BRIGHAM AND WOMEN'S HOSPITAL
| The Lung Center |

SEVERE ASTHMA PROGRAM
Brigham and Women's Hospital
Founding Member, Mass General Brigham

Mass General Brigham
Asthma Center

Update on Severe Asthma 2024

Asthma and Aging

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Disclosures

- **Employment:**

University of Wisconsin

- **Consulting: GSK, AZ**
- **Funding: NIH-NHLBI**

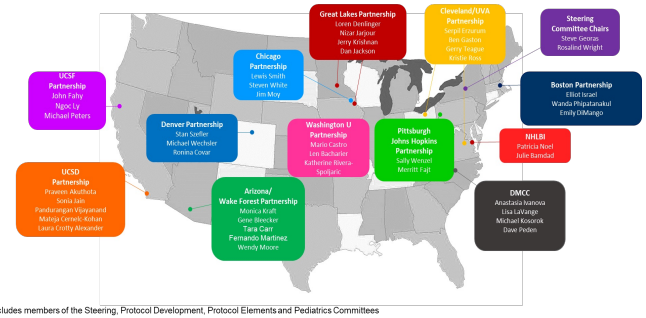
Major NIH Asthma Studies @ UW

NIH National Heart, Lung, and Blood Institute

ACRN

CARE
Childhood Asthma Research & Education Network

SARP



Includes members of the Steering, Protocol Development, Protocol Elements and Pediatrics Committees

ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH

CREW
Children's Respiratory and Environmental Workgroup

SARP
THE SEVERE ASTHMA RESEARCH PROGRAM
WWW.SEVEREASTHMA.ORG

ICAC

AADCRC

CAUSE
Childhood Asthma in Urban Settings

COAST
Childhood Origins of ASThma

PreclSE
PRECISION INTERVENTIONS FOR SEVERE ASTHMA

NIH National Institute of Allergy and Infectious Diseases

AsthmaNet

MESA

Asthma and Aging

- Epidemiology and impact of asthma on the elderly
- Features of asthma in older patients
- Reduced skeletal muscle quality with age
- Asthma and cognitive function
- Cardiovascular events in asthma
- Treatment of the older patient with asthma

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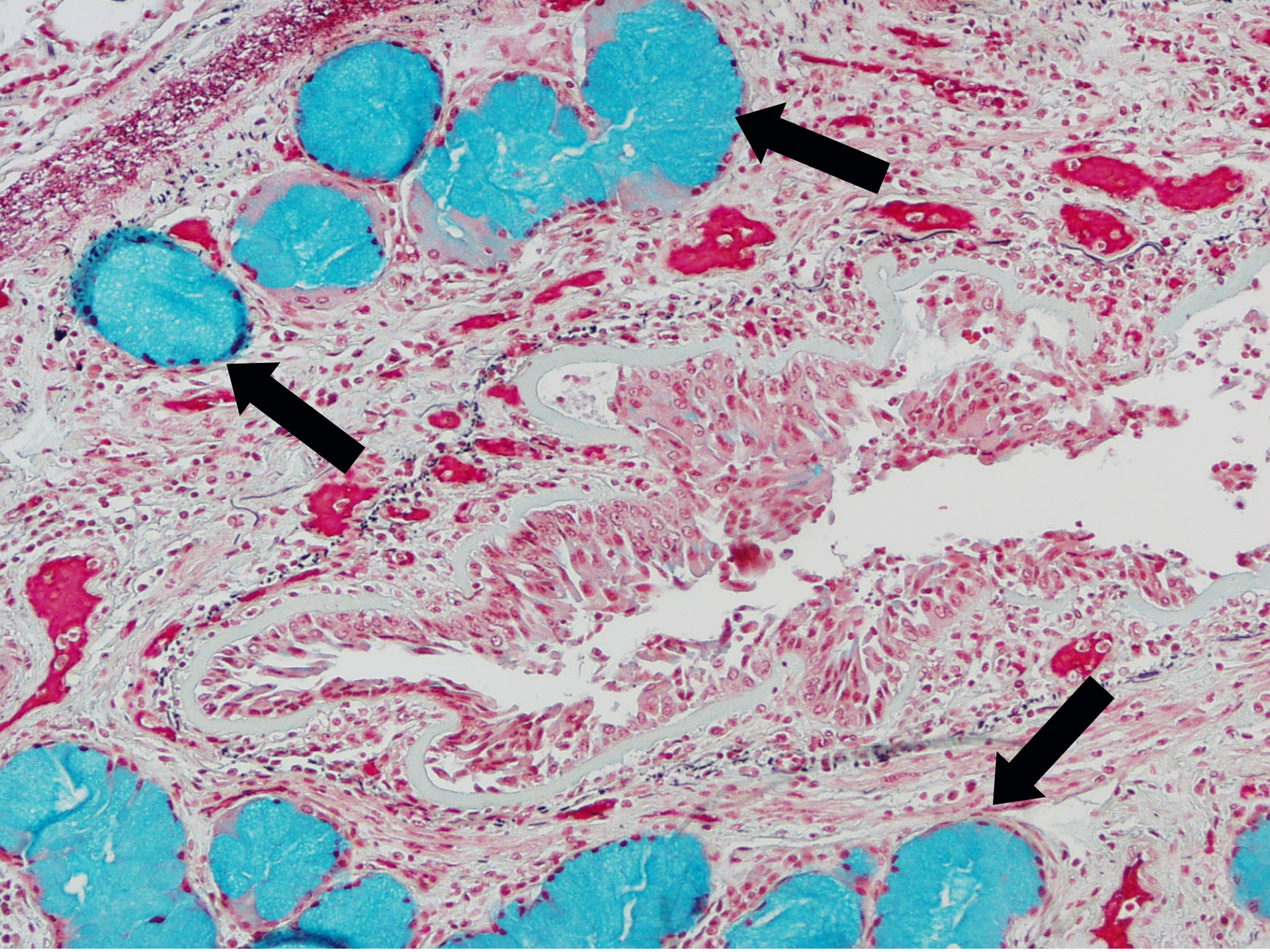
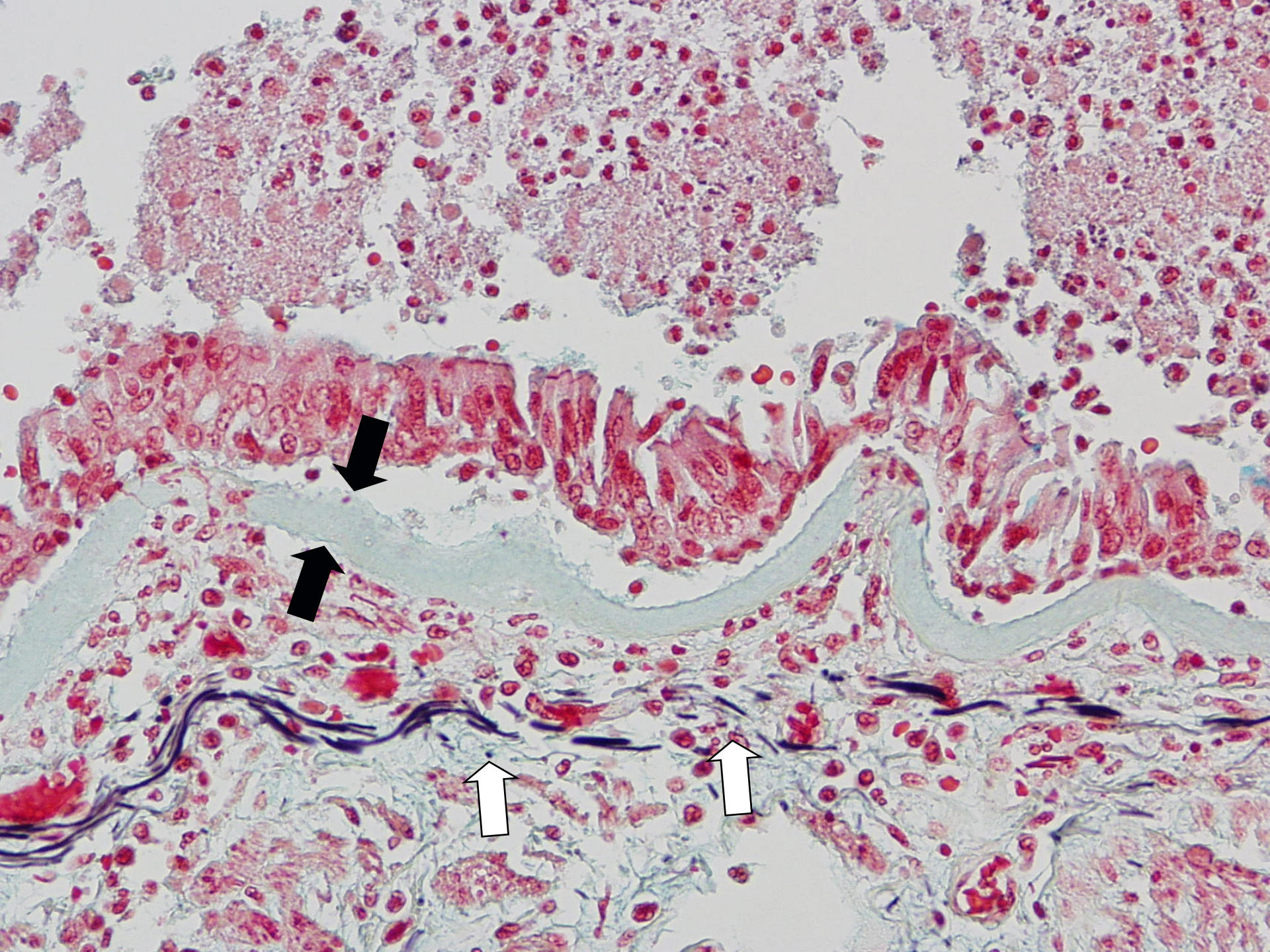
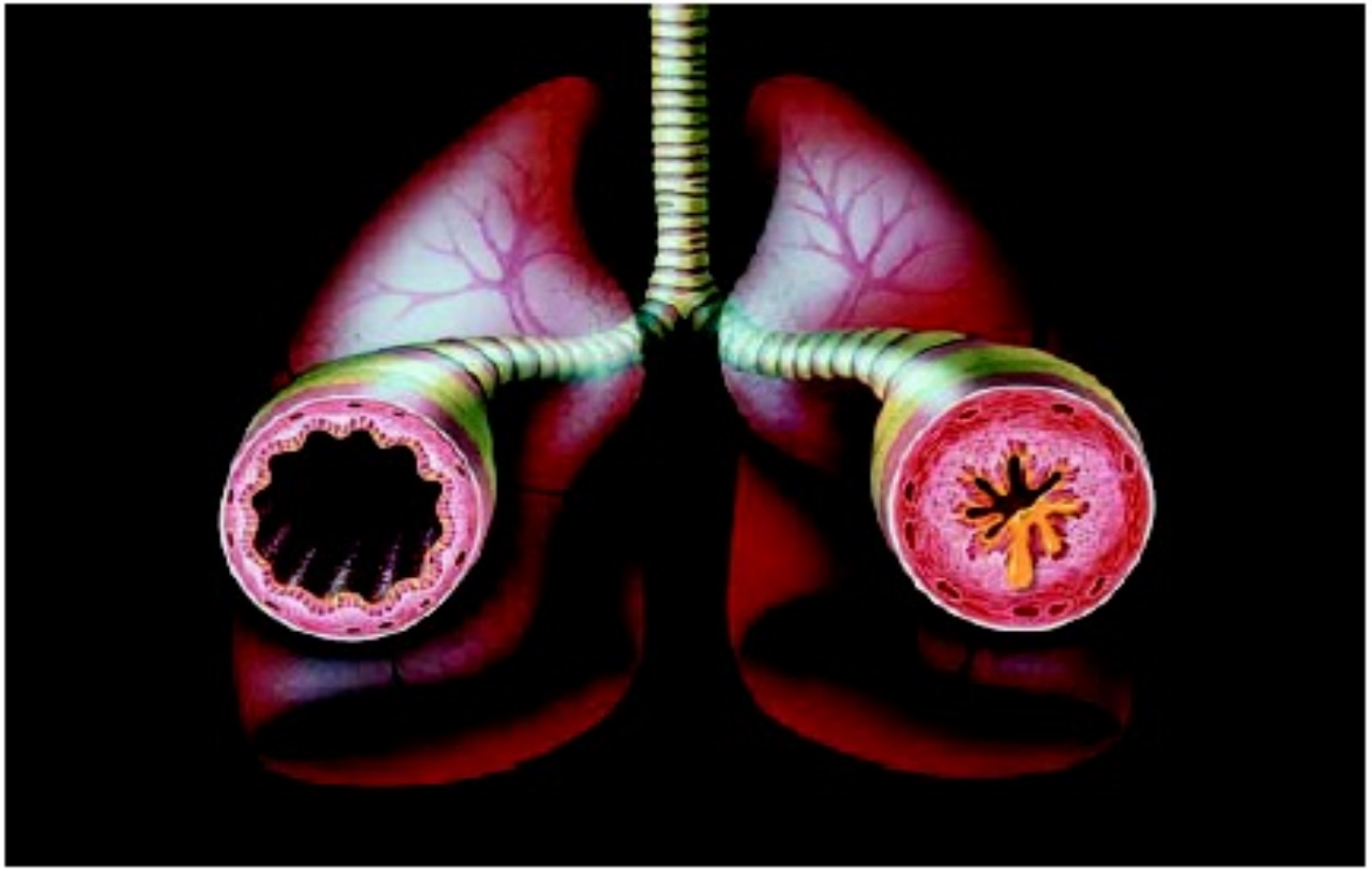
Case history

