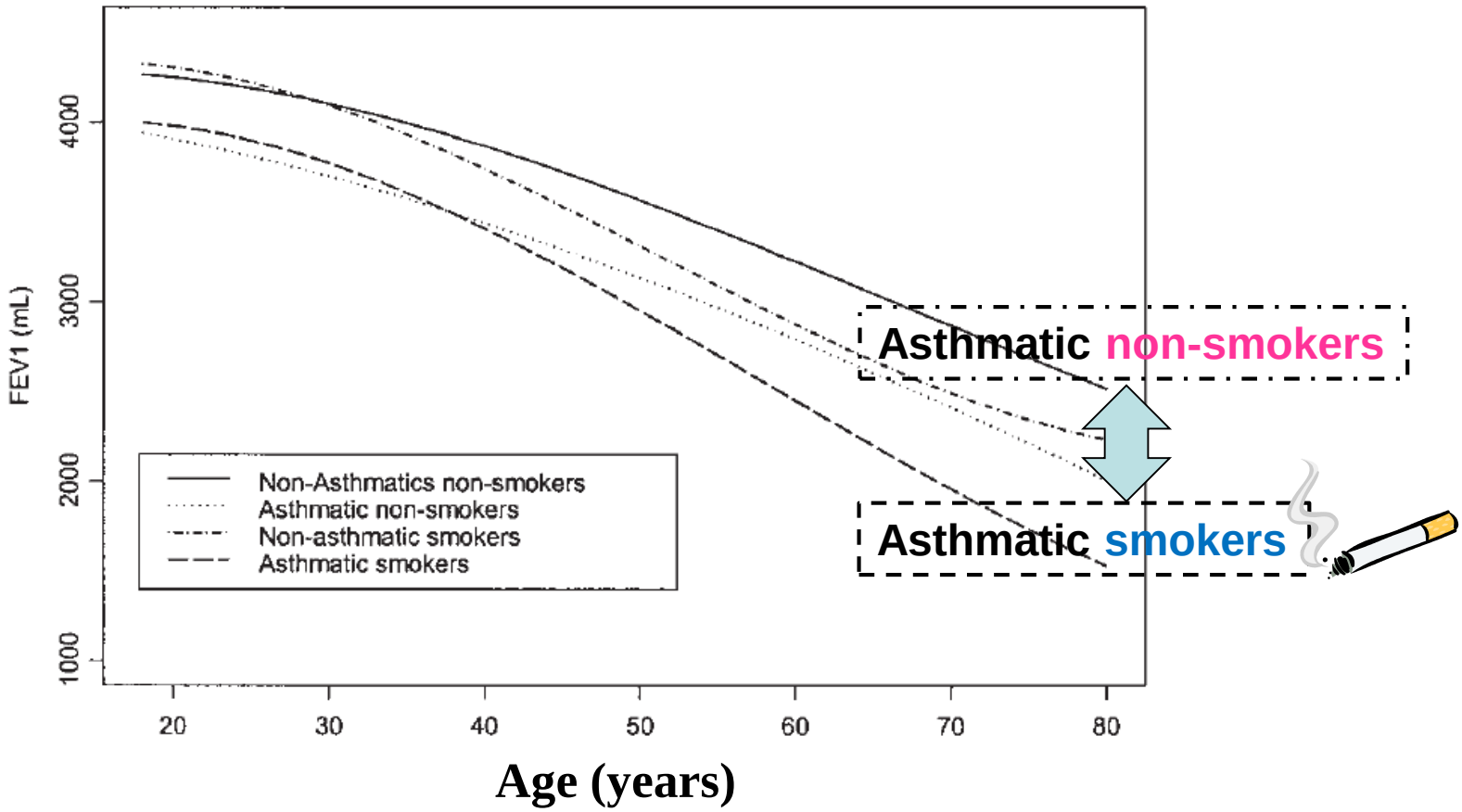
(AL James et al. AJRCCM 2005)

N = 9317 adult

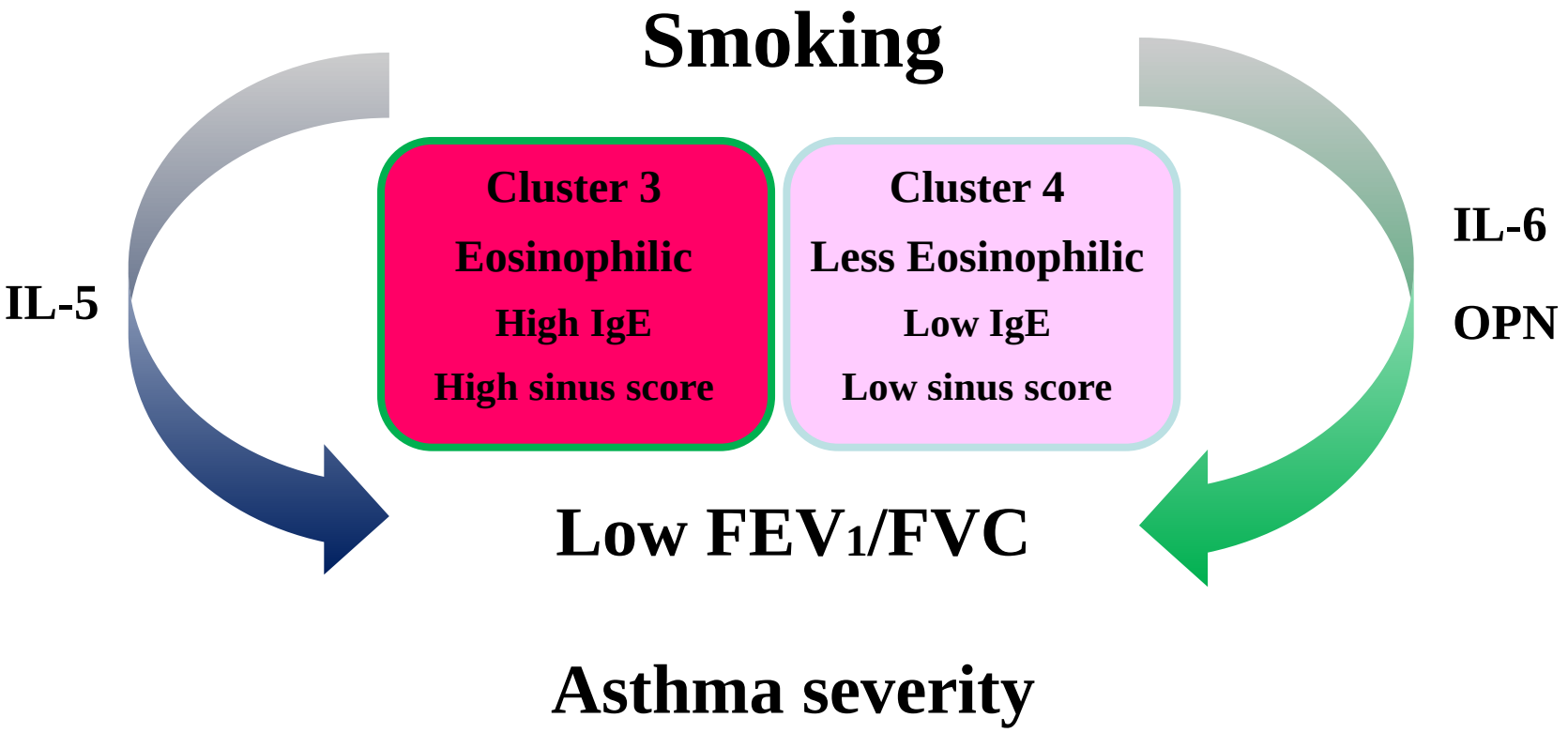
Asthmatic subjects

Smokers **vs.** **Non-smokers**

FEV1 (mL)



Novel hypothesis proposed by cluster analysis



(Konno S, et al. Ann Am Thorac Soc 2018)

