Asthma: Pathogenesis, Risk Factors, and Disease Trajectories

Korea University Guro Hospital
Sang Hyuk Kim

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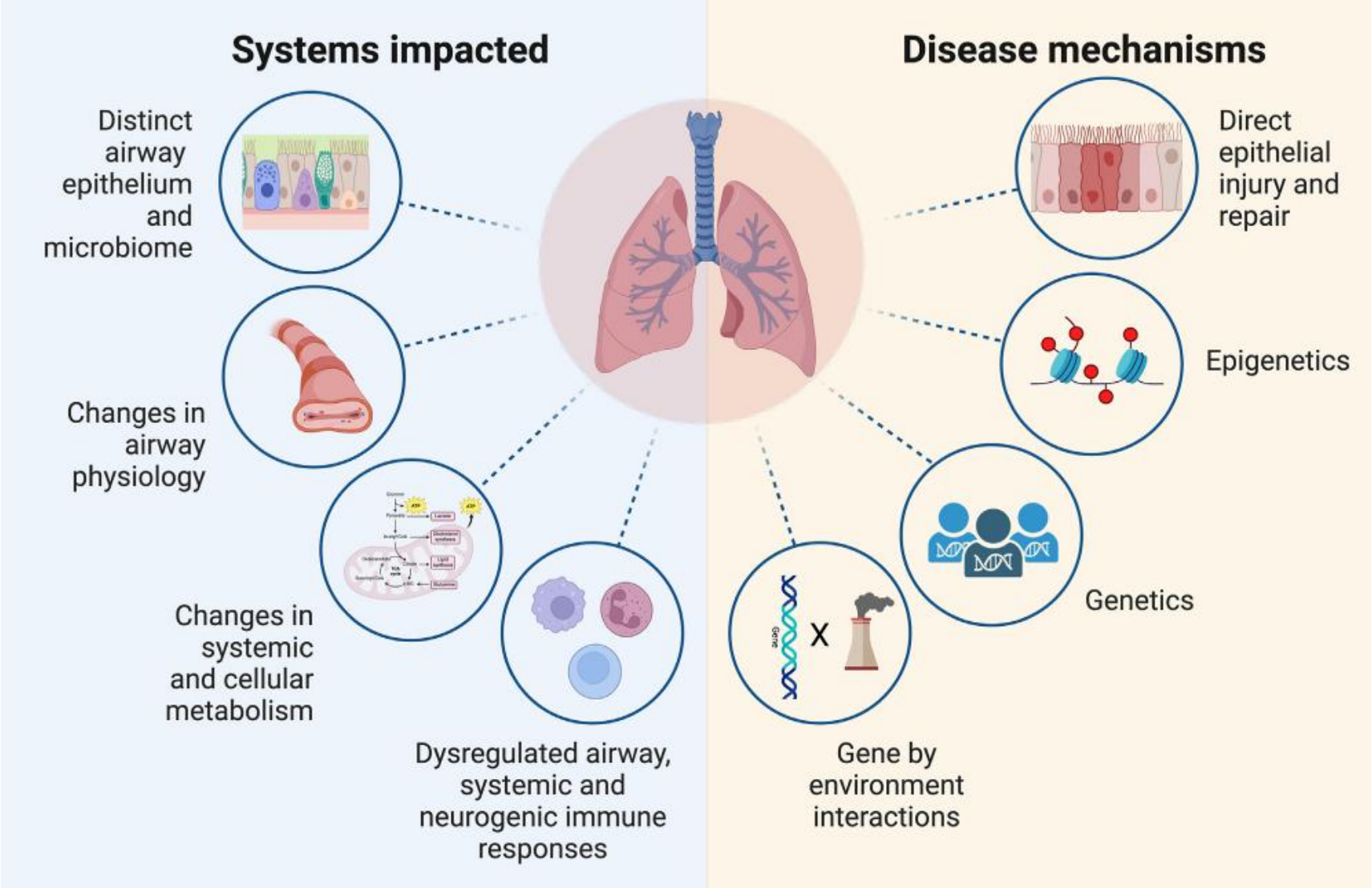
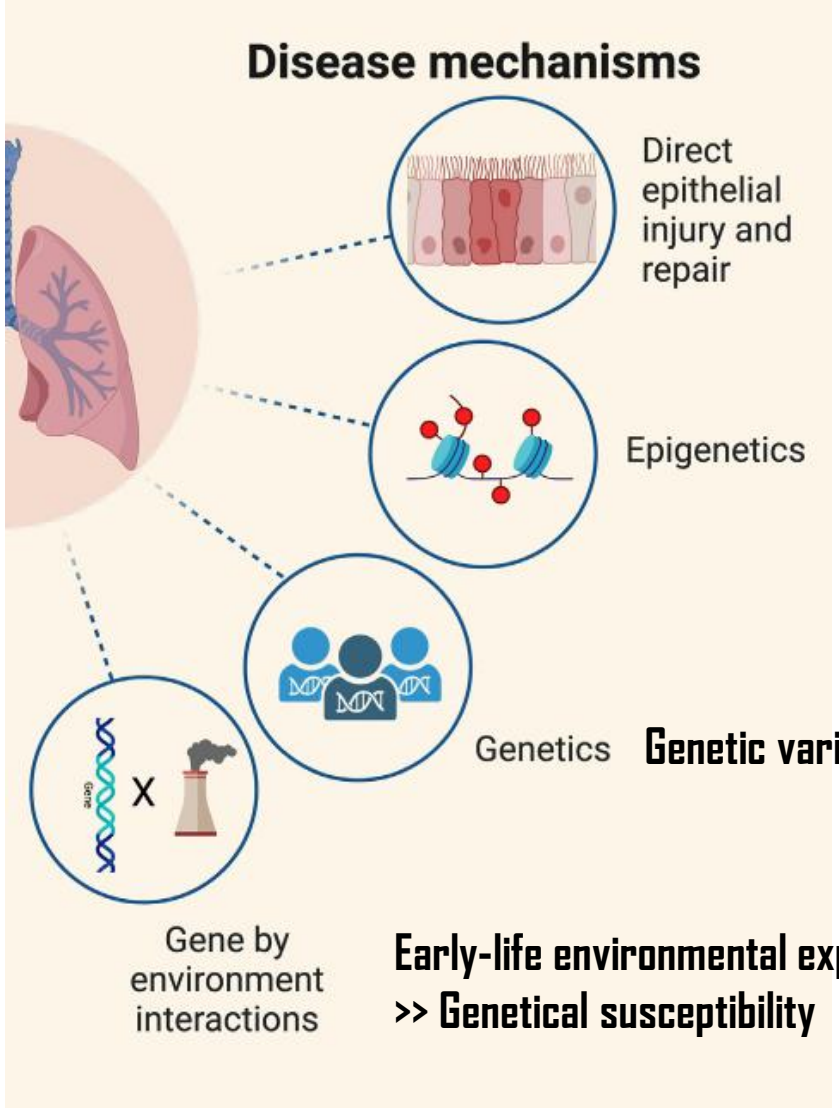
Pathways of asthma development



Hartert et al. JACI 2025

Pathways of asthma development



Abnormal airway epithelium

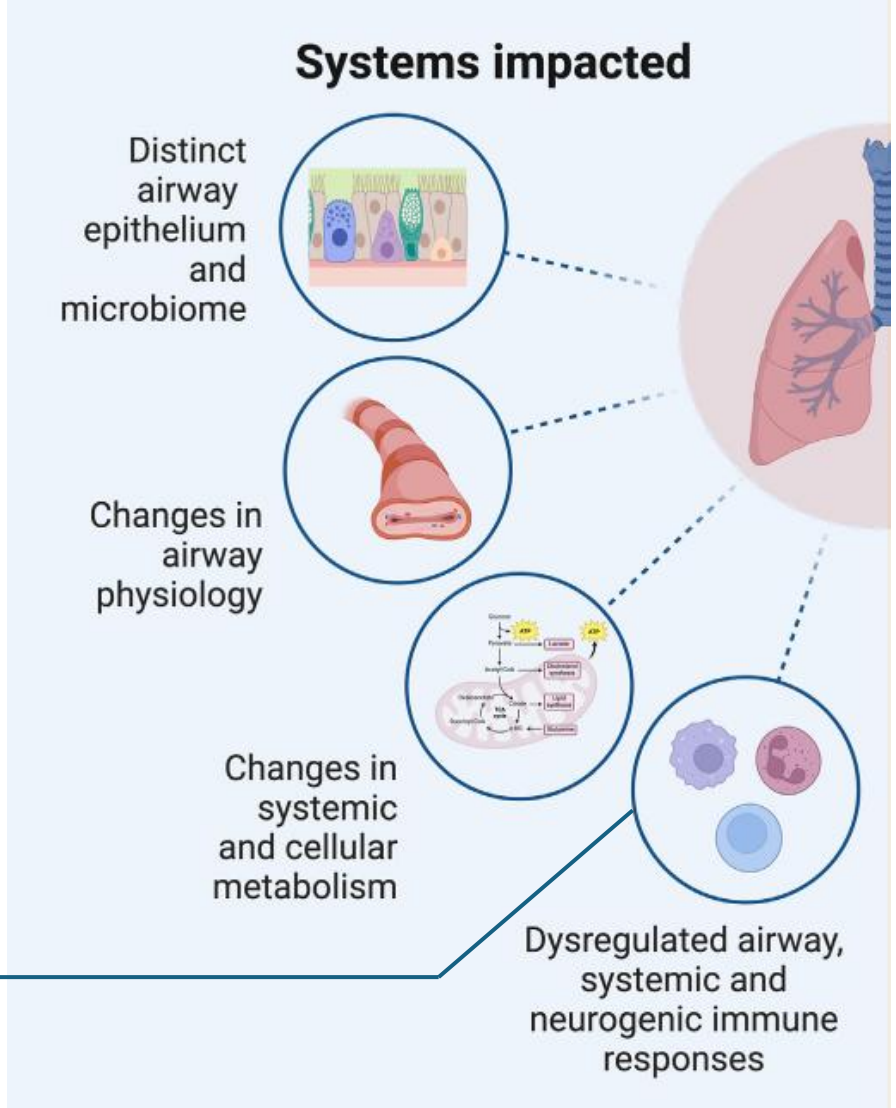
Environnemental exposures induce DNA methylation changes

Genetic variants

Early-life environmental exposures (tobacco smoke, air pollution, farming, respiratory infections)
>> Genetical susceptibility