- 75-year-old woman, never smoker, with long-standing history of asthma,
- Treatment included high dose ICS/ LABA, LTRA, albuterol
- Following a respiratory tract infection, she had significant decline with loss of asthma control and lung functions
- Despite multiple hospitalizations and continued treatment with systemic steroids she had progressive course leading to death





Representation of Airways in Normal Lung and in Asthma

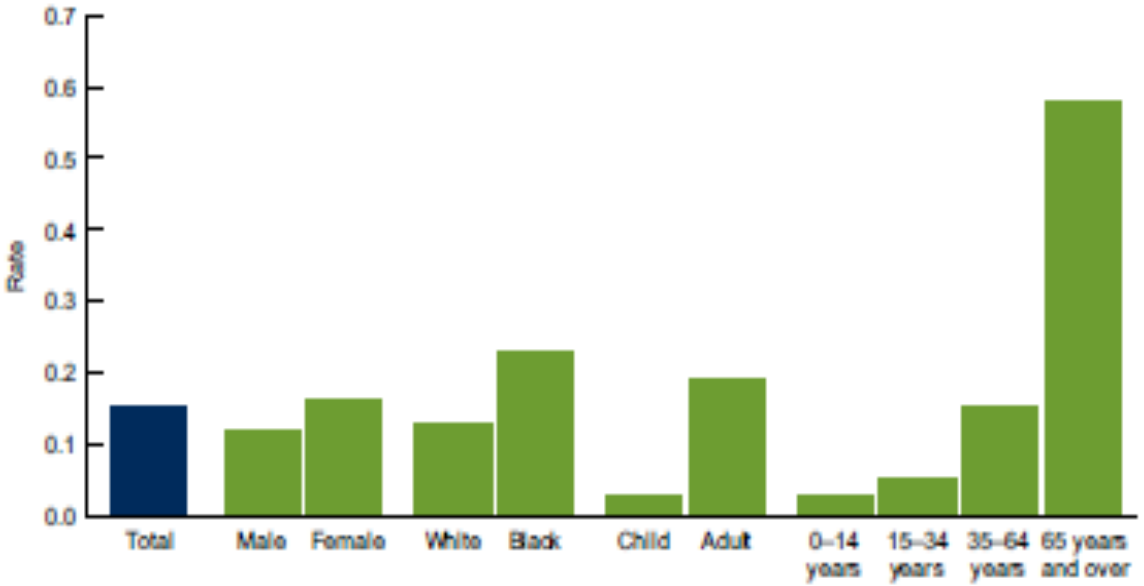


Jeffrey PK. 2001, Am. J. Respir. Crit. Care Med., 164:S28-S38

Asthma Deaths by Demographic (deaths per 1000)

Based on CDC National Vital Statistics : 2007-2009

Older asthma patients have the highest mortality rates from their disease



Dunn et al. Allergy. 2018;73:284–294

Epidemiology and Natural History

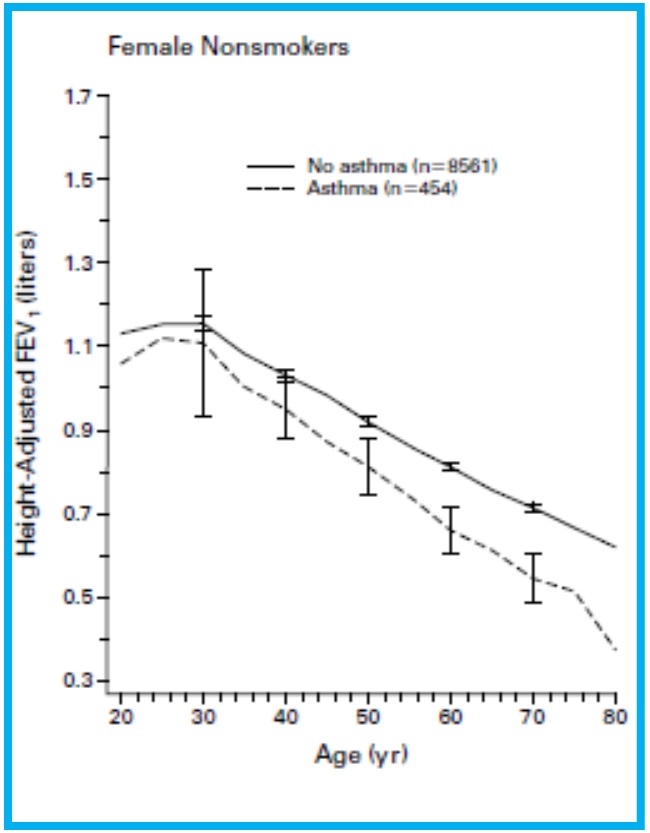
- The prevalence of asthma in subjects older than 60 years range from 3-7%
- Asthma can start in early age and persist into adulthood or may start in the elderly "*de novo*"
- Association with features of atopy (IgE, eosinophil, skin test) is less clear
- Asthma has been linked to accelerated rate of decline in lung function, especially among smokers