Summary I

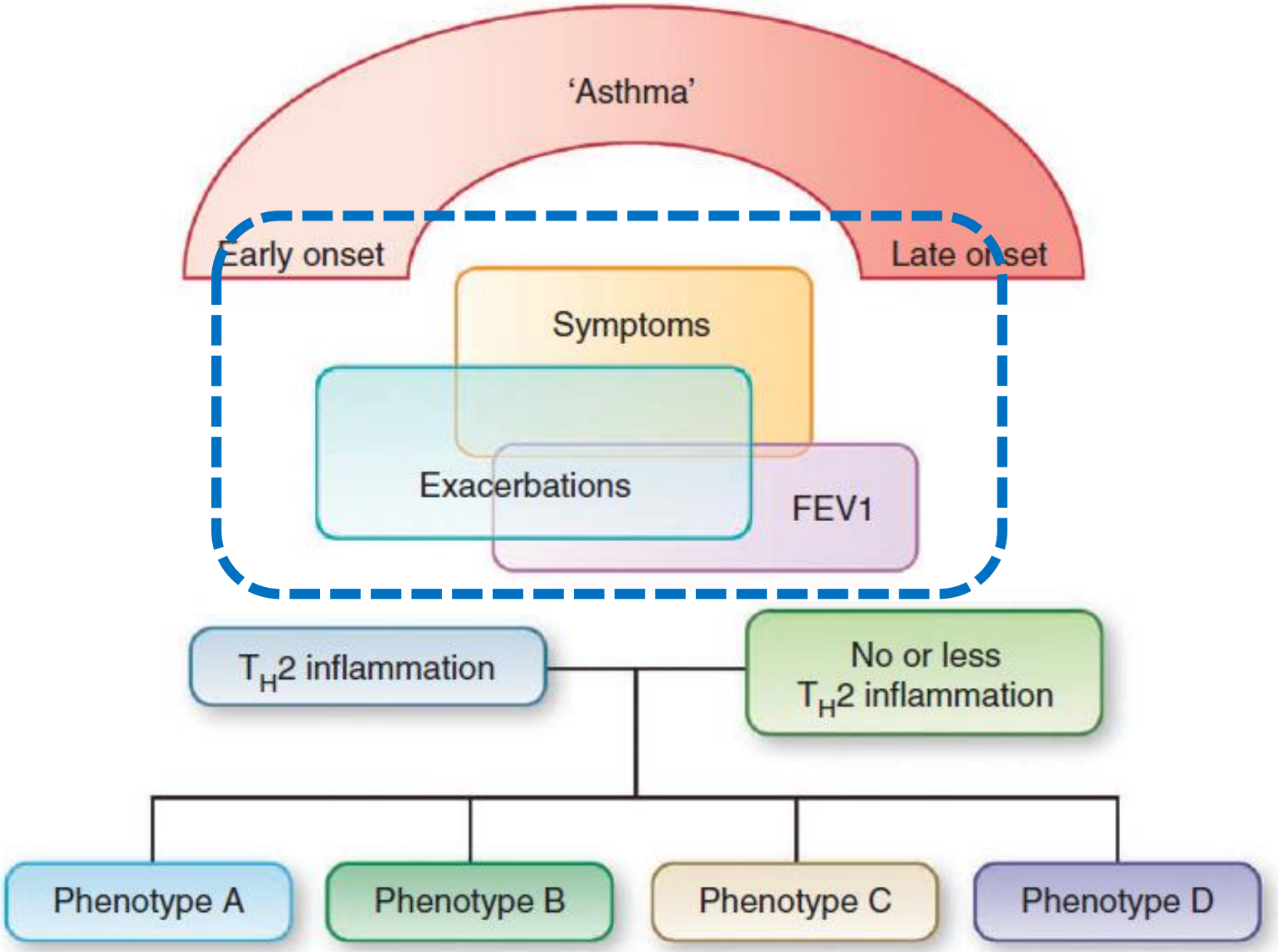
Effect of smoking on asthma phenotypes

- Cluster analysis yielded novel hypotheses regarding the effect of smoking on airway inflammation in severe asthma.

- Two distinct types of pathogenesis may exist in relation to the role of smoking in decline of pulmonary function and eventually in asthma severity.

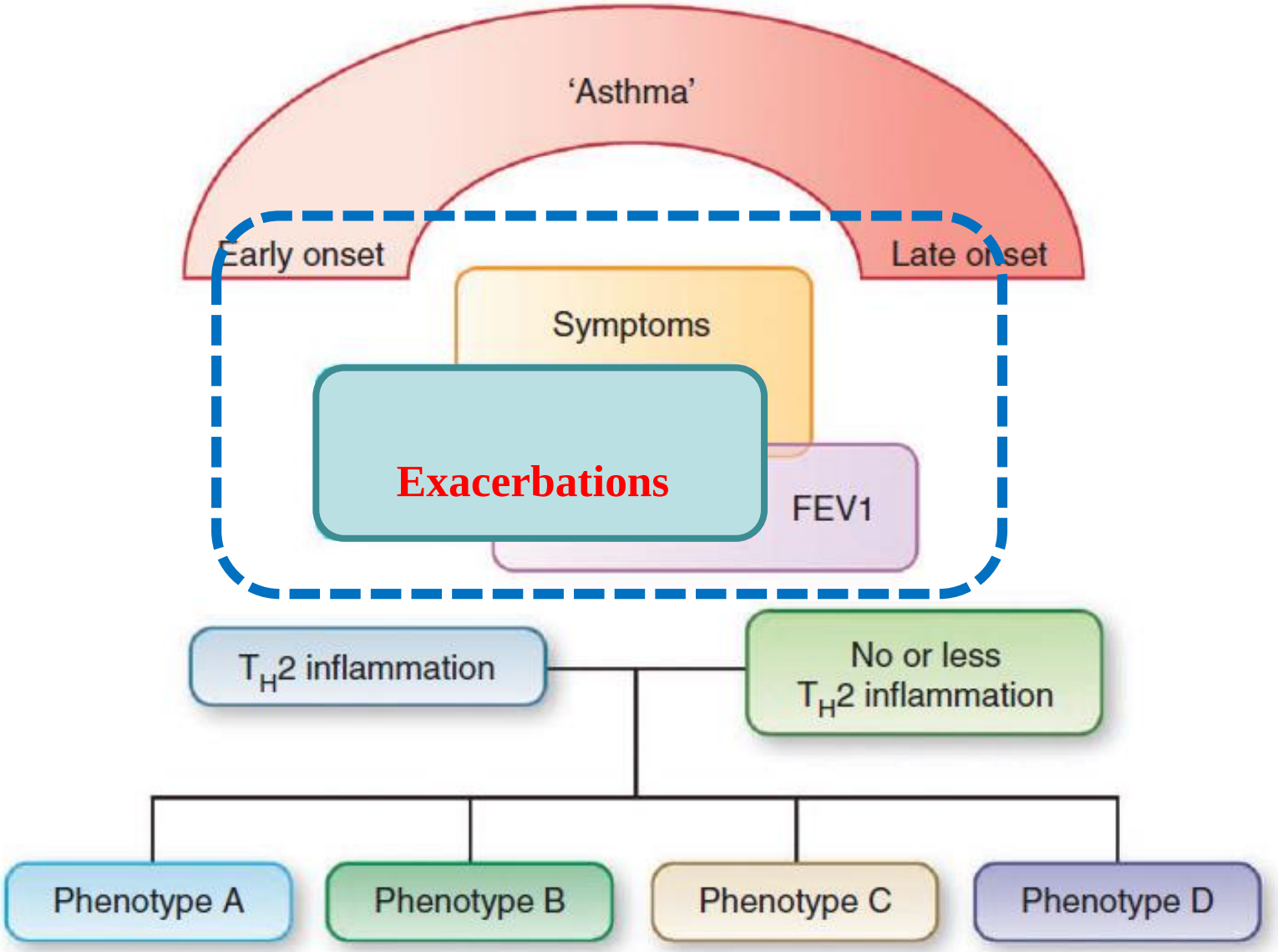
- This might explain the inconclusive results of previous reports regarding the effect of smoking on airway inflammation in asthma.

Goals for asthma treatment



(Wenzel SE. Nat Med. 2012)

Goals for asthma treatment

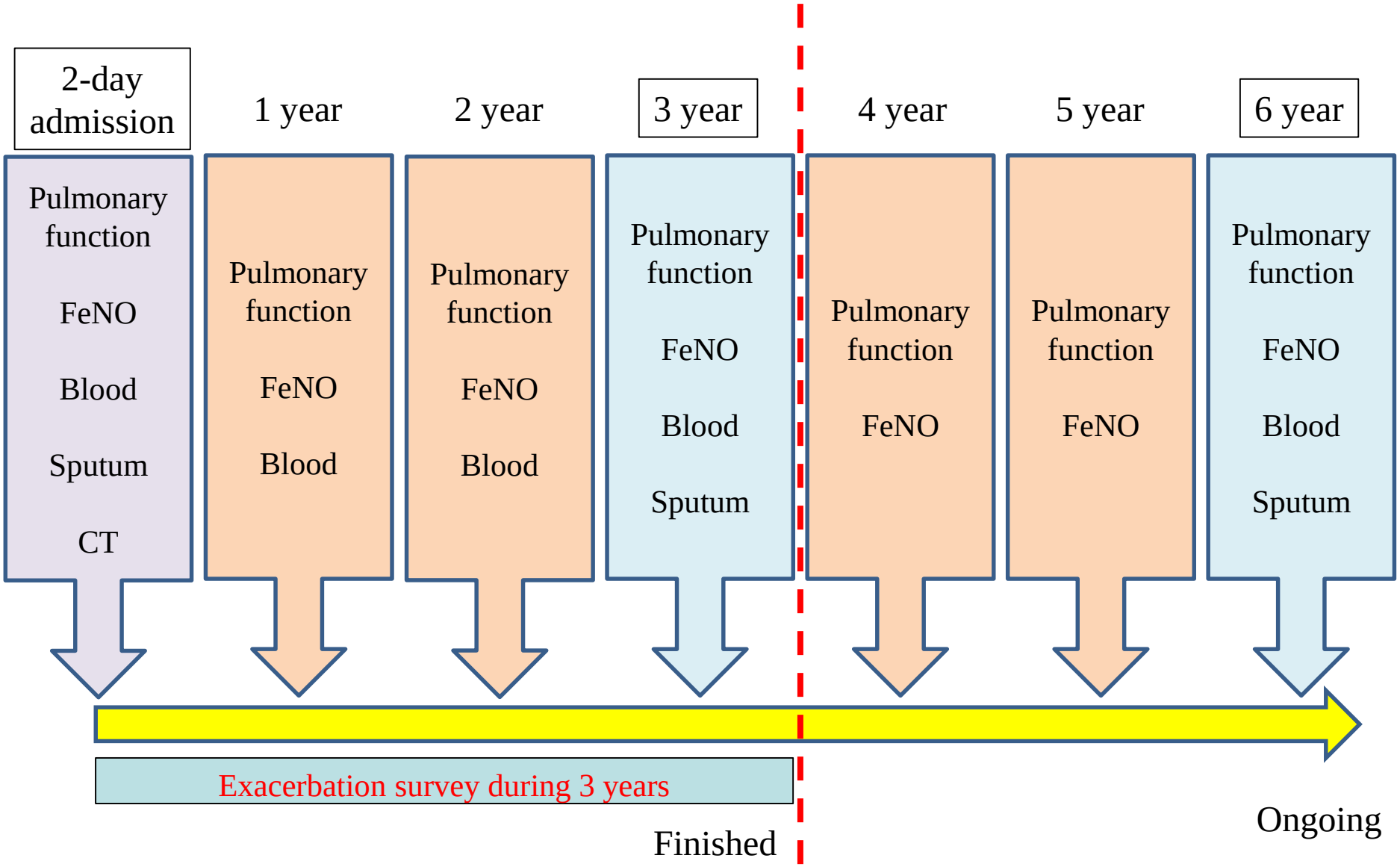


(Wenzel SE. Nat Med. 2012)

Aim

- The aim of this study was to characterize the clinical features associated with asthma exacerbation from data collected during a 3-year follow-up of severe asthmatic subjects.

