Clinical phenotypes of asthma in Korea

Asthma Workshop 2016

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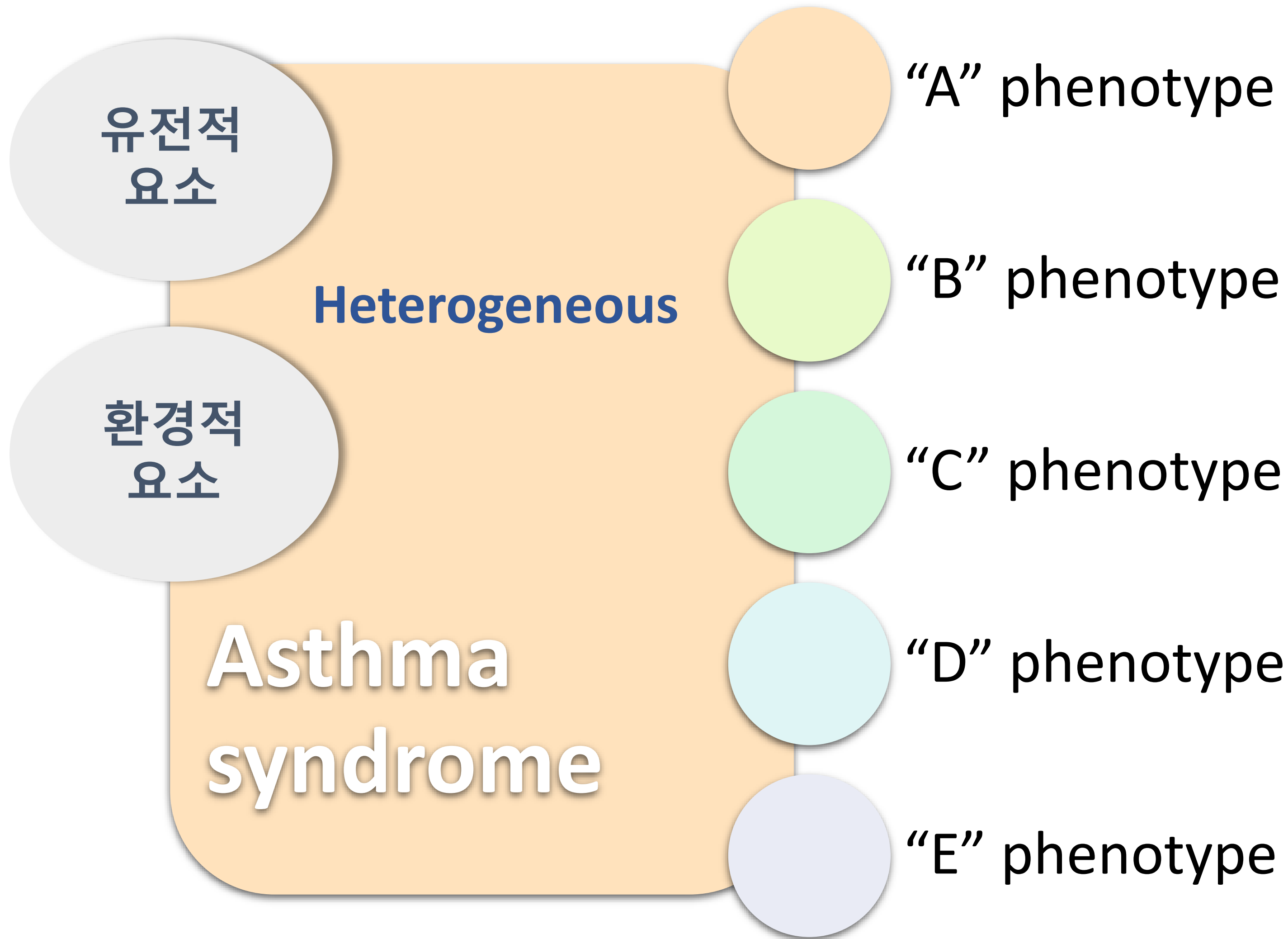
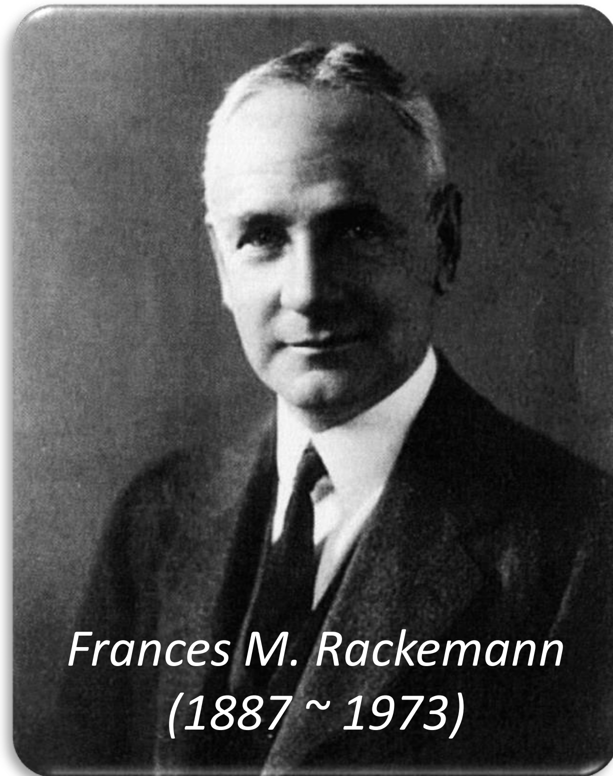
Contents



"유사한 임상양상 (**증상, 악화, 치료반응, 진행속도, 예후**)으로
개체의 구별을 가능하게 하는 특성"

GINA 2014 ~ 2016

The first description of “*phenotype*” in 1940s

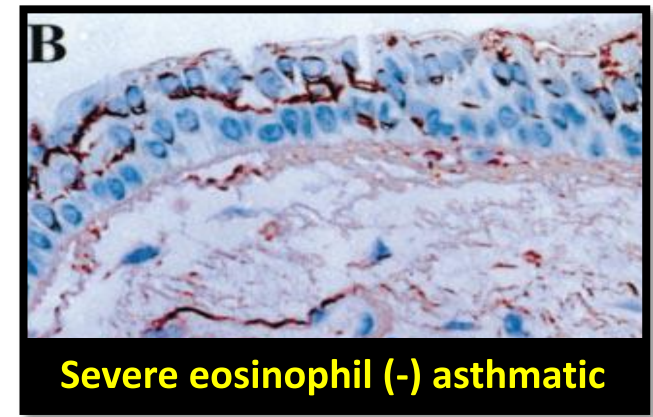


- Extrinsic asthma
- Intrinsic asthma
- ***A key discriminator : age of onset***

J Allergy Clin Immunol, 1940:11:147

Despite the absence of eosinophils and the thinner SBM, FEV1 was marginally lower in eosinophil (-) asthmatics

Severe eosinophil (+) asthmatic



Severe eosinophil (-) asthmatic

1700 1900 1950 1970 1990 2000 2010 2015

Interest in Phenotyping

ICS의 성공

Extrinsic/Intrinsic Asthma

Eosinophilic Asthma

Back to single disease concept

Eosinophilic Asthma

Th2 High Asthma

Th2 Low Asthma

Clustering Studies

Am J Respir Crit Care Med, 2015:192:660

Wenzel et al, Am J Respir Crit Care Med, 1999:156:737

Conventional clinical phenotypes

Category	Phenotype
Trigger-related phenotypes	Exercise-induced
	Environmental allergens
	Aspirin-exacerbated respiratory disease (AERD)
	Infection
	Menses
Clinical or physiological phenotypes	Severity-defined
	Exacerbation-defined
	Fixed obstruction-defined
	Resistance to treatment
	Defined by age of onset
Inflammatory phenotypes	Eosinophilic
	Non-eosinophilic