Hartert et al. JACI 2025

Pathways of asthma development



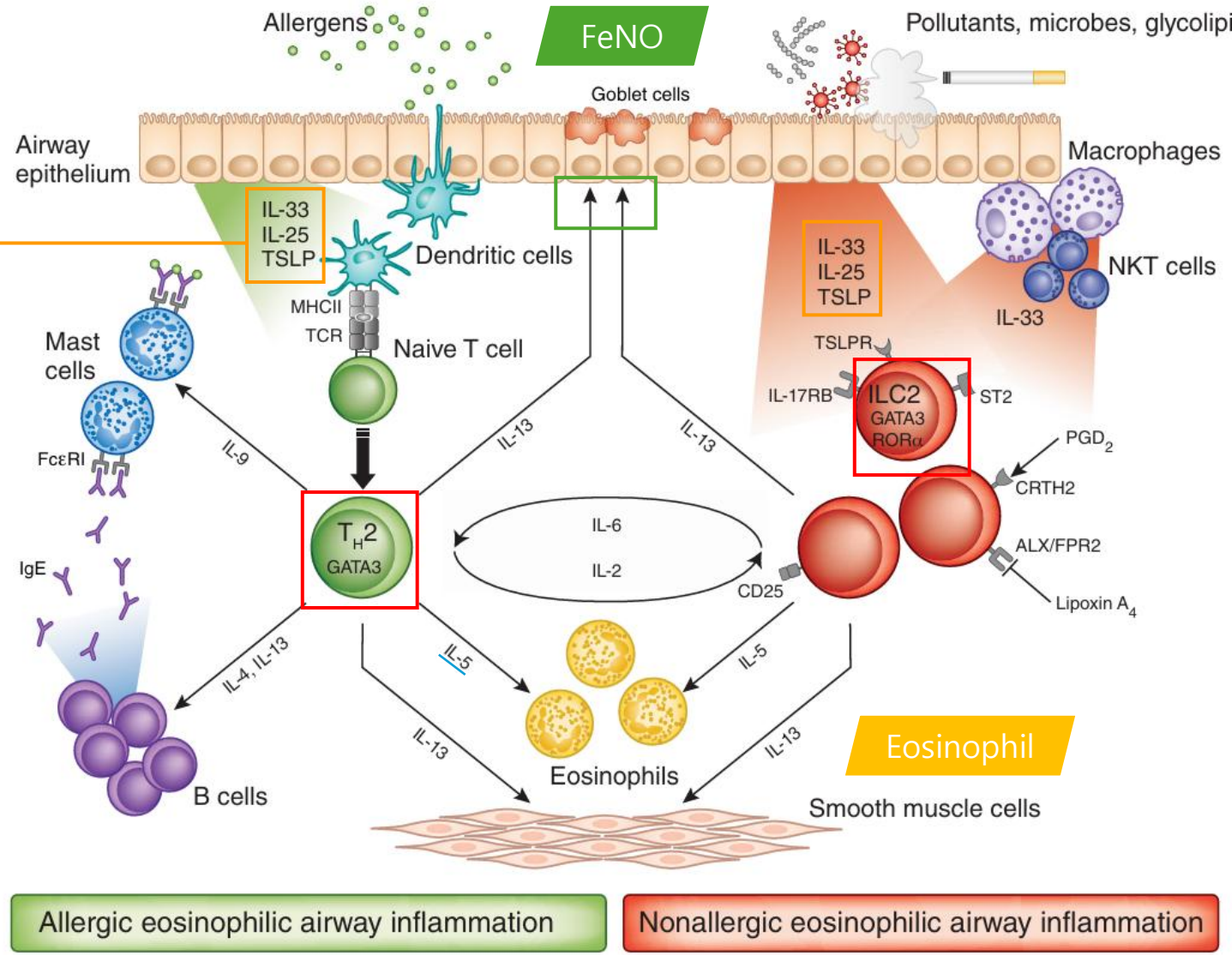
Allergic, eosinophilic

Hartert et al. JACI 2025

Pathogenesis of allergic and eosinophilic asthma

Alarmin Cytokines

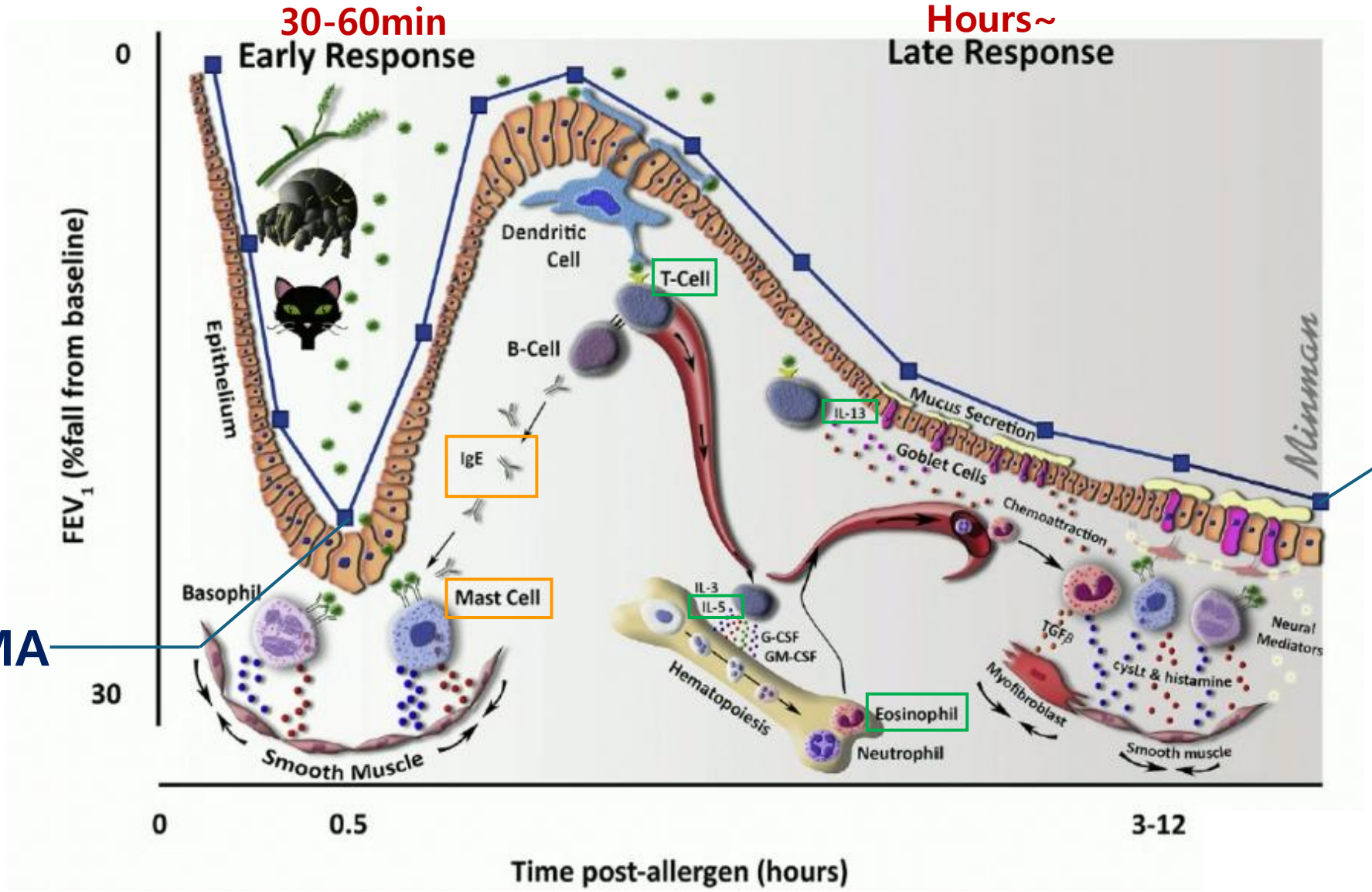
IgE



FeNO	25-50
IgE	100-150
Eosinophil	150-300

Brusselle G. et al. Nature Med 2013

Early and late response



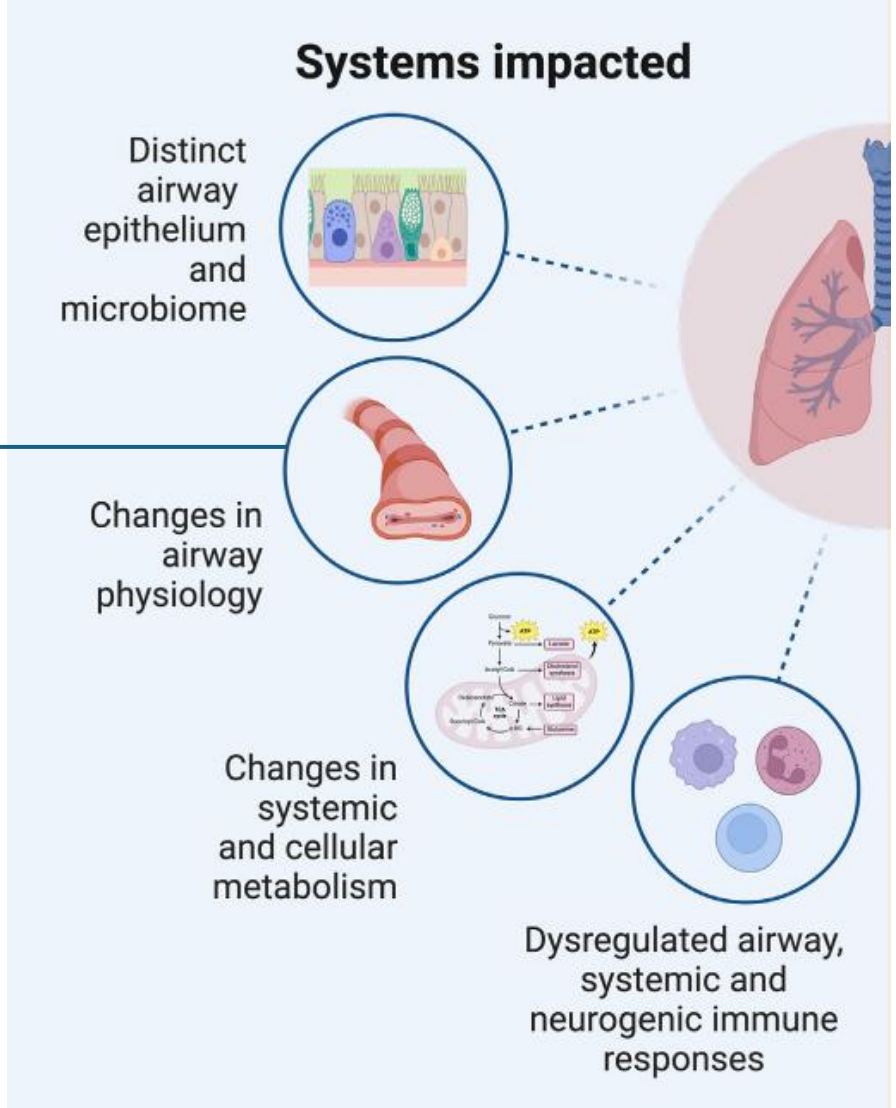
SABA/SAMA

ICS

Diamant Z, et al. JACI 2013

Pathways of asthma development

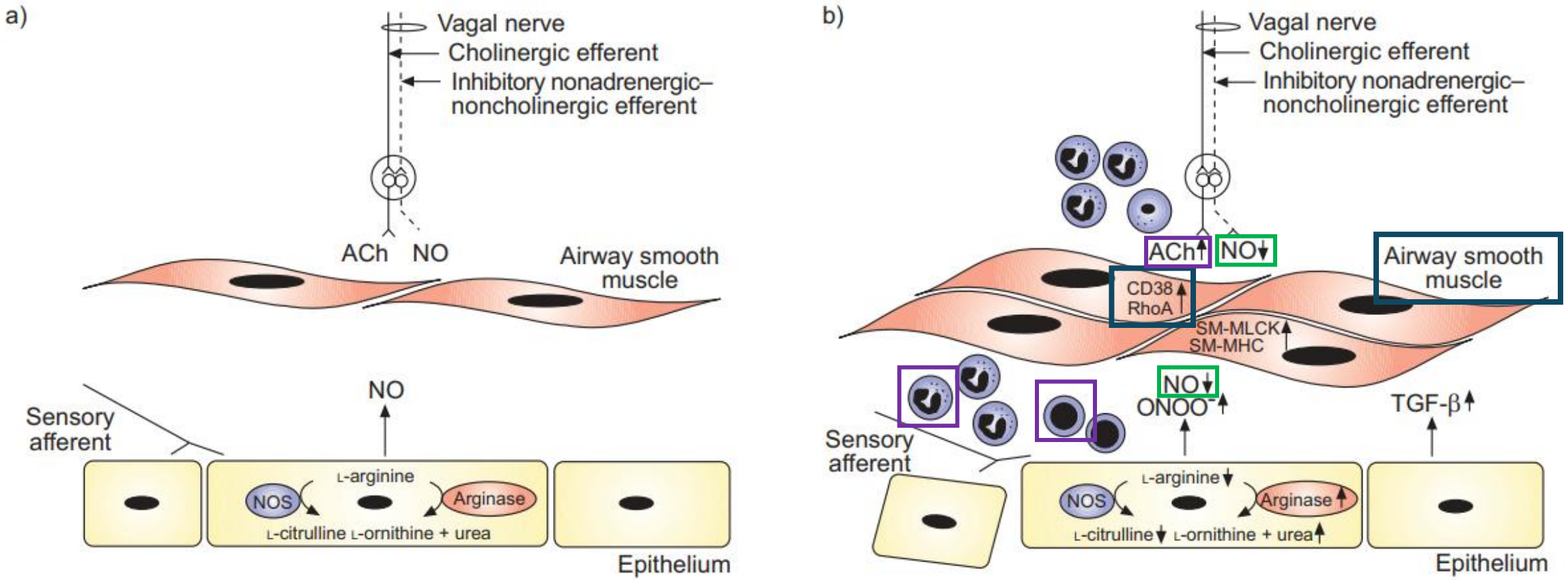
Airway hyperresponsiveness



Hartert et al. JACI 2025

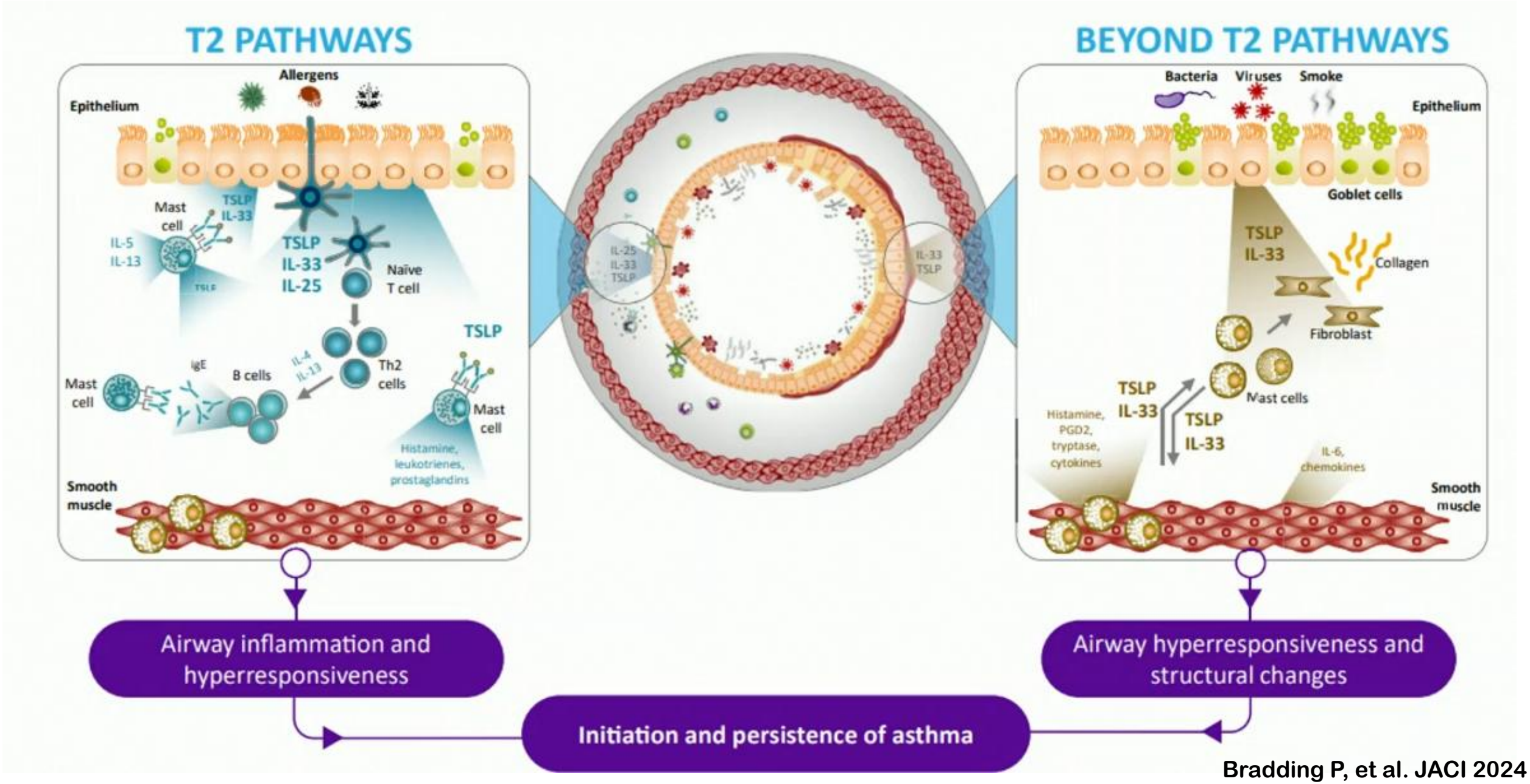
Mechanisms of airway hyperresponsiveness

Low thresholds → Various stimuli → Rapid contraction → Delayed recovery → AHR?