Follow-up protocol in Hi-CARAT



3-year-follow-up

Patients diagnosed with severe asthma (with consent), N=148

→ Patients excluded, N=7:
- Withdrawal, N=3
- Death, N=1
- Severe asthma exacerbation, N=1
- Kidney cancer, N=1
- Idiopathic pulmonary fibrosis, N=1

Examinations performed during the 2-day stay at Hokkaido University Hospital, N=141

→ Patients excluded, N=14:
- Criteria not fulfilled, N=9
- Suspicious of ABPA, N=1
- History of tuberculosis, N=1
- History of lung resection, N=1
- Poor adherence, N=2

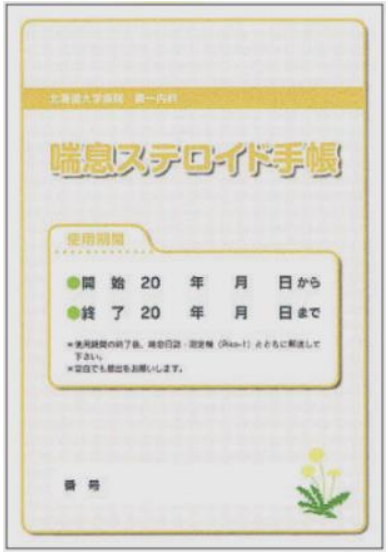
N=127
Analysis of baseline data

→ Lost to follow up, N=10
Unavailable exacerbation data, N=5

N=112
Availability of the 3-year exacerbation data

→ Poor medication adherence (<70%), N=2
Unavailable medication adherence data, N=5

N=105
Analysis of exacerbation data



Assessment of adherence to medications

- We excluded subjects who were assessed by a doctor (Dr. NT) and the CRCs to have poor adherence to their medications and inadequate medication inhalation technique upon their initial visit.
- Subjects with low adherence (< 70%) were excluded from the final analyses.

Medication adherence data

	Year 1			Year 2			Year 3		
Adherence (%)	Oral	Inhaled	Trans-dermal	Oral	Inhaled	Trans-dermal	Oral	Inhaled	Trans-dermal
99-100	80 (72.1%)	75 (67.0%)	4 (50.0%)	82 (78.1%)	69 (63.3%)	6 (66.7%)	78 (76.5%)	74 (69.2%)	4 (57.1%)
90-99	27 (24.3%)	30 (26.8%)	3 (37.5%)	20 (19.0%)	38 (34.9%)	2 (22.2%)	20 (19.6%)	31 (29.0%)	2 (28.6%)
80-90	2 (1.8%)	6 (5.4%)	0	2 (1.9%)	1 (0.9%)	1 (11.1%)	3 (2.9%)	2 (1.9%)	1 (14.3%)
70-80	0	1 (0.9%)	1 (12.5%)	1 (1.0%)	1 (0.9%)	0	1 (1.0%)	0	0
0-70	2 (1.8%)	0	0	0	0	0	0	0	0
All	111	112	8	105	109	9	102	107	7

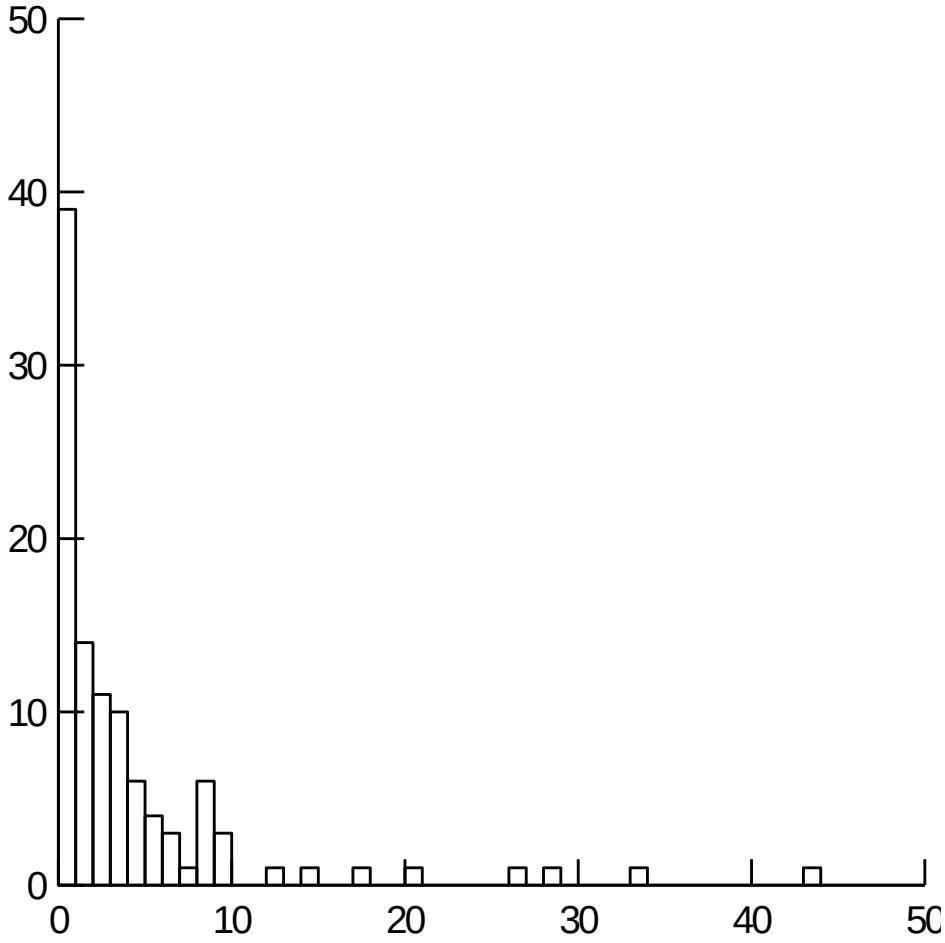
Characteristics (N=105)

Male sex, N (%)	45 (42.9%)
Age at enrollment, years	58.5 ± 12.1
Asthma duration, years	19.7 ± 14.6
Smoking status (Current/Ex/Never)	11/56/38
Pack years	5.5 (0-23.4)
BMI, kg/m^2	25.5 ± 5.0
Daily ICS dose, µg (BUD Eq)	1638 ± 518.8
Maintenance OCS use, N (%)	39 (37.1%)
Atopy, N (%)	65 (61.9%)

Blood eosinophil, cells/µL	197.0 (0.52)
Serum IgE, IU/mL	138.5 (0.70)
Sputum Eosinophil, %	8.0 (0.8-30.6)
FeNO, ppb	30.2 (0.36)
Serum periostin, ng/mL	80.3 (0.21)
FEV_1, %predicted	91.4 ± 18.9
FEV_1/FVC, %	66.3 ± 12.7

Data are shown as mean±SD, median (IQR) , geometric mean ($\log_{10}$ SD) or number (%).

Distribution of exacerbations in 3 years



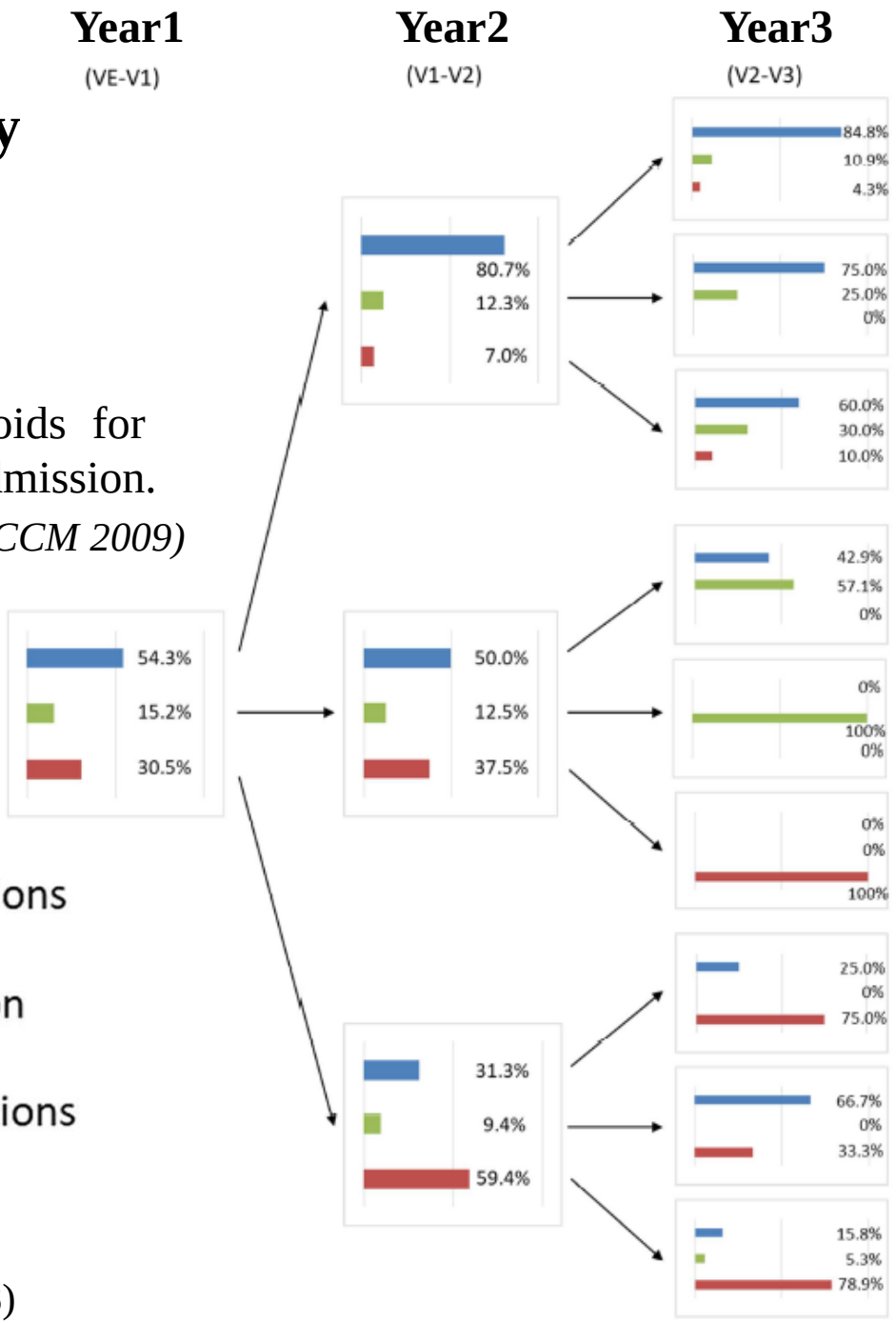
Numbers of exacerbations in 3 years

(Kimura H, et al. *Clin Exp Allergy* 2018)

Exacerbation frequency
— 3-year follow up —

Asthma exacerbation:
the need for systemic corticosteroids for more than 3 days and/or hospital admission.