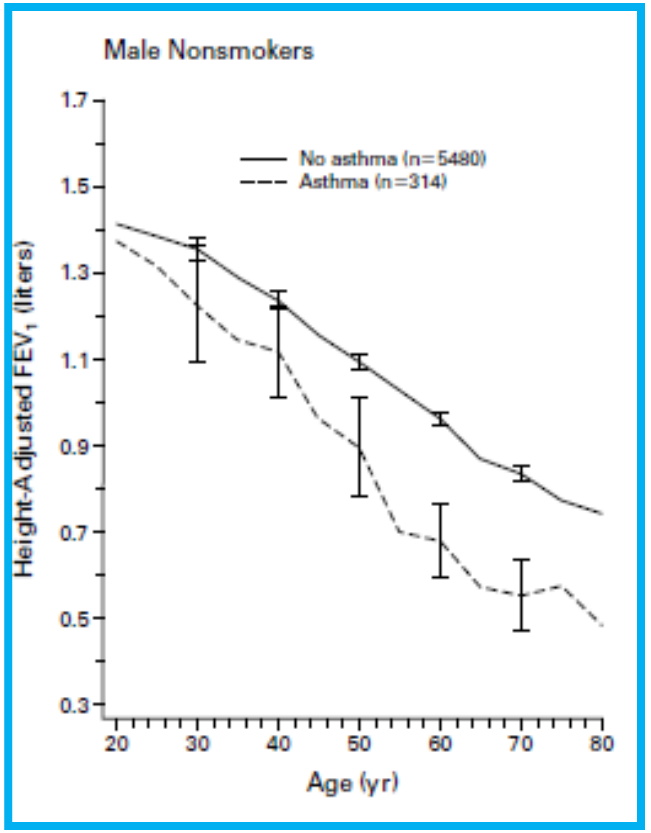
Asthma Patients Had Greater Decline in FEV1 Over Time

Pulmonary function declined among asthma patients over 15- year

17,506 subjects, (1095 had asthma)

The Copenhagen City Heart Study





Lange P et al. N Engl J Med 1998;339:1194-200

Asthma and Aging

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Severe Asthma Research Program (SARP)

- Established by NHLBI in 2001, now in its 4th funding cycle (2019-2024)
- Tasked with improving the understanding of severe asthma to help develop better treatments
- A network of clinical sites and DCC.
- DSMB for reviewing study protocols, monitoring patient safety and adverse events
- Oversight by NHLBI Project Scientists
- UW-Madison has been part of the SARP network since its inception

NIH National Heart, Lung, and Blood Institute

SARP
THE SEVERE ASTHMA RESEARCH PROGRAM
WWW.SEVEREASTHMA.ORG

Subject Characteristics in SARP I cohort

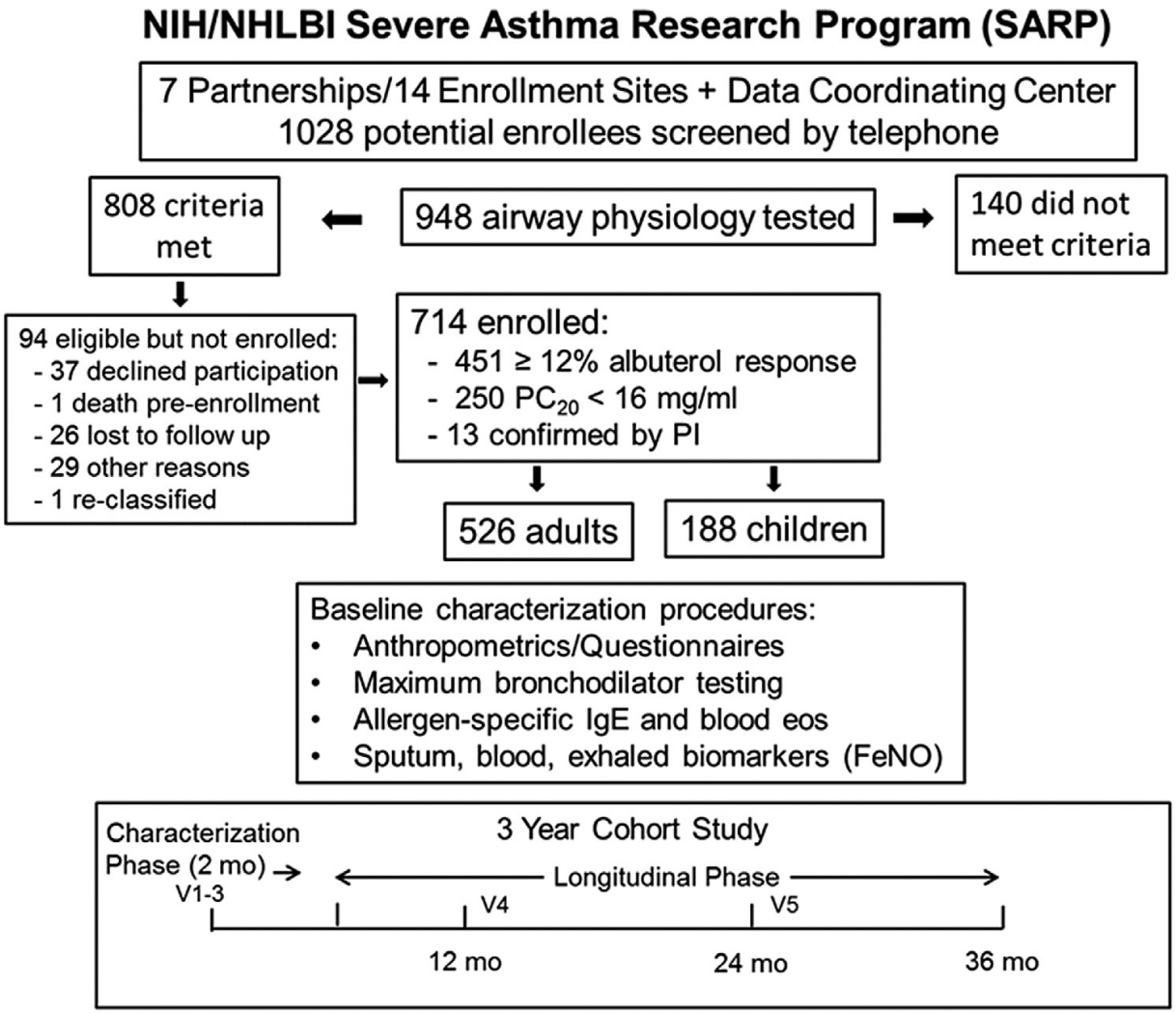
	Mild (n = 164)	Moderate (n=70)	Severe (n=204)	*P* value
Current age (y)	31 ± 12	38 ± 12	41 ± 13	<.0000‡
Age of asthma onset (y)	15 ± 13	18 ± 15	16 ± 16	0.37
Asthma duration (y)	17 ± 11	20 ± 14	25 ± 14	<.0001*
Sex (% female)	72%	56%	64%	0.05
Race (% white/African American/other)	69/25/6	66/29/5	67/26/7	0.92

‡Three-way comparison, significant because of differences between mild vs moderate and severe.
*Three-way comparison significant; all groups are different.

Moore W. et al JACI 2007, 119: 405-13

Features of the SARP III Cohort

(526 adults & 188 children with asthma, 60% severe)

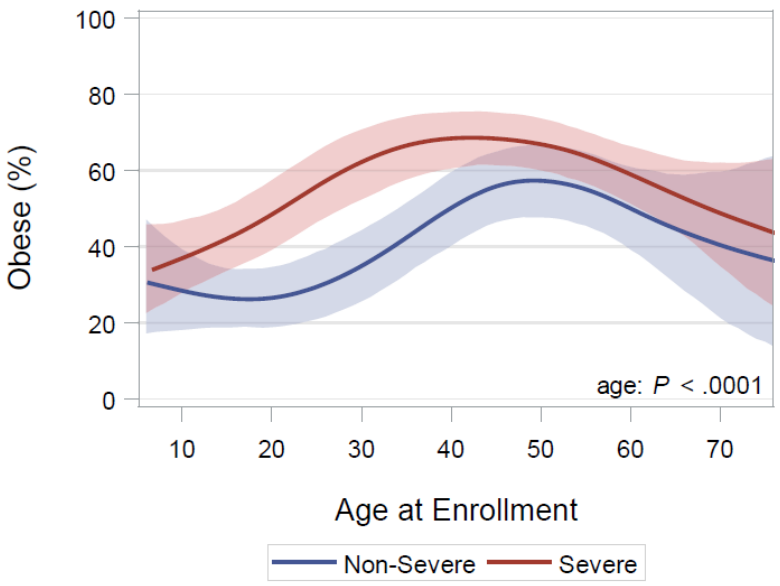


Teague WG, et al. J Allergy Clin Immunol Pract 2018;6:545-54

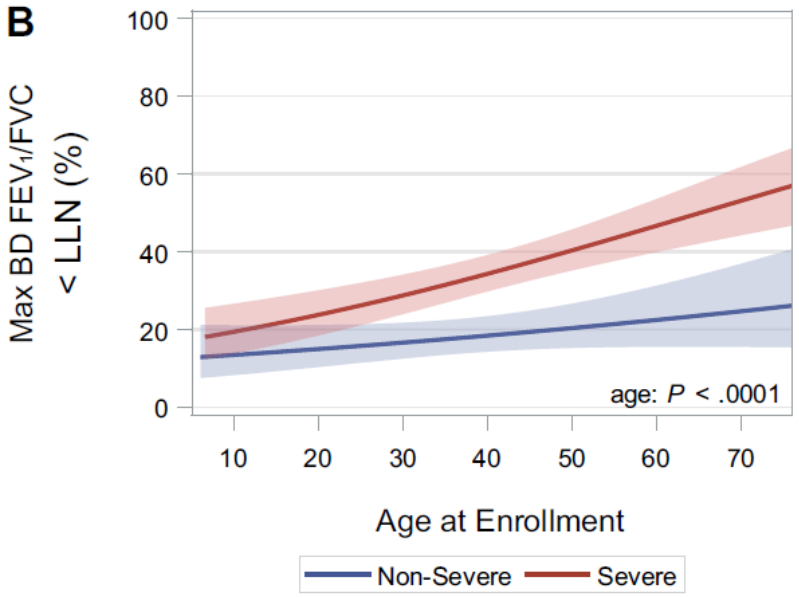
Features of the SARP III Cohort

(526 adults & 188 children with asthma, 60% severe)