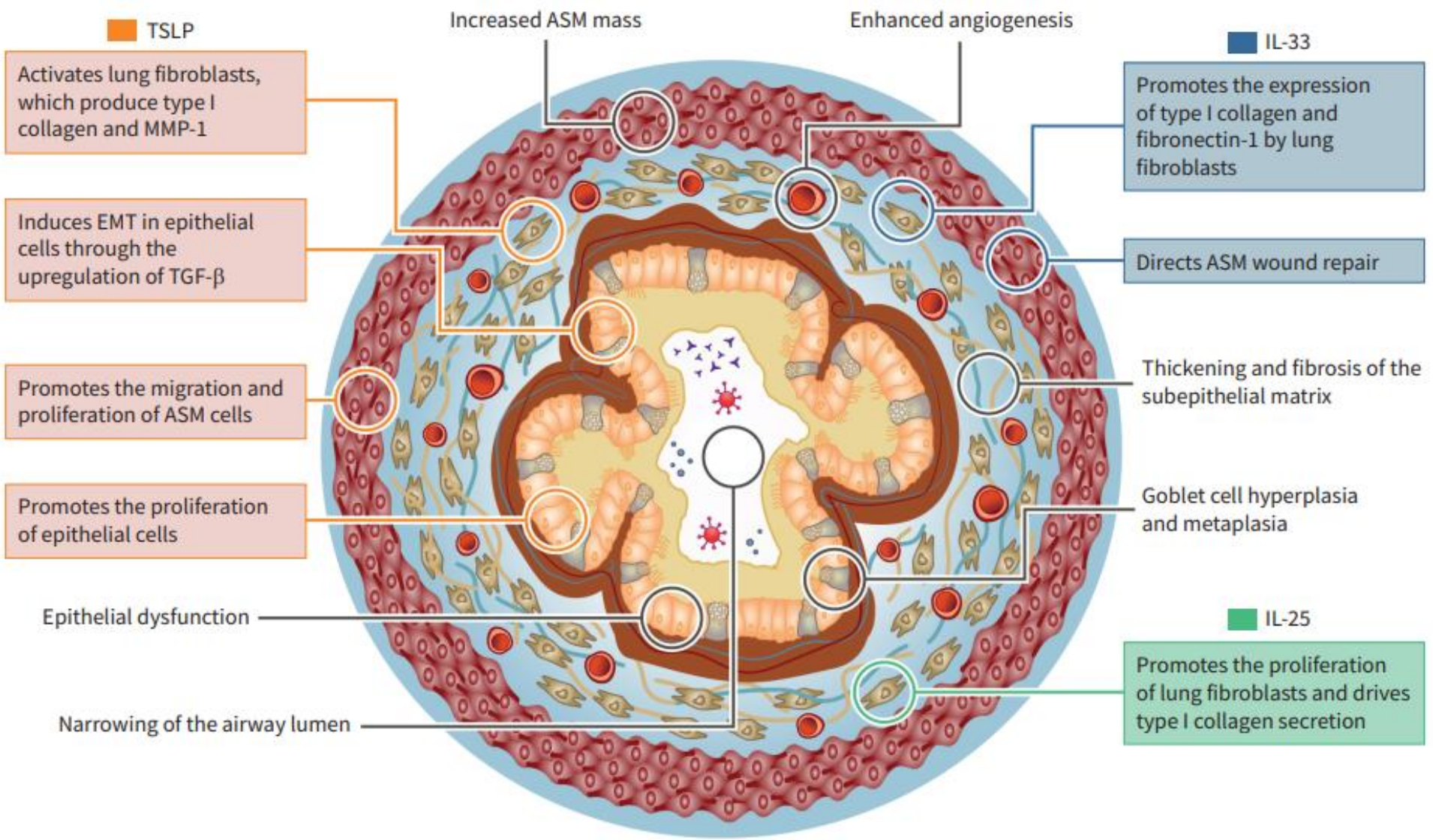
Meurs et al. ERJ 2008

Process of initiation of persistence of asthma



Bradding P, et al. JACI 2024

Pathogenic factors trigger airway remodeling



Varricchi et al. ERK 2023

Summary: Pathogenesis

PATHWAYS OF DEVELOPMENT

T2/Allergic: Allergen → Th2/ILC2 → IL-33, IL-25, TSLP → eosinophils
Non-T2: Bacteria, viruses, smoke → epithelial damage → goblet cells hyperplasia

AIRWAY HYPERRESPONSIVENESS

Mechanism: Low thresholds → rapid ASM contraction → delayed recovery
Neural: ↑ ACh & NO → ↓ inhibition → exaggerated bronchoconstriction

KEY CYTOKINES & BIOMARKERS

IL-33, IL-25, TSLP: alarmin cytokines
FeNO: 25-50 ppb
IgE: 100-150 IU/mL
Eosinophils: 150-300 cells/μL

STRUCTURAL REMODELING

TSLP: Fibroblasts → collagen & MMP-1 → EMT
IL-33: ↑ collagen & fibronectin → subepithelial fibrosis
IL-25: Fibroblast proliferation → airway thickening

BIPHASIC RESPONSE

Early (30-60 min): IgE/mast cells → bronchoconstriction
Late (3-12 hr): Eosinophil influx → prolonged inflammation

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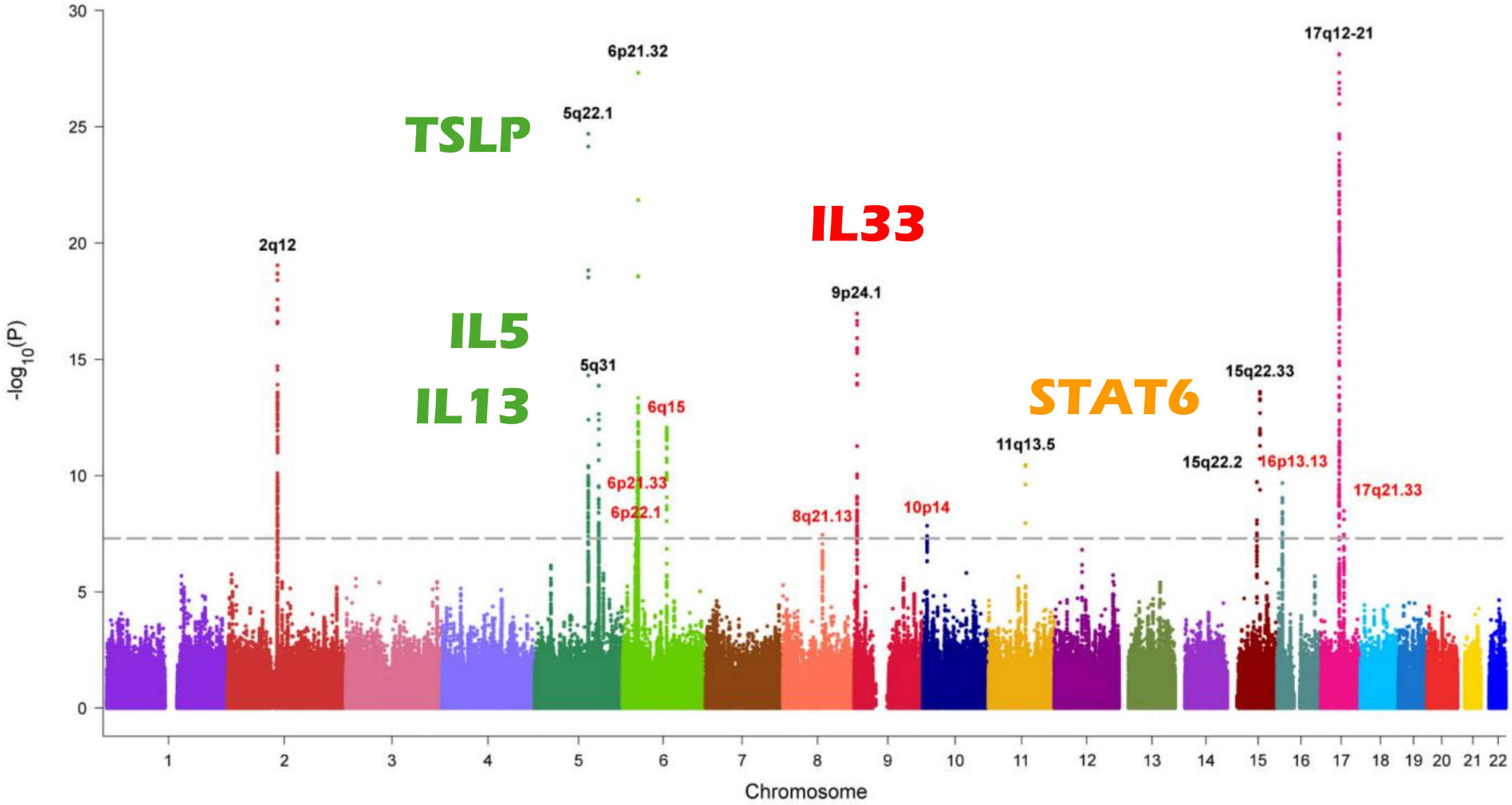
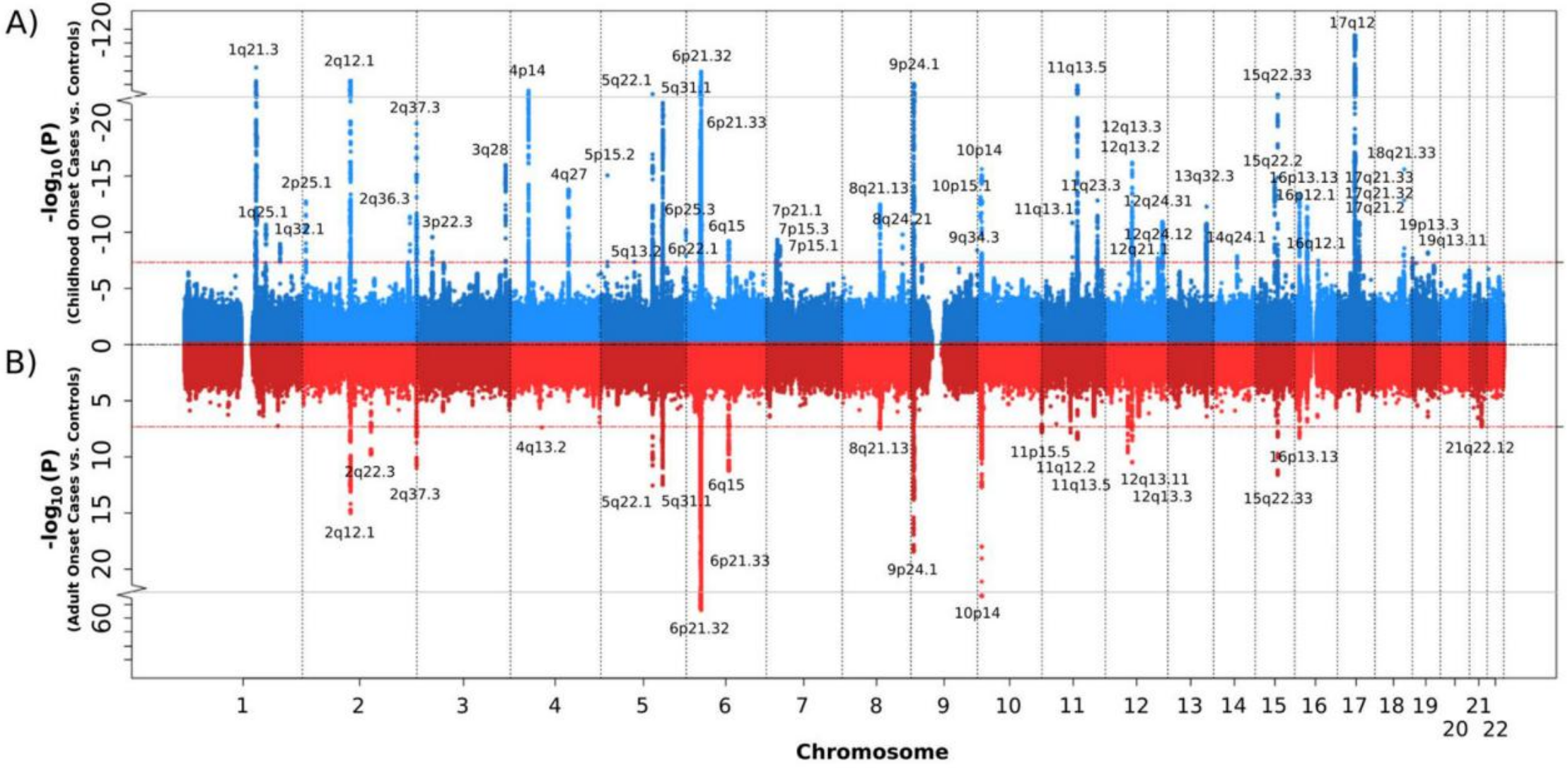
Four risk factors and DALY



