Brigham and Women's Hospital
Founding Member, Mass General Brigham

COPD: beyond cigarette smoking

Craig P. Hersh, MD, MPH
Associate Physician
Channing Division of Network Medicine
and Division of Pulmonary and Critical Care Medicine
Brigham and Women's Hospital
Associate Professor of Medicine
Harvard Medical School

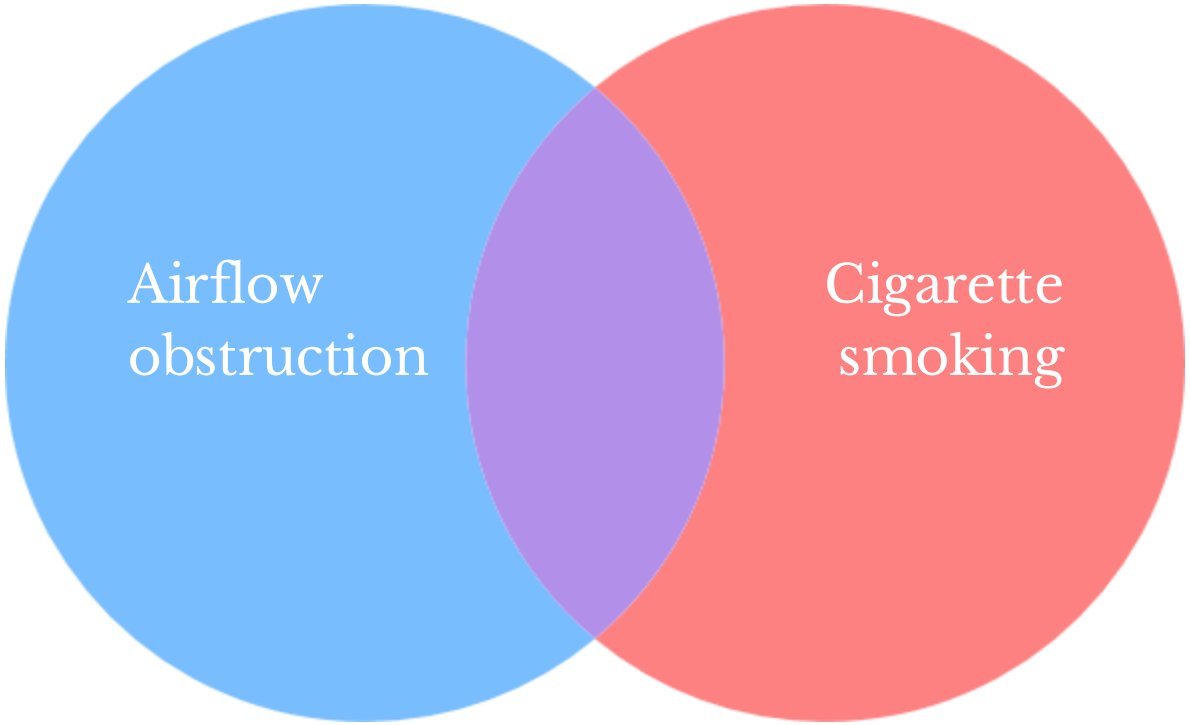
Disclosures

- Grant support:
  - Bayer
- Consulting fees:
  - Apogee Therapeutics, Chiesi, Ono Pharma, Sanofi, Takeda, Verona Pharma

Case presentation

- 66F never smoker presents with COPD
- Exertional dyspnea 1 flight stairs, walks slowly on level
- Mild dry cough
- No asthma or childhood lung disease
- No family history of lung disease
- FEV_1 0.87 (38%), FVC 2.13 (72%), FEV_1/FVC 0.41

COPD: beyond cigarette smoking

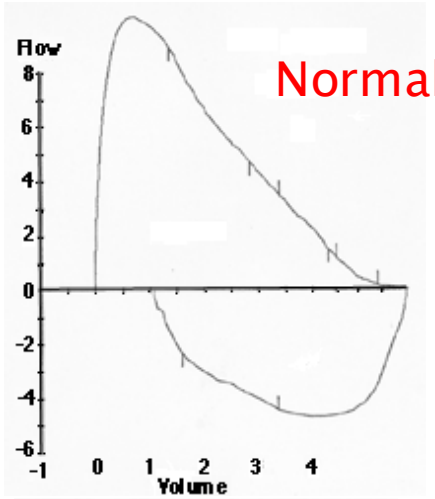


What is COPD?

- Heterogeneous lung condition
- Chronic respiratory symptoms
- Abnormalities of the airways and/or alveoli
- Persistent airflow obstruction

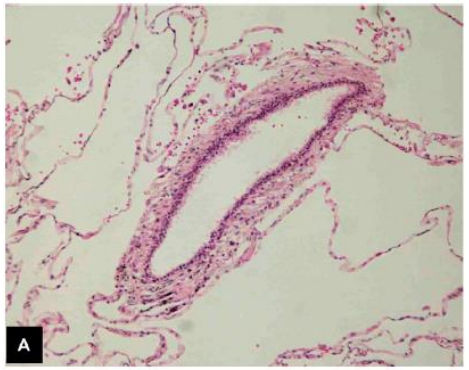
Global Initiative for Chronic Obstructive Lung Disease 2024
www.goldcopd.org