(AJRCCM 2009)



Patients with no exacerbations

Patients with 1 exacerbation

Patients with ≥ 2 exacerbations

(Kimura H, et al. *Clin Exp Allergy* 2018)

Factors associated with the next year asthma exaxcerbartion

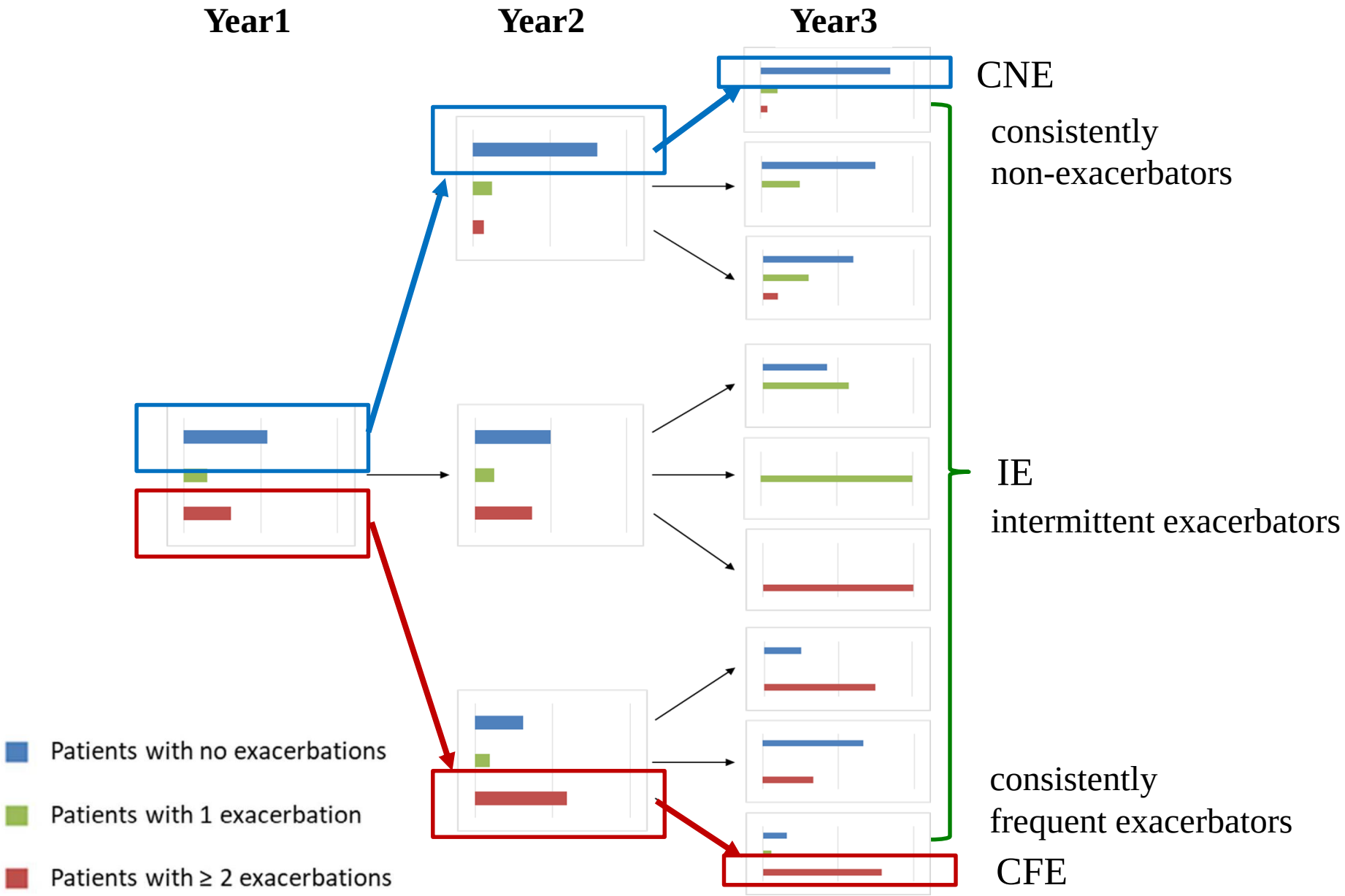
Exacerbation on 2nd year

	OR	95%CI	P-value
Exacerbation during the 1st year	10.1	3.63-28.0	< 0.0001

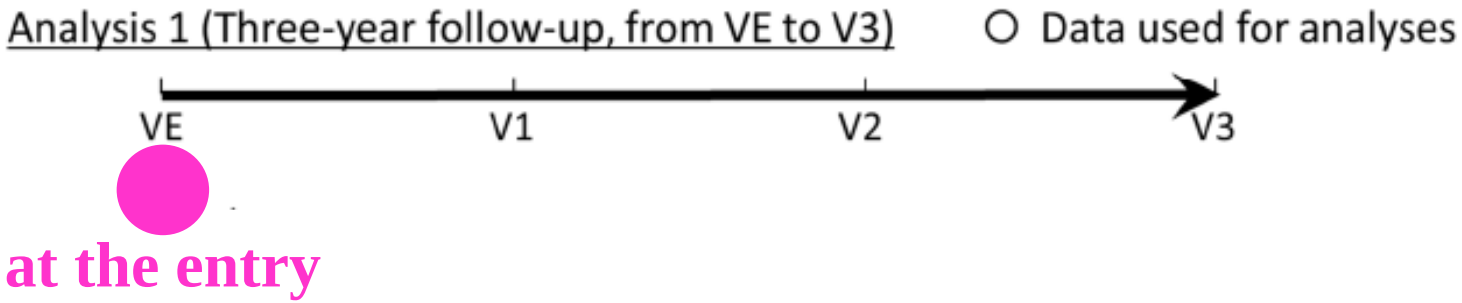
Exacerbation on 3rd year

	OR	95%CI	P-value
Exacerbation during the 1st and 2nd year	33.7	7.90-144.2	< 0.0001

Logistic regression analysis
Adjusted by age, gender, yearafter diagnosis of exacerbation, atopy, BMI, smoking status


Year1
Year2
Year3
CNE
consistently
non-exacerbators
IE
intermittent exacerbators
consistently
frequent exacerbators
CFE
Patients with no exacerbations
Patients with 1 exacerbation
Patients with ≥ 2 exacerbations

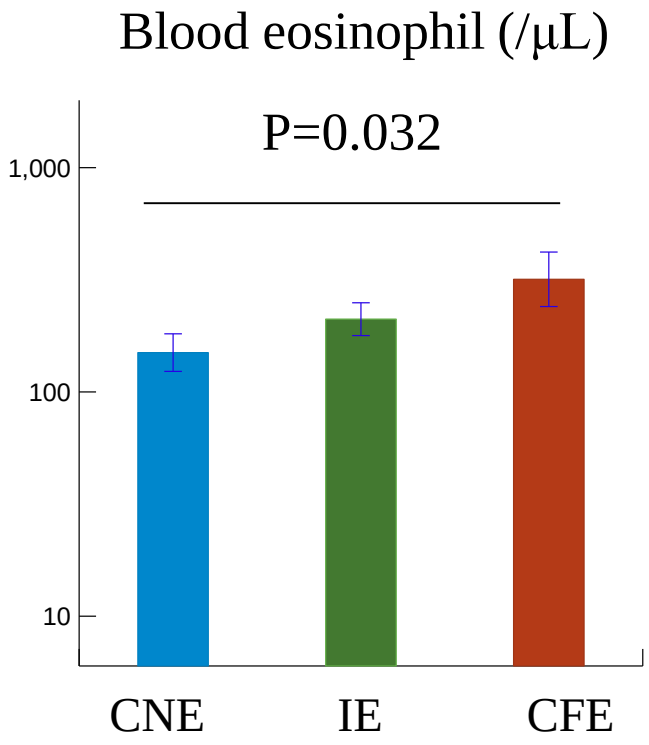
3-Year Follow up

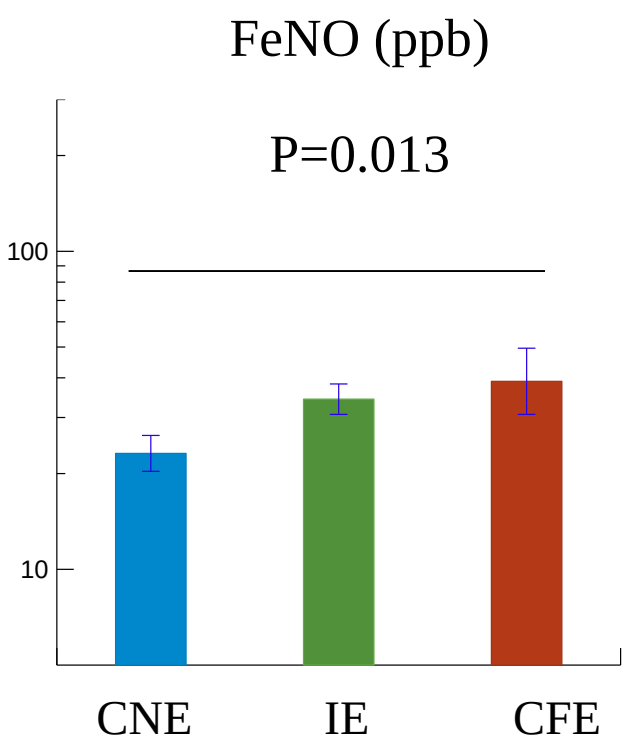


Th2 biomarkers

- **Blood eosinophils (μL)**
- **Sputum eosinophils (%)**
- **Total serum IgE**
- **FeNO**
- **Serum periostin**