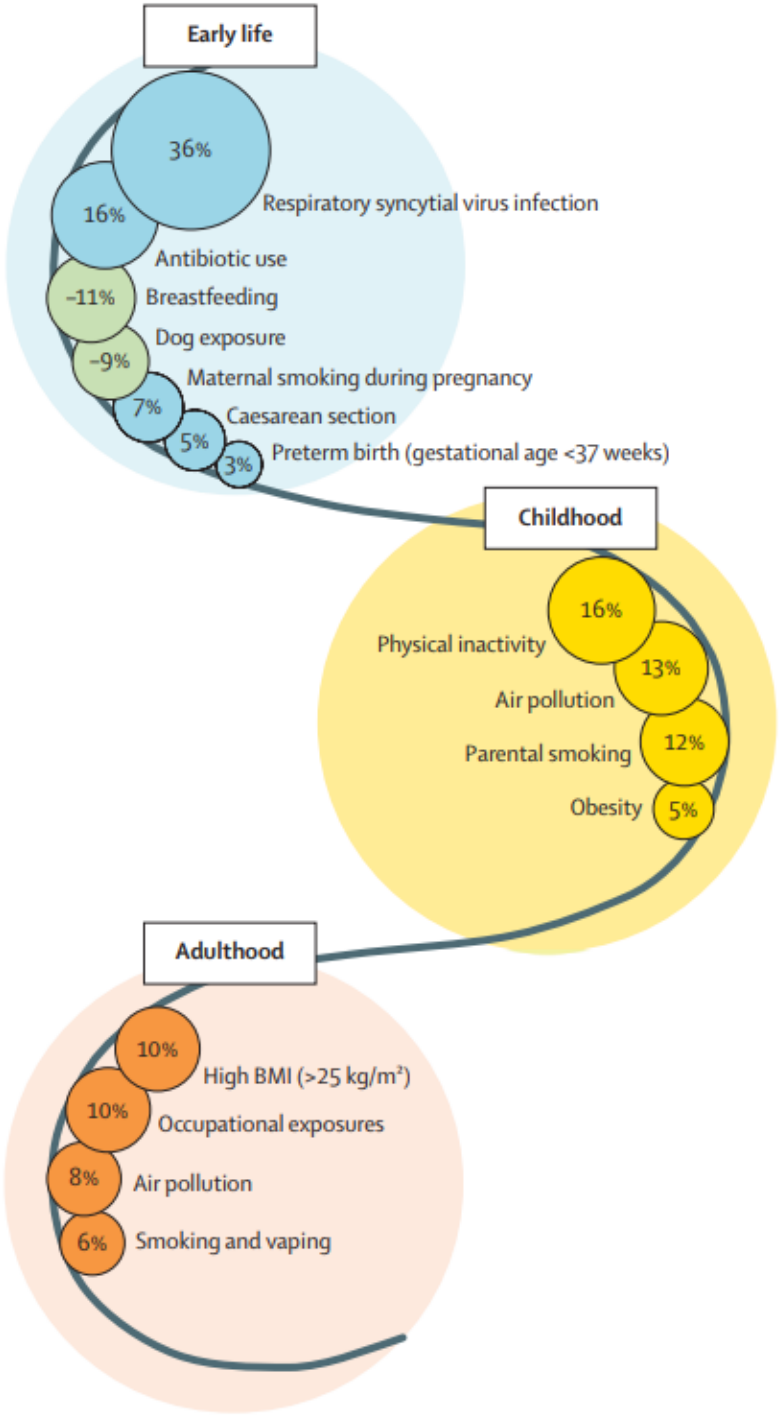
F. Demenais et al, Nature Genetics 2018

GWAS of childhood onset and adult onset asthma



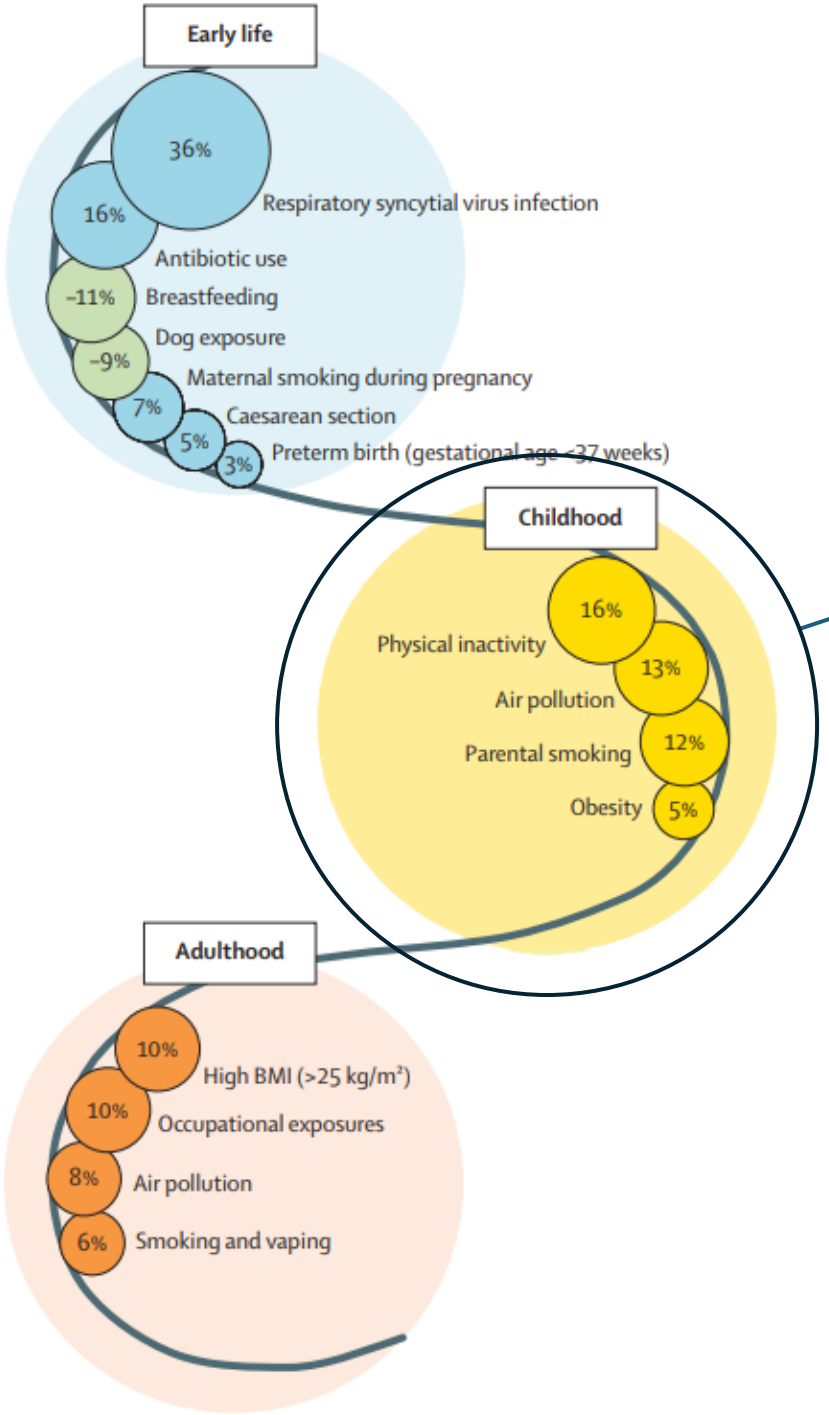
Pividori et al, Lancet RM 2019

Environmental risk factors for asthma throughout life



G. Koppelman et al, Lancet RM 2025

Environmental risk factors for asthma throughout life

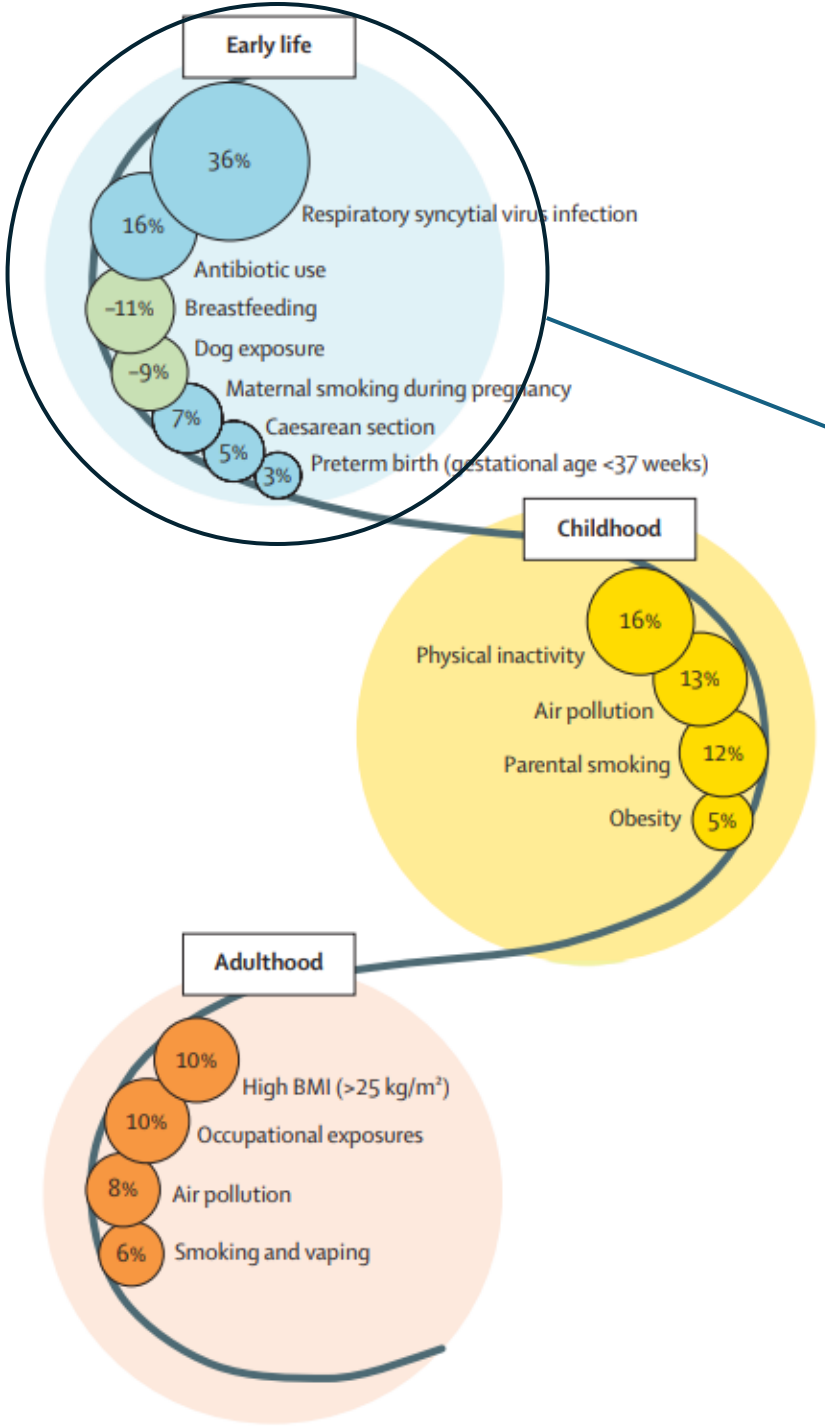


Pre- & Perinatal Factors

Physical inactivity
Air pollution
Parental smoking
Obesity

G. Koppelman et al, Lancet RM 2025

Environmental risk factors for asthma throughout life



Pre- & Perinatal Factors

RSV infection

Antibiotic use

Breastfeeding

Dog exposure

Maternal smoking

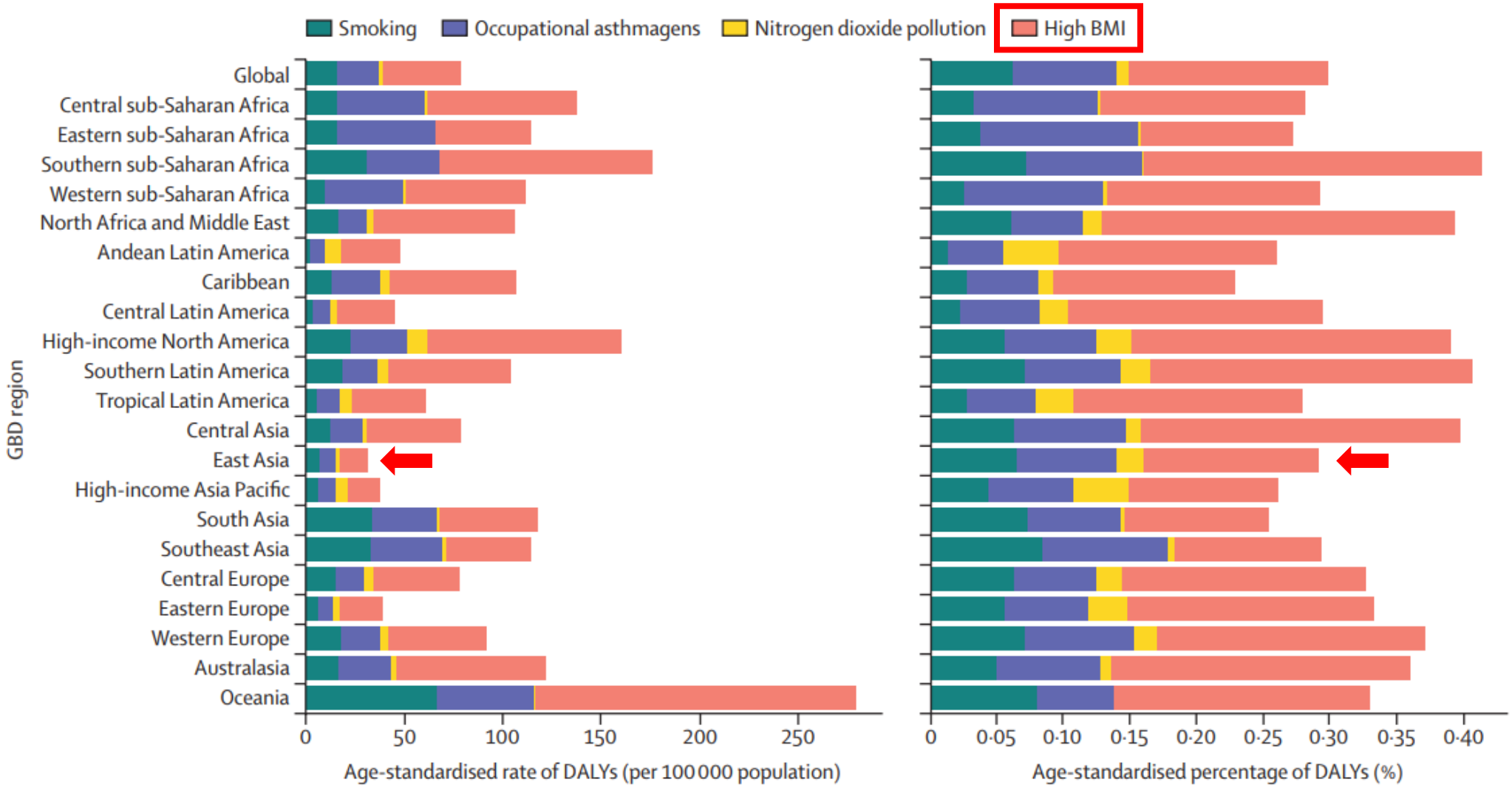
Caesarean section

Preterm birth: HR 1.3 to 3.0

Maternal age < 20

G. Koppelman et al, Lancet RM 2025

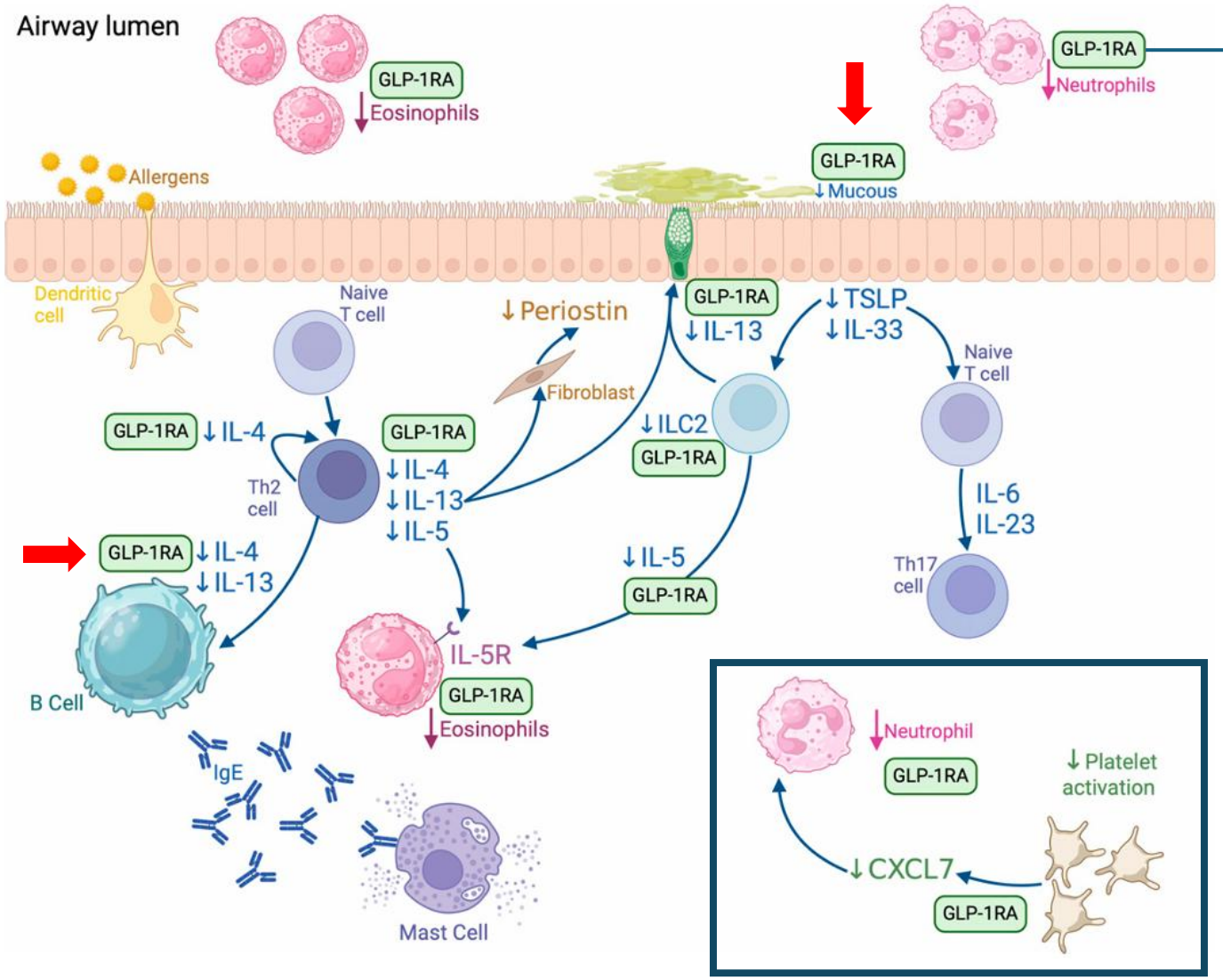
Four risk factors and DALY



GBD 2021 Asthma and Allergic Diseases Collaborators, Lancet RM 2025

Obesity and Asthma

Potential impact of GLP-1R agonists on T2 and non-T2 inflammation



Mechanical benefit

Immunommodulation

Glucagon-Like Peptide-1 Receptor Agonist in the Treatment of Adult, Obesity-related, Symptomatic Asthma (GATA-3) (GATA-3)

ClinicalTrials.gov ID NCT05254314

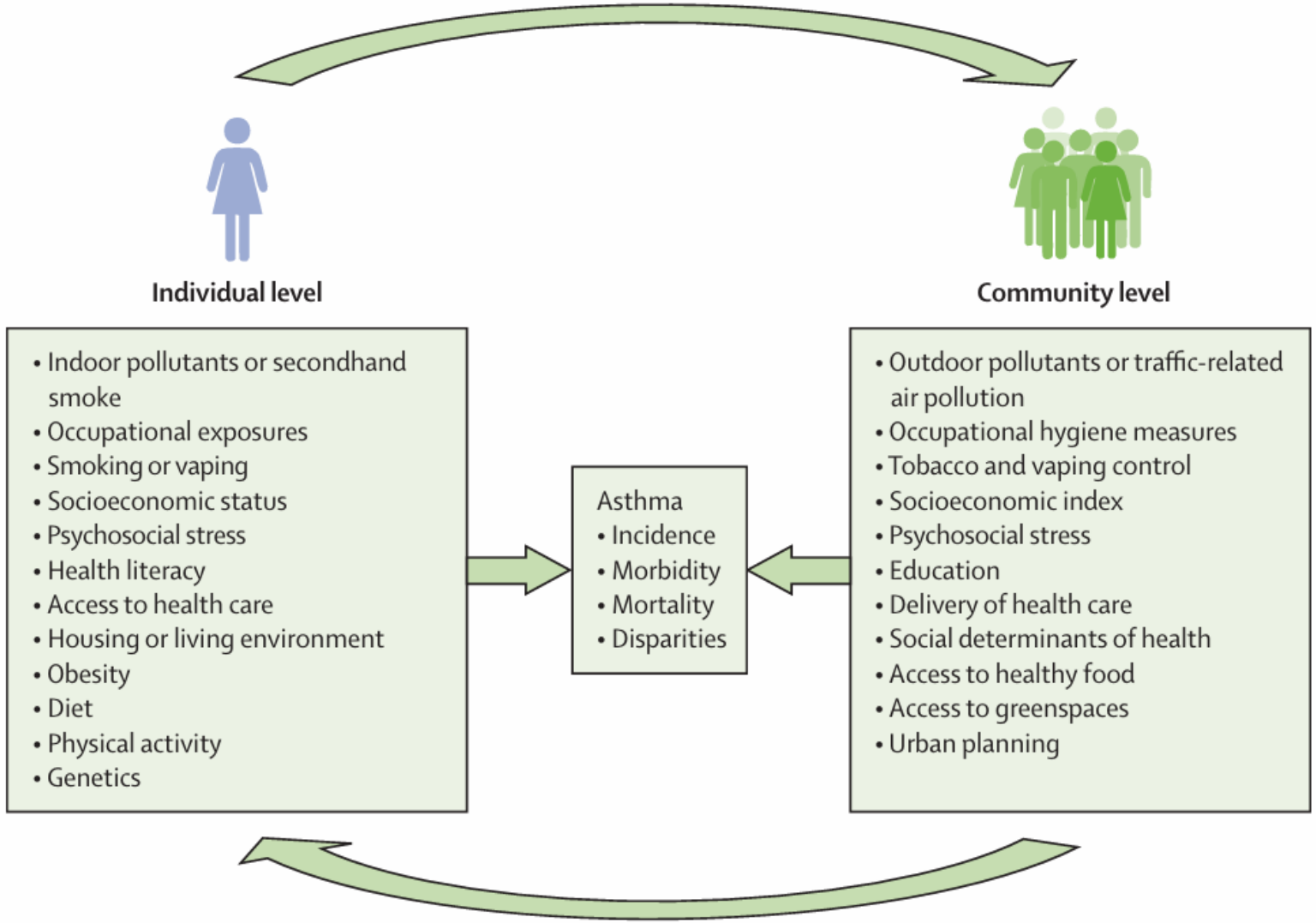
Sponsor Vanderbilt University Medical Center

Information provided by Katherine Cahill, MD, Vanderbilt University Medical Center (Responsible Party)

Last Update Posted 2025-02-20

Meghan D. Althoff et al. AJRCCM 2024

Environmental and lifestyle factors at individual and community level