Multiple pathologies of COPD

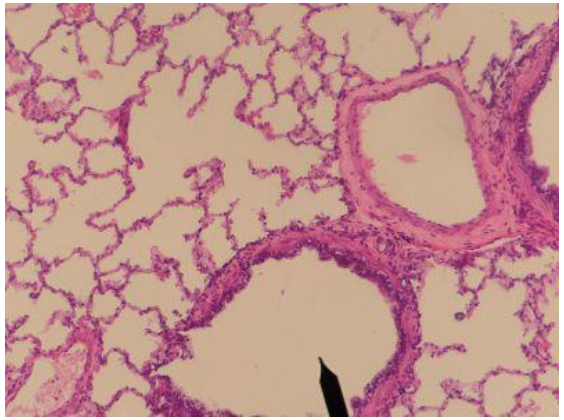


Normal spirometry

Emphysema

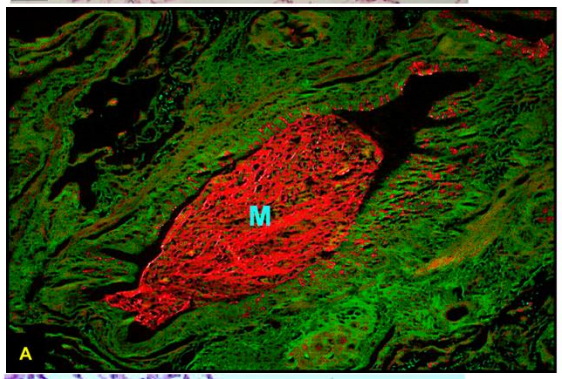


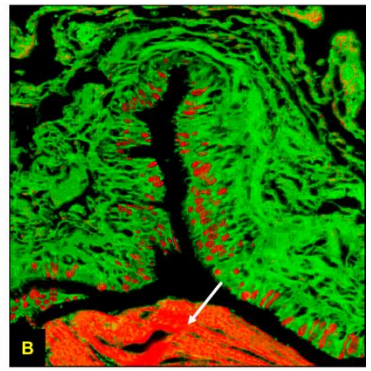
Normal

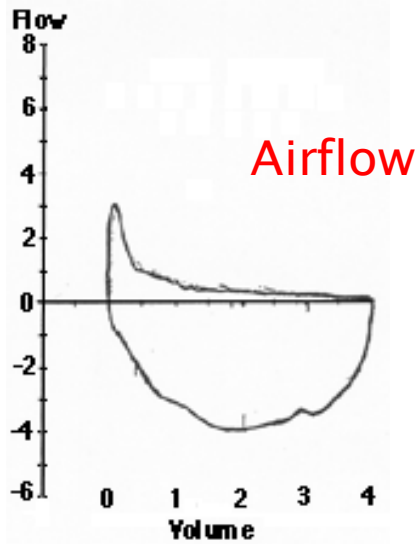


histology-world.com

Mucus metaplasia

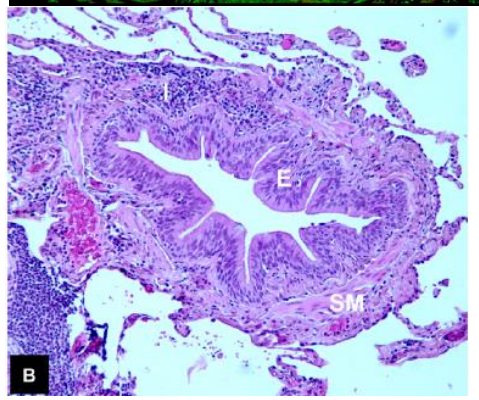






Airflow obstruction

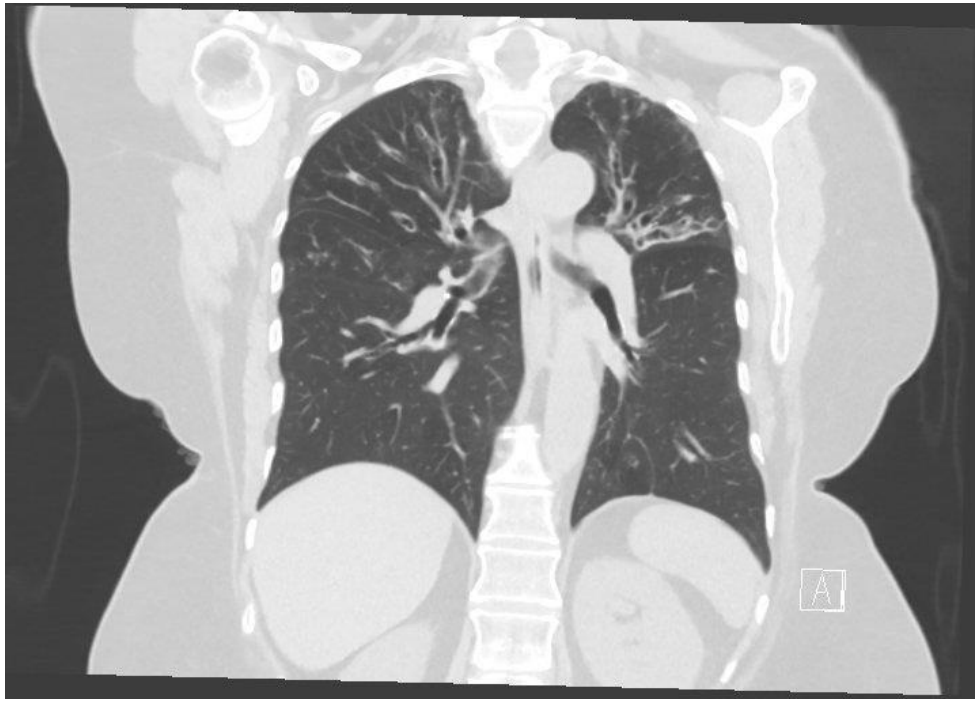
Small airway disease



Kim V, Proc Am Thorac Soc 2008;5:478

COPD: differential diagnosis

- Asthma with fixed obstruction
- Bronchiectasis
- Post-tuberculosis
- Obliterative bronchiolitis
- Diffuse panbronchiolitis



How to define a smoker?

CDC

≥ 100 cigarettes in lifetime

Most COPD Studies

≥ 10 pack-years

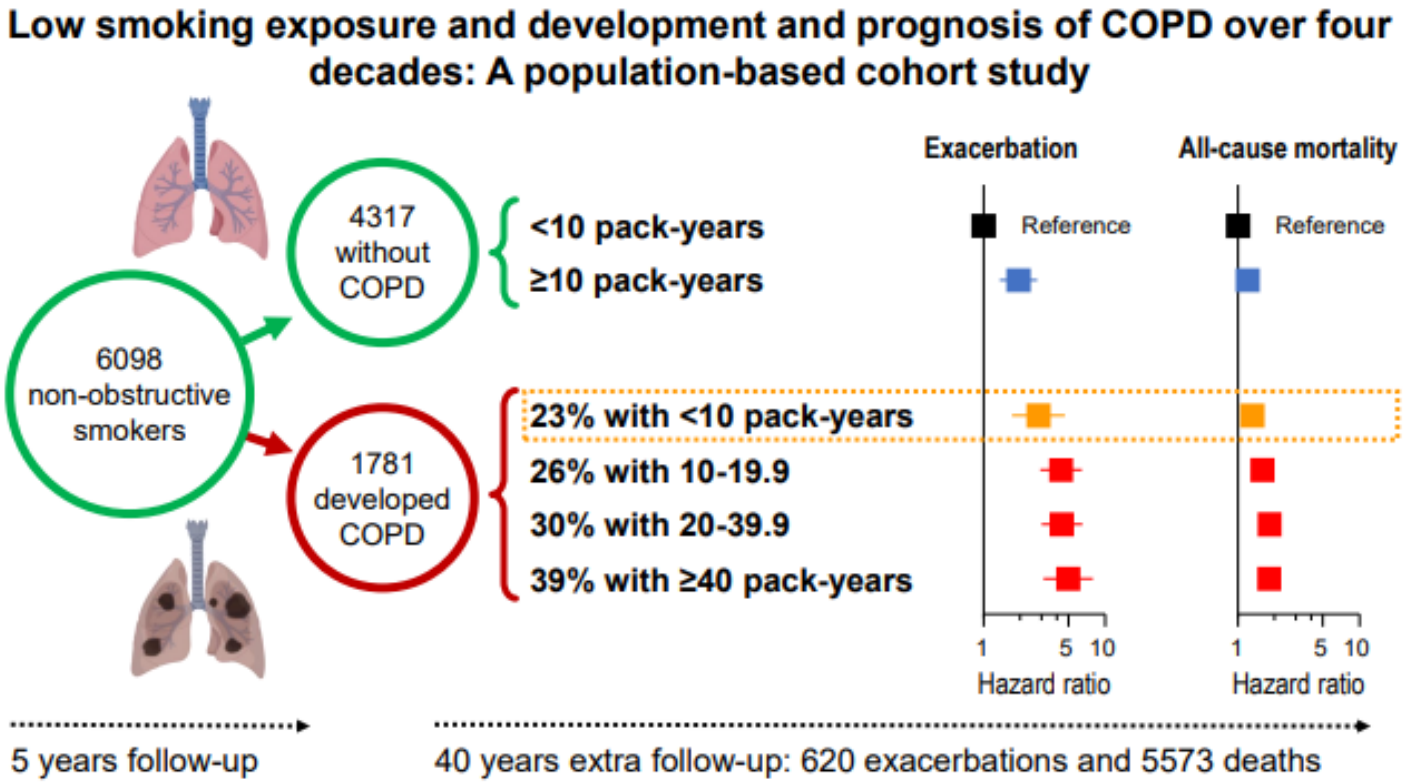
https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm

How to define a smoker?