Sally Wenzel, Lancet 2006:368:804

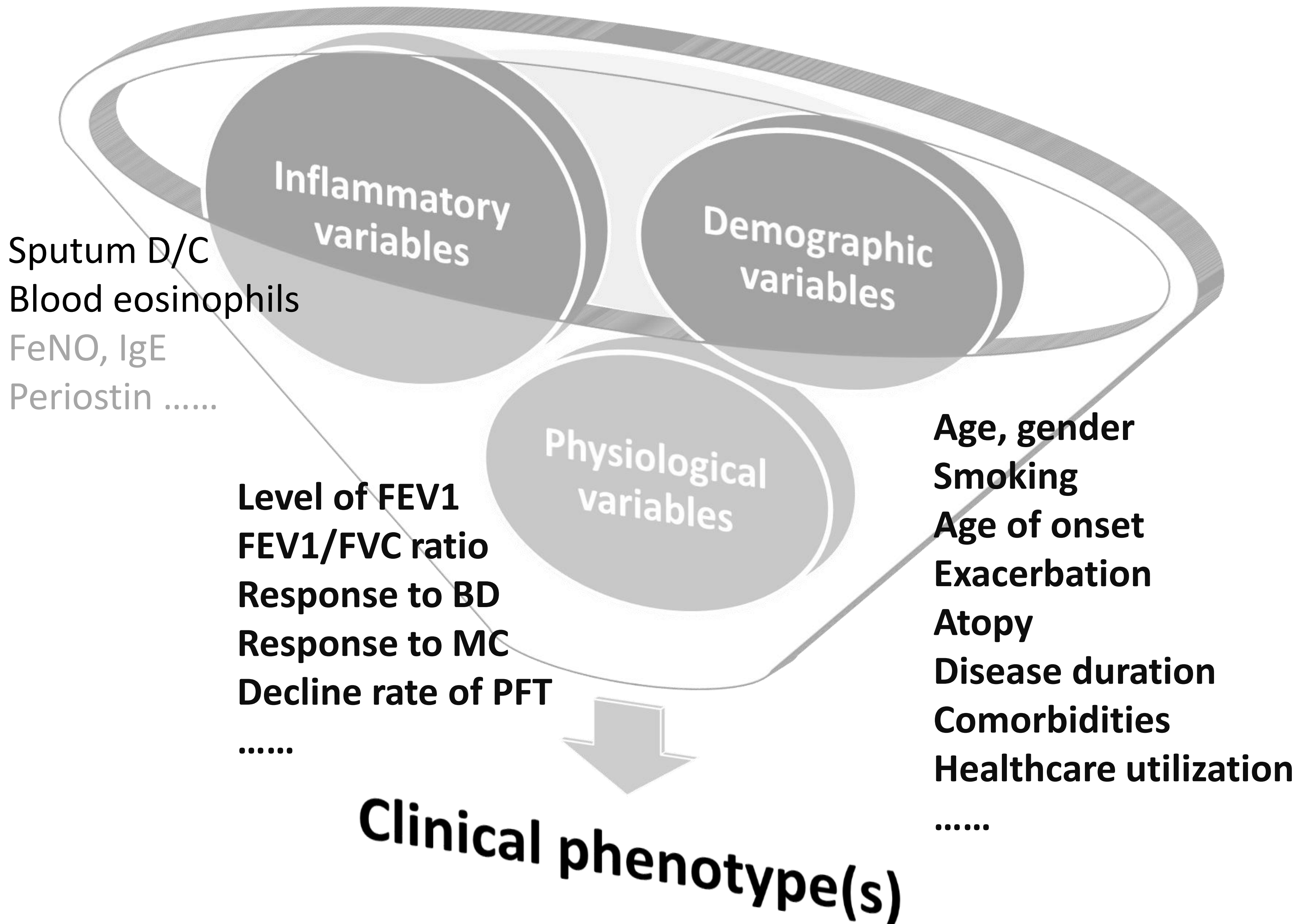
Approaches to phenotyping

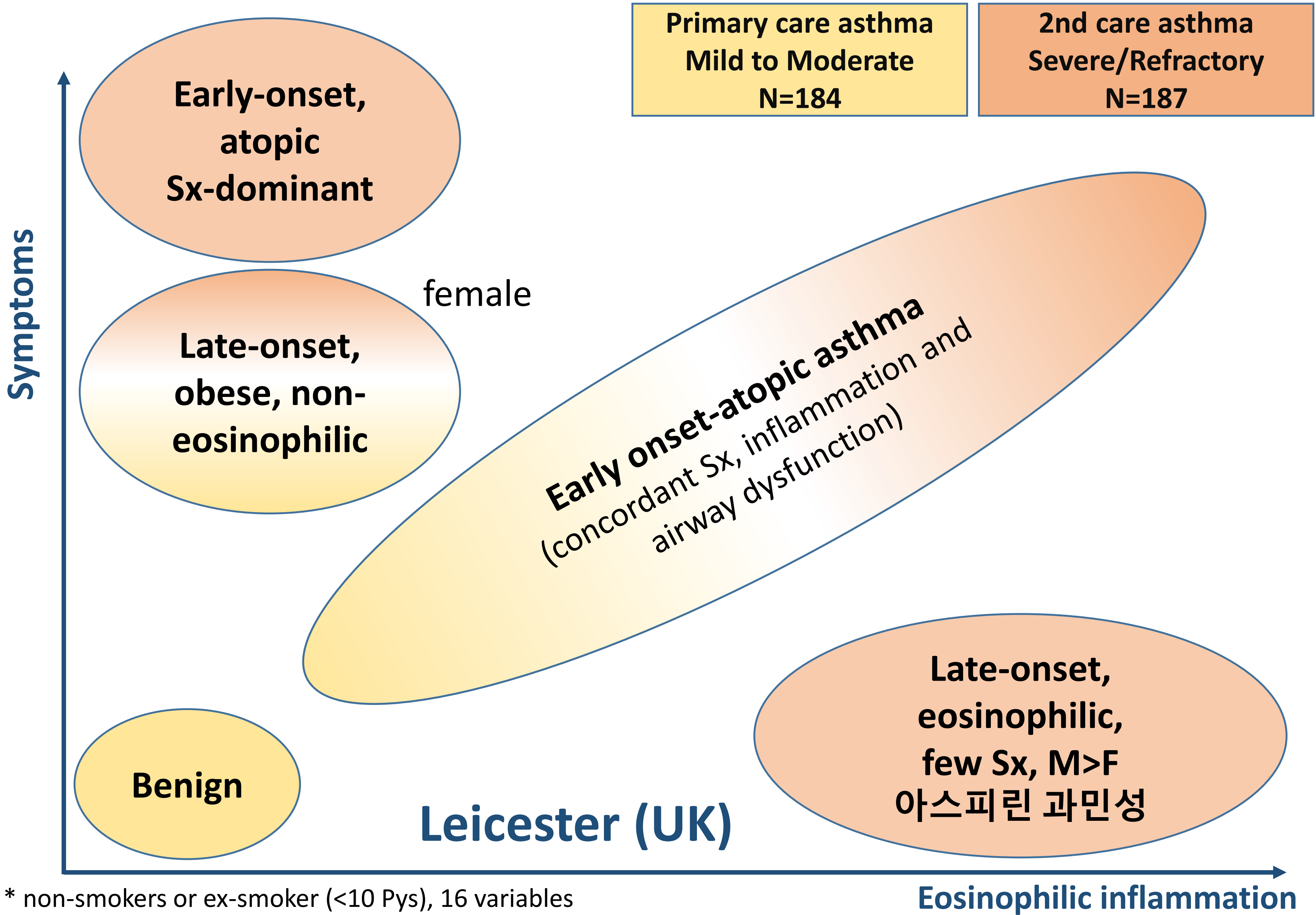
전통적 기법 (Biased approaches)

- Usually focus on a single dimension of the disease
- Based on hypothesis from preconceived ideas

현대적 기법 (객관적 통계기법 적용, Unbiased approaches)

- **Based on unsupervised, multi-dimensional variables**
- **From relatively well-defined cohort, No *a priori* hypotheses**
- **Care selection of variables(factors) a/w asthma is important**
- **ex) cluster analysis, latent class analysis …**


Inflammatory variables
Demographic variables
Physiological variables
Sputum D/C
Blood eosinophils
FeNO, IgE
Periostin ……
Level of FEV1
FEV1/FVC ratio
Response to BD
Response to MC
Decline rate of PFT
……
Age, gender
Smoking
Age of onset
Exacerbation
Atopy
Disease duration
Comorbidities
Healthcare utilization
……
Clinical phenotype(s)



* non-smokers or ex-smoker (<10 Pys), 16 variables
Sputum eosinophil 포함, not included physiological measures (FEV1)

Haldar et al, Am J Respir Crit Care, 2008:178:218

Discordant symptom Monitoring inflammation could down-titration of CS

현재 GINA 의 추천방식

Symptom-based approach may be sufficient

Primary care asthma Mild to Moderate N=184	2nd care asthma Severe/Refractory N=187

Early-onset, atopic Sx-dominant

Late-onset, obese, non-eosinophilic

female

Early onset-atopic asthma (concordant Sx, inflammation and airway dysfunction)

Concordant disease

Monitoring inflammation could allow targeted CS to lower AE frequency

Discordant inflammation

Benign

Late-onset, eosinophilic, few Sx, M>F 아스피린 과민성

Leicester (UK)

Symptoms

Eosinophilic inflammation

* non-smokers or ex-smoker (<10 Pys), 16 variables
Sputum eosinophil 포함, not included physiological measures (FEV1)

Haldar et al, Am J Respir Crit Care, 2008:178:218

Clinical phenotypes of SARP cohort (US)

* N=726 (≥12 years), mild to severe, non-smokers, 34 variables
not include markers a/w inflammation in all pts

Cluster 1 (110, 15.1%)

- **Early-onset, atopic**, normal lung function
- Age (27세), F (80%), No controller(40%)

Cluster 2 (321, 44.2%)

- **Early-onset, atopic**, preserved lung function
- Age (33세), F (67%), No controller(26%)

Cluster 3 (59, 8.1%)

- **Late-onset**, **obese**(BMI>30, 58%), **older women (71%)**, **non-atopic,**
- Age (50세), 폐기능에 비해 증상이 많음

Cluster 4 (120, 16.6%)

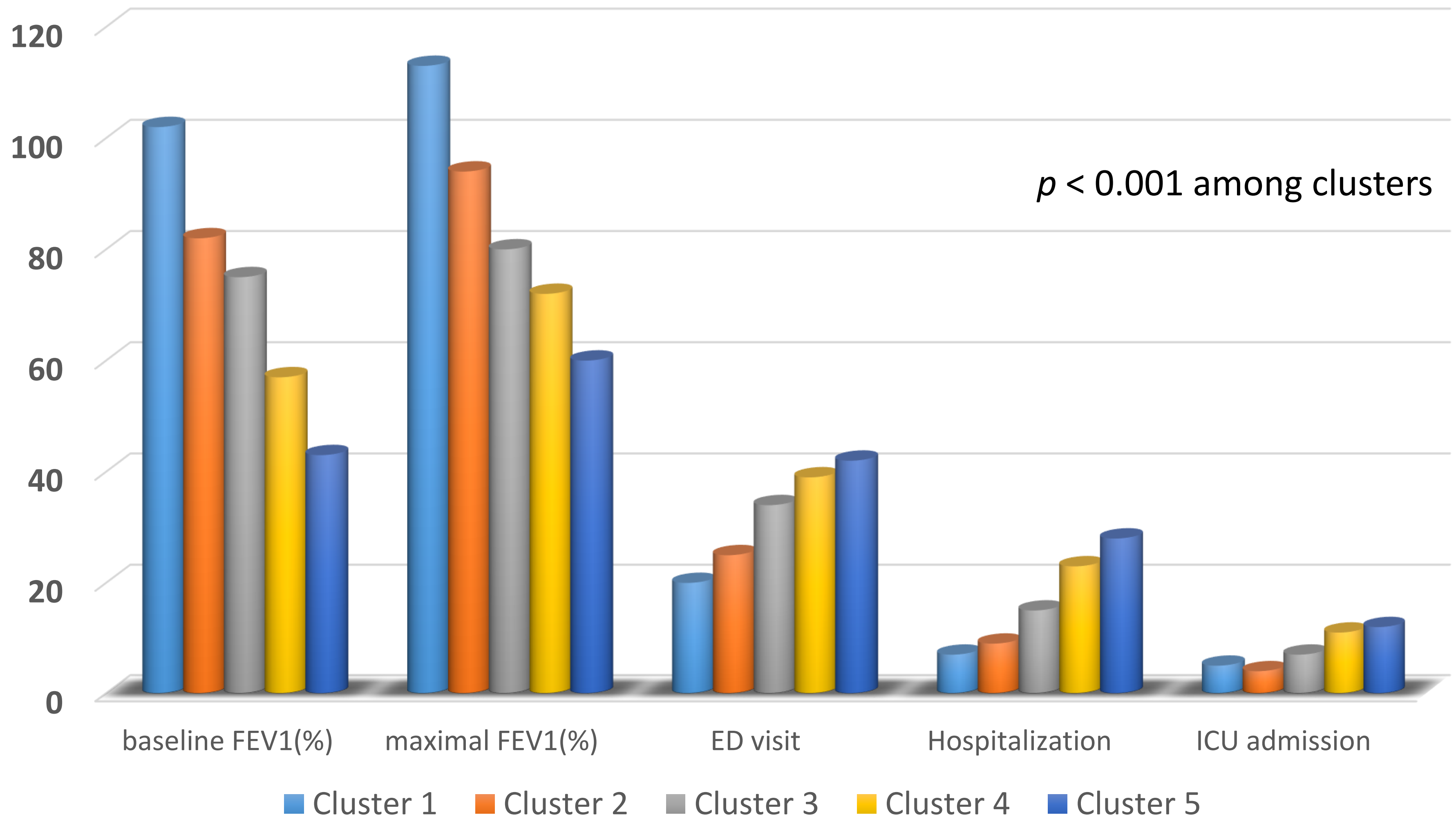
- Severe, **early-onset, atopic,** post-BD FEV1 < 80% (60%)
- Age (38세), F (53%), nearly fully-reversible, long duration

Cluster 5 (116, 16%)

- Severe, **late-onset, non-atopic, fixed airflow**
- Age (49세), F (63%), **longest duration**

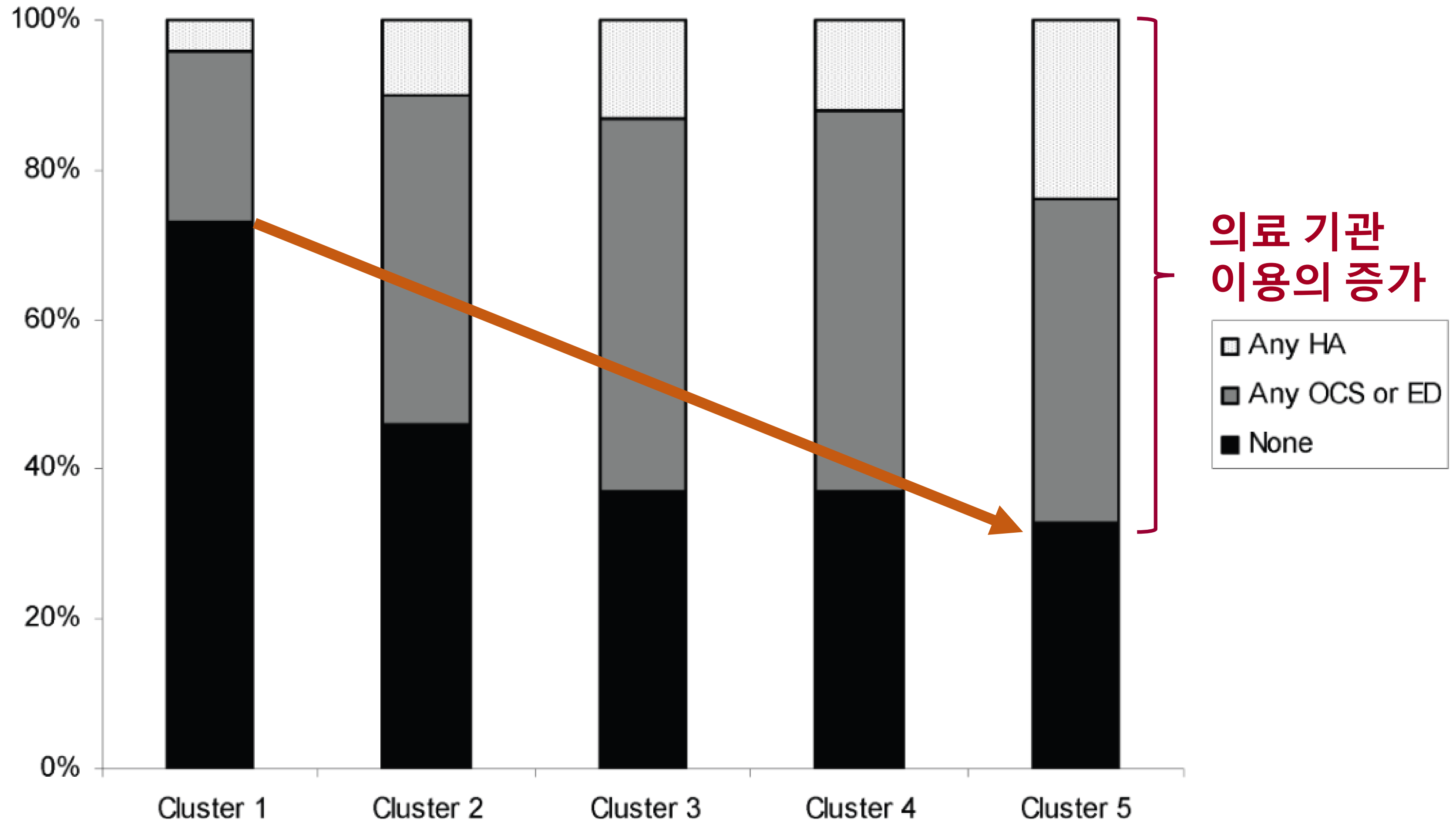
Wendy Moore et al, Am J Respir Crit Care, 2010:181:315

PFT and HCU according to clusters (phenotypes)



Wendy Moore et al, Am J Respir Crit Care, 2010:181:315

다른 천식 코호트에 적용 (재현성 평가)



Application of SARP algorithm to an urban population (NY), non-smoker

PLOS ONE, 2012:7(9):e44540

Phenotypes of adult-onset asthma from Amsterdam

: age of onset > 18 yr, n=200, mild~severe, mean age: 54

- female (60.5%)
- non-atopic (55%)
- Smoker (> 10 PY) 포함
- **Severe (38.5%)**
- **2차/3차 병원**

Using Ward's and K-means cluster analysis
35 variables including sputum eosinophilia