Biomarkers according to exacerbation status



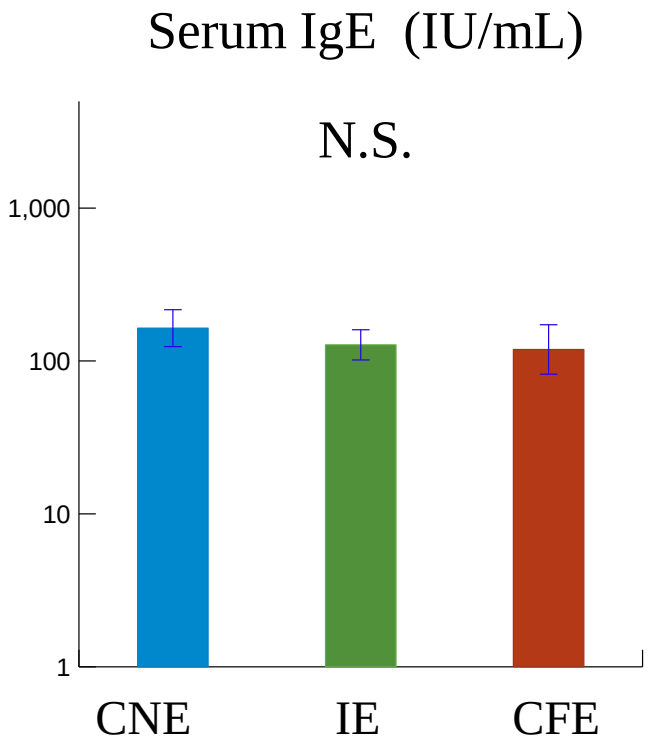


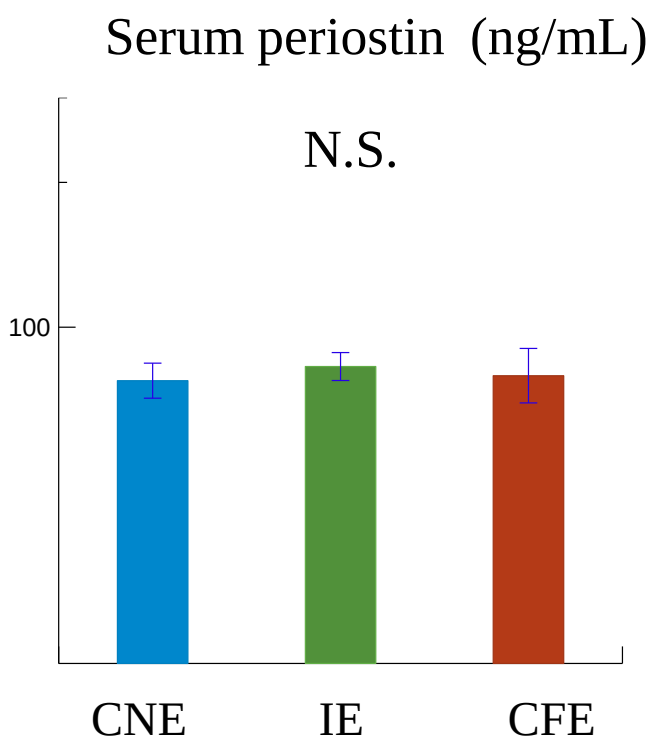
Data are shown as mean±SD
Jonckheere-Terpstra trend tests

CNE: consistently non-exacerbators
IE: intermittent exacerbators
CFE: consistently frequent exacerbators

(Kimura H, et al. *Clin Exp Allergy* 2018)

Biomarkers according to exacerbation status





Data are shown as mean±SD
Jonckheere-Terpstra trend tests

CNE: consistently non-exacerbators
IE: intermittent exacerbators
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(Kimura H, et al. *Clin Exp Allergy* 2018)

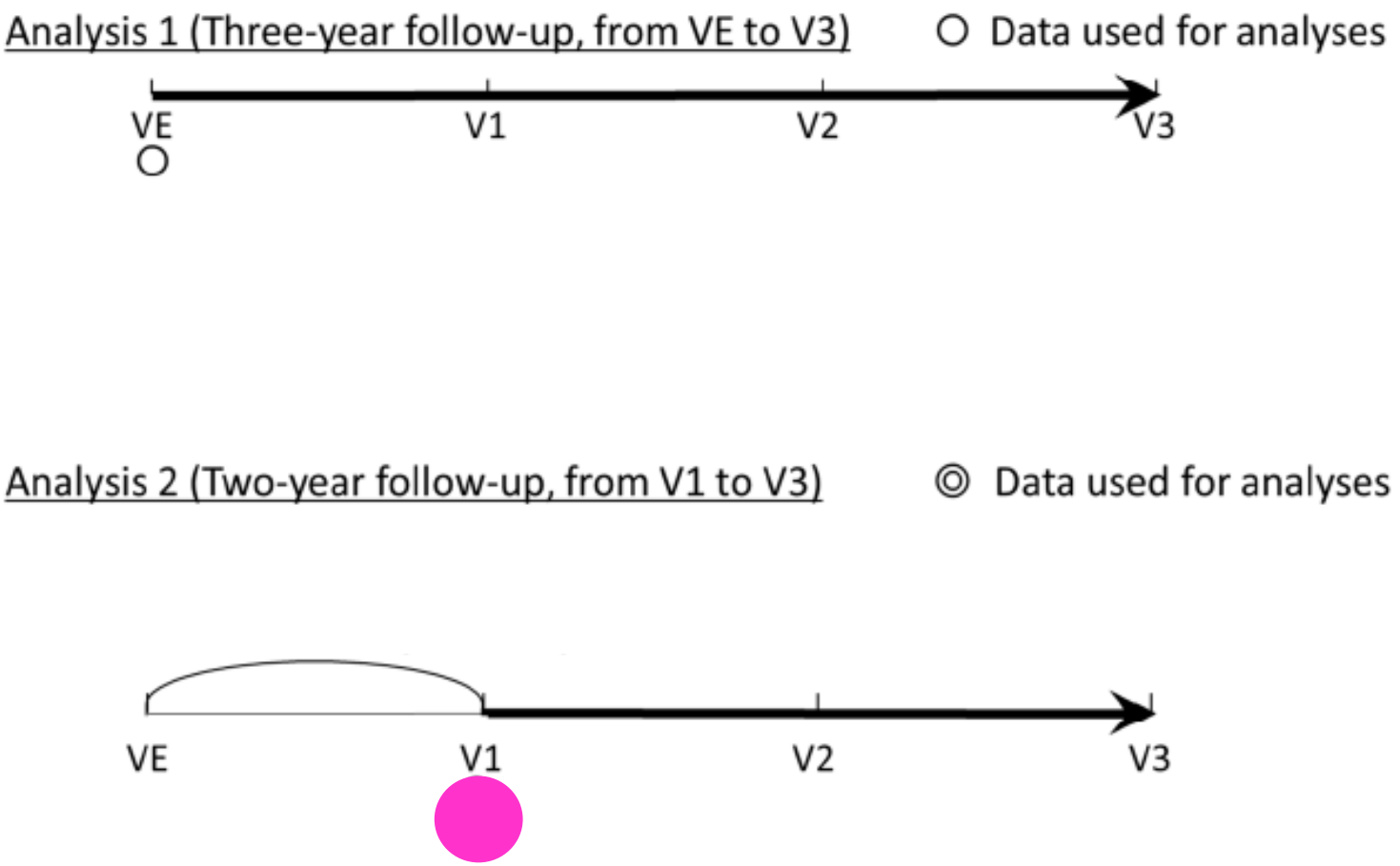
Characteristics according to exacerbation status