CDC	Most COPD Studies
≥ 100 cigarettes in lifetime	≥ 10 pack-years = 73,000 cigarettes

https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm

Is 10 pack-year threshold appropriate?

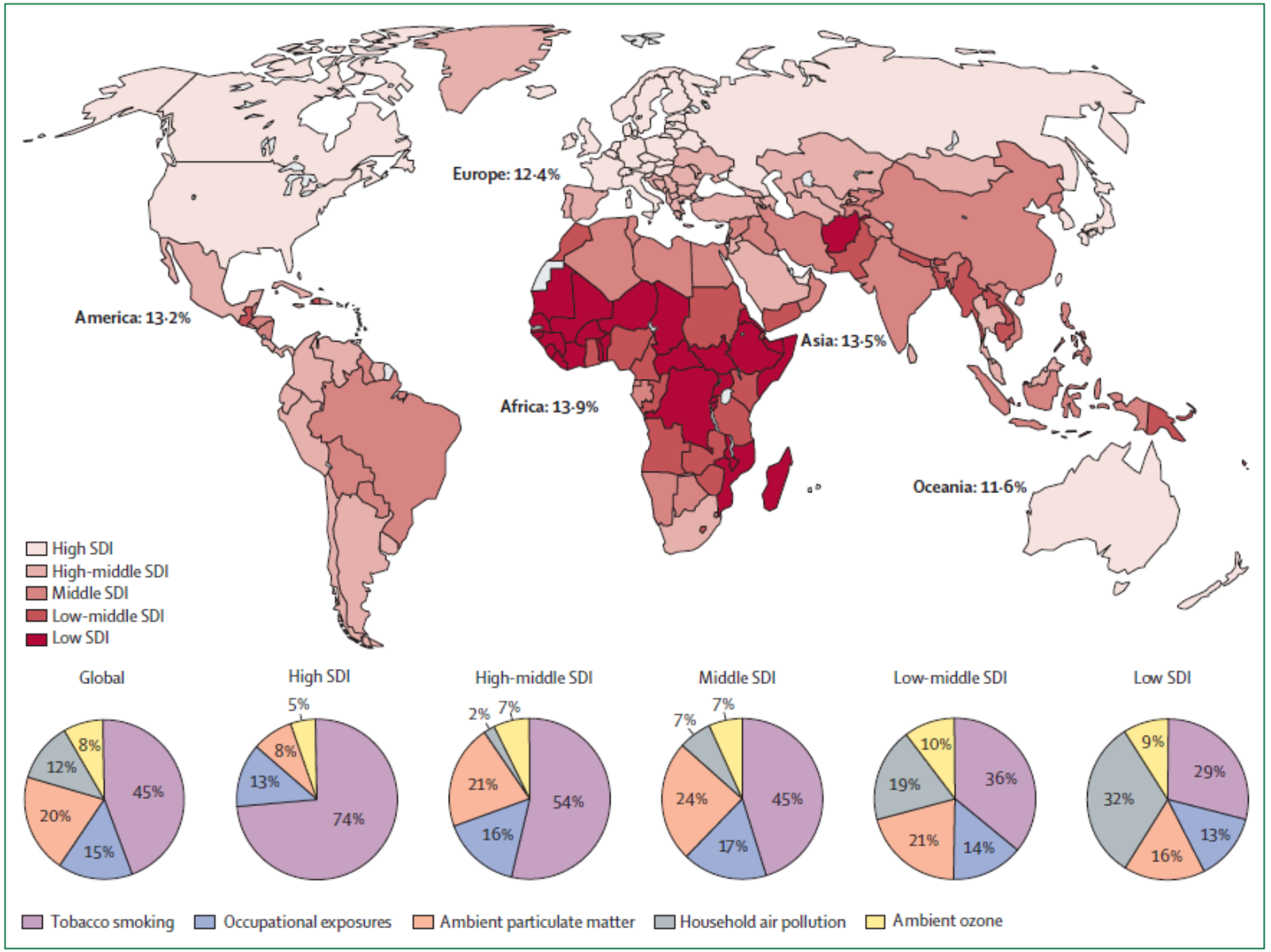


Limitations of 10 py cutoff:

- Younger/early COPD
- Developing world
- Decreasing smoking rates

Colak Y, ERJ 2024;64:2400314

Exposures and COPD worldwide



Yang IA, Lancet Respir Med 2022;10:497

COPD Etiotypes

Proposed Taxonomy (Etiotypes) for COPD

Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

COPD Etiotypes

Proposed Taxonomy (Etiotypes) for COPD

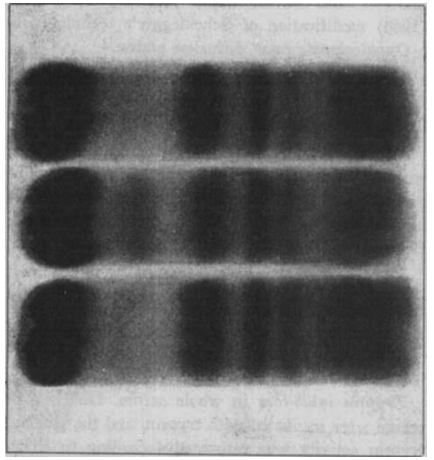
Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

Alpha-1 antitrypsin deficiency

- *SERPINA1* gene on chromosome 14
- Autosomal co-dominant
- Prevalence in USA >100,000 (3x CF)
- 10-15% diagnosed



Laurell and Eriksson 1963

Table. Commonly Identified Pi Phenotypes With the Corresponding Range of Serum α_1-Antitrypsin Concentration in mg/dL (and μM), Predicted Prevalence in the United States, and Disease Association

Phenotype	Range of Serum AAT Concentration, mg/dL (μM)[a]	US Predicted Prevalence[b]	Disease Association
PiMM	102-254 (19-47)	NA	None
PiMS	86-218 (16-40)	1:17	No proven association
PiMZ	62-151 (11-28)	1:48	Lung disease
PiSS	43-154 (8-28)	1:922	Lung disease
PiSZ	38-108 (7-20)	1:1299	Lung and liver disease
PiZZ	≤29-52 (≤5-10)	1:6211	Lung and liver disease