Inflammation-guided Mx가 Sx-guided Mx 보다 더 중요할 듯

- **Severe eosinophilic inflammation-predominant (34.5%)**
  - **Persistent airflow limitation**, F (71%), 중등도 이상의 ICS,
  - AE > 3/yr (29%), **폐기능에 비해 상대적으로 적은 Sx**

- **Frequent Sx, High HCU and low sputum eosinophils (20.5%)**
  - **Obese women** (BMI 30.4), 고용량 ICS, AE > 3/yr (53.7%), GERD (++)
  - **폐기능 정도에 비해 잦은 증상발현**, **low sputum eosinophils**

- **Mild to moderate, well-controlled (45%)**
  - M (52%), **low sputum eosinophils**, low Sx score, normal lung fx

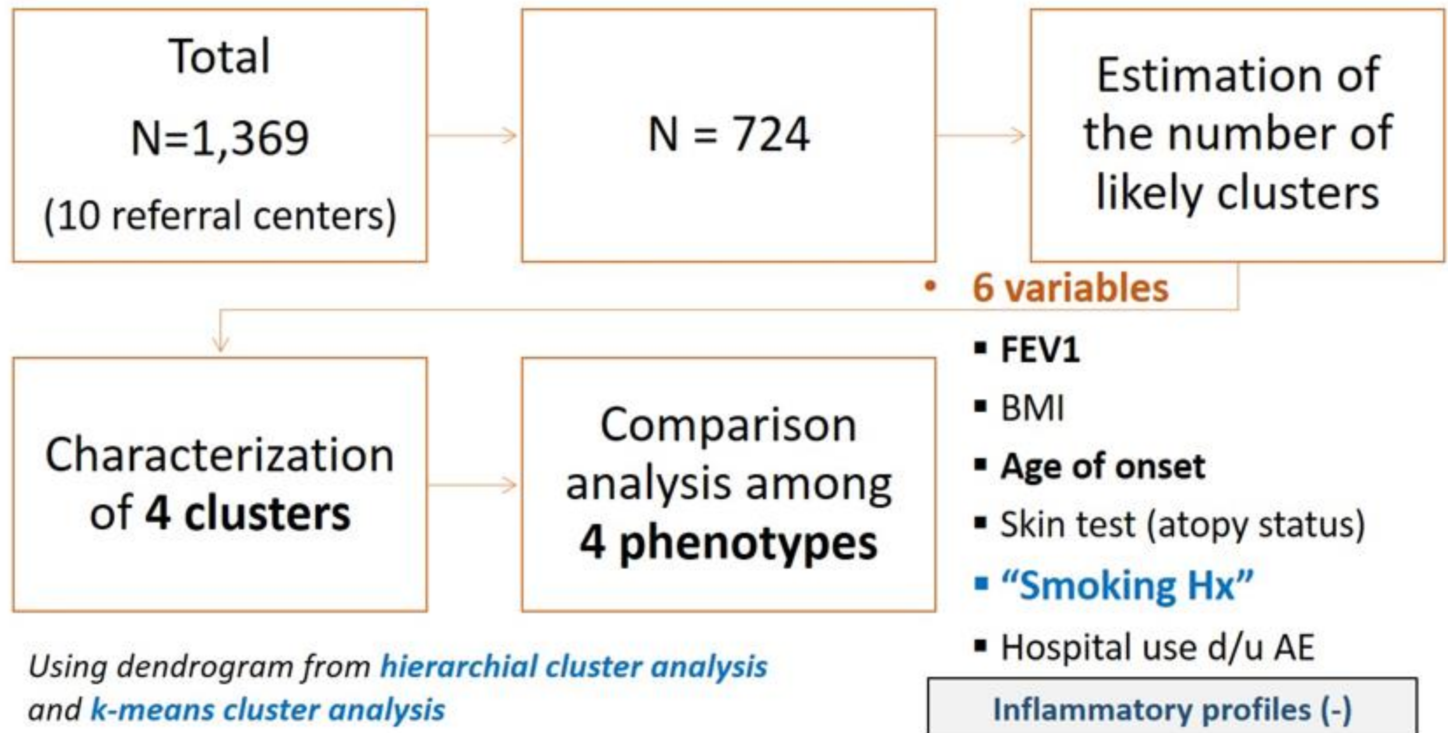
Allergy, 2013:68(5):674

Phenotypes observed commonly from western cohorts

- 다양한 중증도의 early-onset, atopic/allergic phenotype
- 중등도 이상의 late-onset, non-atopic, F > M obesity-related phenotype (잦은 증상이 특징)
- Later-onset/more severe → less atopic
- Discordant phenotypes btw Sx, PFT and/or inflammation

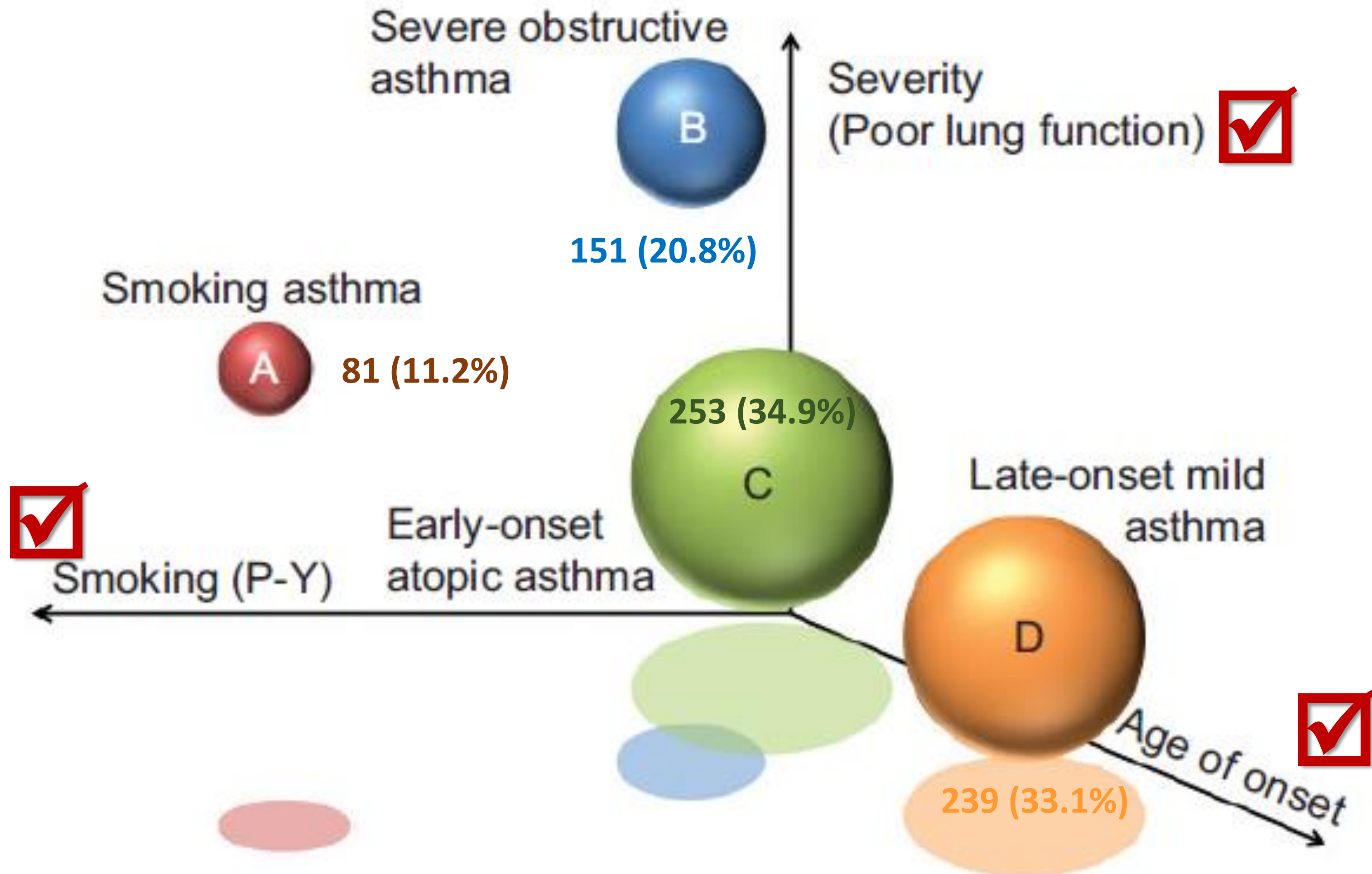
Identification of asthma clusters in two independent Korean adult asthma cohorts

Tae-Bum Kim*,¶¶, An-Soo Jang#,¶¶, Hyouk-Soo Kwon*, Jong-Sook Park#, Yoon-Seok Chang¶, Sang-Heon Cho¶, Byoung Whui Choi+, Jung-Won Park§, Dong-Ho Namƒ, Ho-Joo Yoon**, Young-Joo Cho##, Hee-Bom Moon*, You Sook Cho* and Choon-Sik Park#,¶¶ for the COREA Study Group



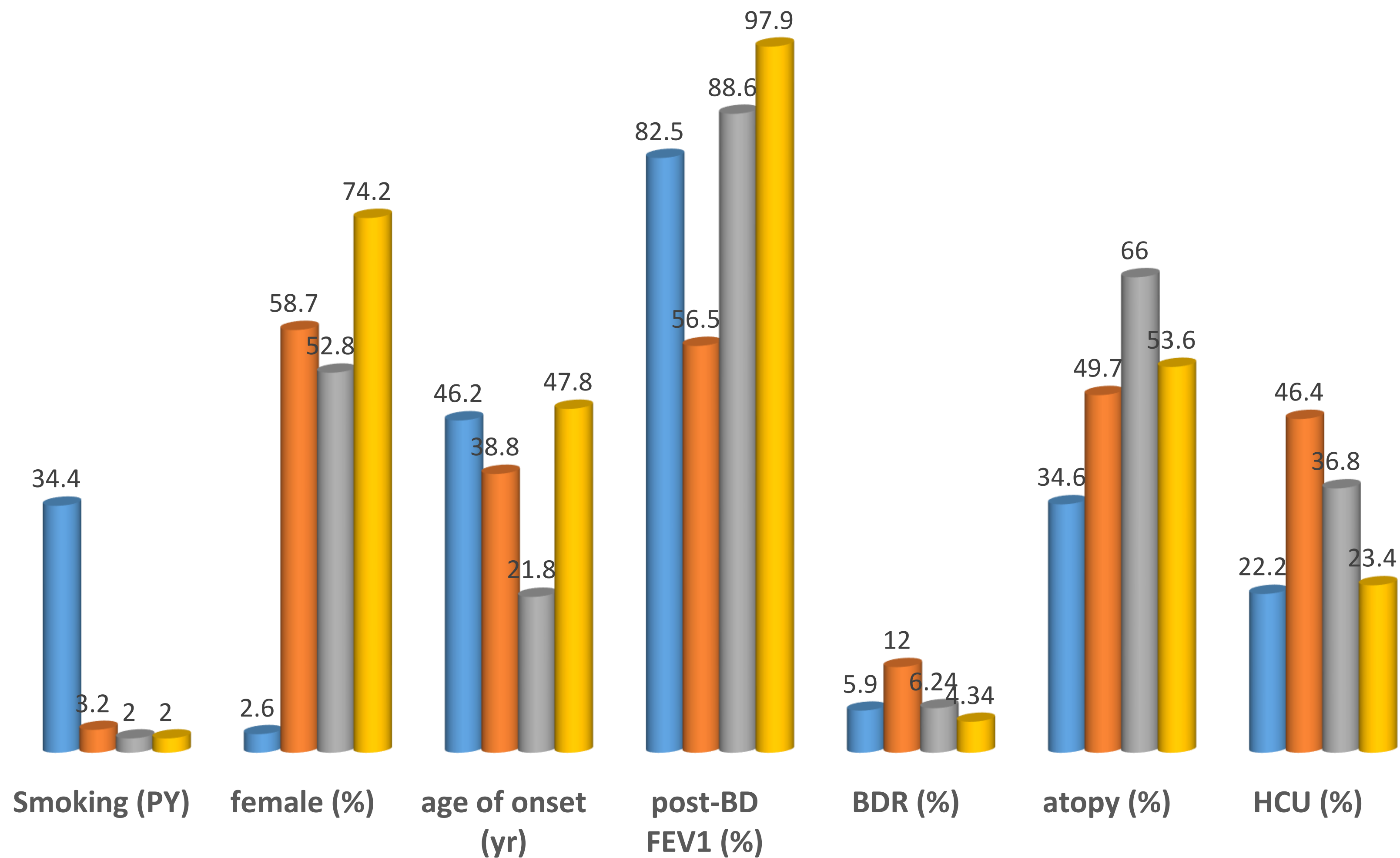
Eur Respir J, 2013:41:1308

4 distinct clinical phenotypes
(COREA cohort, mild to severe)