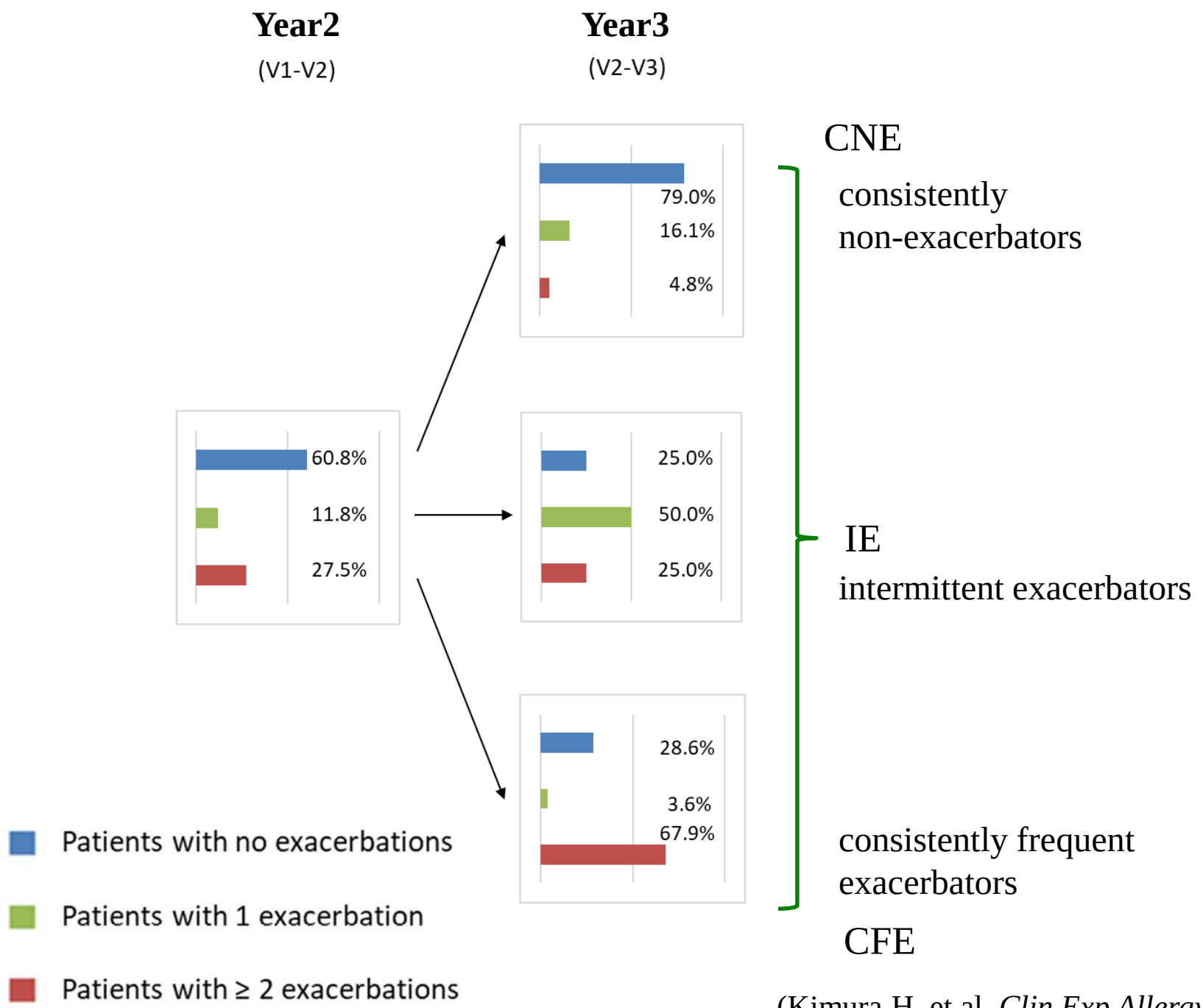
		Type of exacerbation				
	All (N = 105)	CNE (N = 39)	IE (N = 51)	CFE (N = 15)	*P*-value	*P* for trend*
Male sex, N (%)	45 (42.9)	14 (35.9)	26 (51.0)	5 (33.3)	.259	n/a
Age at enrolment, y	58.5 ± 12.1	57.3 ± 11.8	60.0 ± 12.2	56.3	.456	n/a
Asthma duration, y	19.7 ± 14.6	16.8 ± 11.1	22.0 ± 16.5	19.3 ± 15.4	.242	n/a
Smoking status (Current/Ex/Never)	11/56/38	4/17/18	7/29/15	0/10/5	.272	n/a
Pack years	5.5 (0-23.4)	4.5 (0-17.1)	7.4 (0-30.9)	4.0 (0-11.6)	.237	n/a
Pack years ≥10, N (%)	46 (43.8)	14 (35.9)	25 (49.0)	7 (46.7)	.448	n/a
Body mass index, kg/m^2	25.5 ± 5.0	25.7 ± 5.9	25.5 ± 3.9	24.7 ± 5.7	.795	n/a
Daily ICS dose, μg[a]	1638 ± 518.8	1674.4 ± 462.7	1611.3 ± 455.4	1640 ± 819.2	.852	n/a
Maintenance OCS use, N (%)	39 (37.1)	13 (33.3)	17 (33.3)	9 (60.0)	.141	n/a
Atopy, N (%)	65 (61.9)	26 (66.7)	30 (58.8)	9 (60.0)	.740	n/a
ACT	21.0 (17.0-23.0)	22.0 (18.3-23.8)	20.0 (16.3-23.0)	20.0 (15.3-20.8)	.107	.039
AQLQ	5.5 (4.9-6.3)	5.7 (4.9-6.3)	5.5 (4.9-6.3)	5.1 (4.3-6.1)	.341	.160

CNE IE CFE

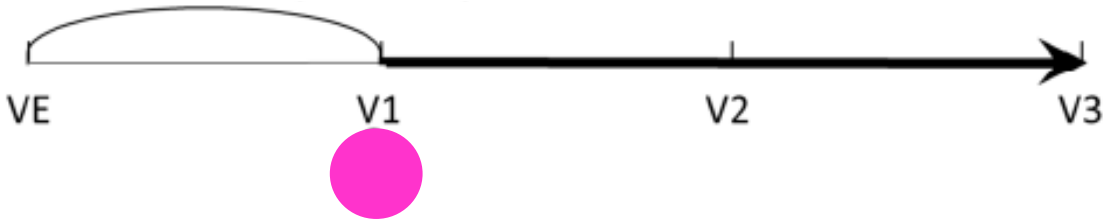
(Kimura H, et al. *Clin Exp Allergy* 2018)

3-Year Follow up



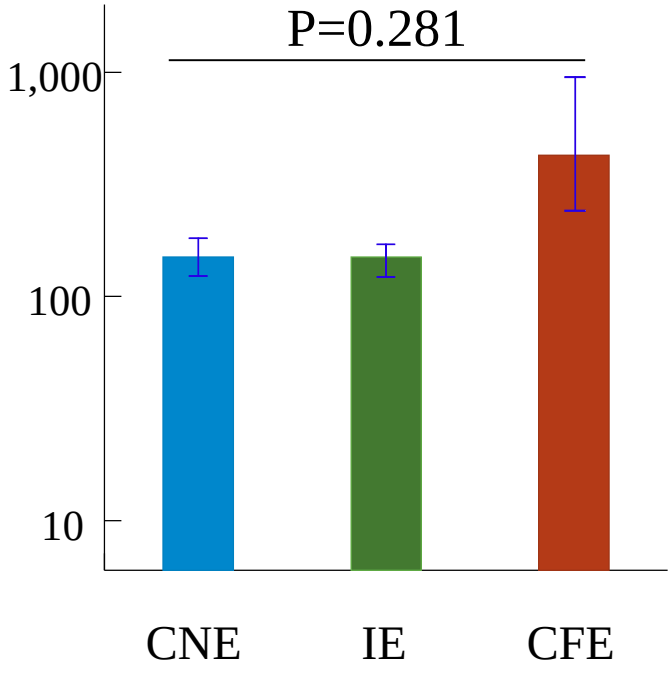


(Kimura H, et al. *Clin Exp Allergy* 2018)

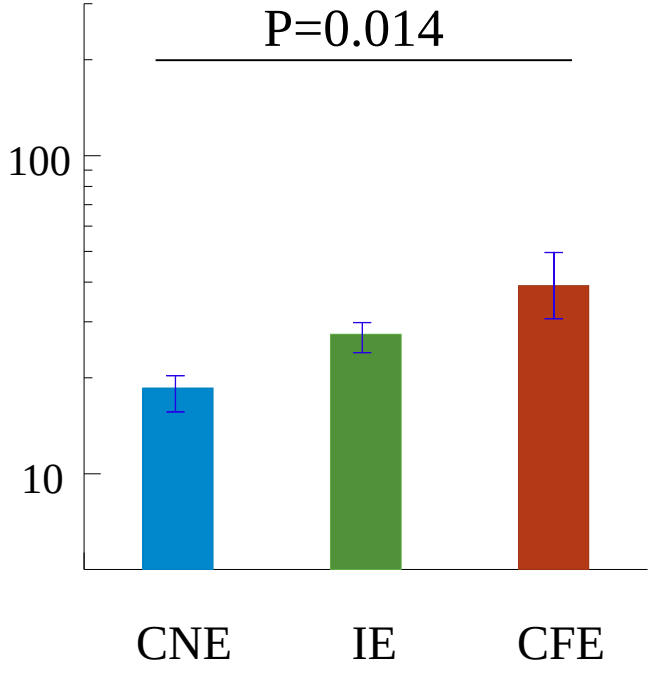


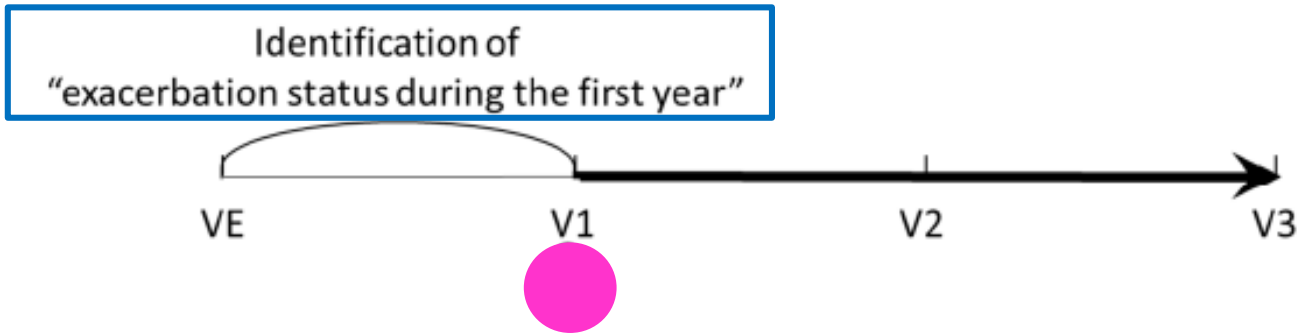
Data at visit 1

Blood eosinophils (/µL)