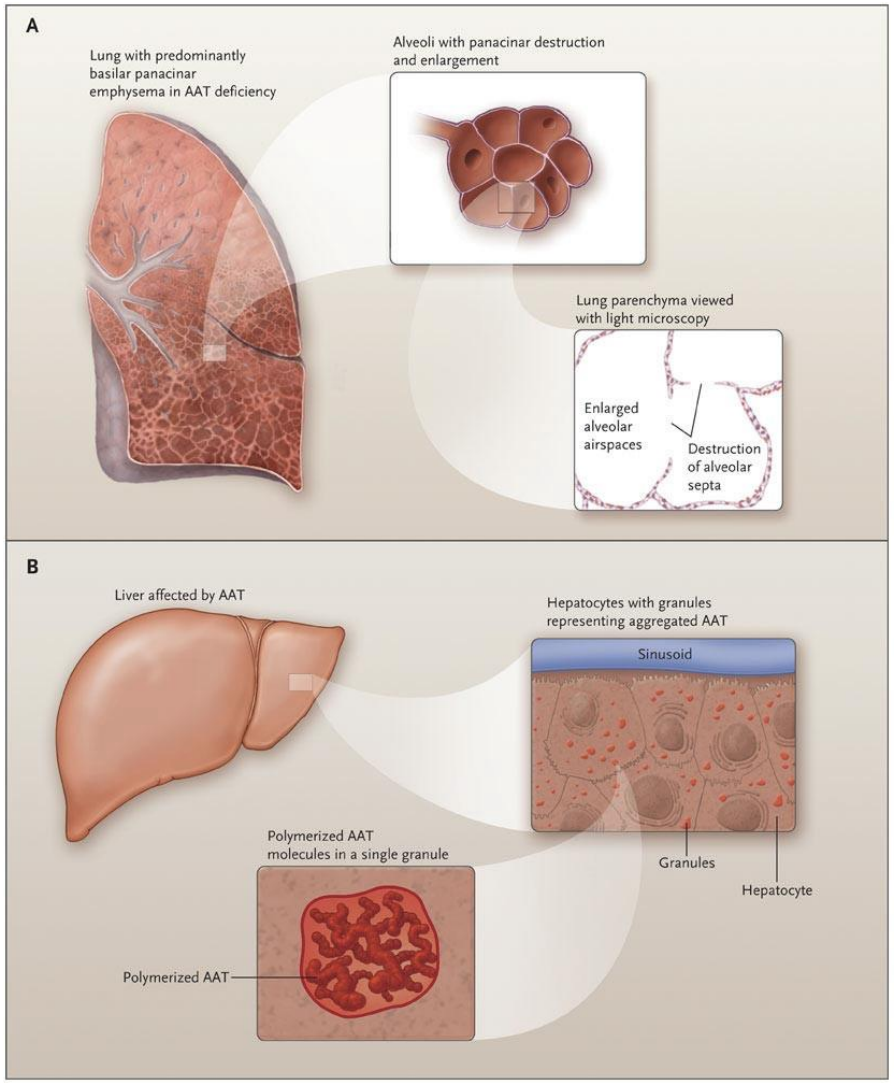
Abbreviation: AAT, α_1-antitrypsin.

[a] From Bornhorst et al 2013.[2]

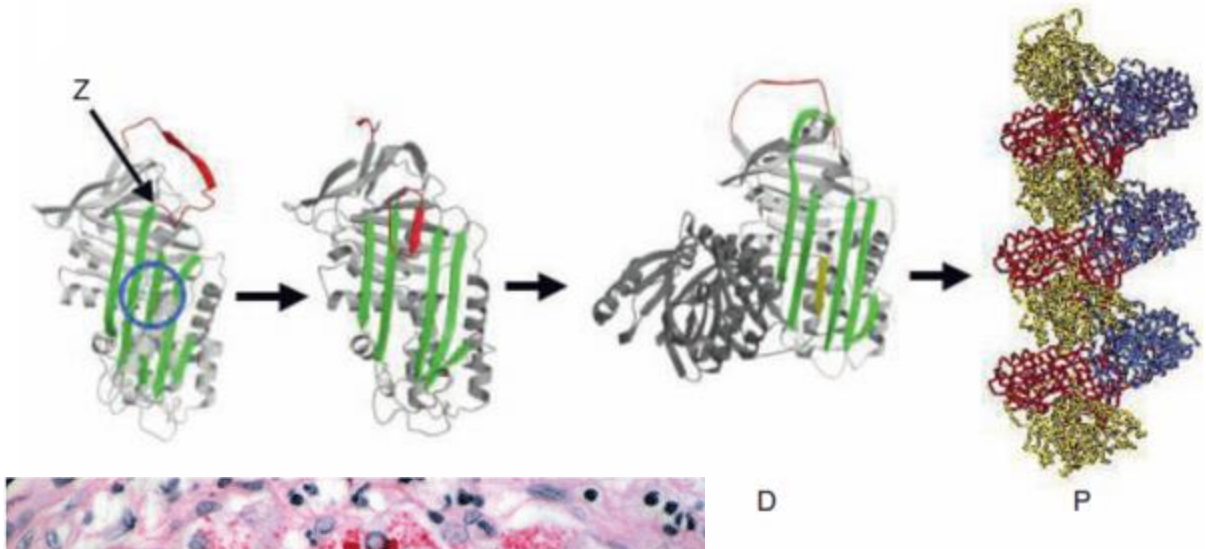
[b] From de Serres et al 2014.[3]