Age had significant effect on obesity



More airway obstruction with age

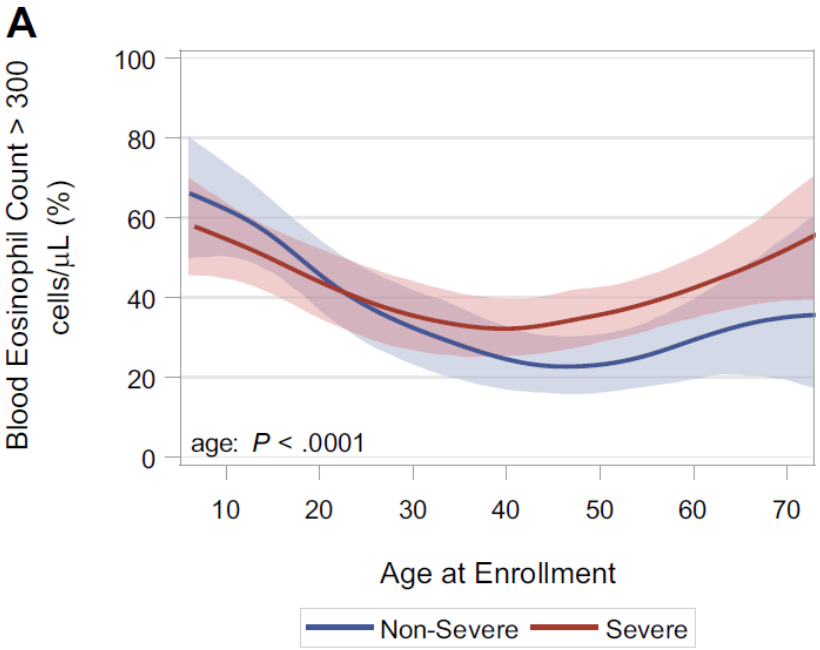


Teague WG, et al. J Allergy Clin Immunol Pract 2018;6:545-54

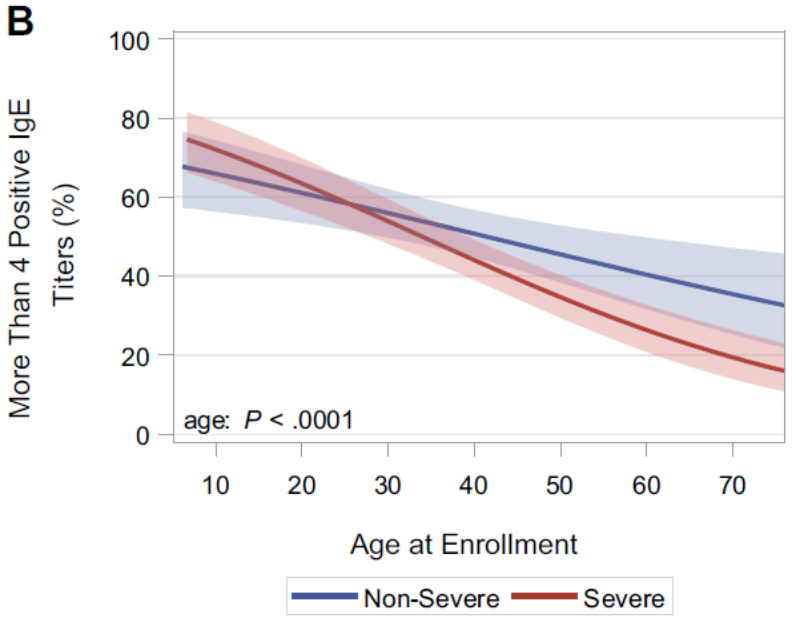
Features of the SARP III Cohort

(526 adults & 188 children with asthma, 60% severe)

Age had significant effect on EOS > 300



Less frequent positive IgE test with age



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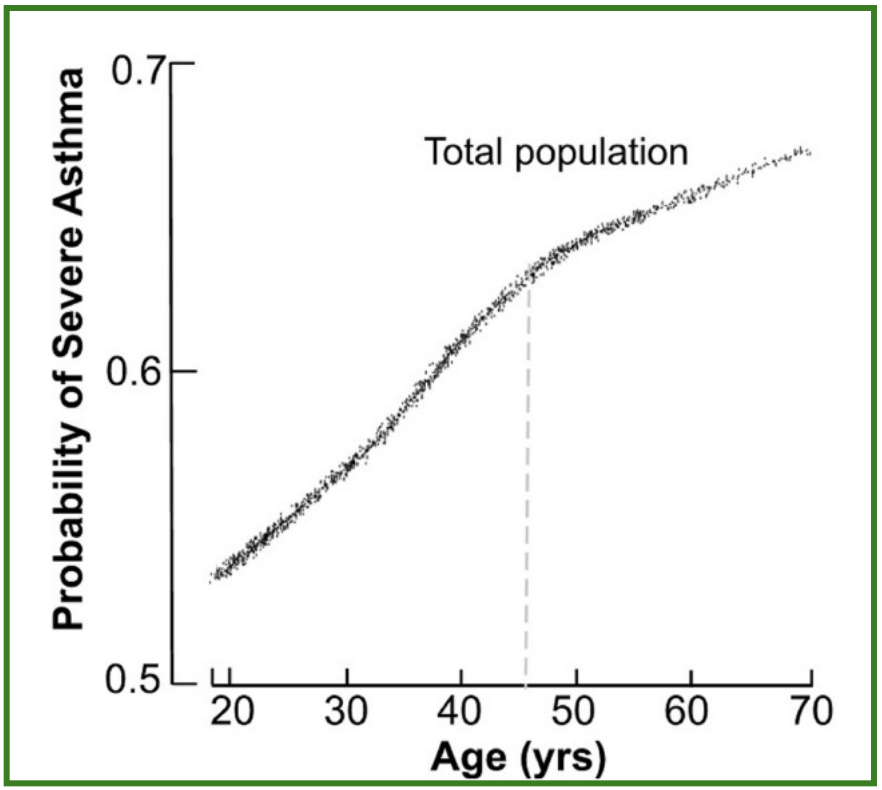
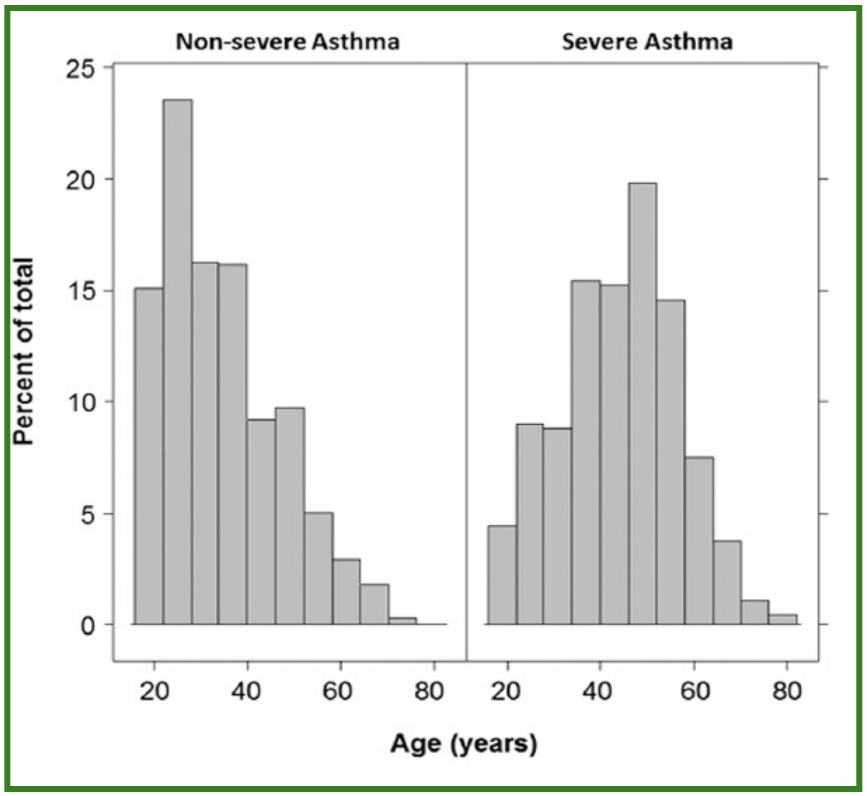
Teague WG, et al. J Allergy Clin Immunol Pract 2018;6:545-54

Asthma Is More Severe in Older Adults

Cross-sectional study of adult SARP participants
(n=1130; 454 with severe asthma)