G. Koppelman et al, Lancet RM 2025

Summary: Risk factor

GENETIC SUSCEPTIBILITY

Key loci:
TSLP (5q22.1), IL5 & IL13 (5q31), IL33 (9p24.1), STAT6 (12q13.5), chr17q12-21
Childhood vs Adult onset: Overlapping but distinct genetic profiles

GLOBAL DISEASE BURDEN (DALYs)

Leading contributors: High BMI (obesity), occupational asthmagens, smoking, NO_2 pollution
Regional variation: East Asia shows low absolute rates but high proportional obesity burden

ENVIRONMENTAL RISK FACTORS

Early life: RSV infection (36%), antibiotic use (16%), maternal age <20
Protective: Breastfeeding (-11%), dog exposure (-9%)
Childhood: Physical activity (16%), air pollution (13%), parental smoking (12%)
Adulthood: High BMI (10%), occupational exposures (10%), smoking (6%)

OBESITY-RELATED ASTHMA

Emerging therapy: GLP-1R agonists (e.g., semaglutide)
Mechanisms: Weight loss + direct anti-inflammatory effects
T2 pathway: ↓ IL-4, IL-13, IL-5 via Th2 & ILC2 modulation
Non-T2: ↓ neutrophils, ↓ CXCL7, ↓ platelet activation

INTERVENTION TARGETS

Individual: Smoking cessation, obesity management, occupational protection
Community: Air quality control, tobacco policies, urban planning, health equity

CLINICAL TRIAL

GATA-3 (NCT05254314): GLP-1R agonist for adult obesity-related symptomatic asthma
Dual benefit: Mechanical (weight ↓) + immunomodulation

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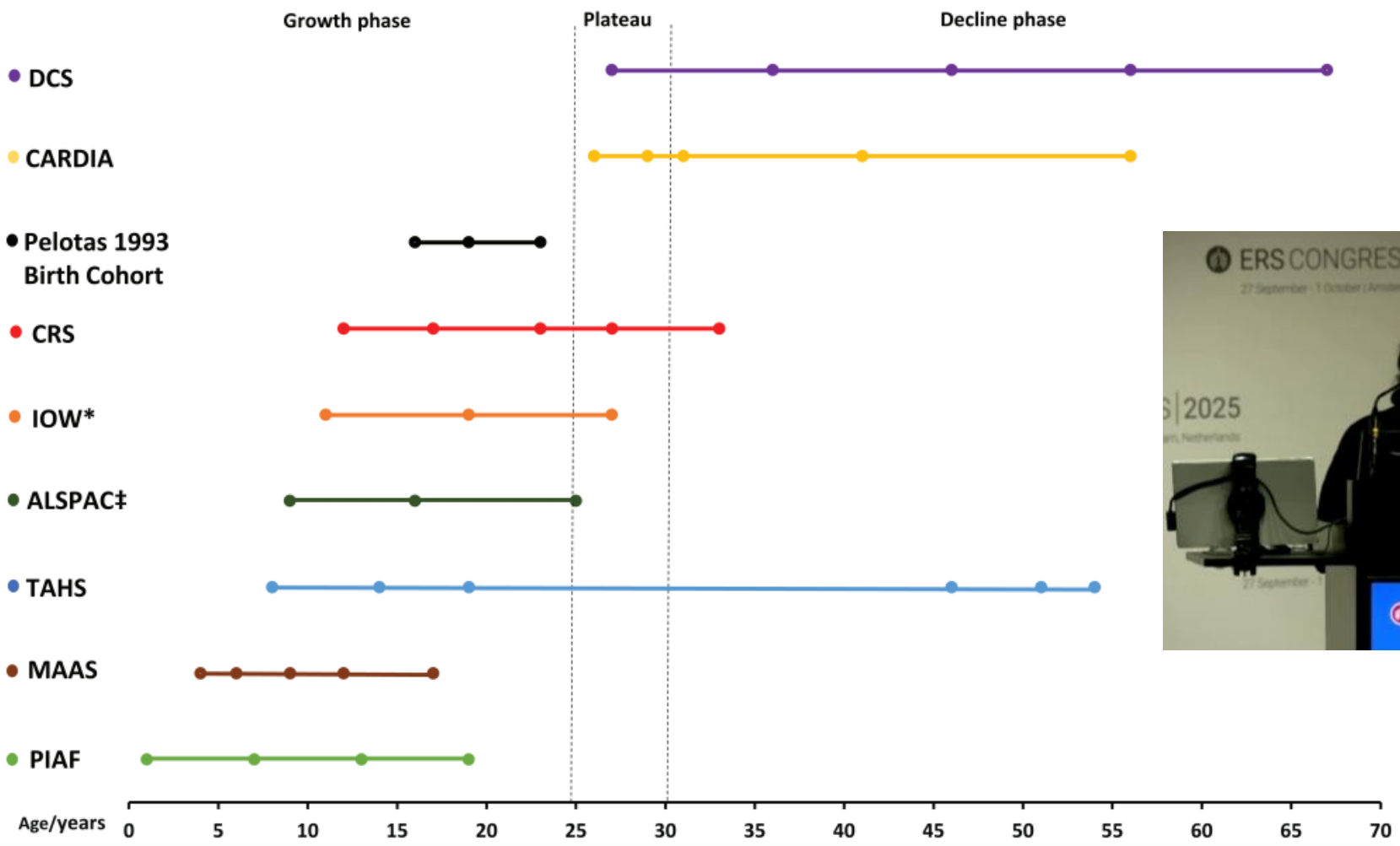
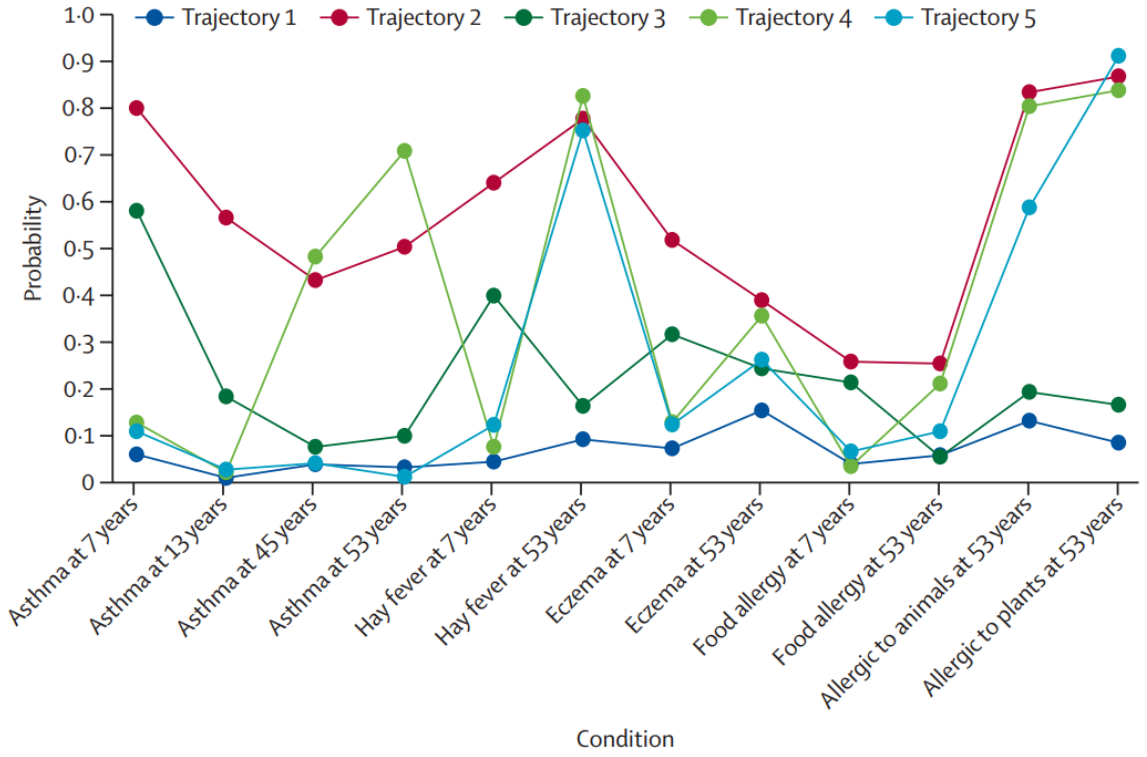
Timepoint measurement of lung function among studies