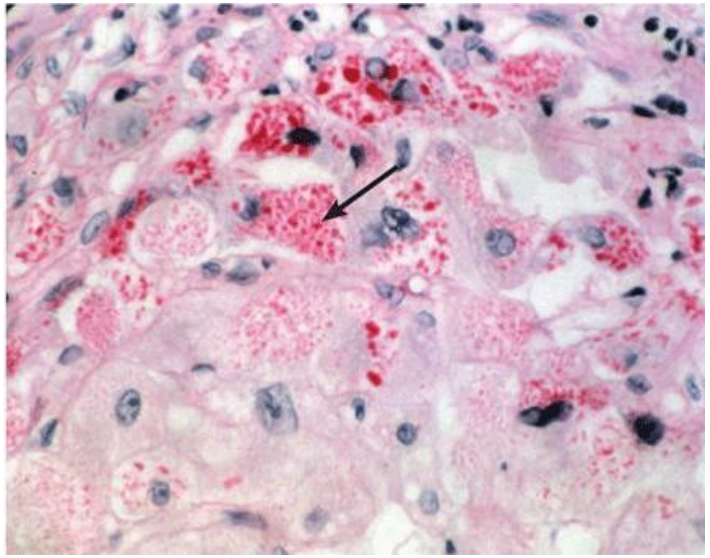
Hurley and O'Connor, JAMA 2018

AATD Pathophysiology - Liver



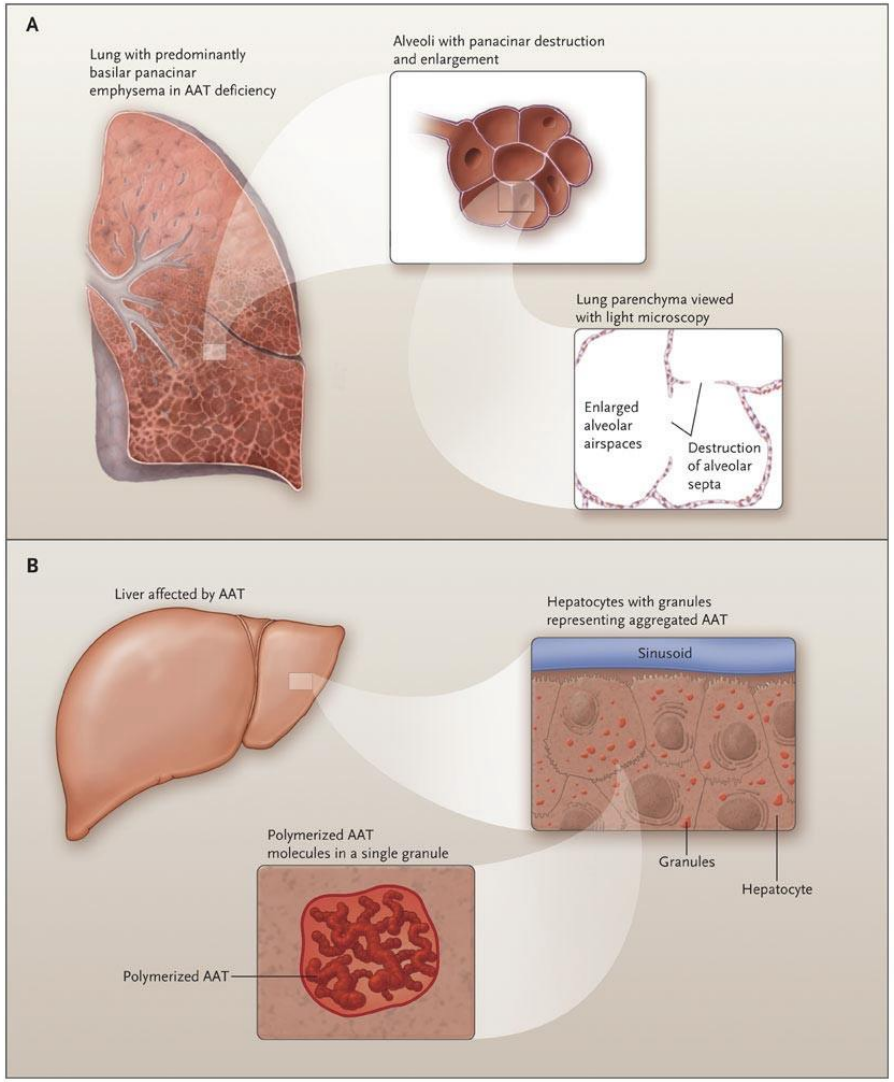
Silverman and Sandhaus, NEJM 2009



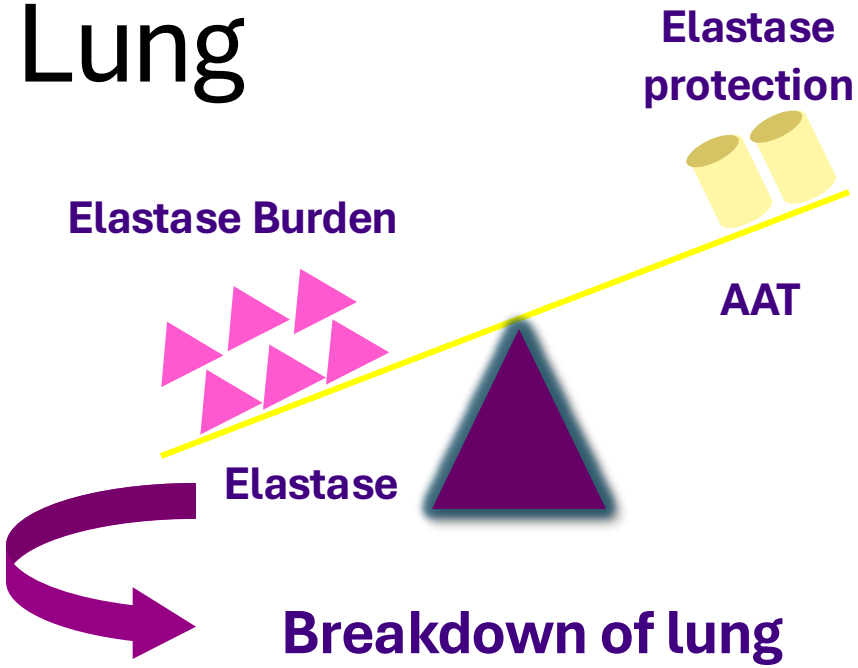


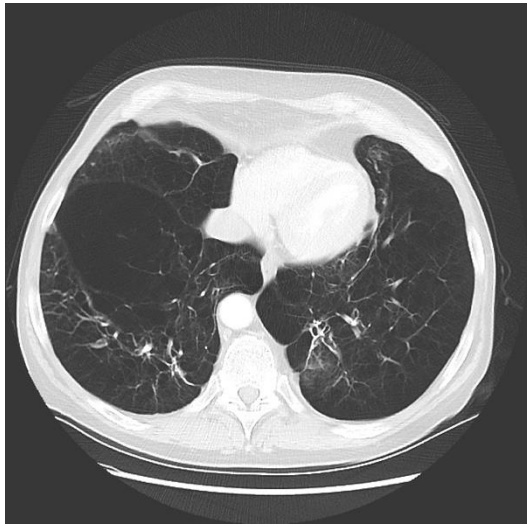
Lomas, Clin Med 2005
Stoller, Cleve Clin J Med 2016