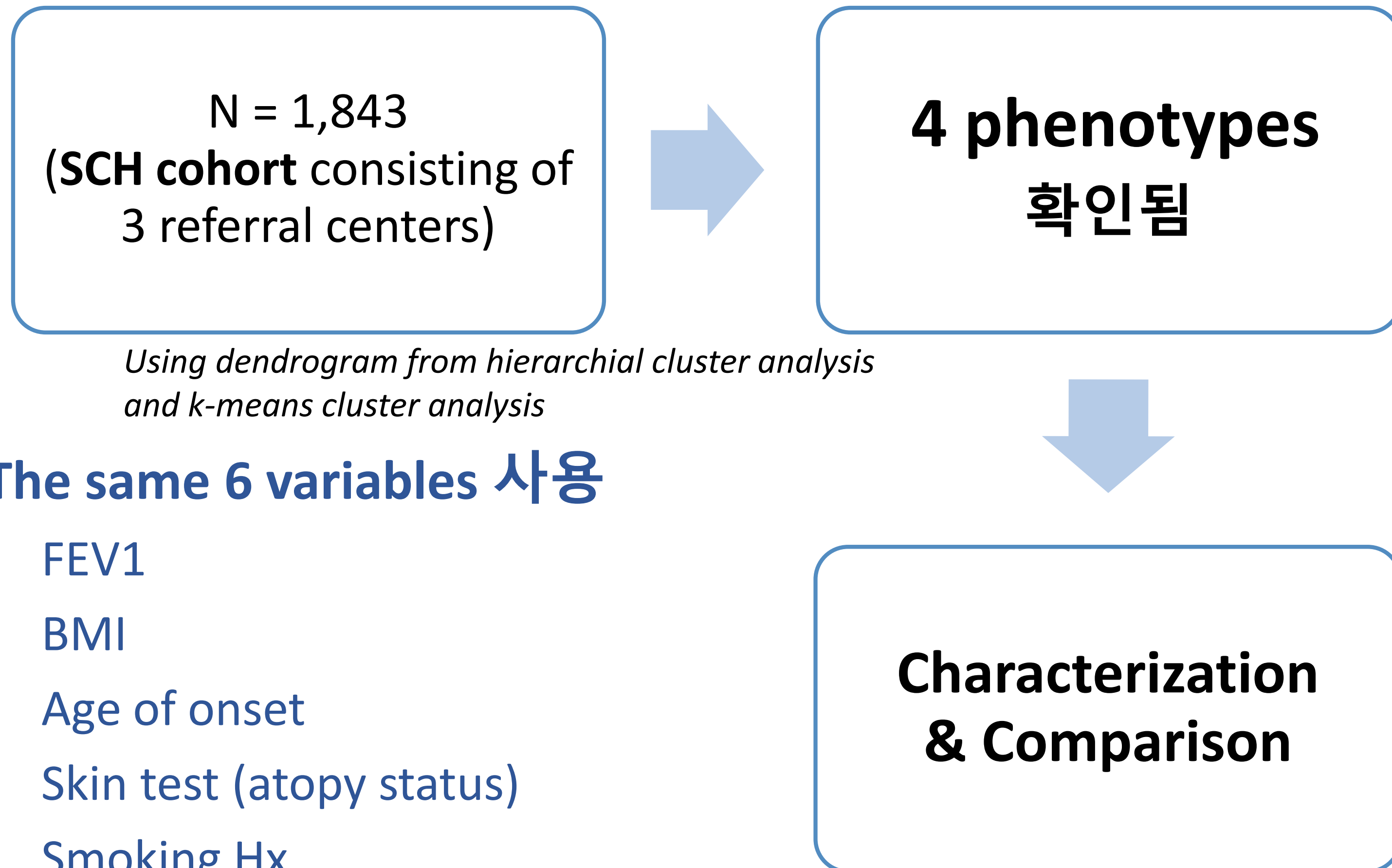
Eur Respir J 2013:41:1308

Comparison among phenotypes from COREA cohort



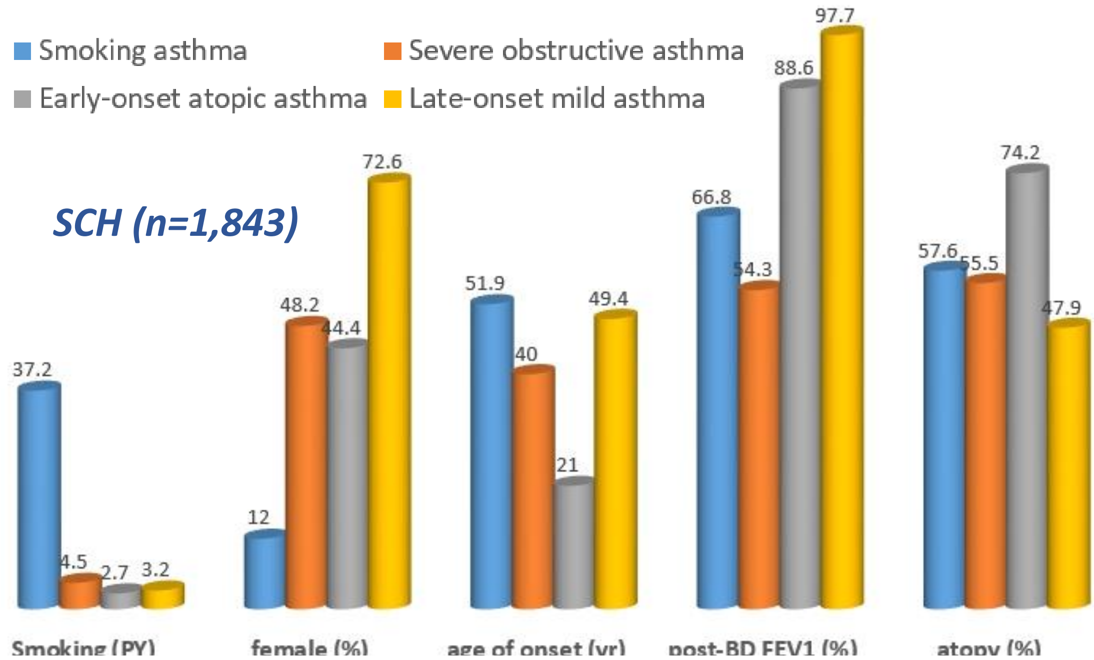
Eur Respir J 2013:41:1308

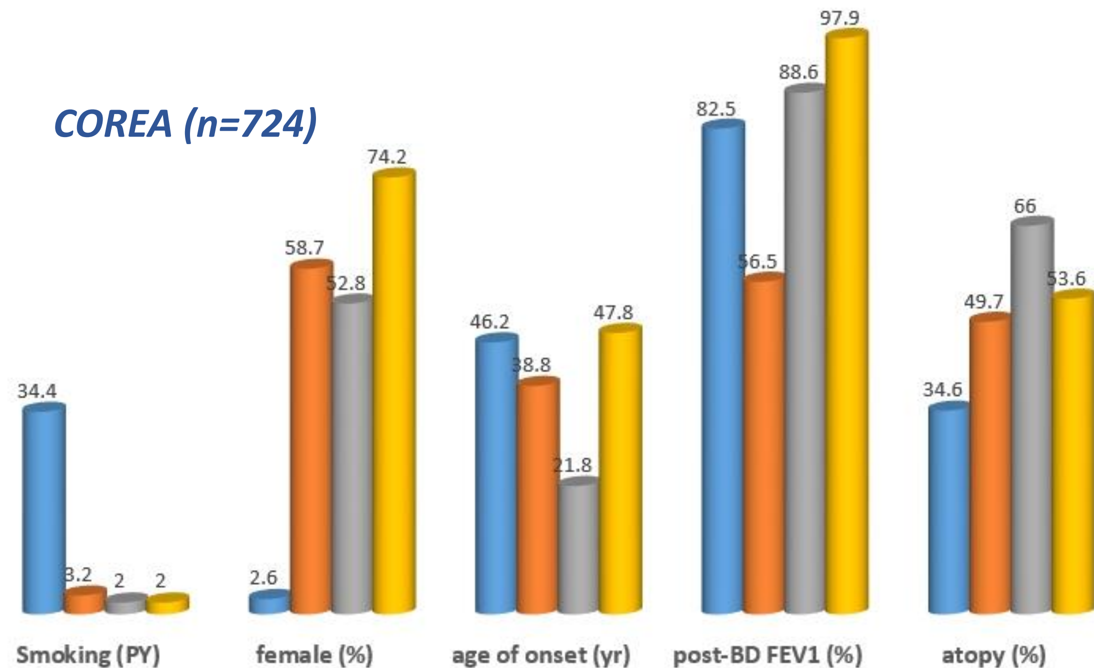
재현성 평가 (SCH cohort 에 적용)



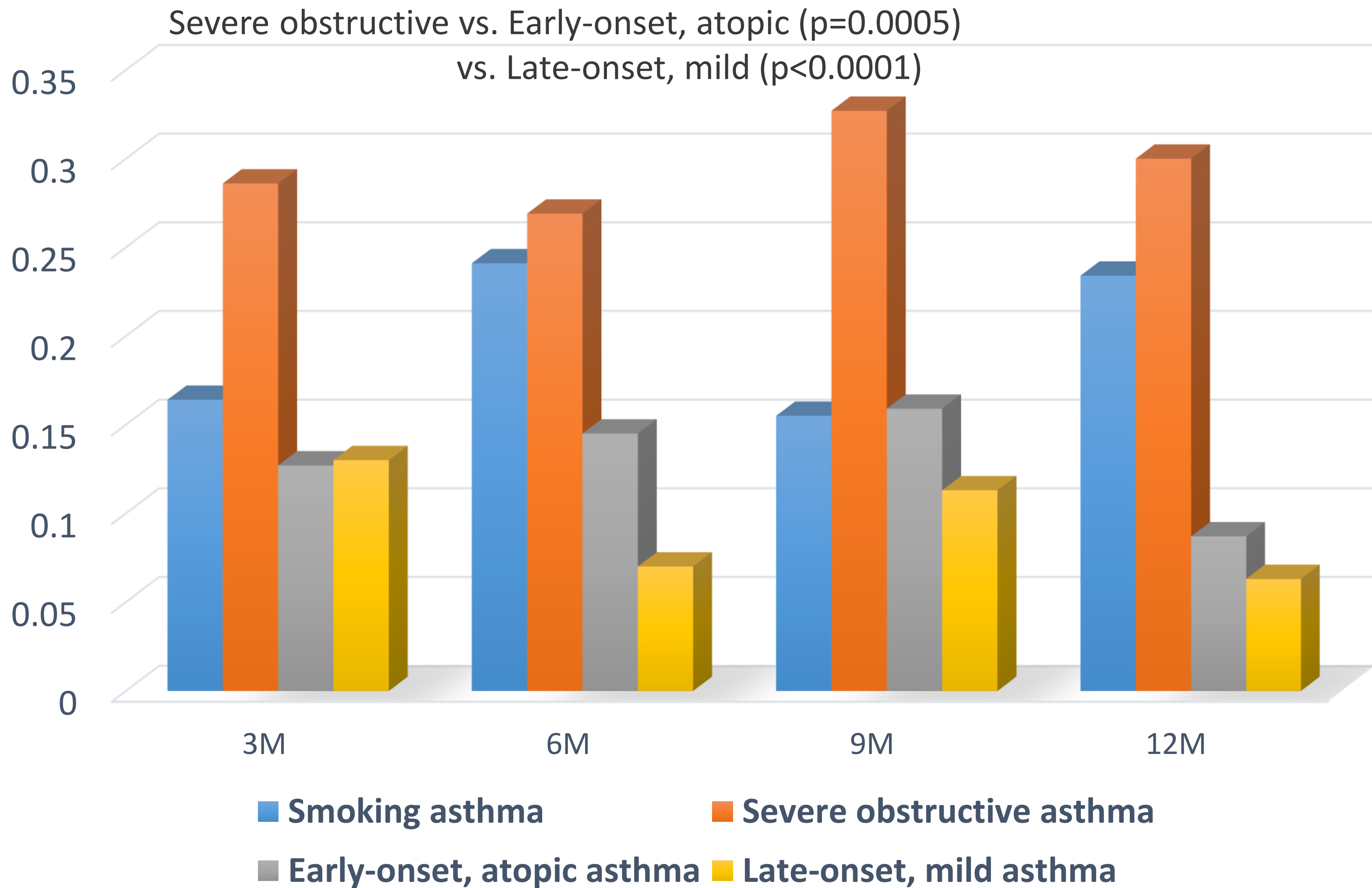
Ann Allergy Asthma Immunol, 2009:103:311
Eur Respir J, 2013:41:1308

COREA cohort	SCH cohort
A smoking asthma (11.2%)	A' (11.8%)
B severe obstructive asthma (20.8%)	B' (25.9%)
C early-onset atopic asthma (34.9%)	C' (31.8%)
D late-onset mild asthma (33.1%)	D' (30.5%)





% of systemic CS use during 12-month FU



PLOS One 2013:8(12):e83540

BTS Severe Refractory Asthma Registry (n=349)

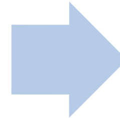
	Cluster 1 (117, 34%)	Cluster 2 (72, 21%)	Cluster 3 (52, 15%)	Cluster 4 (54, 15%)	Cluster 5 (54, 15%)
Age (yr)	40	47	43	49	50
Age of onset	13	39	27	40	25
BMI	27.9	36	27	26.3	28
Pack-year	4	12	10	17.5	15
Atopy (%)	68.7	61.1	44.2	53.7	50.9
Bl. eos. no.	280	320	200	870	210
IgE	322	151	162	638	267
Pre-FEV1/FVC	58.1	72.5	76.6	57.5	53.7
Pre-FEV1(%)	58.8	77	88.4	58.8	52.8
BDR (%)	24.8	12.9	11.3	19.2	18.8
Admission (%)	31.8	16.7	7.7	9.6	9.4
	Early-onset Atopic	**Late-onset Obese**	**Discordant btw Sx and Inflam/PFT**	**Late-onset Eosinophilics short-duration**	**Non-eos, long-duration marked fixed airflow obs**