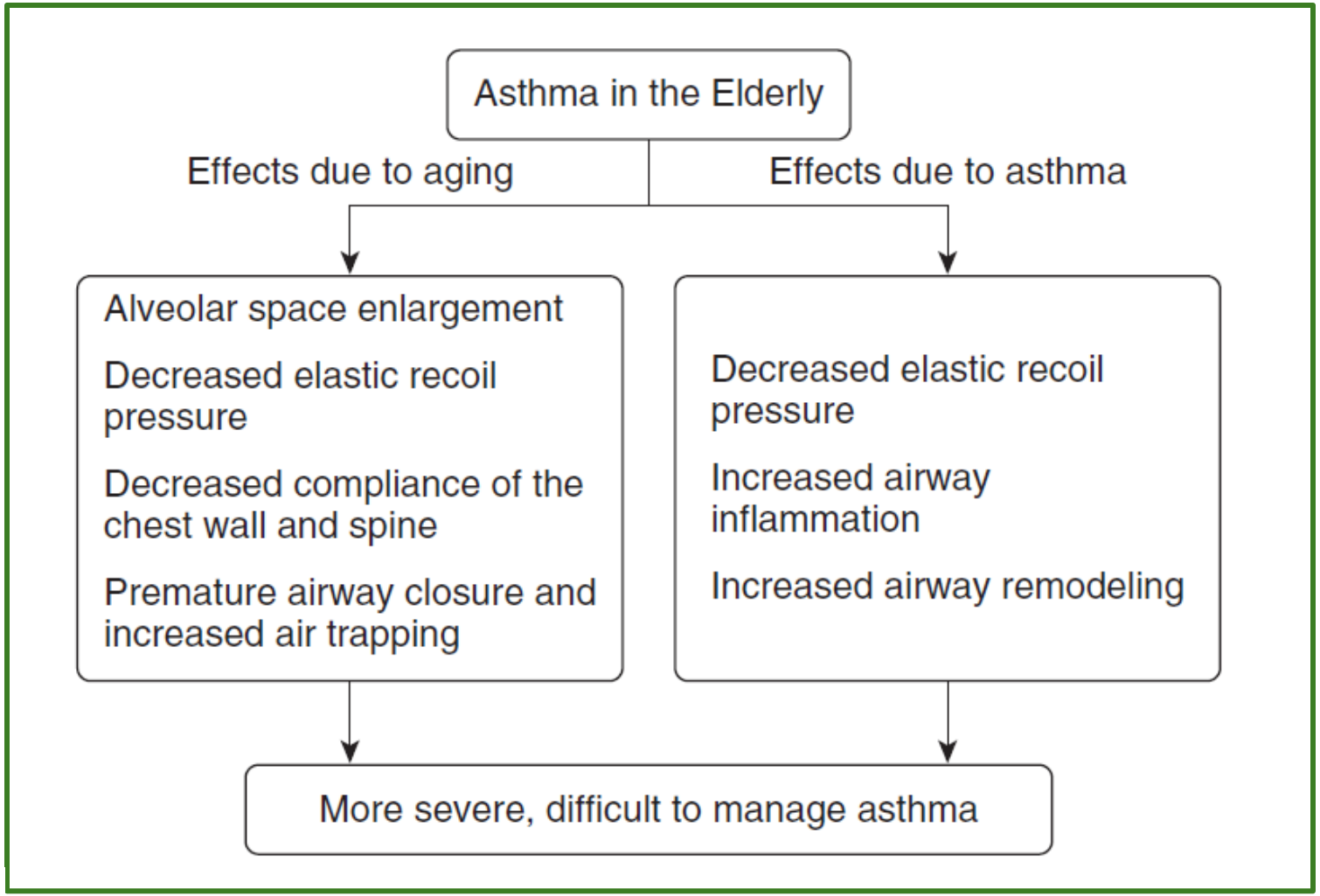


Probability of severe asthma increased with each year of life

SARP

Zein J. et al. PLOS ONE. July 22, 2015

ATS Workshop Report: Evaluation & Management of Asthma in the Elderly



Skloot et al. Ann Am Thorac Soc 13: 2064–2077, 2016

ATS Workshop Report: Evaluation & Management of Asthma in the Elderly

Feature	Characteristics in the elderly
Spirometry	Frailty influences results, limited predicted values
BD response	Less pronounced
Methacholine Challenge	Frequent contra-indications
Atopy	Less common
Co-morbidities	More common
Sputum cellularity	More neutrophilic

Skloot et al. Ann Am Thorac Soc 13: 2064–2077, 2016

Diagnosis

- History: dyspnea, wheezing, cough and chest tightness, allergies, rhinitis, sinusitis
- Examination: confirm wheezing, rhinitis, evaluate alternative diagnoses
- Pulmonary function studies:
  - Spirometry (baseline, post albuterol, post steroid trial)
  - PEFR (personal best, variability)
  - Lung volumes, DLCO (smokers, abn. CXR)
  - Methacholine challenge

Diagnostic Testing

- Chest X-ray
- Chest CT scan
- CBC (eosinophils)
- Exhaled NO
- IgE level
- Allergy skin, or RAST testing
- ECG
- Sputum examination

Differential diagnosis

- COPD
- Bronchiectasis
- ILD
- Lung cancer
- Pulmonary embolism or thromboembolic Disease
- Broncholithiasis
- Heart failure
- GERD
- Recurrent aspiration
- Vocal cord dysfunction
- Dysfunctional breathing
- Deconditioning
- Muscles weakness

➢ These conditions can mimic some of the symptoms of asthma

➢ Asthma patients can also have one or more of the above conditions in **addition** to asthma

Asthma and Aging

- Epidemiology and impact of asthma on the elderly
- Features of asthma in older patients
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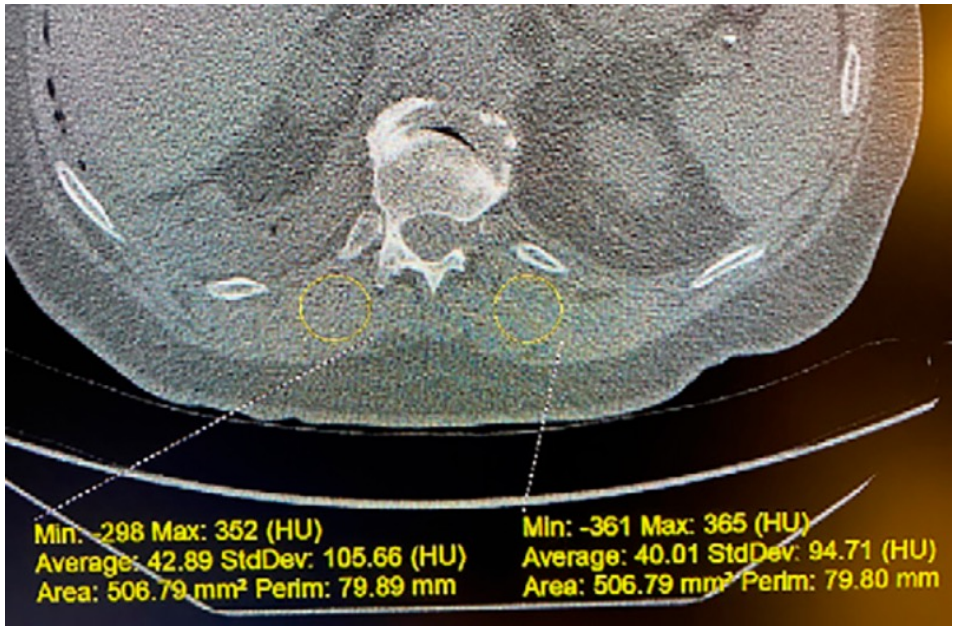
Skeletal Muscle Adiposity in Asthma

NIH National Heart, Lung, and Blood Institute

- Paraspinous muscle density (PSMD) measured from chest CT from the SARP cohort
- 219 patients with asthma (67% women, BMI 32)
- 37 control (51% women, BMI 26)



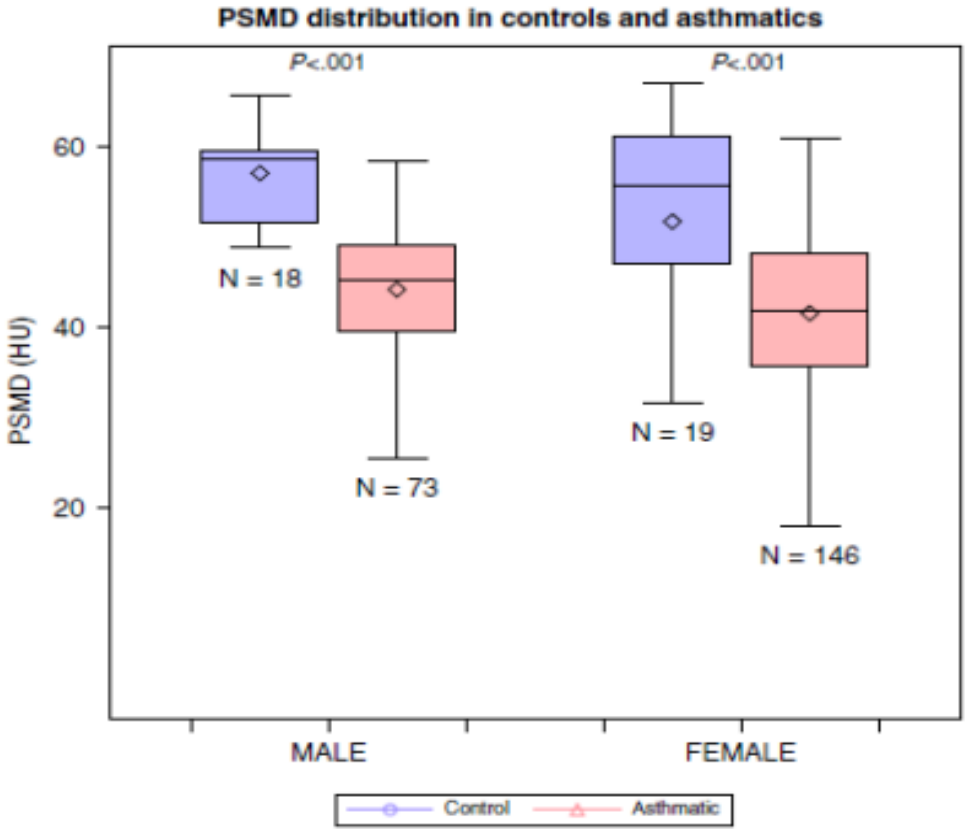
SARP

Tattersall M, et al. Am J Respir Crit Care Med 207: 475–484, 2023

Skeletal Muscle Adiposity in Asthma

National Heart, Lung, and Blood Institute

- Patients with asthma had lower muscle density than controls
- Female asthma patients with the lowest muscle density had greater decline in FEV1 over 5 years