AATD Pathophysiology - Lung



Silverman and Sandhaus, NEJM 2009





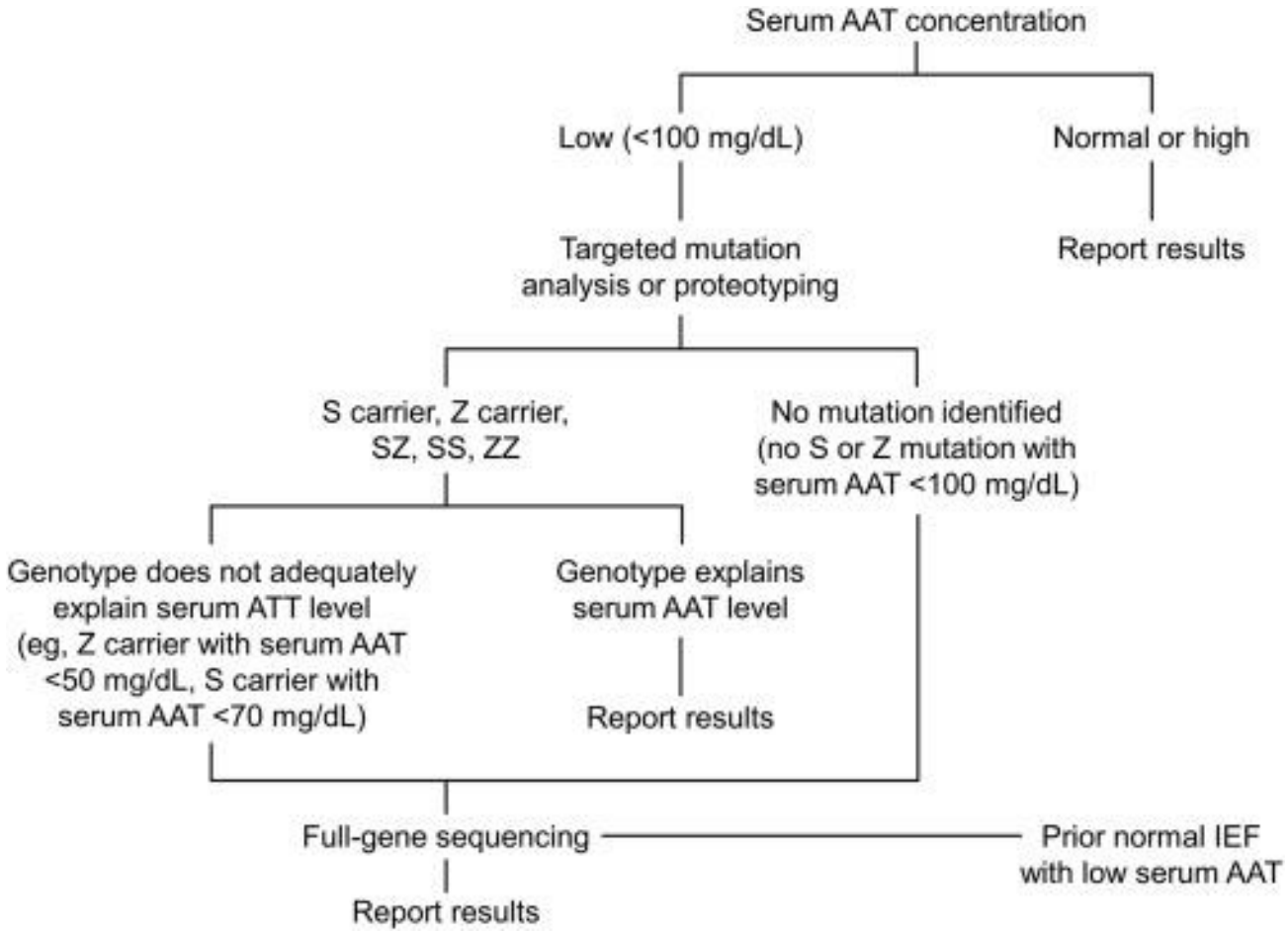
Radiopedia.org

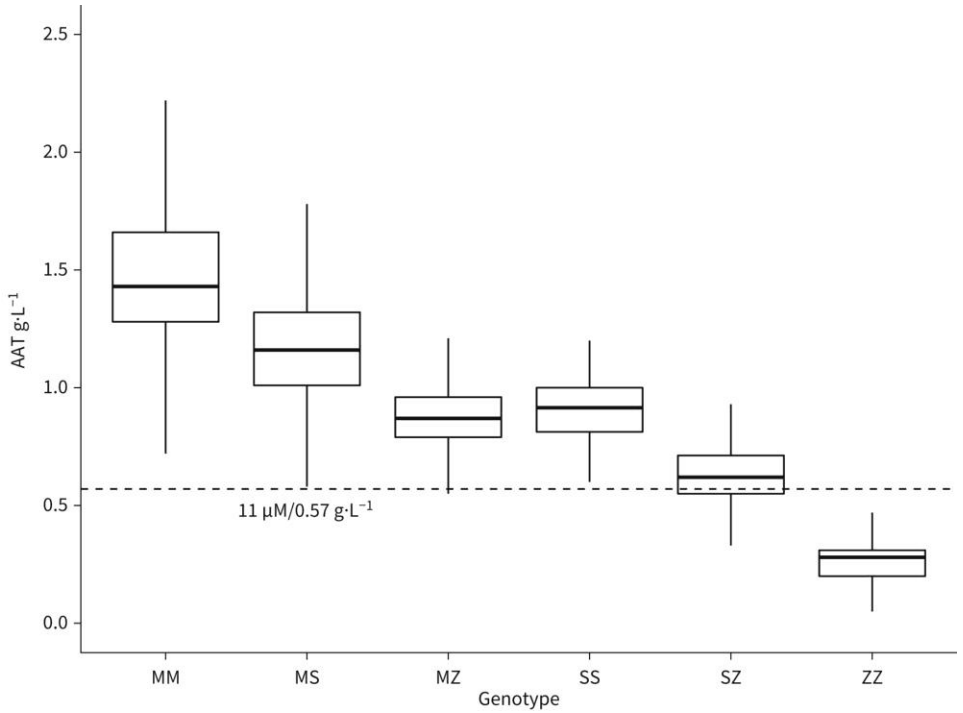
Who to test

- Everyone with COPD
- Unexplained chronic liver disease
- Unexplained bronchiectasis
- Necrotizing panniculitis
- Granulomatosis with polyangiitis
- Parents, siblings, children
- Asthma with fixed airflow obstruction?

Sandhaus et al., Chron Obstr Pulm Dis 2016

How to test



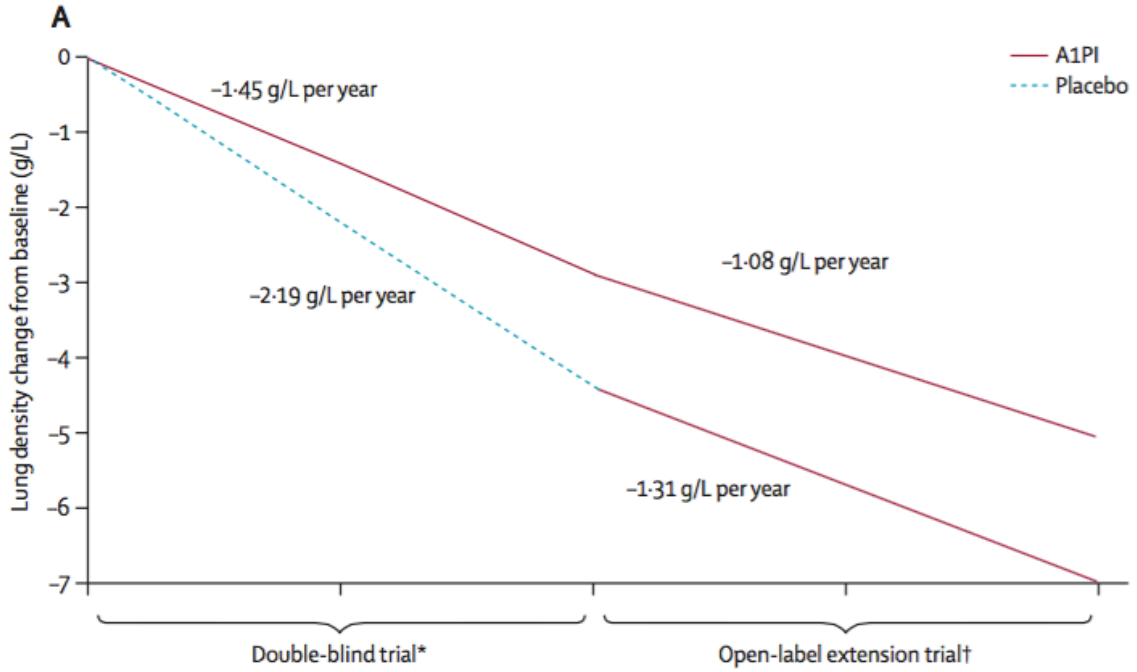


Alessandro N. Franciosi et al. Eur Respir J 2022;59:2101410

Graham R et al., J Mol Diagn 2015

RAPID trial: RCT of augmentation therapy

- n=180
- AAT level ≤ 11μM
- Ex-smokers
- FEV1 35-70%
- Randomized 1:1 α1PI vs. placebo
- 2 yr randomized, 2 yr open label
- 1º endpoint: CT lung density



- Slowed decline in lung density
- Estimate 5.8 yr delay in time to death or transplant
- No difference in FEV1, symptoms, exercise capacity

Chapman et al., Lancet 2015;386:360-8

Alpha-1 augmentation therapy

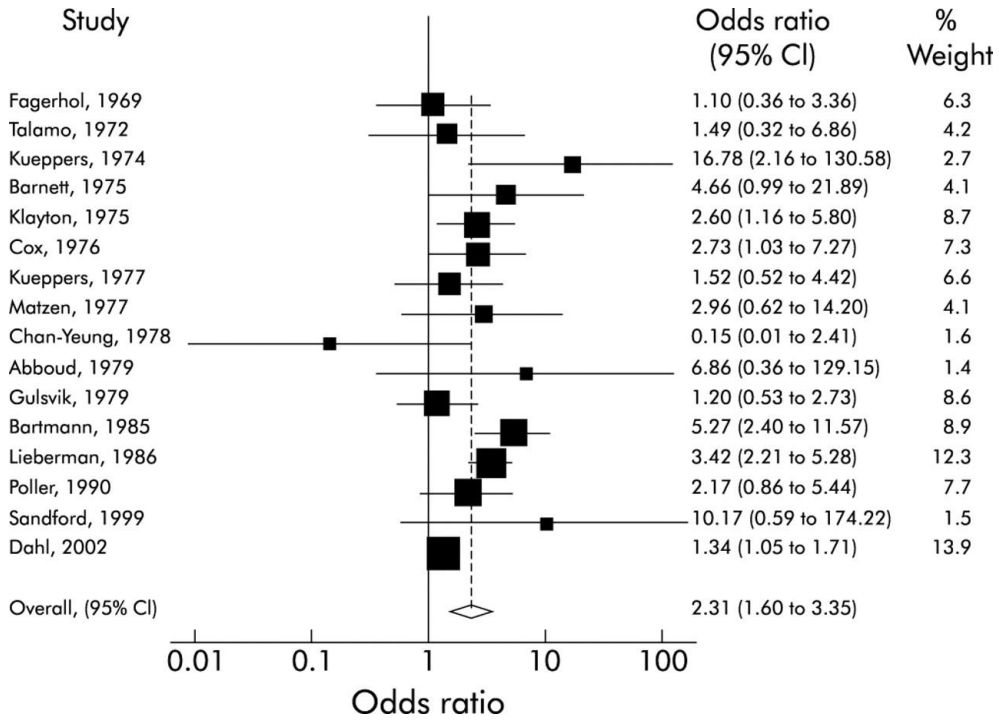
Indications
Adults
ZZ genotype (or Z-Null)
Reduced FEV1
Emphysema
Necrotizing panniculitis