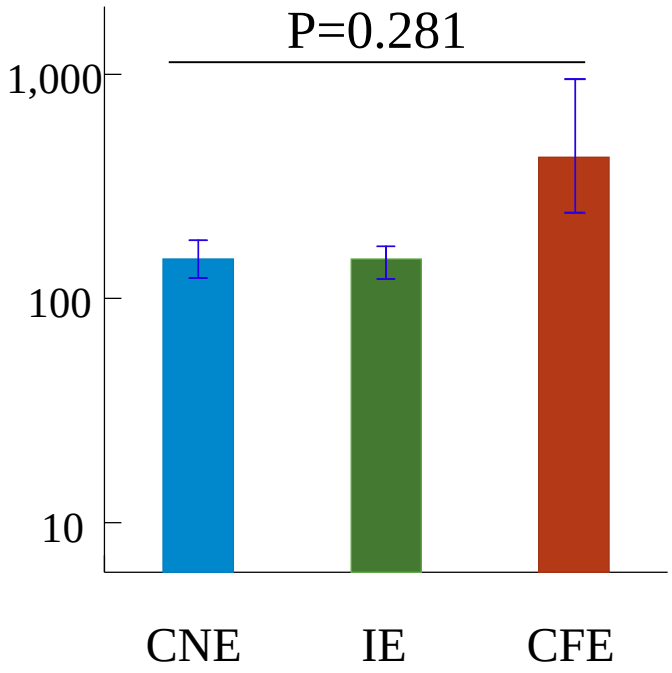
FeNO (ppb)



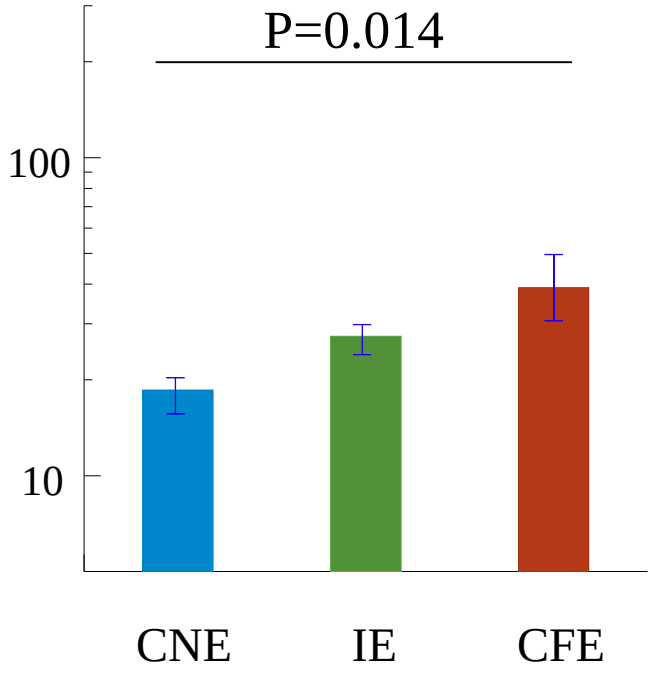


Data at visit 1

Blood eosinophils (/µL)



FeNO (ppb)



Multivariate Analysis

Table 5. Comparison of the blood eosinophil count and FeNO among exacerbation status groups in two-year follow-up after Visit 1 (Analysis 2)

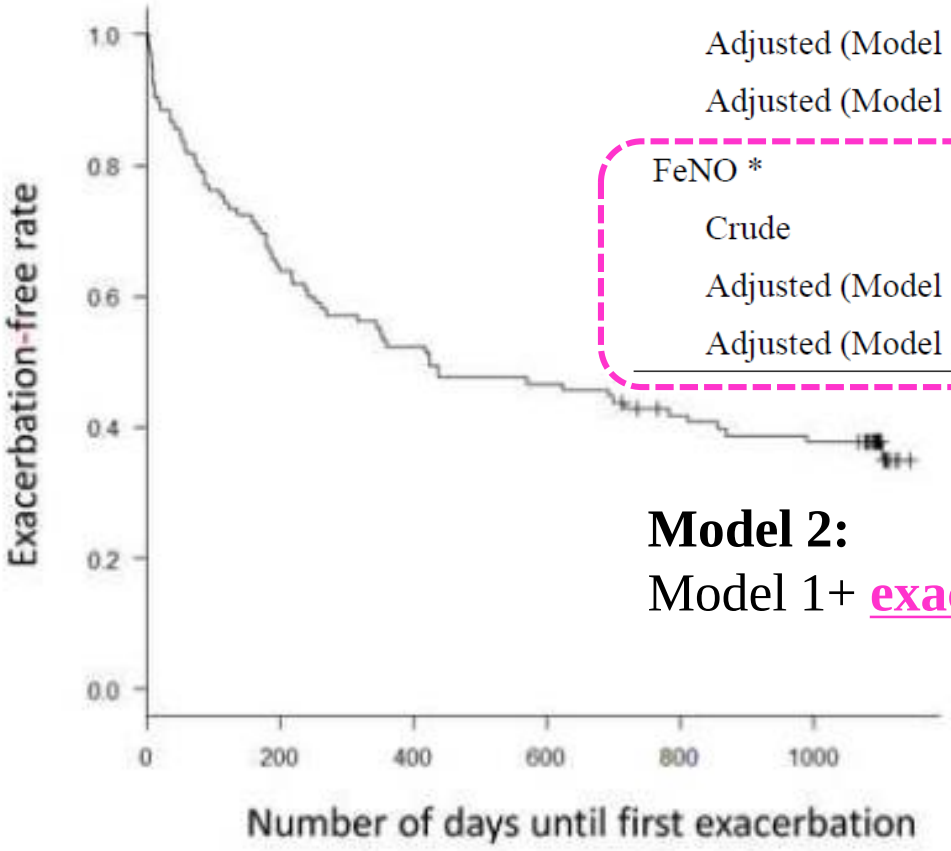
	Type of exacerbation					
	CNE (N = 49)	IE (N = 34)	CFE (N = 19)	P-value, Crude	P-value Model 1	P-value Model 2
Blood eosinophil count, cells/μL *	190.6 (0.50)	181.7 (0.46)	289.2 (0.38)	0.281	0.428	0.778
FeNO, ppb *	19.8 (0.27)	26.1 (0.36)	35.3 (0.36)	0.014	0.016	0.017

- **Crude**
- **Model 1:** Age, gender, BMI smoking status
- **Model 2:** Model 1+ **exacerbation status during the 1st year**

(Kimura H, et al. *Clin Exp Allergy* 2018)

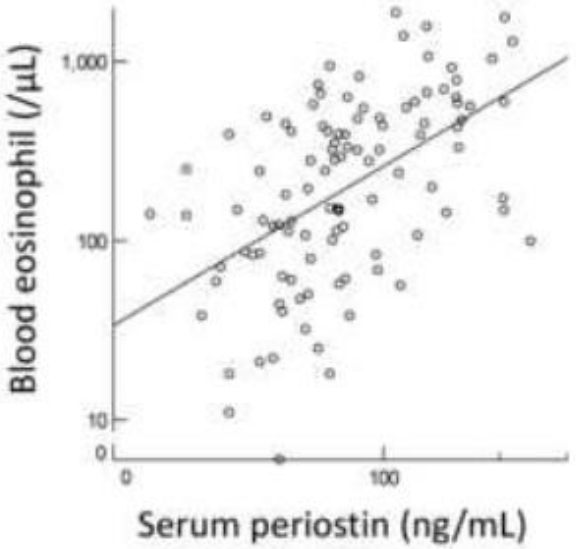
Cox Proportional Hazard model

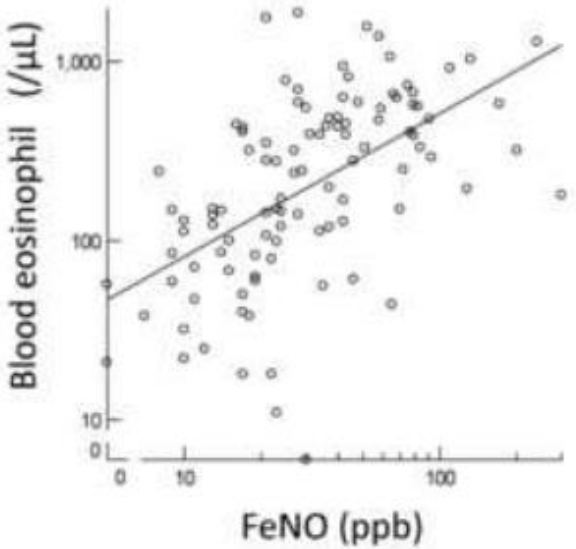
	HR	95% CI	P-value
Blood eosinophil count *			
Crude	1.27	0.70-2.31	0.433
Adjusted (Model 1) †	1.43	0.74-2.79	0.291
Adjusted (Model 2) ‡	1.20	0.62-2.31	0.584
FeNO *			
Crude	2.96	1.29-6.81	0.011
Adjusted (Model 1) †	2.84	1.18-6.85	0.020
Adjusted (Model 2) ‡	2.78	1.14-6.81	0.025



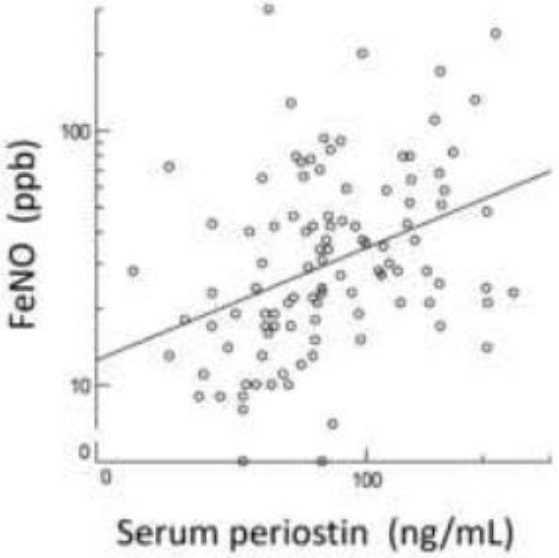
Model 2:
Model 1+ **exacerbation status during the 1st year**