PLOS ONE, 2014:9(7):e102987

Identification of Subtypes of Refractory Asthma in Korean Patients by Cluster Analysis

An Soo Jang · Hyouk-Soo Kwon · You Sook Cho · Yun Jeong Bae · Tae Bum Kim · Jong Sook Park · Sung Woo Park · Soo-Taek Uh · Jae-Sung Choi · Yong-Hoon Kim · Hyeon-Kyu Hwang · Hee-Bom Moon · Choon Sik Park

2,187 from Korean asthma cohort (SCH cohort)



86 with refractory asthma

Hierarchial cluster analysis & *k*-means cluster analysis

- **5 variables**
  - FEV1/FVC ratio
  - BMI
  - Age of onset
  - Smoking amount
  - PC20 of methacholine

- Female : 61.6%
- **BMI : 23.3**
- Age of onset: 39.9
- **Less atopic (42%)**
- **Smoker/ex-smoker (39%)**
- **FEV1/FVC = 63.8 (%)**
- **FEV1 = 62.1(%)**
- Blood eos % (5.9%)

Lung, 2013:191:87

Long duration severe obstruction

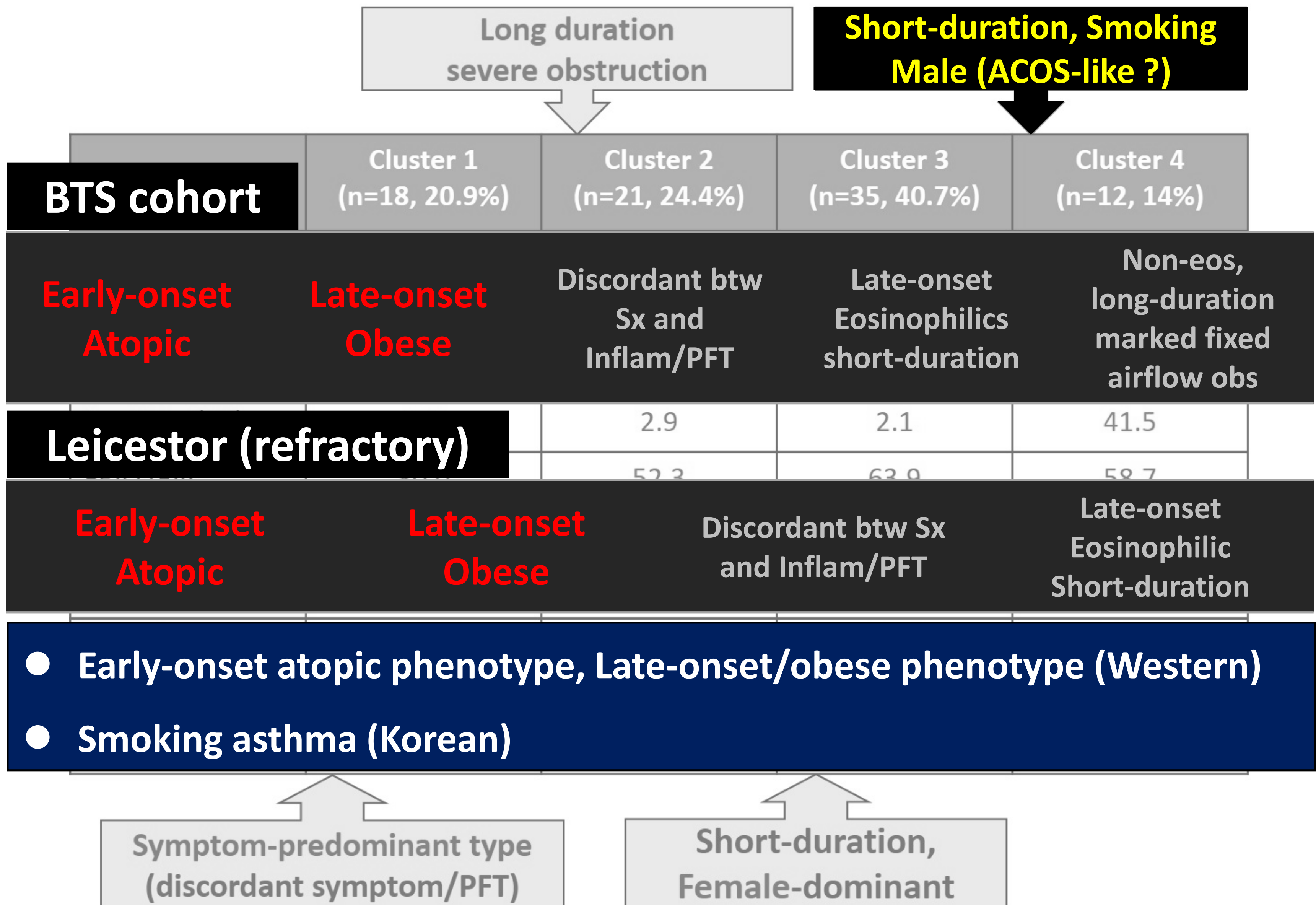
Short-duration, Smoking Male (ACOS-like ?)

	Cluster 1 (18, 20.9%)	Cluster 2 (21, 24.4%)	Cluster 3 (35, 40.7%)	Cluster 4 (12, 14%)
% Female	50	62	80	25
Age of onset	25.2	24.1	51.9	54.4
Sx duration (yr)	13.3	24.4	5.5	5.5
Smoking (PY)	5.0	2.9	2.1	41.5
FEV1/FVC	80.0	52.3	63.9	58.7
FEV1(% pred)	79.5	48.6	61.4	61.5
PC20 (mg/mL)	7.0	4.2	2.6	5.7
Atopy (%)	55.5	33.3	37.1	41.6
객담 호산구(%)	18.6	7.9	11.2	18.1
객담 중성구(%)	49.1	64.6	55.0	48.5

Symptom-predominant type (discordant symptom/PFT)

Short-duration, Female-dominant

Lung, 2013:191:87



PLOS ONE, 2014:9(7):e102987
Lung, 2013:191:87

Classification and implementation of asthma phenotypes in elderly patients

Heung-Woo Park, MD [*,†]; Woo-Jung Song, MD [*,†]; Sae-Hoon Kim, MD [‡]; Hye-Kyung Park, MD [§]; Sang-Heon Kim, MD [||]; Yong Eun Kwon, MD [¶]; Hyouk-Soo Kwon, MD [#]; Tae-Bum Kim, MD [#]; Yoon-Seok Chang, MD [‡]; You-Sook Cho, MD [#]; Byung-Jae Lee, MD [**]; Young-Koo Jee, MD [††]; An-Soo Jang, MD [‡‡]; Dong-Ho Nahm, MD [§§]; Jung-Won Park, MD [||||]; Ho Joo Yoon, MD [||]; Young-Joo Cho, MD [¶¶]; Byoung Whui Choi, MD [##]; Hee-Bom Moon, MD [#]; and Sang-Heon Cho, MD [*,†]

N=872 (> 65세), 9 centers in Korea, since 2009 : cluster analysis

Variables

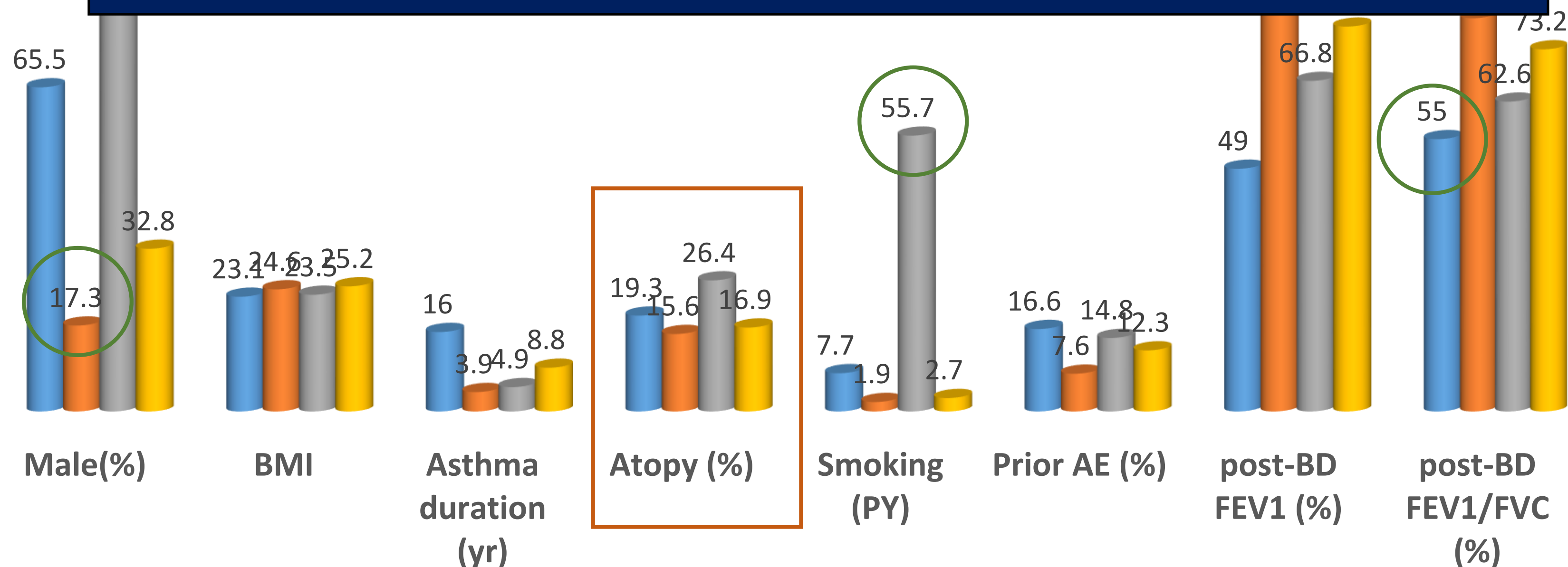
- Demographic factors
- Asthma Sx duration
- BMI
- **Smoking Hx**
- Atopy
- Presence of chronic sinusitis
- Hx of previous AE
- Post-BD lung function
- Assessment of congitivs Fx and depression

Ann Allergy Asthma Immunol, 2015:114:18

Comparison among phenotypes from elderly cohort

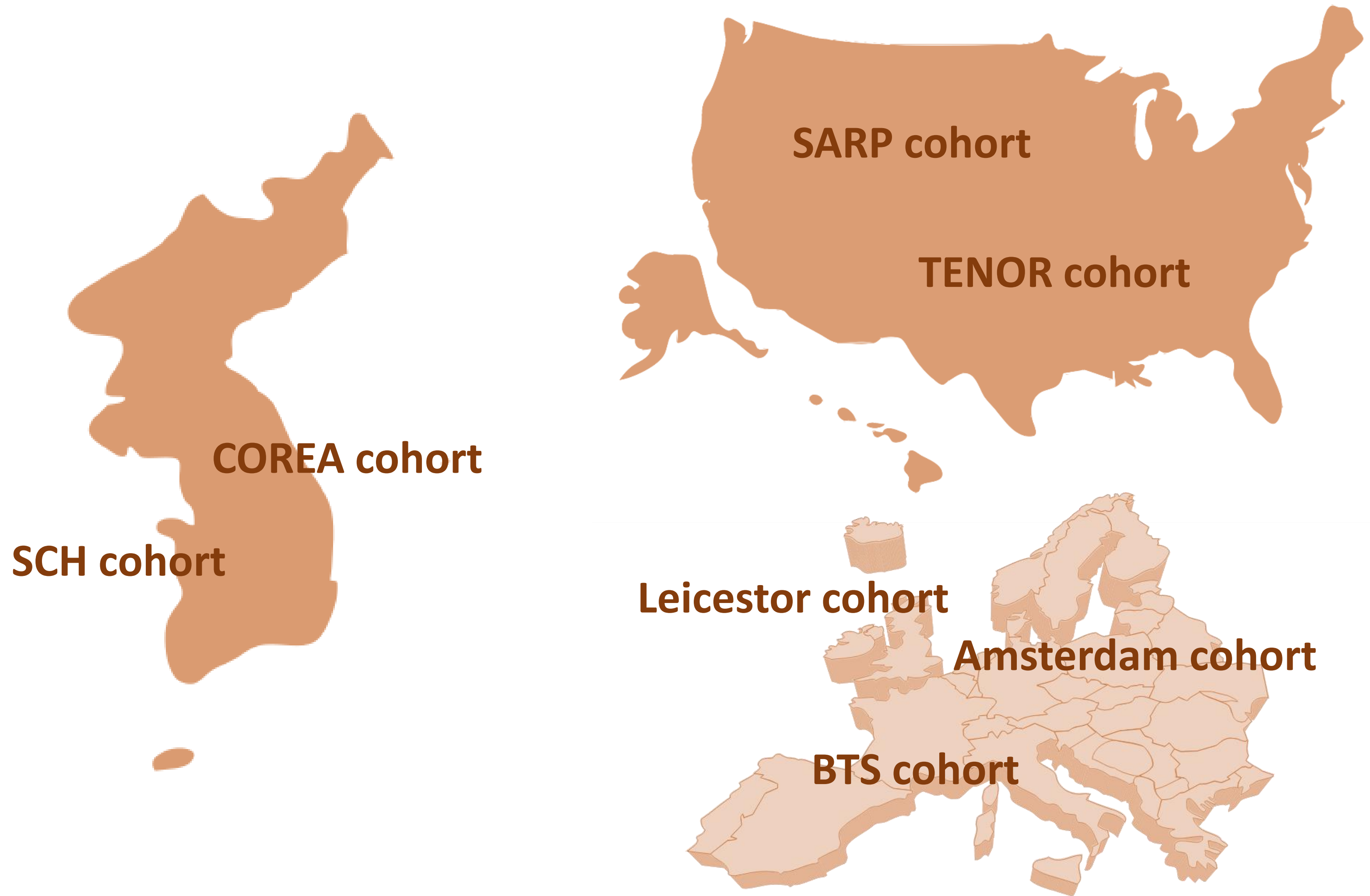
- Long duration and marked airway obstruction (n=145)
- Female dominance and normal lung function (n=237)
- Smoking male dominance and reduced lung function (n=182)
- High BMI and borderline lung function (n=308)

- Early-onset atopic phenotype, Late-onset/obese phenotype (Western)
- Smoking asthma (Korean)



Ann Allergy Asthma Immunol, 2015:114:18

Several differences… Why?