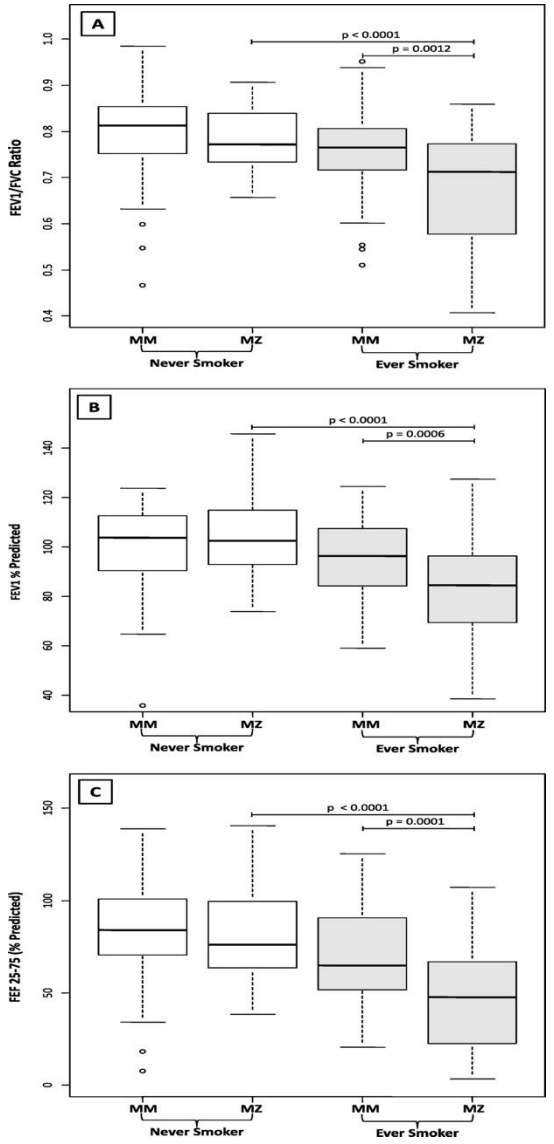
Contraindications
MZ genotype
Bronchiectasis with normal lung function
Normal lung function
Selective IgA deficiency
After liver transplant

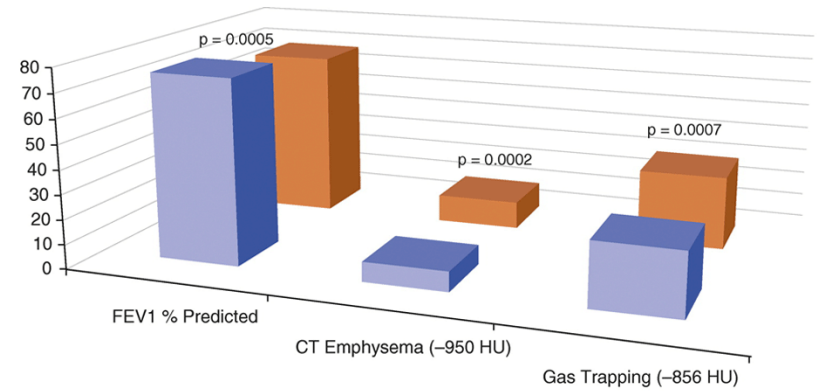
Questions/controversies
Current smokers
Emphysema with normal FEV1
Bronchiectasis with reduced lung function
Other genotypes with level ≤11µM
Other dosing regimens

Adapted from Sandhaus et al., Chron Obstr Pulm Dis 2016

Alpha-1 MZ heterozygote risk







	FEV1 % Predicted	CT Emphysema (–950 HU)	Gas Trapping (–856 HU)
PI MM	75	8	26
PI MZ	68	11	30

Hersh CP*, Dahl M*, Thorax 2004;59:843-849
Molloy K, AJRCCM 2014;189:419
Foreman MG, AnnalsATS 2017;14:1280

COPD Etiotypes

Proposed Taxonomy (Etiotypes) for COPD

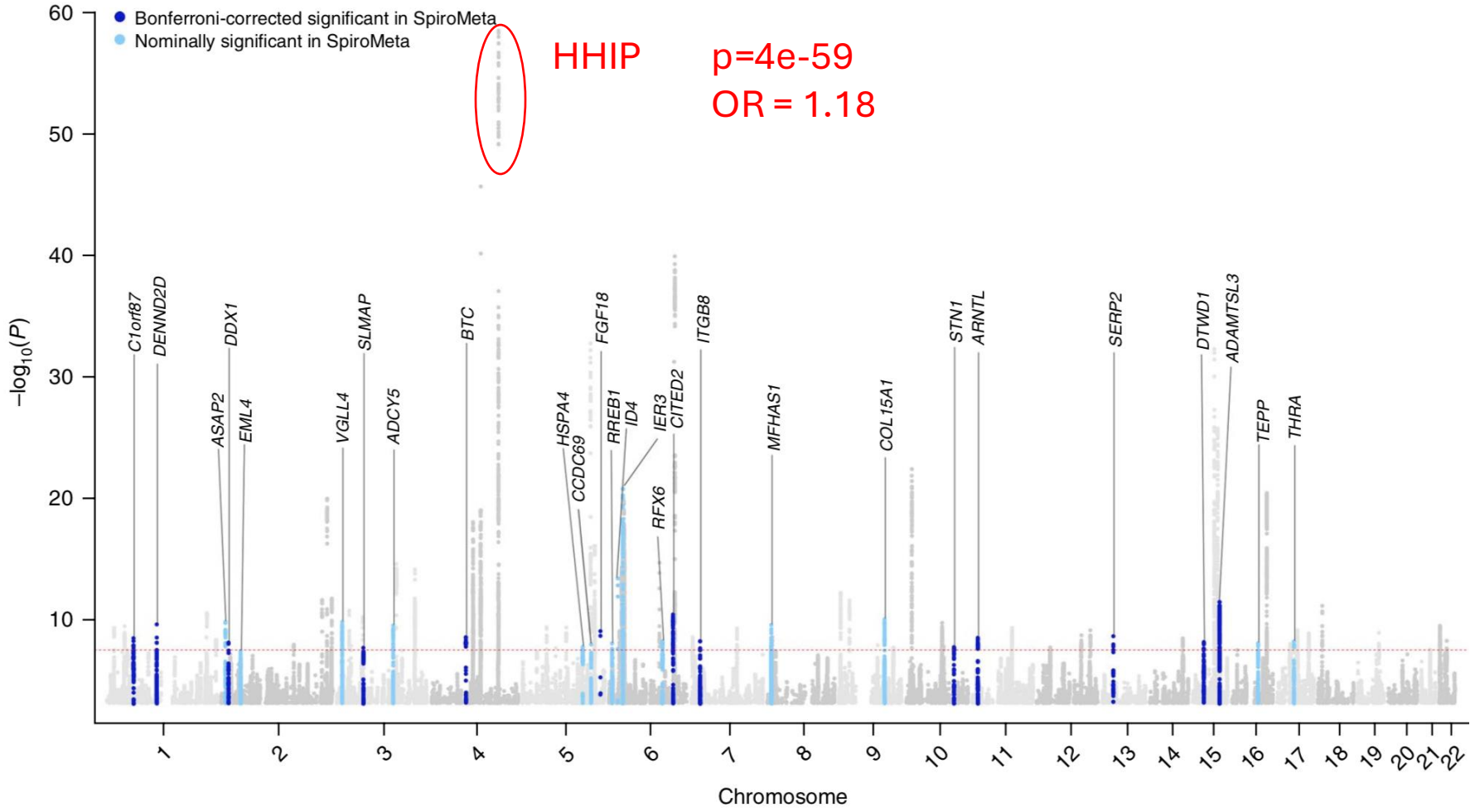
Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