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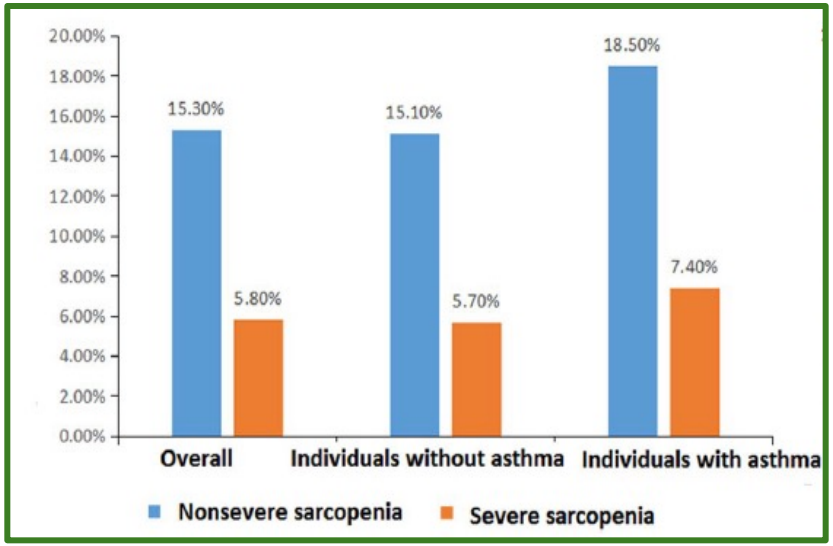
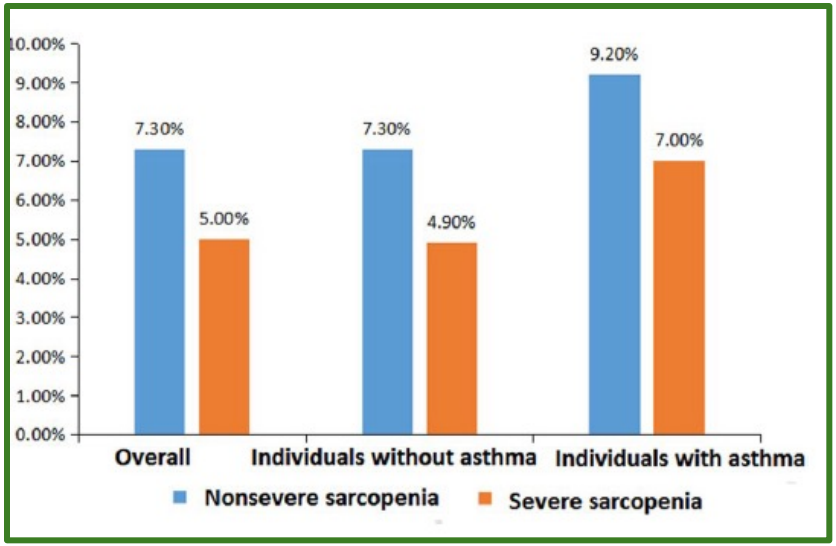
Tattersall M, et al. Am J Respir Crit Care Med 207: 475–484, 2023

Greater Prevalence of Sarcopenia in Patients with Asthma

China Health and Retirement Longitudinal Study
(15,400 people, 60-103 years old)



Study on global AGEing and adult health
(10,263 people, 60-102 years old)



Hu et al; BMC Geriatrics. 2022; 22:703

Sarcopenia, Asthma Prevalence, Lung Function and Comorbidity

- Prevalence of sarcopenia and severe sarcopenia was around18% and 7% in older asthmatics
- Sarcopenia increased with age, and among females
- Sarcopenia was associated with more frequent asthma-related symptoms, especially dyspnea
- Sarcopenia was accompanied by increased risk of airway obstruction and reduced PEFR
- Depression was more frequent in those with sarcopenia

Hu et al; BMC Geriatrics. 2022; 22:703

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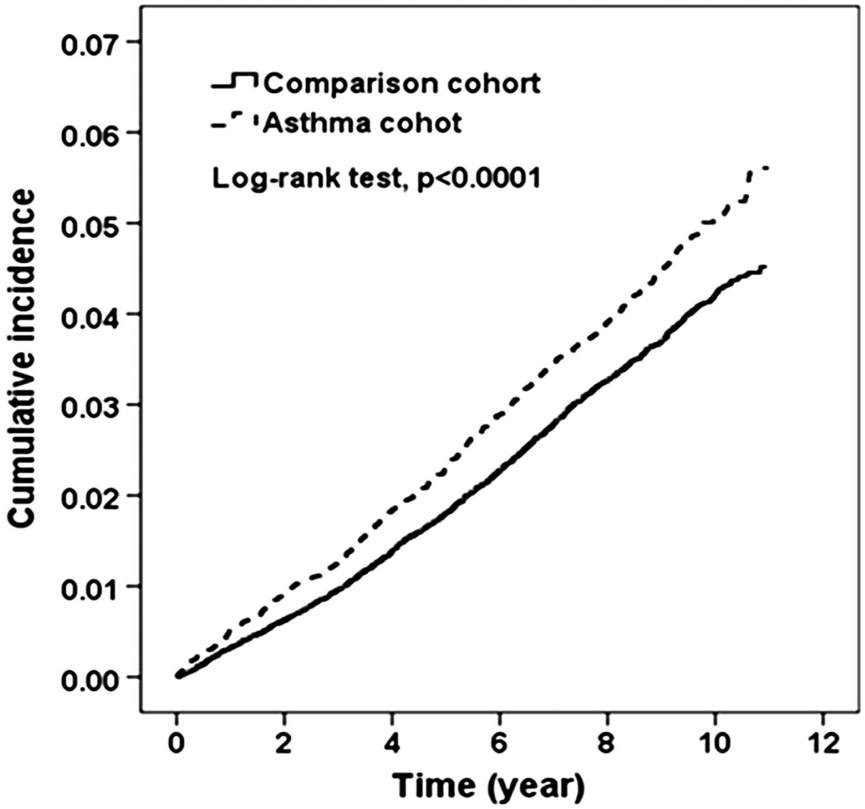
Does asthma increase the risk of dementia?

- Cohort study using National Health Insurance Research Database in Taiwan
- 12,771 patients newly diagnosed asthma (2001-2003)
- Average age 54 years, 54% women
- 51,084 people without asthma (control)
- Follow up to the date of dementia diagnosis, or to 2011

Peng Y-H et al. J Epidemiol Community Health 2015;69:123-128

Cumulative incidence for dementia in asthma *versus* control *(Kaplan-Meier analysis)*

- Asthma patients had 1.27-fold greater risk of developing dementia
- Asthma further increased the incidence of dementia in those with other risk factors (e.g. stroke, head injury)
- Increased risk with poor asthma control



Peng Y-H et al. J Epidemiol Community Health 2015;69:123-128

Incidence and hazard risk (HR) for dementia is associated with asthma severity (ER visits and admissions per year)

Average ER Visits and Admission for Asthma	Incidence (per 1000 person years)	HR
≤1	4.86	1.22
2	22.47	3.17
>2	51.19	6.18

Peng Y-H et al. J Epidemiol Community Health 2015;69:123-128

Allergic diseases and risk of incident dementia and Alzheimer's disease

- Korean national health insurance data
- Adults (≥40 years, n= 6,785,948) without history of dementia
- 260,705 dementia cases diagnosed over the following 8 yrs

- **Hazard risk of dementia was**
  - 1.20 in asthma,
  - 1.10 in allergic rhinitis, and
  - 1.16 in atopic dermatitis

Hee-Kyung Joh, et al ANN NEUROL 2023;93:384–397

Allergic diseases and risk of incident dementia and Alzheimer's disease

- All three allergic conditions were associated with increased risk of dementia.
- Asthma had the greatest risk