Okyere et al. Respirology 2021

Longitudinal trajectories of asthma and allergic diseases

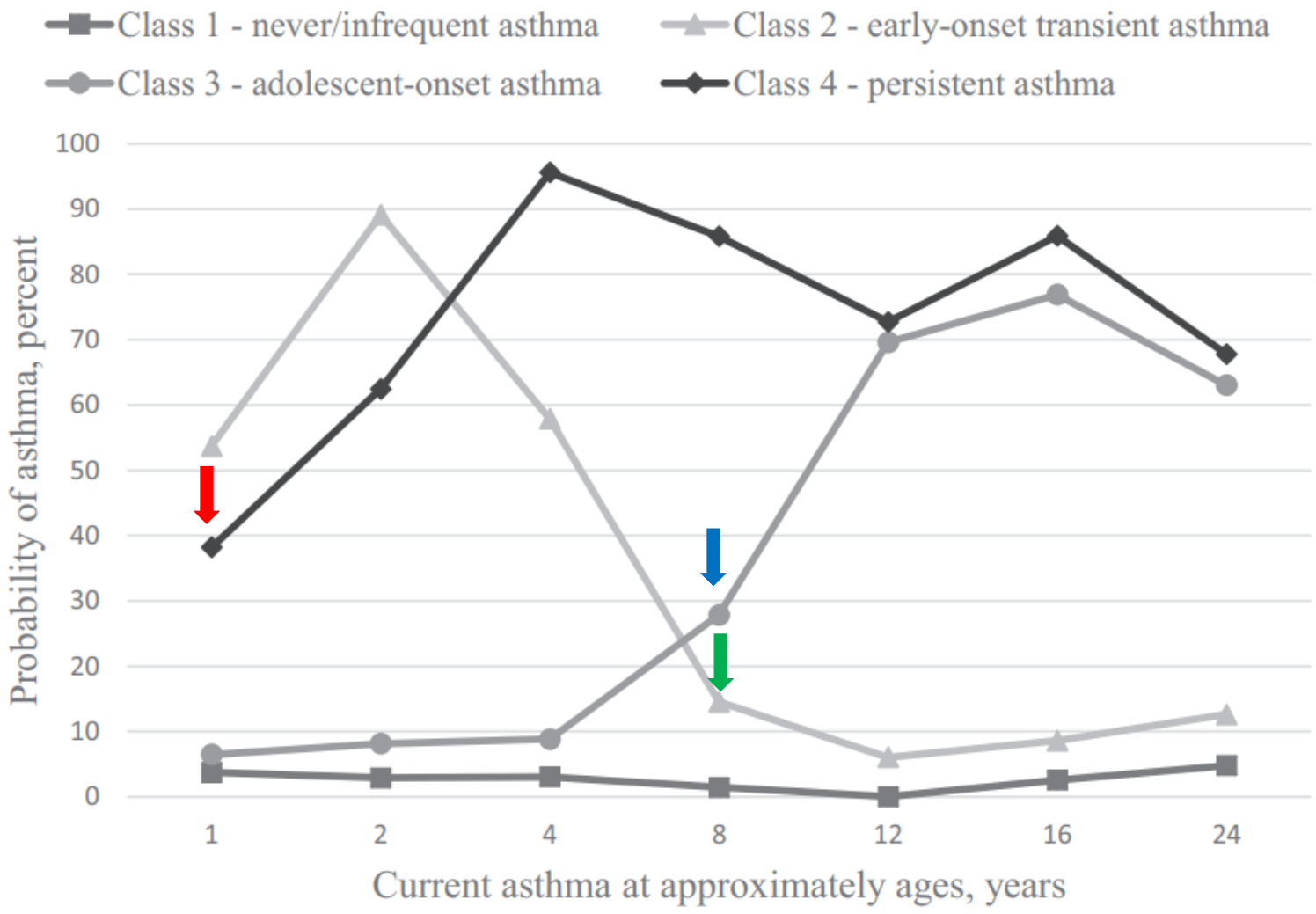
Asthma | Allergic rhinitis | Eczema | Food | Environment



	Asthma and allergy trajectories				
	Minimal or least asthma and allergies	Early-onset persistent asthma and allergies	Early-onset remitted asthma and allergies	Late-onset asthma and allergies	Late-onset hay fever, no asthma
Asthma at 7 years	0·059	0·80	0·58	0·13	0·11
Asthma at 13 years	0·0084	0·57	0·18	0·020	0·026
Asthma at 45 years	0·037	0·43	0·074	0·48	0·040
Asthma at 53 years	0·031	0·50	0·098	0·71	0·010
Hay fever at 7 years	0·043	0·64	0·40	0·073	0·12
Hay fever at 53 years	0·09	0·78	0·16	0·83	0·75
Eczema at 7 years	0·071	0·52	0·32	0·13	0·12
Eczema at 53 years	0·15	0·39	0·24	0·35	0·26
Food allergy at 7 years	0·038	0·26	0·21	0·033	0·065
Food allergy at 53 years	0·057	0·25	0·05	0·21	0·11
Allergic to animals at 53 years	0·13	0·83	0·19	0·80	0·59
Allergic to plants at 53 years	0·083	0·87	0·16	0·84	0·91