(Kimura H, et al. *Clin Exp Allergy* 2018)

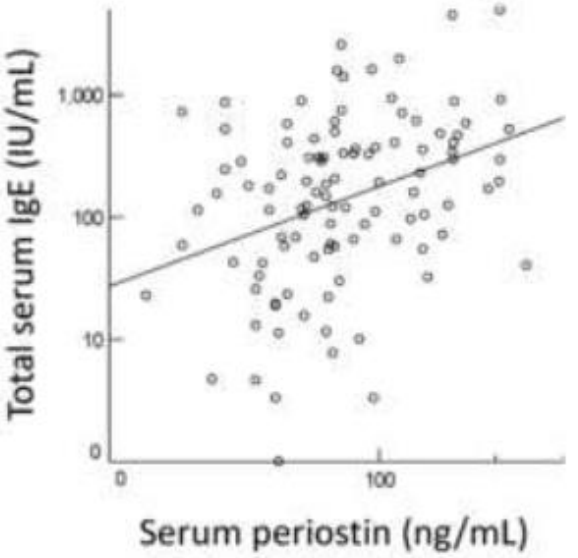

Blood eosinophil (/μL)
1,000
100
10
0
0
100
Serum periostin (ng/mL)


Blood eosinophil (/μL)
1,000
100
10
0
0
10
100
FeNO (ppb)

(C)


FeNO (ppb)
100
10
0
0
100
Serum periostin (ng/mL)

(D)


Total serum IgE (IU/mL)
1,000
100
10
0
0
100
Serum periostin (ng/mL)

Increased periostin associates with greater airflow limitation in patients receiving inhaled corticosteroids

(Kanemitsu Y, et al. JACI 2013)

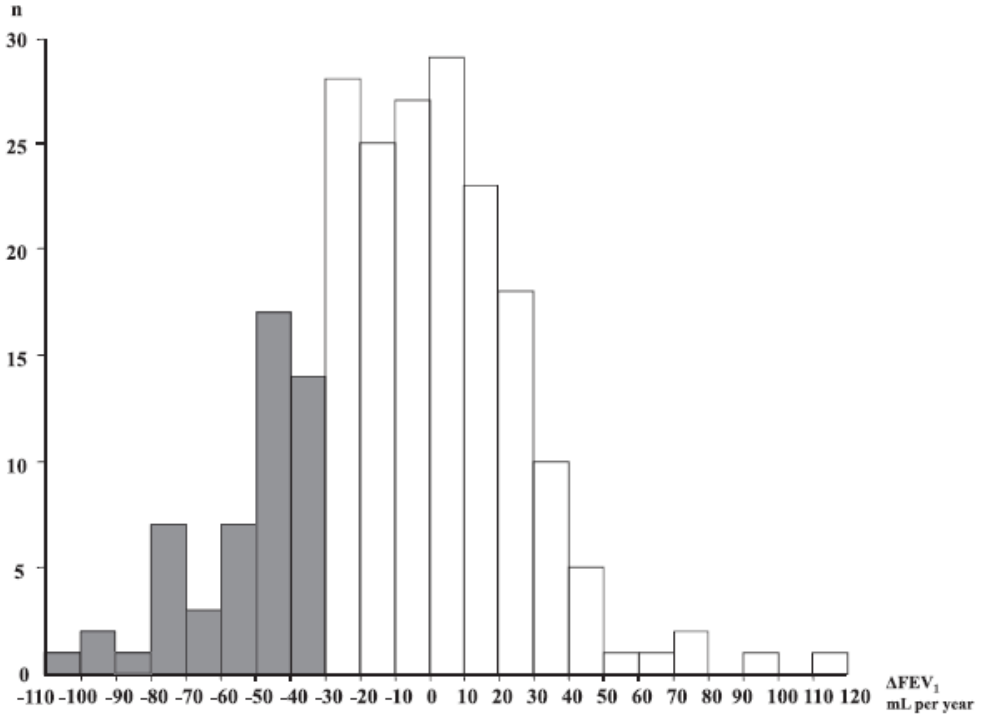


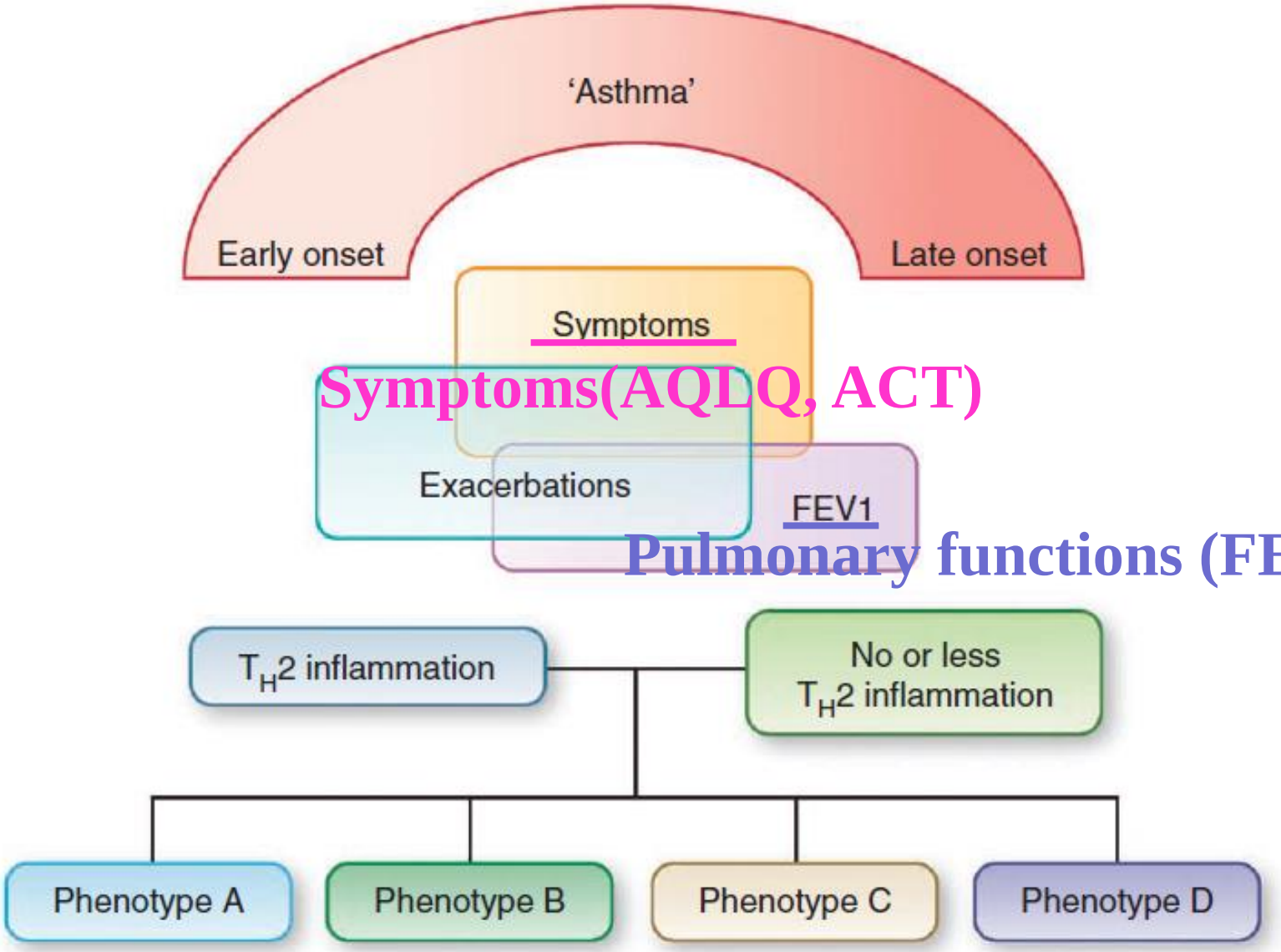
TABLE IV. Estimated effects of clinical indices and serum periostin on a decline in FEV_1 of 30 mL or greater per year

	Univariate analysis			Multivariate analysis		
	Estimates	95% CI	*P* value	Estimates	95% CI	*P* value
Treatment step, 5 vs 2 to 4*	1.63	0.51 to 2.60	.004	1.24	0.078 to 2.30	.04
History of admission due to asthma	1.09	0.37 to 1.90	.003	0.70	−0.11 to 1.50	.09
ICS daily maintenance dose (μg)	0.001	0.00 to 0.002	.01	—		
Chronic sinusitis	0.82	0.11 to 1.53	.03	0.61	−0.15 to 1.37	.12
Smoking history, ex vs never	0.87	−0.002 to 1.74	.05	0.98	0.030 to 1.93	.04
Log serum periostin (ng/mL)	2.96	0.78 to 5.13	.008	—		
Periostin group, high vs low†	1.03	0.33 to 1.72	.004	0.87	0.11 to 1.63	.03

Summary II

- Fifteen patients (14.3%) were frequent exacerbators in 3 years analysis among 105 severe asthmatics.
- Frequent exacerbators displayed high blood eosinophils and FeNO levels.
- Frequent exacerbations in previous year were significant associated factors with frequent exacerbations in next years.
- FeNO levels were significant associated factors with frequent exacerbations independent of exacerbations in previous year.

Future Planning



(Wenzel SE. Nat Med. 2012)

Thank you very much for your kind attention.

Hokkaido University