비만
(obesity)

Sex Hormonal change
(남<녀)

Oxidative stress,
systemic inflammation 증가 (IL-6, CRP 등)

동반질환 (GERD, OSA)

Non-Th2 inflammation

Adipokines 의 변화
(adiponectin 감소, leptin 증가)

기계적 요소
(ERV, FRC, FVC, FEV1 감소)

천식
(asthma)

- 스테로이드에 대한 낮은 반응
- 중증 천식 환자의 비중이 높음
- Less-atopic/non-eosinophilic
- **Weight reduction 고려 or 다른 치료?**

Respir Med, 2013:107:1287
Annals ATS, 2013:10:S138

Diseases Concomitant With Asthma in Middle-Aged and Elderly Subjects in Korea: A Population-Based Study

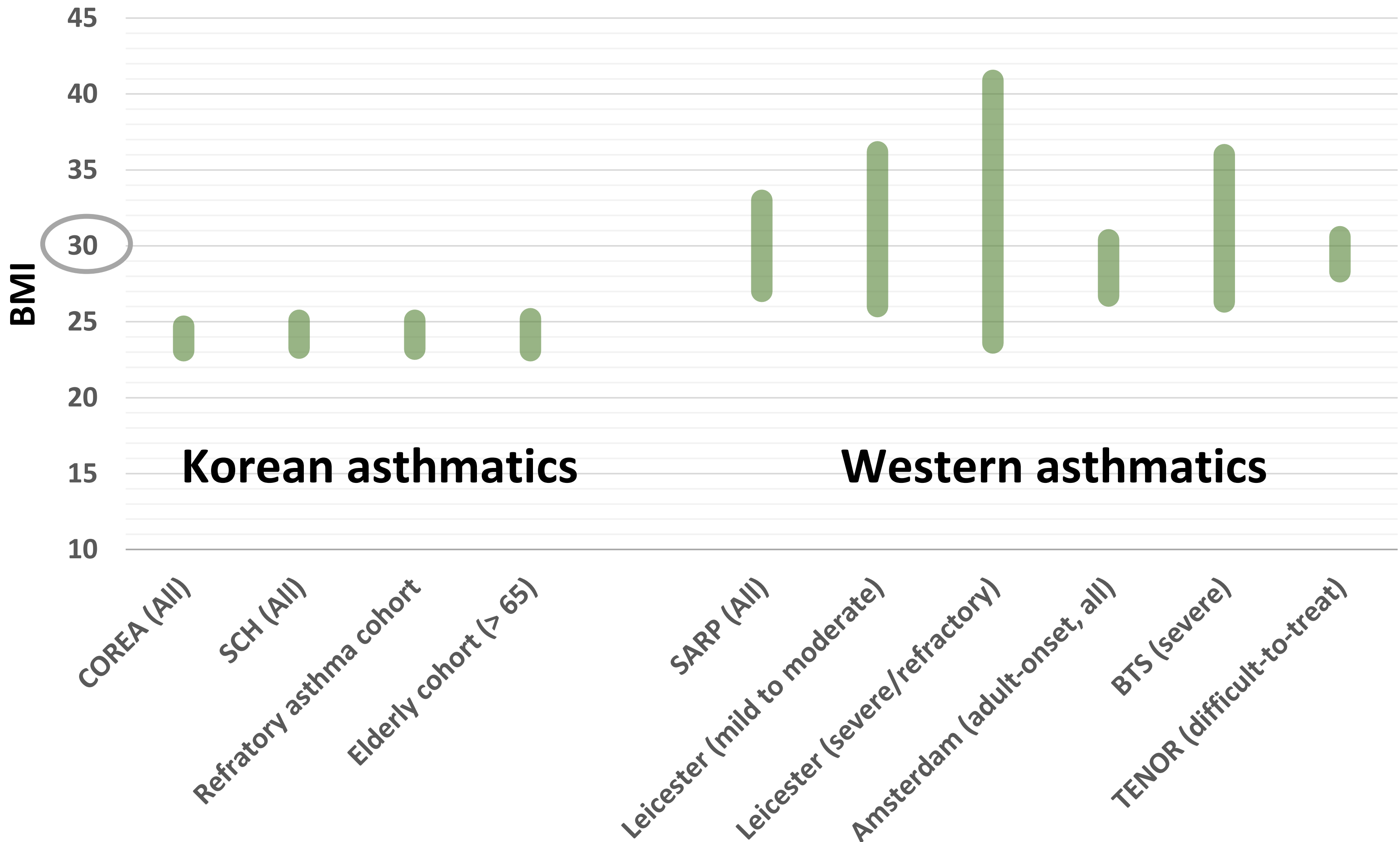
Jinkyeong Park,[1] Tae-Bum Kim,[2,4,5] Hyejin Joo,[3] Jae Seoung Lee,[3,4,5] Sang Do Lee,[3,4,5] Yeon-Mok Oh[3,4,5*]

- From 4th Korean National Health and Nutrition Survey database
- 195 (4.4%) with self-reported ever-asthma
- 444 (10%) with history of wheezing

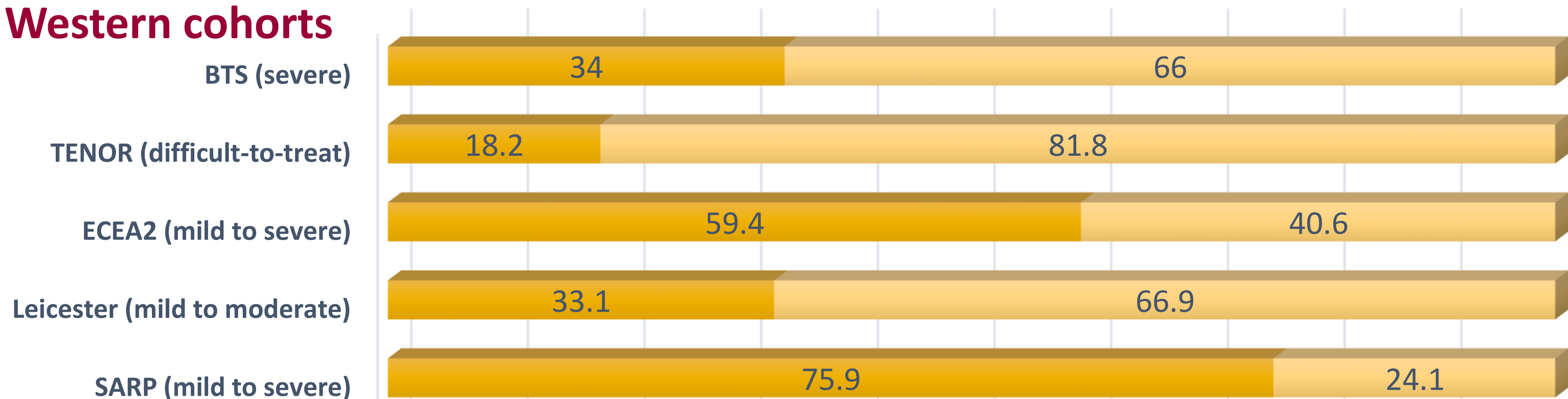
	Self-reported ever-asthma	Wheezer
Obesity	OR 1.61 (95% CI: 1.08 ~ 2.40)	OR 1.56 (95% CI: 1.17 ~ 2.09)

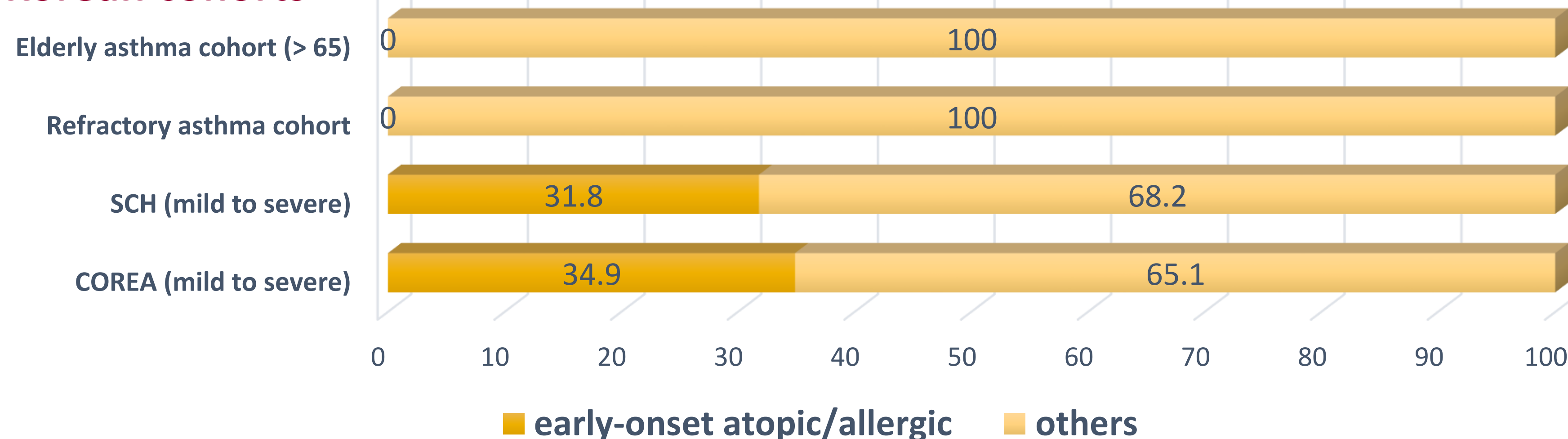
Allergy Asthma Immunol Res, 2013:5(1):16

There was a distinct obesity-asthma phenotype only in western populations

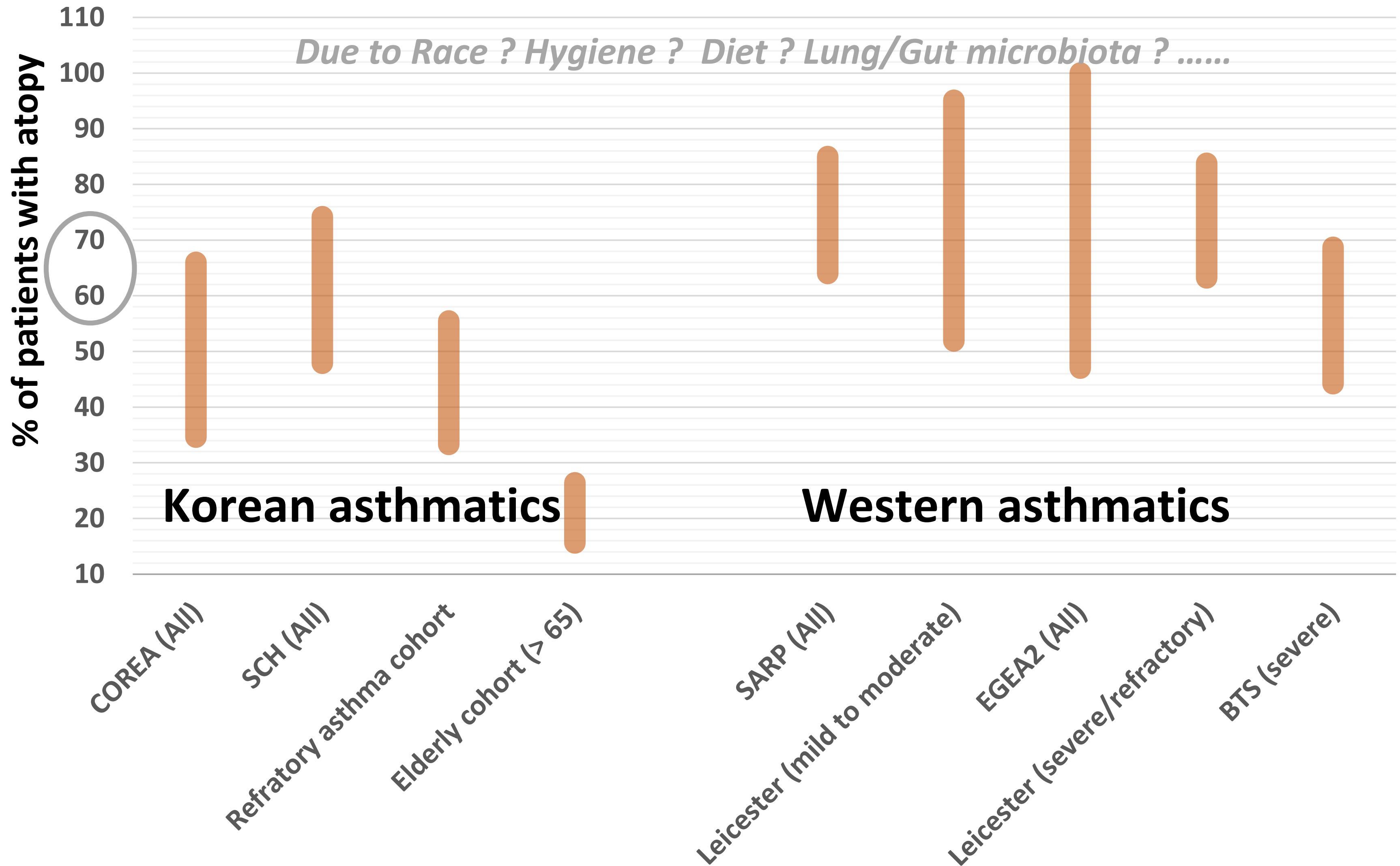


The proportion of the early-onset atopic/allergic phenotype in Korean and Western cohorts