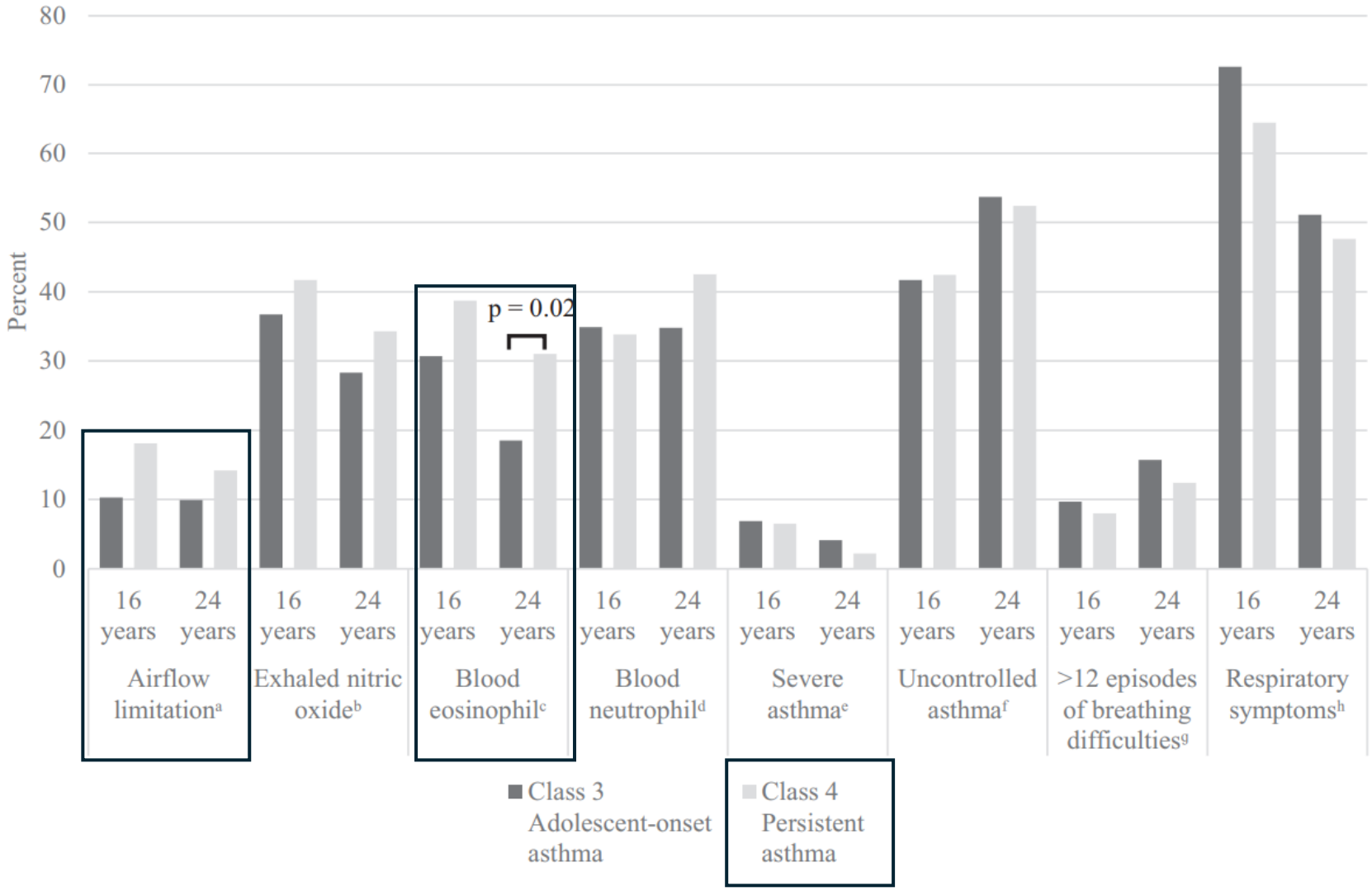
Bui et al. Lancet RM 2021

Trajectories of infancy to young adulthood



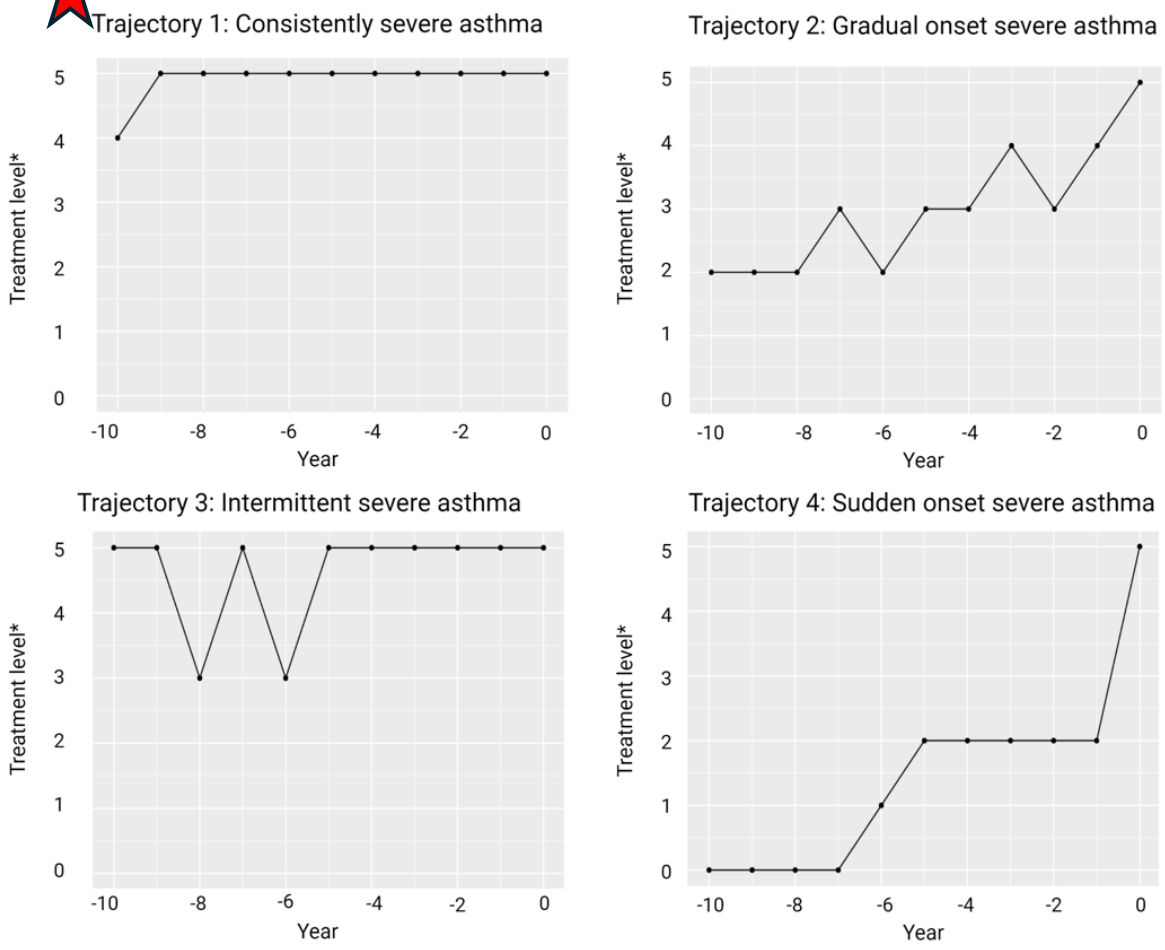
Odling et al. JACI pract 2021

Comparison adolescent-onset asthma vs. persistent asthma

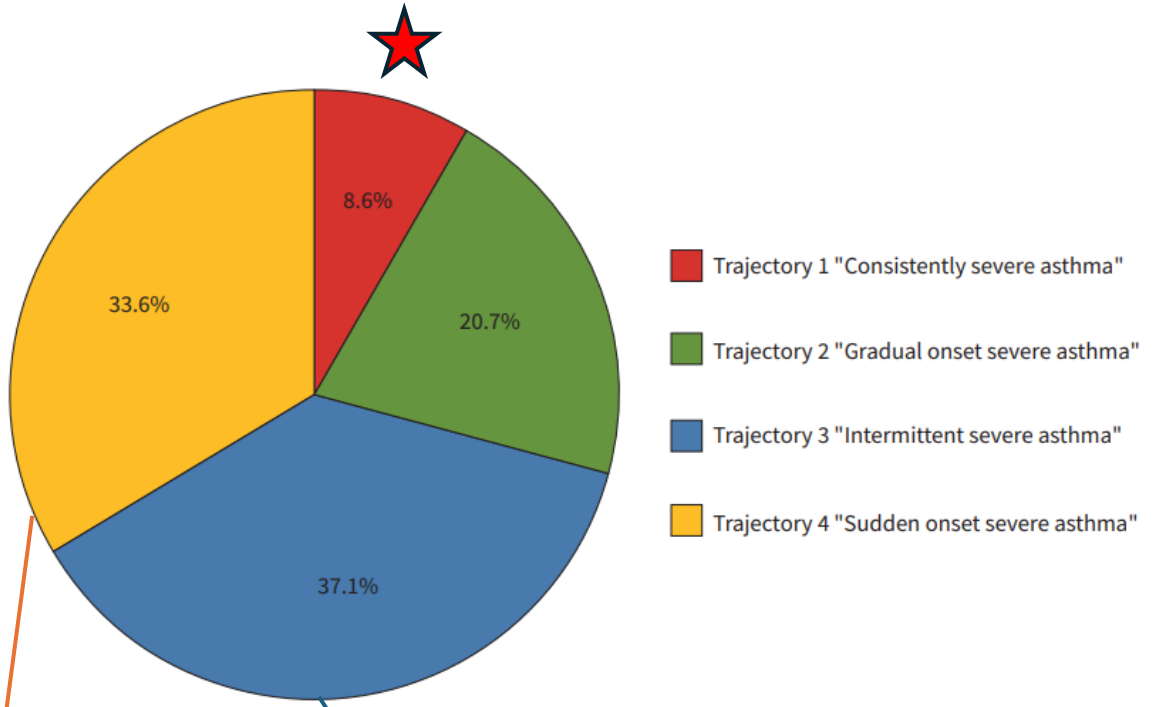


Odling et al. JACI pract 2021

Severe asthma trajectory



*Treatment level defined as 0: no asthma treatment, 1: only SABA (no ICS), 2: <400 average daily dose of µg budesonide or equivalent, 3: ≥400 µg average daily dose of budesonide or equivalent, 4: ≥800 µg average daily dose of budesonide or equivalent, 5: ≥1600 µg average daily dose of budesonide or equivalent, + second controller OR filled OCS ((≥ 1825 mg a year) in combination with ≥ 800 µg average daily dose of budesonide or equivalent OR ≥ 1 dispensation of biologics (anti-IgE/anti-IL5)

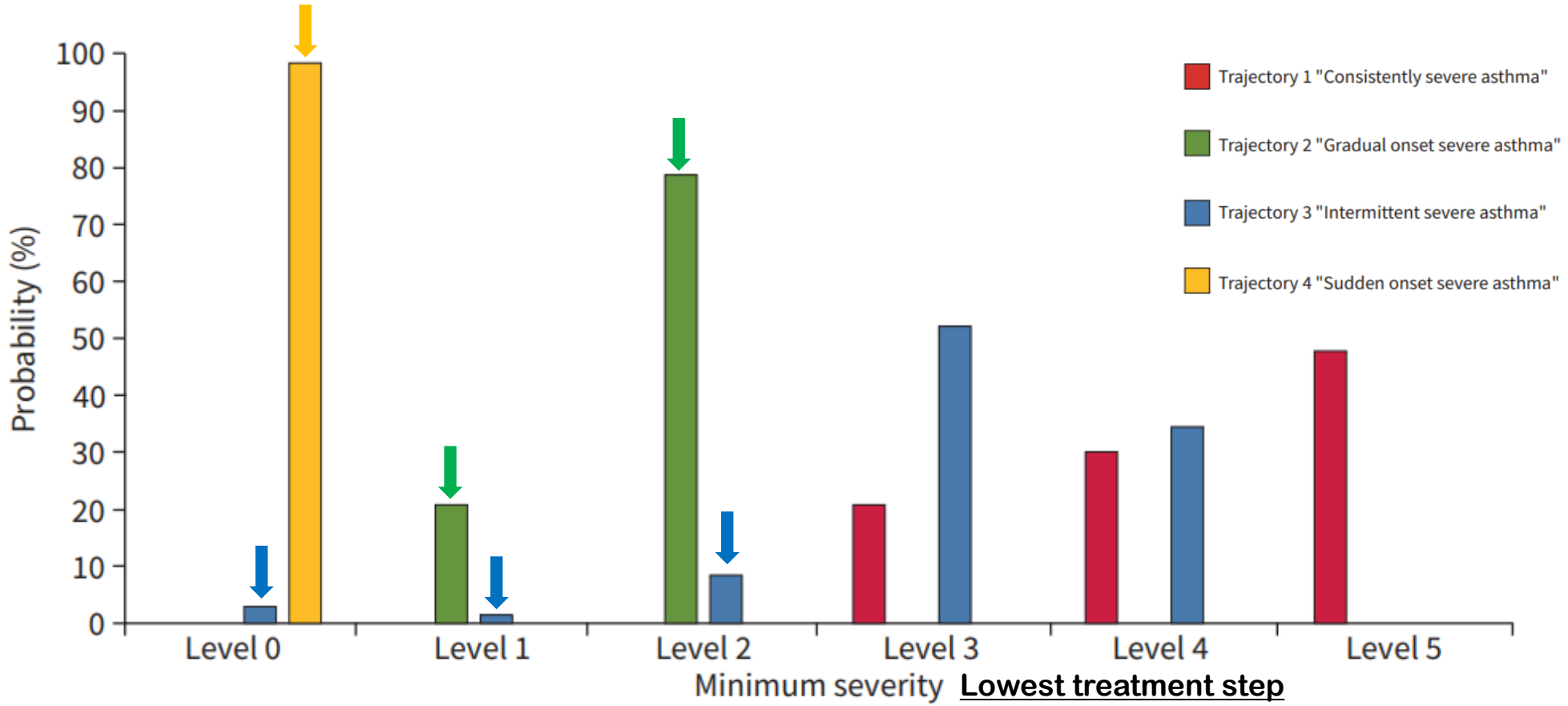


Exacerbation driven

Late onset phenotype

Bulow et al. ERJ 2023

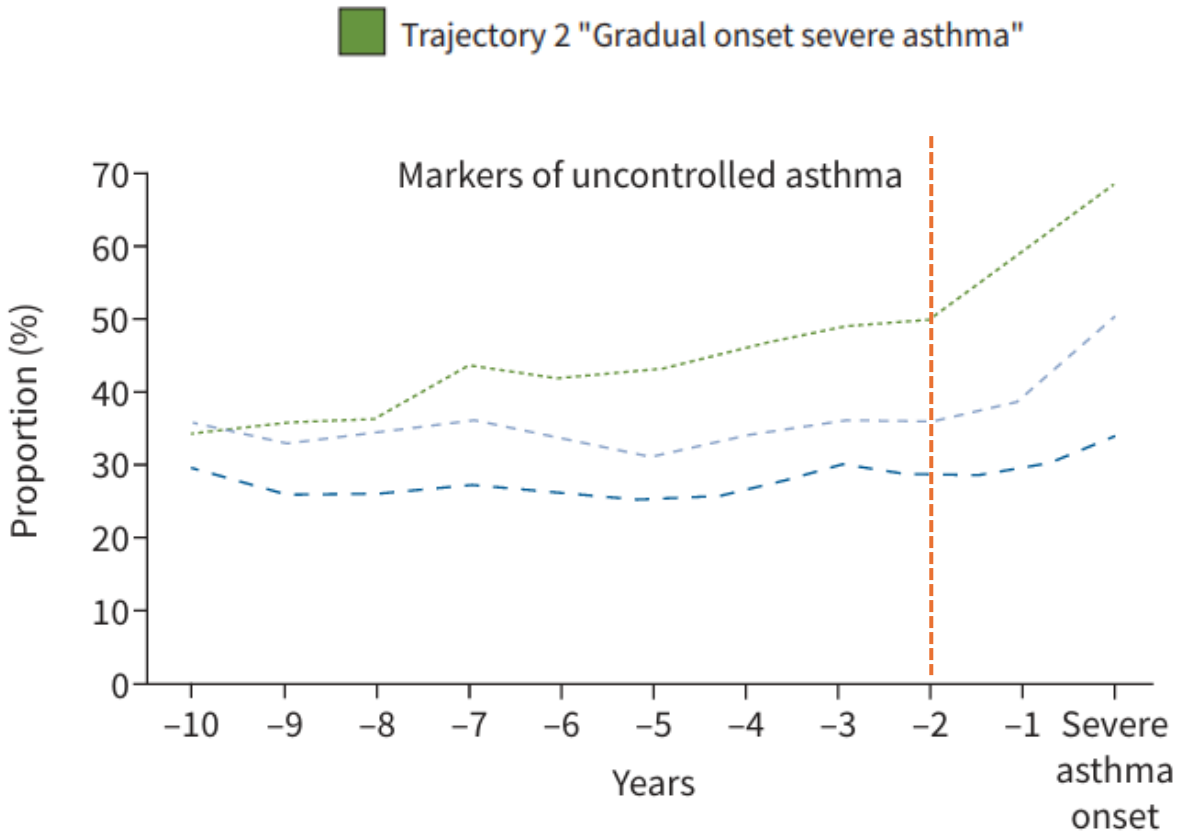
Severe asthma trajectory

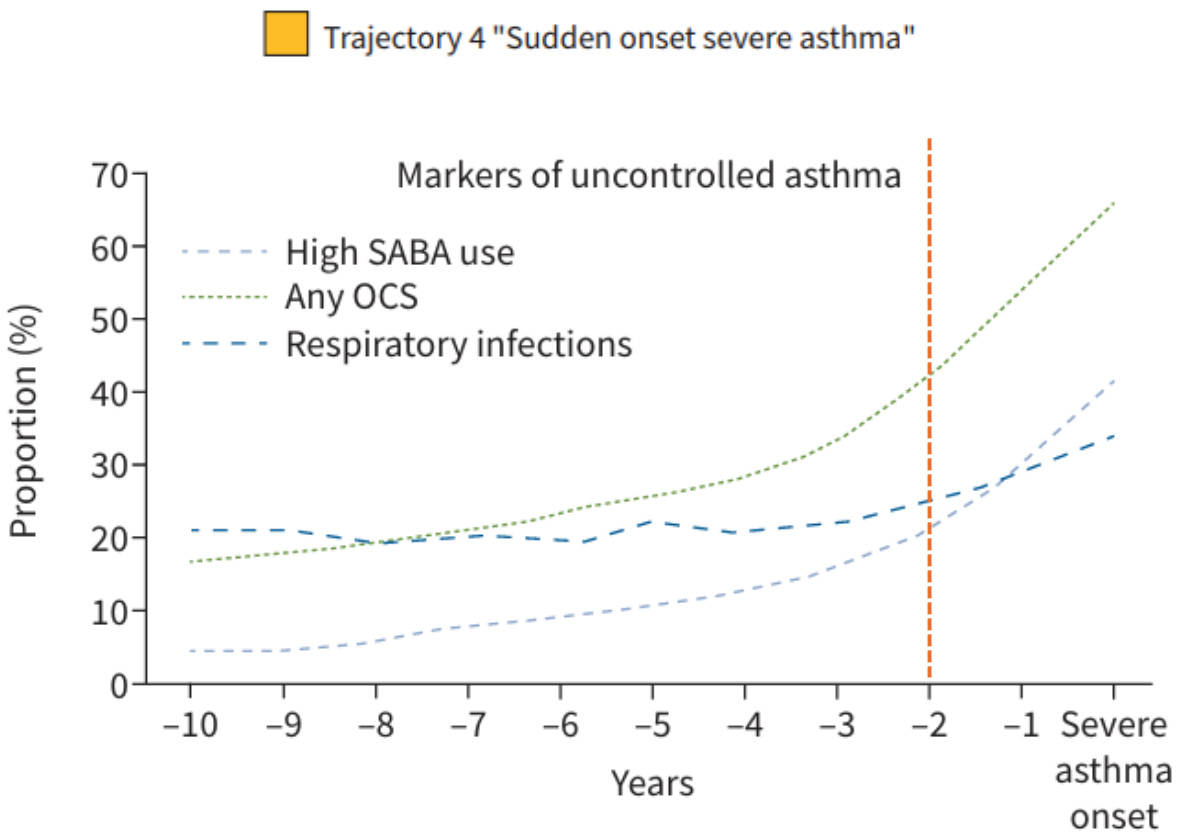


	Lowest treatment step					
Trajectory 1	0	0	0	21	31	49
Trajectory 2	0	21	79	0	0	0
Trajectory 3	3	1	9	52	35	0
Trajectory 4	100	0	0	0	0	0