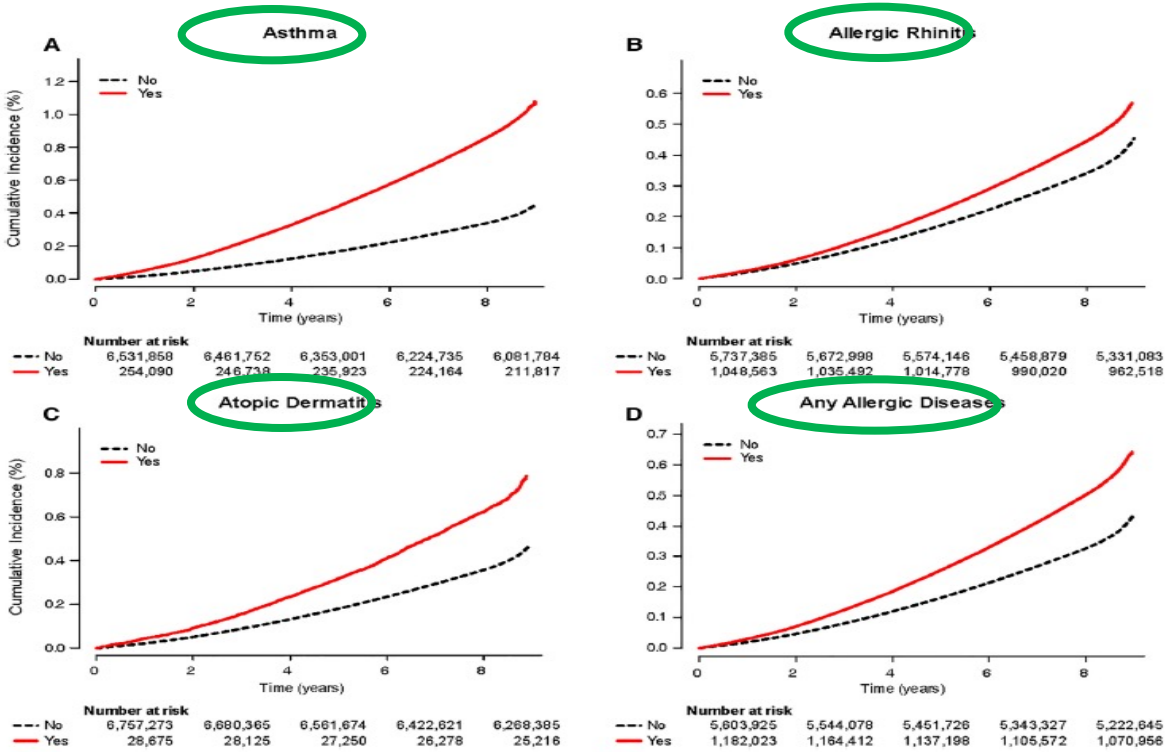


FIGURE 1: Kaplan–Meier curves of cumulative incidence of all-cause dementia up to 9-years' follow-up, stratified by allergic diseases. Cumulative incidence plots of all-cause dementia according to asthma (A), allergic rhinitis (B), atopic dermatitis (C), and any allergic diseases (D). All *p*-values <0.001 for the log-rank test. [Color figure can be viewed at www.annalsofneurology.org]

Hee-Kyung Joh, et al ANN NEUROL 2023;93:384–397

Risk of dementia among older patients with asthma

- Longitudinal study using the National Health Insurance Research Database in Taiwan
- 11,030 asthma participants >45 years of age
- 44,120 matching controls
- Enrollment 1998 to 2008
- Follow-up assessment in 2011

Chen M-H et al. JAMDA 2014;15:763-767

Asthma is associated with >2-fold increased incidence of dementia

	Asthma	Controls	P Value
Number	11,020	44,120	
Age	60.88	60.88	
Sex (% women)	58.3	58.3	
Any dementia (per 1000-person- year)	590 **(6.79)**	1091 **(3.08)**	<0.001
Alzheimer's disease (per 1000-person-years)	77 **(0.87)**	118 **(0.33)**	<0.001

Chen M-H et al. JAMDA 2014;15:763-767

Asthma is associated with increased hazard risk (HR) of developing dementia

	<65 Years	≥65 Years	Total
	HR (95% CI)	HR (95% CI)	HR 95% (CI)
Asthma	**2.48** (**1.80–3.41**)	**2.06** (**1.74–2.44**)	**2.17** (**1.87–2.52**)
Depression	3.74 (2.84–4.92)	2.79 (2.36–3.30)	3.12 (2.71–3.60)
Alcohol-related disorders	0.65 (0.16–2.64)	2.03 (1.08–3.81)	1.56 (0.88–2.77)
Diabetes	1.31 (1.03–1.68)	1.13 (1.00–1.28)	1.18 (1.05–1.31)
Cerebrovascular diseases	2.39 (1.85–3.08)	1.50 (1.33–1.68)	1.63 (1.46–1.82)
Use of ICS	1.11 (0.79–1.57)	0.96 (0.81–1.15)	0.98 (0.84–1.15)

Chen M-H et al. JAMDA 2014;15:763-767

Incidence & prevalence of Alzheimer's and any dementia among asthma patients in a large Medicare data base (n=5,406,732)

	Controls n = 4,359,060 n (%)	Cases/ 100,000 (Controls)	Asthma n = 578,846 n (%)	Cases/ 100,000 (Asthma)	P value
2 yr Alzheimer's Incidence	48,186 **(1.0)**	1105	8153 **(1.2)**	1408	<0.001
Ever Alzheimer's (Prevalence)	258,635 **(5.4)**	5409	53,175 **(7.8)**	7834	<0.001
2 yr Any Dementia Incidence	193,314 **(4.3)**	4435	37,594 **(5.5)**	6495	<0.001
Ever Dementia (Prevalence)	616,256 **(12.9)**	12,887	137,478 **(20.3)**	20,255	<0.001

In Asthma there was:

- *20% increased 2-year incidence, and*
- *> 40% increased prevalence of Alzheimer's disease*

Bartels C, et al. Table published in Adv Exp Med Biol. 2023;1426:185-214.

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MESA Multi-ethnic study of atherosclerosis

NIH National Heart, Lung, and Blood Institute

- NHLBI-Funded cohort study of ethnically diverse population

- 6,792 participants, 53% women, average age 62, were free of CVD at baseline
  - 156 with persistent asthma, on controller medications
  - 511 with intermittent asthma, not on controller medications
  - 6125 without asthma

- Research Questions: does greater asthma severity lead to more CVD events?

Matt Tattersall, DO
Assistant Professor of Medicine
Division of Cardiology

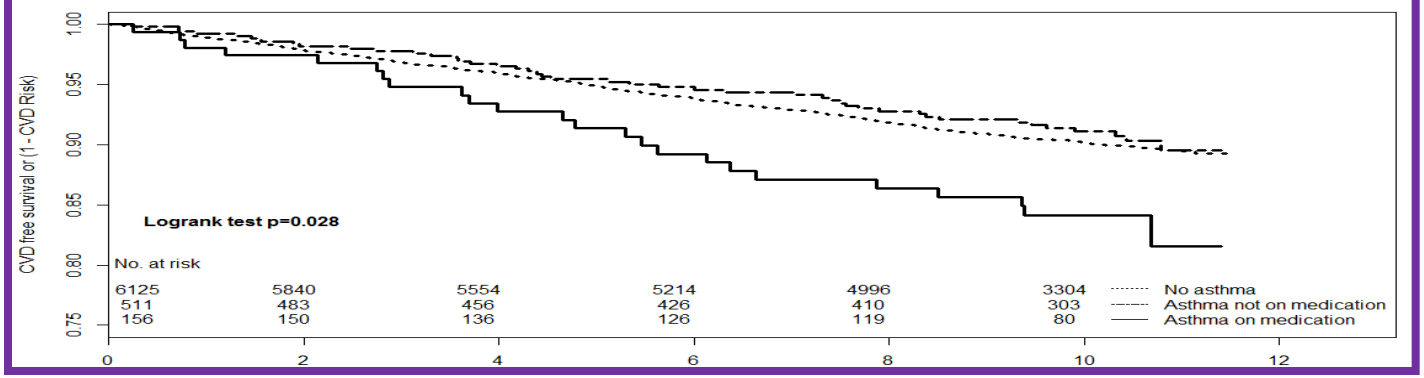
Tattersall MC, et al. Arterioscler Thromb Vasc Biol. 2015 Jun;35(6):1520-5.

MESA Multi-ethnic study of atherosclerosis

NIH National Heart, Lung, and Blood Institute

Model 1: Adjusted for age, race, sex

Full Model: Model 1 + cholesterol, blood pressure, smoking, diabetes, BP meds, cholesterol meds, BMI, family history, income



	Persistent Asthma *		Intermittent Asthma *	
Model	**Hazard Ratio**	**P value**	**Hazard Ratio**	**P value**
Model 1	1.72	0.010	1.13	0.452
Full Model	1.59	0.040	1.10	0.655

* Patients without asthma as reference

Tattersall MC, et al. Arterioscler Thromb Vasc Biol. 2015 Jun;35(6):1520-5.