Lower rate of patients with atopy in Korean cohorts



Smoking and incidence of asthma

Black women's Health Study. US
(from 1995 to 2001, 1,523/46,182)

Smoking Status	Cases	Person-Years	Basic Model (Age and Questionnaire Cycle) [*HR (95% CI)*]	Multivariable Model [*HR (95% CI)*]*
Never active or passive	142	84,071	1.0	1.0
Passive only	677	284,103	1.36 (1.13–1.63)	1.21 (1.00–1.45)
Exposed before age 20 only	225	105,193	1.26 (1.02–1.56)	1.17 (0.94–1.45)
Exposed at age 20 or older only	180	72,745	1.39 (1.11–1.74)	1.24 (0.99–1.56)
Exposed before and after 20	272	106,165	1.43 (1.16–1.75)	1.18 (0.96–1.46)
Former smoker	423	139,885	1.71 (1.41–2.08)	1.36 (1.11–1.67)
Current smoker	281	85,741	1.72 (1.40–2.11)	1.43 (1.15–1.77)

Smoker 의 경우, 약 40% 정도 smoking 에 의해 adult-onset asthma의 위험도가 증가
Age > 50세의 women에 위험도가 더 증가

A specific phenotype

Am J Respir Crit Care Med, 2015:191:168

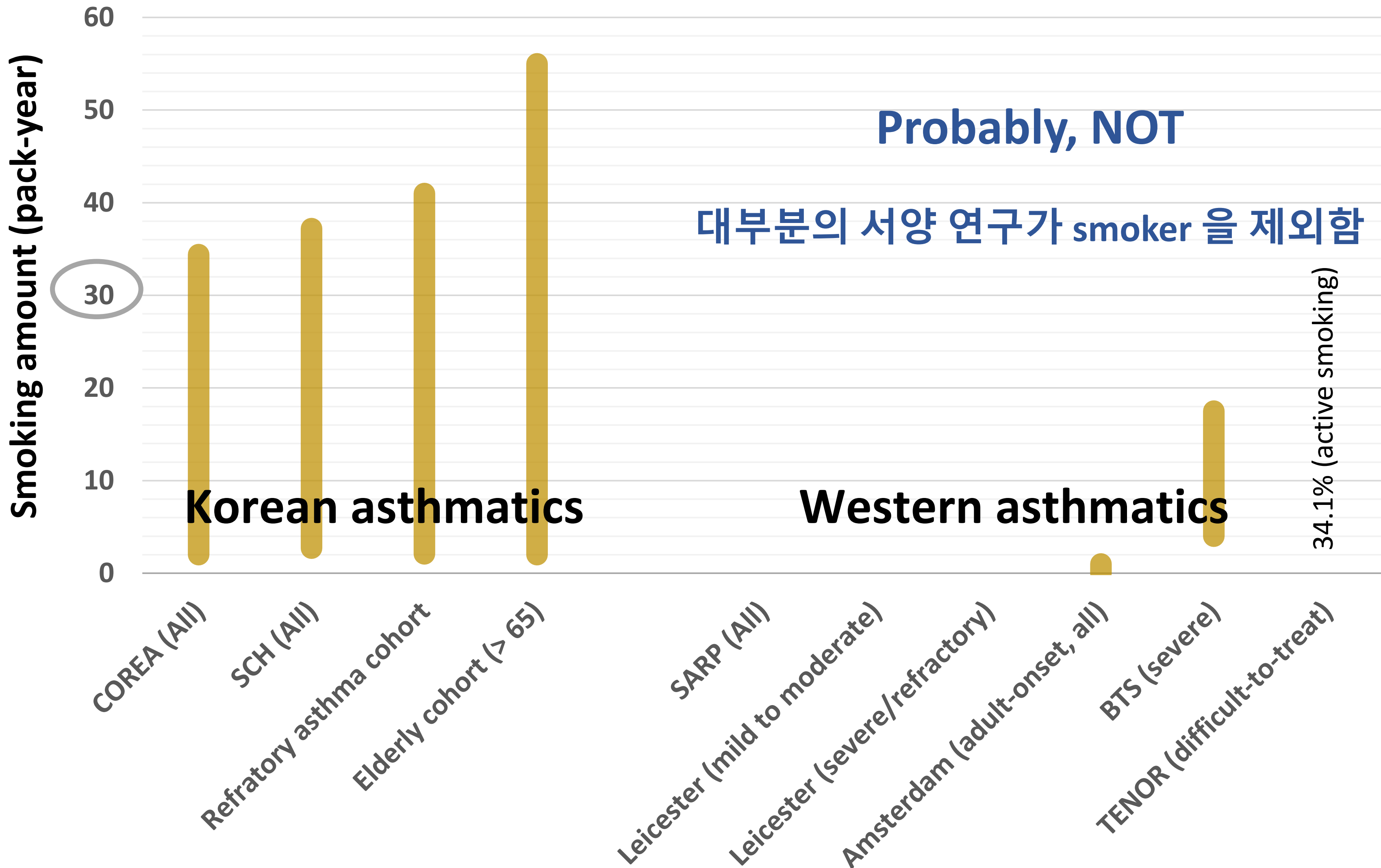
Difference of asthma control days by smoking history

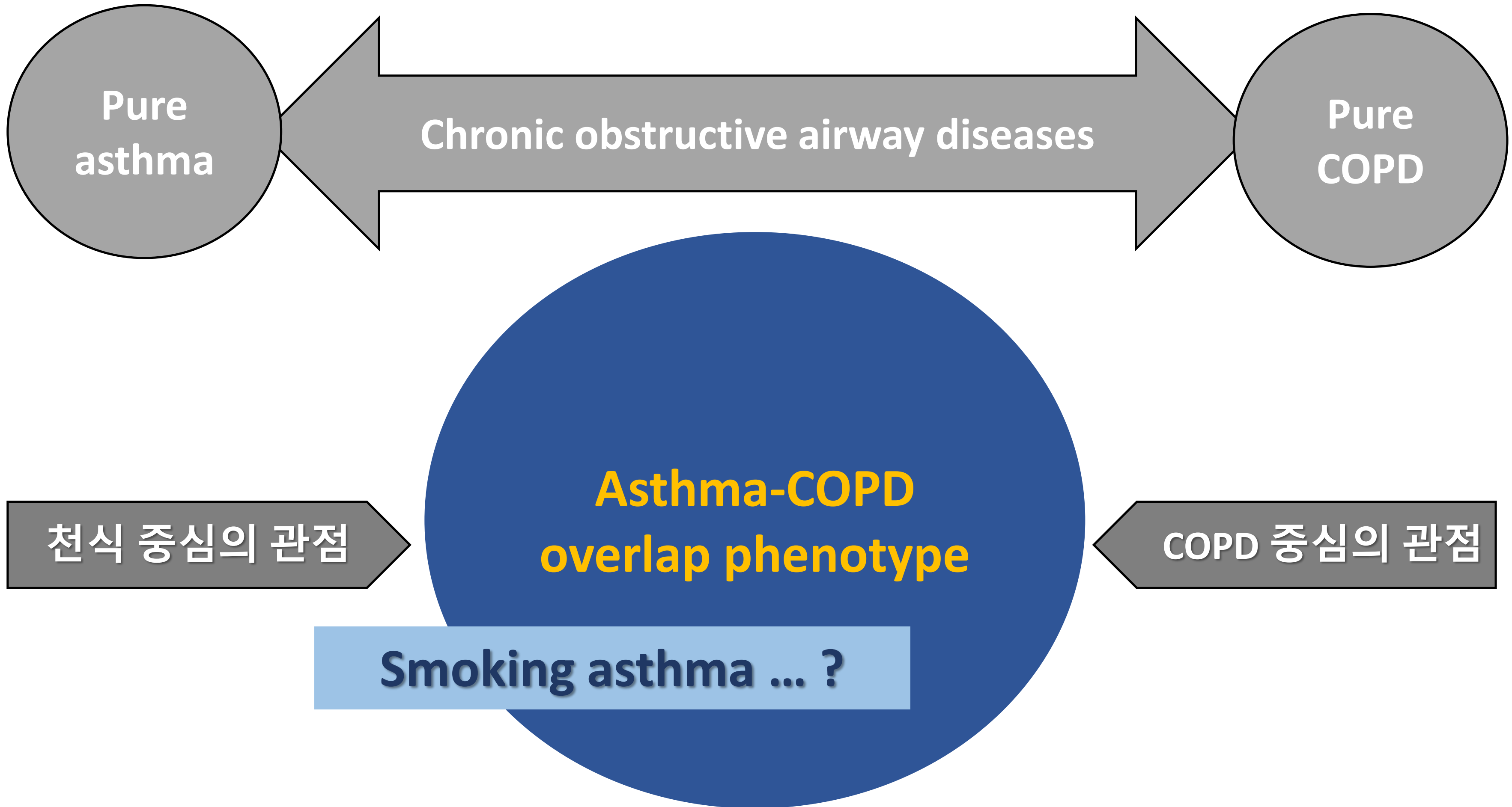
Treatment	No.	Percentage of asthma control days during period II			
		Mean (SD)	LS mean (95% CI)*	Difference in LS mean vs placebo (95% CI)*	Difference in LS mean vs fluticasone (95% CI)*
Smoking history ≤ median (11.4 pack years)					
Montelukast	186	53.37 (37.19)	47.29 (41.57 to 53.01)	3.90 (−3.97 to 11.77)	−10.35 (−18.18 to −2.52)
Fluticasone	155	63.04 (36.77)	57.64 (51.52 to 63.76)	14.25 (6.02 to 22.48)	
Placebo	152	49.13 (38.80)	43.39 (37.14 to 49.64)		
Smoking history > median (11.4 pack years)					
Montelukast	148	47.35 (39.28)	43.24 (37.03 to 49.45)	8.67 (0.59 to 16.74)	2.16 (−5.89 to 10.21)
Fluticasone	174	44.63 (39.10)	41.08 (35.31 to 46.84)	6.51 (−1.24 to 14.25)	
Placebo	171	39.13 (36.90)	34.57 (28.74 to 40.40)		

Smoking 정도에 따라 asthma 조절을 위한 치료제에 대한 반응에 차이(+)

J Allergy Clin Immunol, 2013:131:763

A distinct smoking-asthma phenotype exists only in Korean populations ?





NEJM 2015:373:1241

국내 cluster analysis 의 smoking asthma

Mean	COREA (n=81, 11.2%) (mild to severe)	SCH (n=217, 11.8%) (mild to severe)	Refractory asthma cohort (n=12, 13,9%)	Elderly cohort (age > 65) (n=182, 20.8%)
Male	97.4%	88.0%	75%	96.2%
Age of onset	**46.2세**	**51.9세**	**54.4세**	NA
Sx duration	NA	NA	**5.5년**	**3.9년**
Smoking (갑년)	**34.4**	**37.2**	**41.5**	**55.7**
BMI	24.7	24.8	25.4	23.2
Atopy	**34.6%**	57.6%	**41.6%**	**15.6%**
Post-BD FEV1(%)	82.5	66.75	61.5	66.8
Post-BD FEV/FVC	71.44	**64.8**	**58.7**	**62.6**
AE in the past year	NA	NA	NA	14.8%

Asthma-COPD overlap with late-onset asthma…?