Bulow et al. ERJ 2023

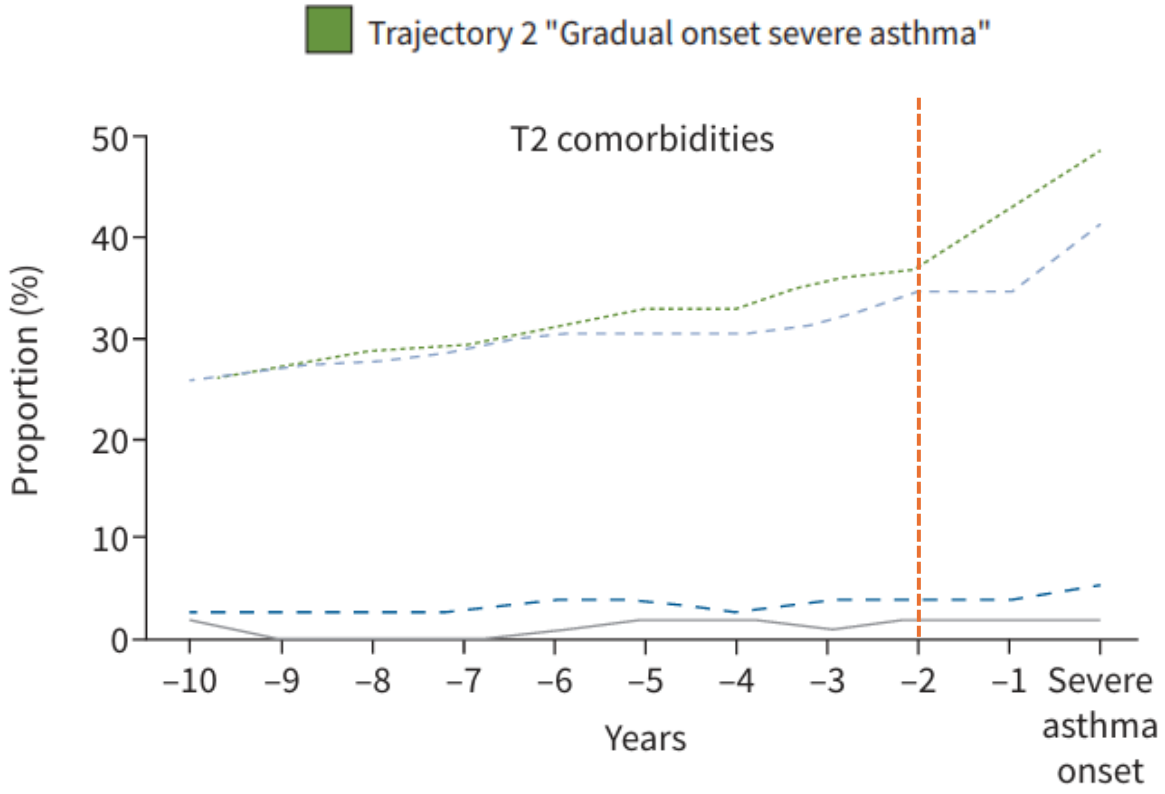
Severe asthma trajectory: markers of uncontrolled asthma

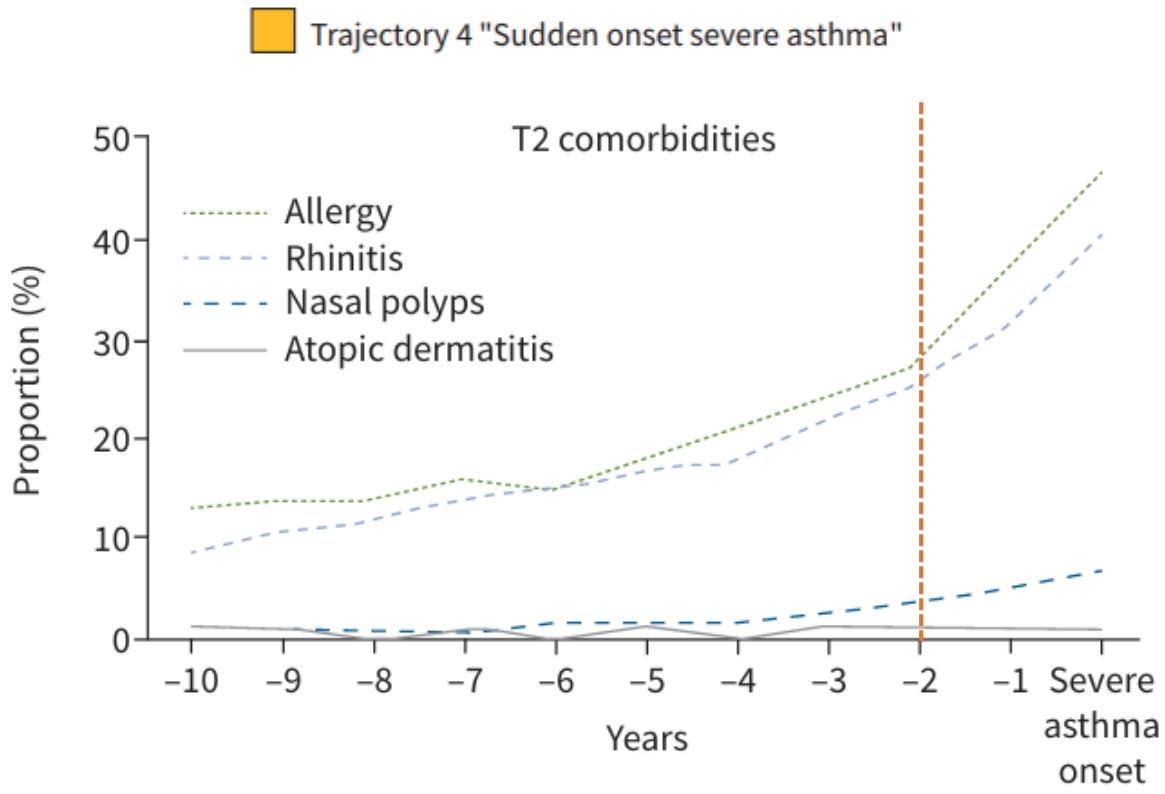




Bulow et al. ERJ 2023

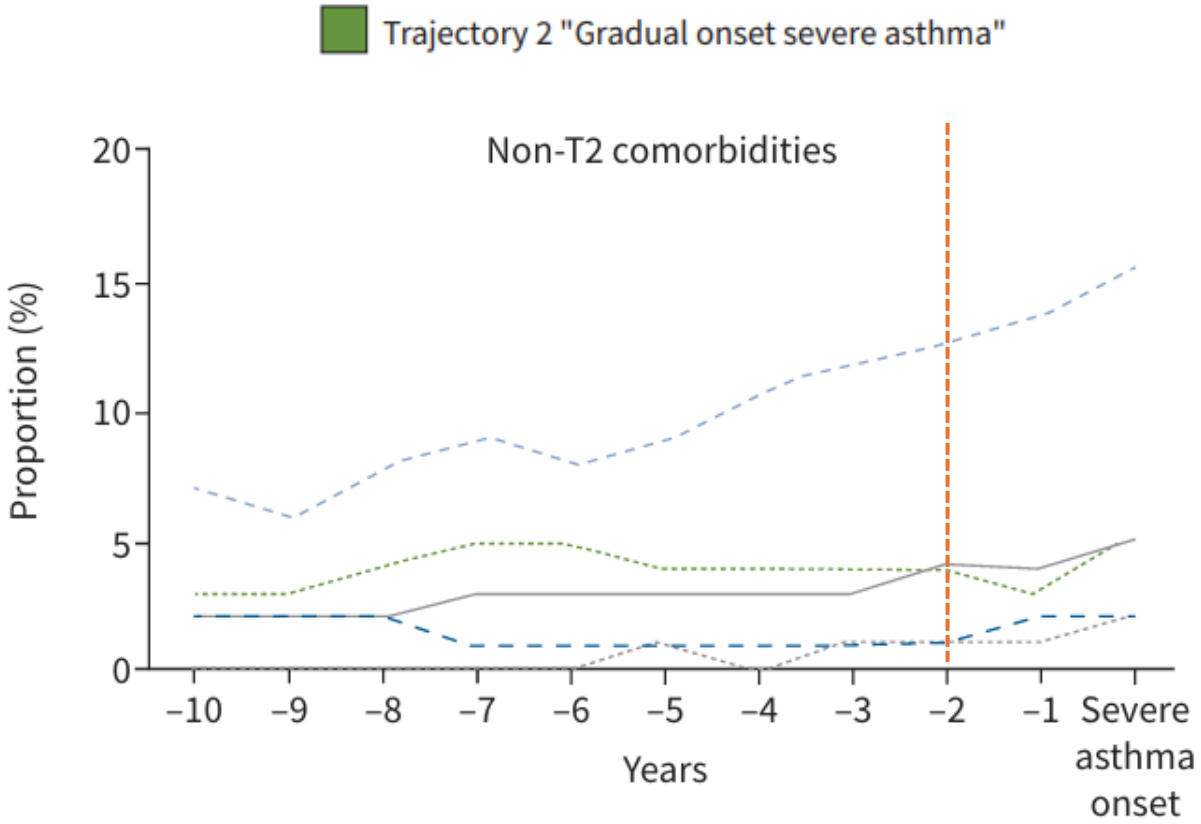
Severe asthma trajectory: T2 comorbidities

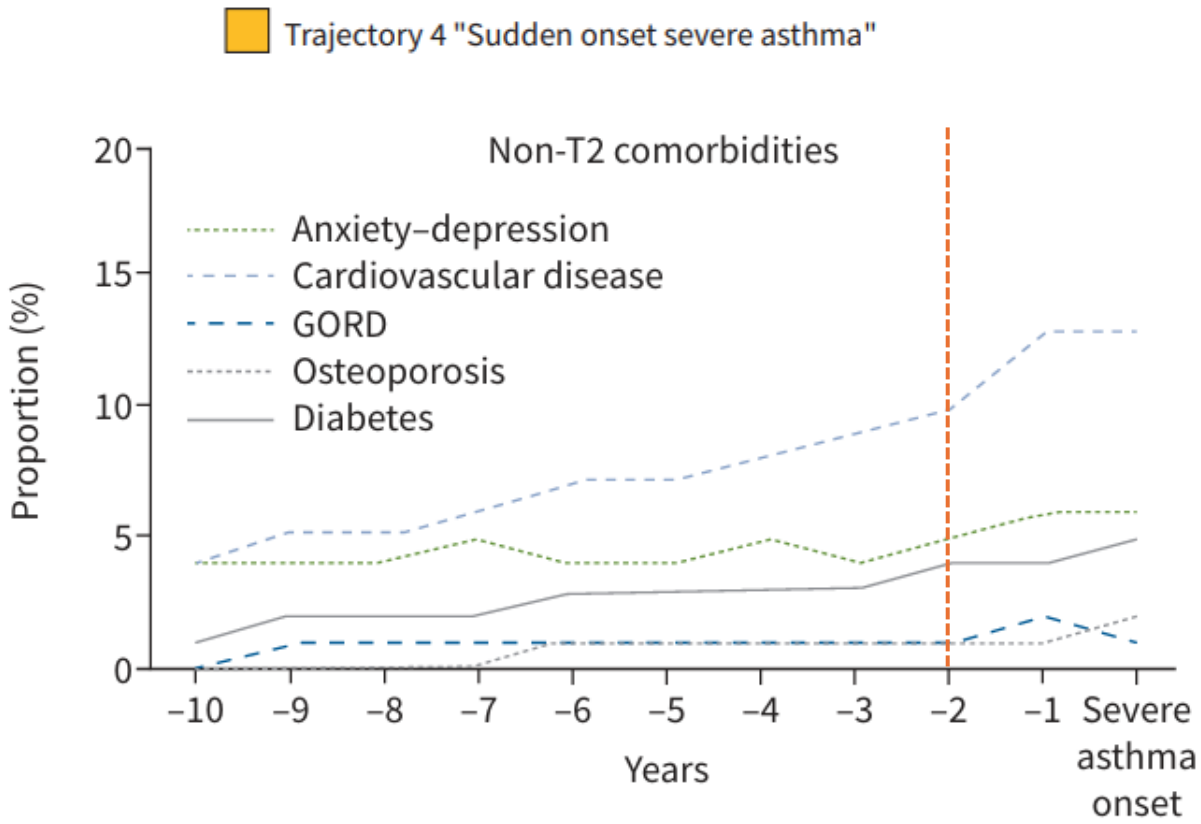




Bulow et al. ERJ 2023

Severe asthma trajectory: non-T2 comorbidities





Bulow et al. ERJ 2023

Summary: Trajectory

Trajectory Heterogeneity

3-5 distinct patterns

Vary by onset age, persistence, remission

Consistent phenotypes across cohorts

Severe Asthma Evolution

Four pattern: Consistent, gradual, intermittent, sudden

Exacerbation-driven, late-onset phenotypes predominate

Trajectories predict treatment escalation

Common Trajectory Pattern

Early-onset transient: Childhood peak, adolescent resolution

Adolescent-onset: Latter onset, distinct features

Persistent: High burden

Clinical Implication

Early identification

SABA, OCS predict progression

Comorbidities patterns emerge years before severe onset

Summary

Pathogenesis

✓Pathway development ✓Key cytokines/biomarkers ✓Biphasic response
✓Airway hyperresponsiveness ✓Structural remodeling

Risk Factors

✓Genetic susceptibility ✓Environmental risk factors
✓Intervention target ✓global disease burden ✓Obesity related asthma

Disease Trajectories

✓Trajectory heterogeneity ✓Common trajectory pattern
✓Severe asthma evolution ✓Clinical implication