Persistent Asthma Is Associated With Carotid Plaques

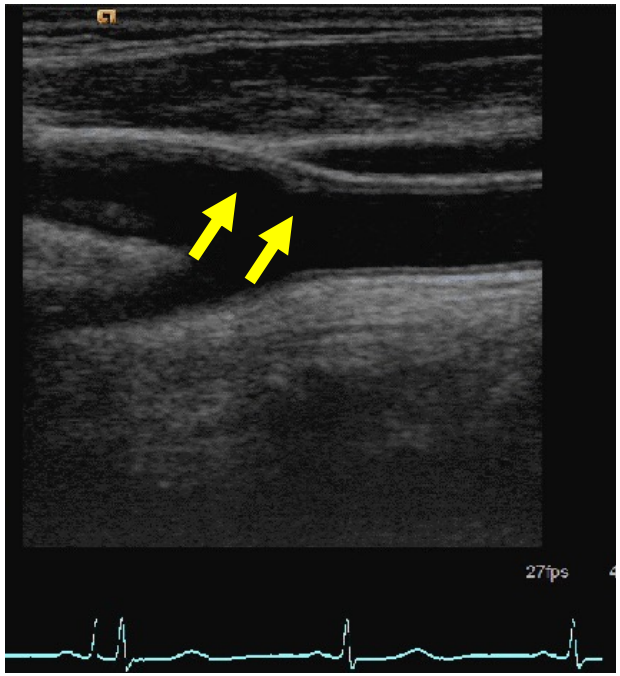
- Carotid ultrasound was done to detect plaques in MESA

- 5029 participants, 53% women, mean age 62 years
  - 109 with persistent asthma, on controller medications
  - 388 with intermittent asthma, not on controller medications
  - 4532 without asthma

- Research Questions: is greater asthma severity associated with more plaques? What is the role of systemic inflammation?

Tattersall et al . J Am Heart Assoc. 2022

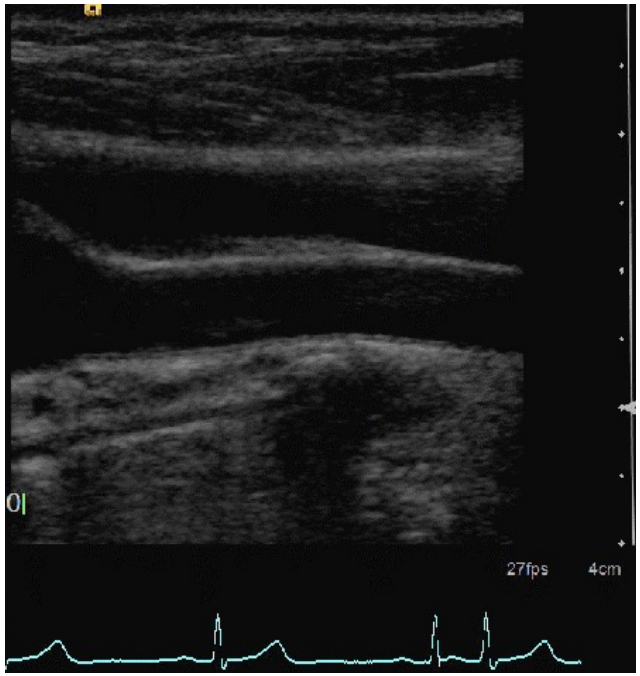
Persistent Asthma Is Associated With Carotid Plaques



58yo Female: asthma

Carotid bulb plaque

Mean intimal thickness 0.641 mm



55yo Female: non-asthma

No plaque

Mean intimal thickness 0.489 mm

Courtesy of Dr. Matt Tattersall (UW Madison)

More Plaques and Higher Serum Inflammatory Markers in Persistent Asthma

- **Carotid plaques** were present in
  - 50.5 0f Control subjects
  - 49.5% of Intermittent Asthma
  - 67% of Persistent asthma
- Patients with persistent asthma had higher serum levels of:
  - *IL6*
  - *CRP*
- **Total Plaque Score** correlation with asthma phenotype persisted after adjusting for IL6 and CRP levels
- Other factors are likely to contribute to this relationship

Variables	No asthma	Intermittent asthma	Persistent asthma
IL-6, pg/mL	1.52 (1.21)	1.60 (1.21)	1.89 (1.61)*
CRP, mg/L	3.61 (5.53)	4.54 (6.84)*	6.49 (11.22)*

Data are given as mean (SD). CRP indicates C-reactive protein; and IL-6, interleukin 6.

*Significantly different from no asthma group at the $P<0.05$ level.

Tattersall et al . J Am Heart Assoc. 2022

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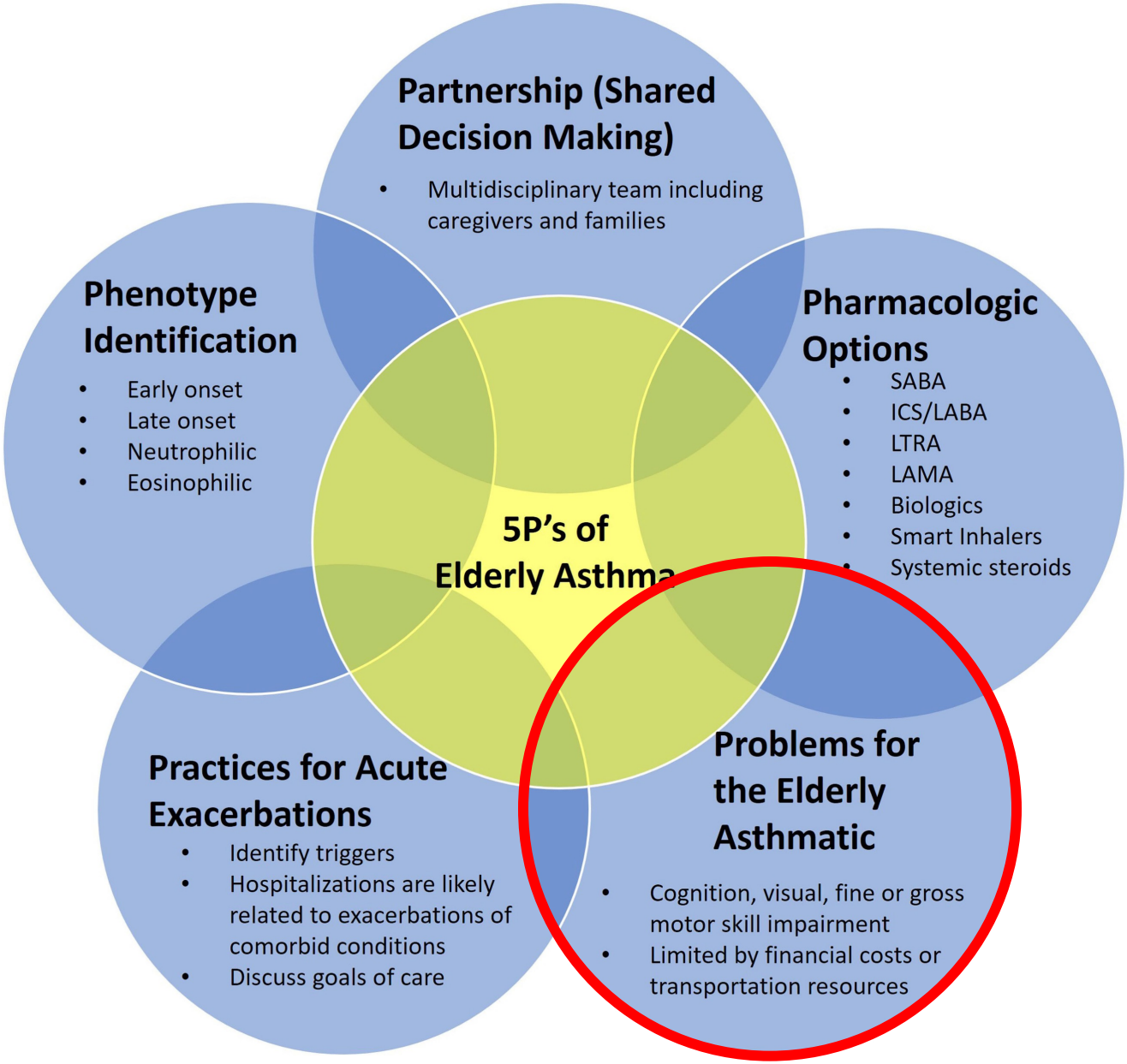
Management of Asthma in the Elderly

- **Education**: open communications, set goal clear plans, involve family, ensure understanding, partnership in care
- **Monitoring:** symptoms, objective measures
- **Avoiding triggers**: environmental control, vaccines, smoking cessation
- **Medications**: adverse effect and drug interactions are greater in the elderly



Khosa et al. Journal of Asthma and Allergy 2023:16 33–43

Adverse Effects of Beta Agonists

- Adverse effect of beta agonists (dose-dependent) are more common in the elderly, and they include:
  - tremor
  - anxiety
  - palpitation and arrhythmias
  - increase oxygen demands of the heart (ischemia)

- **To reduce side effects**
  - Teach MDI technique and recheck on return visit
  - Use spacers
  - Consider combination drugs when appropriate to simplify the regimen

Adverse effects of Inhaled steroids

- Cough & thrush
- Laryngomalacia (hoarseness)
- Pneumonia
- Dermal thinning, bruising
- Osteoporosis
- Cataract/ glaucoma

- **To reduce side effects**
  - Teach MDI technique and recheck on return visit
  - Use spacers
  - Use lowest dose possible (step down when appropriate)

Adverse effects of systemic corticosteroids

- Fluid retention, CHF
- Hypokalemia
- Adrenal suppression
- Peptic ulcer
- Osteoporosis
- Skin thinning
- Myopathy
- Diabetes Mellitus
- Cataract /Glaucoma
- Depression
- Infections
- Arthralgia and myopathy on withdrawal

- Consider biologics in patients with recurrent exacerbations or severe asthma requiring systemic steroids
- While biologics do not suggest an upper age for use, data in elderly patients are limited


Thank you !