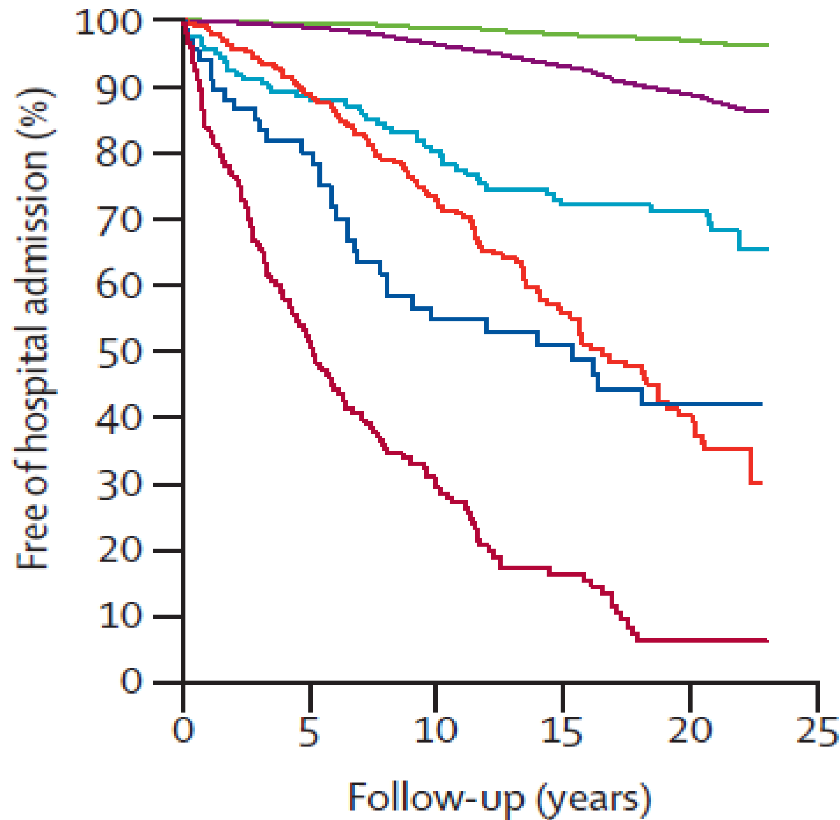
Asthma-COPD overlap with late asthma onset 군의 급격한 폐기능의 감소

	Decline in FEV_1, in mL per year	p value	p value	p value	p value
Healthy never-smokers	20·9 (1·2)	Reference	0·15	<0·0001	0·19
Ever-smokers without asthma or COPD	20·7 (1·4)	0·88	0·13	<0·0001	0·17
Asthma	25·6 (3·3)	0·15	Reference	0·0003	0·77
COPD	39·5 (2·5)	<0·0001	0·0003	Reference	0·02
ACO with early asthma onset	27·3 (5·0)	0·19	0·77	0·02	Reference
ACO with late asthma onset	49·6 (3·0)	<0·0001	<0·0001	0·003	0·0001
Male sex (reference: female sex)	4·8 (1·2)	<0·0001	..	..	..

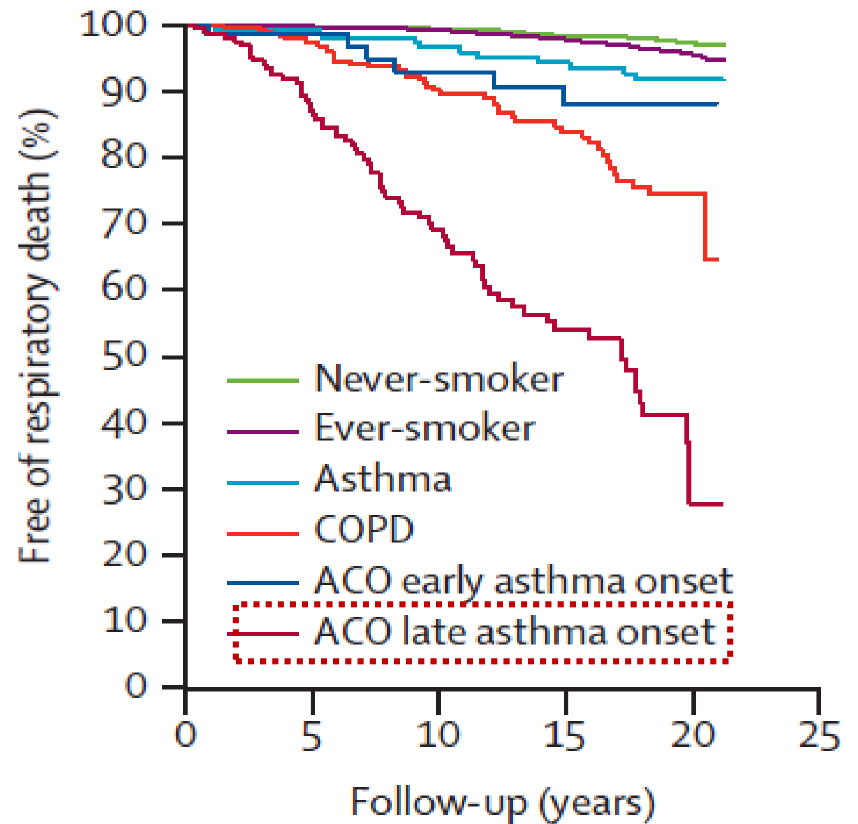
From Copenhagen City Heart Study
Age criteria (early vs. late) : 40 years

Lancet Respir Med, 2016:4:454

급성악화로 인한 입원



호흡기관련 사망



Lancet Respir Med, 2016:4:454

	ACO with early asthma onset (n=68)	ACO with late asthma onset (n=202)
Male sex	31 (46%)	106 (52%)
Age (years)	57 (14)	68 (8)
FEV_1		
Mean (L)	1·79 (0·94)	1·29 (0·58)
% of predicted value	58 (22)	51 (19)
FEV_1 to FVC ratio (%)	58 (9)	54 (10)
Change in FEV_1 after bronchodilator (mL)	65 (–57 to 163)	70 (–15 to 140)
Body-mass index (kg/m²)	25 (4)	25 (4)
High-sensitivity C-reactive protein concentration ≥3 mg/L	24/58 (41%)	88/175 (50%)
Chronic bronchitis	33/68 (49%)	102/199 (51%)
Wheezing	63/68 (93%)	165/199 (83%)
Night-time respiratory symptoms	32/68 (47%)	72/199 (36%)
mMRC dyspnoea scale ≥2	34/68 (50%)	137/200 (69%)
At least five respiratory infections during past 10 years	12/67 (18%)	23/197 (12%)
Medication for airway disease	53/68 (78%)	177/202 (88%)
Frequent episodes of bronchitis in childhood	33/67 (49%)	33/198 (17%)
Asthma, hay fever, or eczema as child	39/68 (57%)	17/197 (9%)
Occupational exposures to dust and fumes	21/68 (31%)	78/199 (39%)
Smoking		
Never	12/68 (18%)	8/200 (4%)
Former	18/68 (26%)	69/200 (35%)
Current	38/68 (56%)	123/200 (62%)
Smoking history (pack-years)	23 (23)	34 (22)

비슷한 폐기능

From Copenhagen City Heart Study

Age criteria (early vs. late) : 40 years

"Smoking asthma" cluster from Korean population 와 유사한 임상적 특징을 갖는다

비슷한 BMI

낮은 아토피 비율

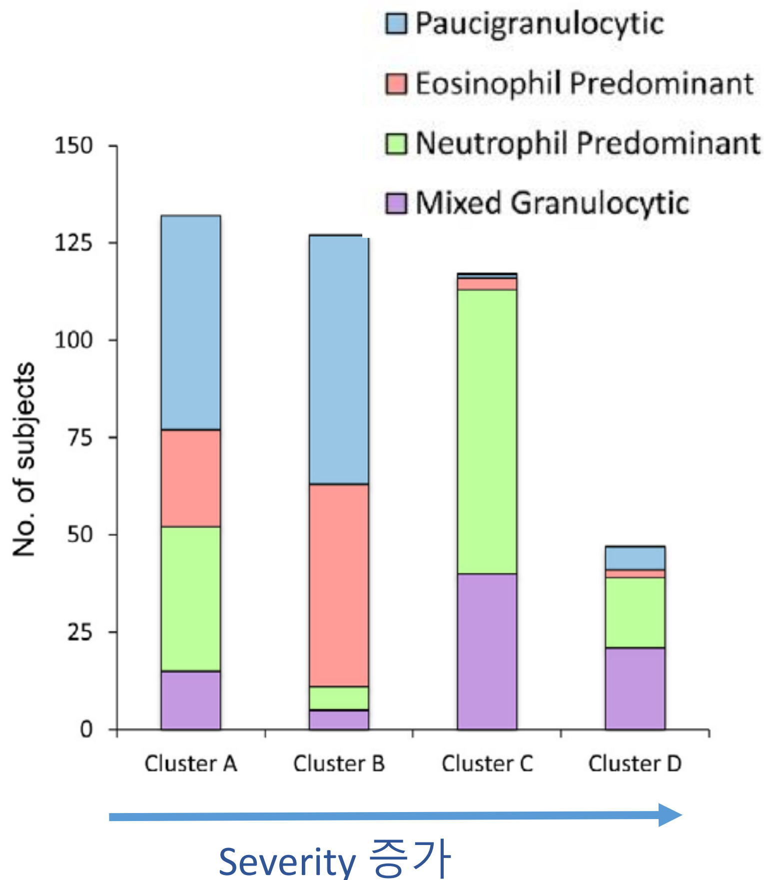
대부분의 환자(97%)가 흡연
평균 30갑년 이상

Lancet Respir Med, 2016:4:454

Study	Early onset asthma 포함	중증도	Study setting	Cluster 분석에 포함된 biomarker와 연관된 변수
Leicestor	Yes	Mild ~ severe	CS + L (1yr)	**Sputum eosinophil**
SARP	Yes	Mild ~ severe	CS	None
Amsterdam	No	Mild ~ severe	CS	**Sputum eosinophil, IgE**
TENOR	Yes	Difficult-to-treat	L (1 yr)	**IgE**
BTS refractory asthma registry	Yes	Severe refractory	L (3 yr)	**Blood eosinophil count, IgE**

국내 연구는 분석변수로 biomarker와 연관된 변수를 이용하지 않았음

Importance of inflammation in clinical phenotyping



	A	B	C	D
age	27	**35**	**42**	50
Female (%)	73	**61**	**62**	43
BMI >30(%)	28	**46**	**50**	57
Late-onset (%)	37	**41**	**52**	60
Pre-FEV1(%)	97	**73**	**76**	47
Post-FEV1(%)	107	**86**	**88**	61
Change in FEV1 (%)	12	**20**	**19**	31
IgE	120	**178**	**135**	118
Aspirin 과민성 (%)	10	**9**	**11**	10
High-dose ICS(%)	16	***26***	***41***	66
Hospitalization(%)	5	***4***	***9***	17

유사해 보이는 B, C 는 다른 inflammatory profiles을 가지며 치료에 대한 반응이 다음

* N=423 (≥12 years), mild to severe, non-smokers
15 Variables including blood and blood eosinophil and neutrophil (%)

Wendy Moore et al, J Allergy Clin Immunol, 2014:133:1557

Wrap up (1)

□ **A statistical, unbiased clustering approach** seems to be standard

□ **In Korean asthma phenotypes,** (compared with western)

유사점	❑ **가장 흔한 early-atopic/allergic phenotype** ❑ **later-onset, more severe phenotype : non-atopic** ❑ **Discordant phenotype btw Sx and inflammation/lung fx**
차이점	❑ **Smoking asthma (+)** : ACO with late-onset asthma ? ❑ **Obesity-related phenotype (-)** ❑ **Lower proportion of early-onset atopic/allergic phenotype**

Wrap up (2)

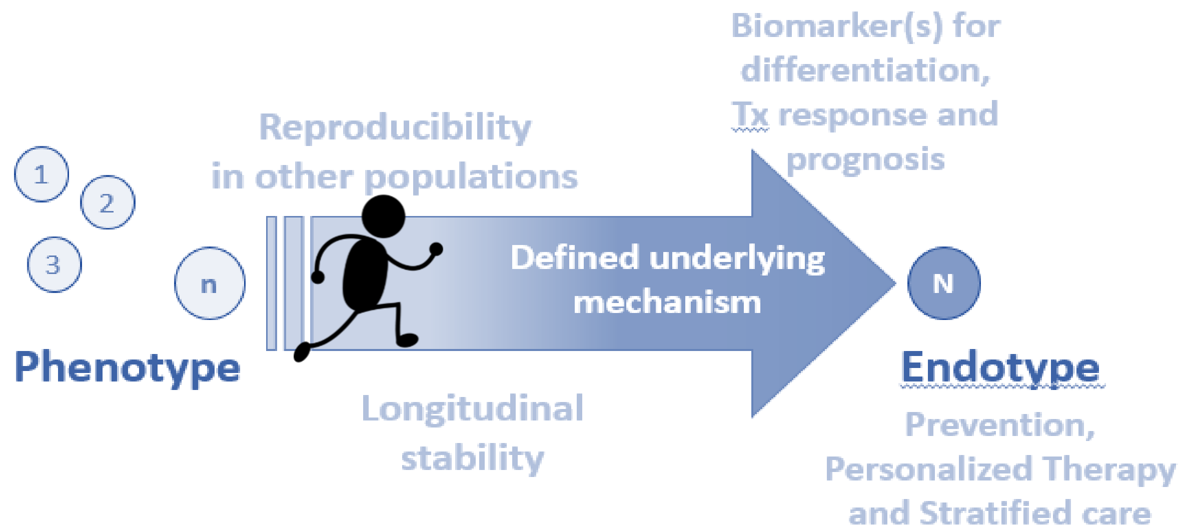
Where are we?

□ We **don't still have a well-established methodology** for phenotyping

- 어떤 임상 변수들을 선택하나? 동일한 가중치갈는가?
- Inflammatory markers/biomarkers 는 무엇으로?

□ **Reproducibility/Stability, Long-term outcomes ?! :** few evidences

□ **Clinical implication of a given phenotype ??** : none



Thank you for your attention