Genome-wide association study

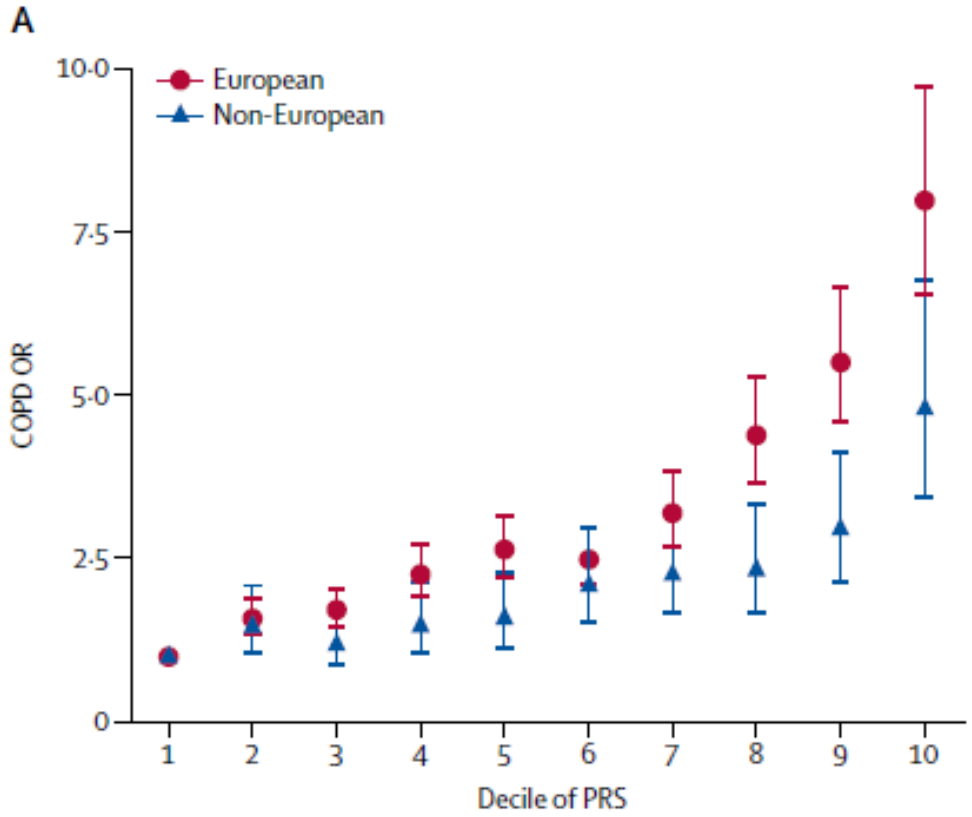
36k cases, 222k controls



Sakornsakolpat P, Nat Genet 2019;51:494-505

Polygenic risk score (PRS)

Summing small effects:
2.5 million genetic variants



<u>Predicting COPD</u>

- PRS: AUC 0.67
- Clinical risk factors: 0.76
  - age, sex, pack-years
- PRS + Clinical: 0.80

Moll M, Lancet Respir Med 2020

COPD Etiotypes

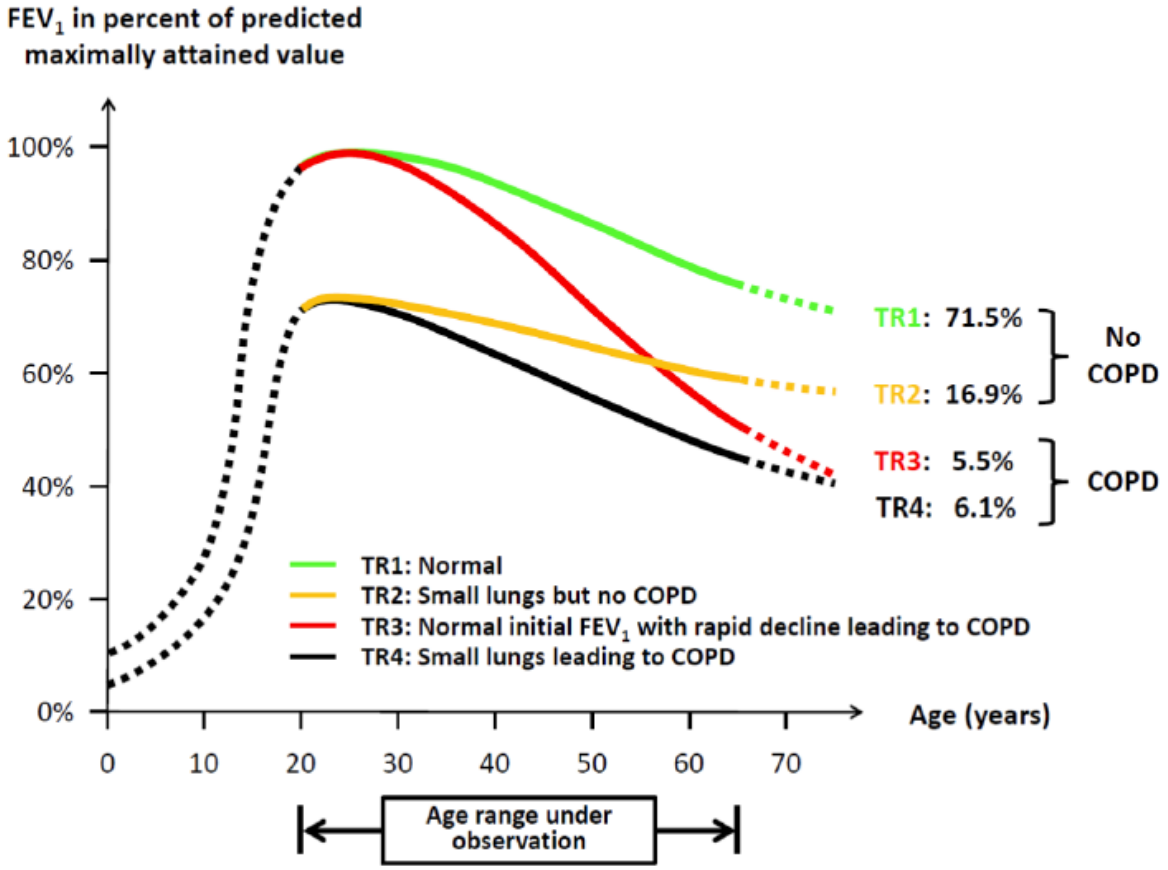
Proposed Taxonomy (Etiotypes) for COPD

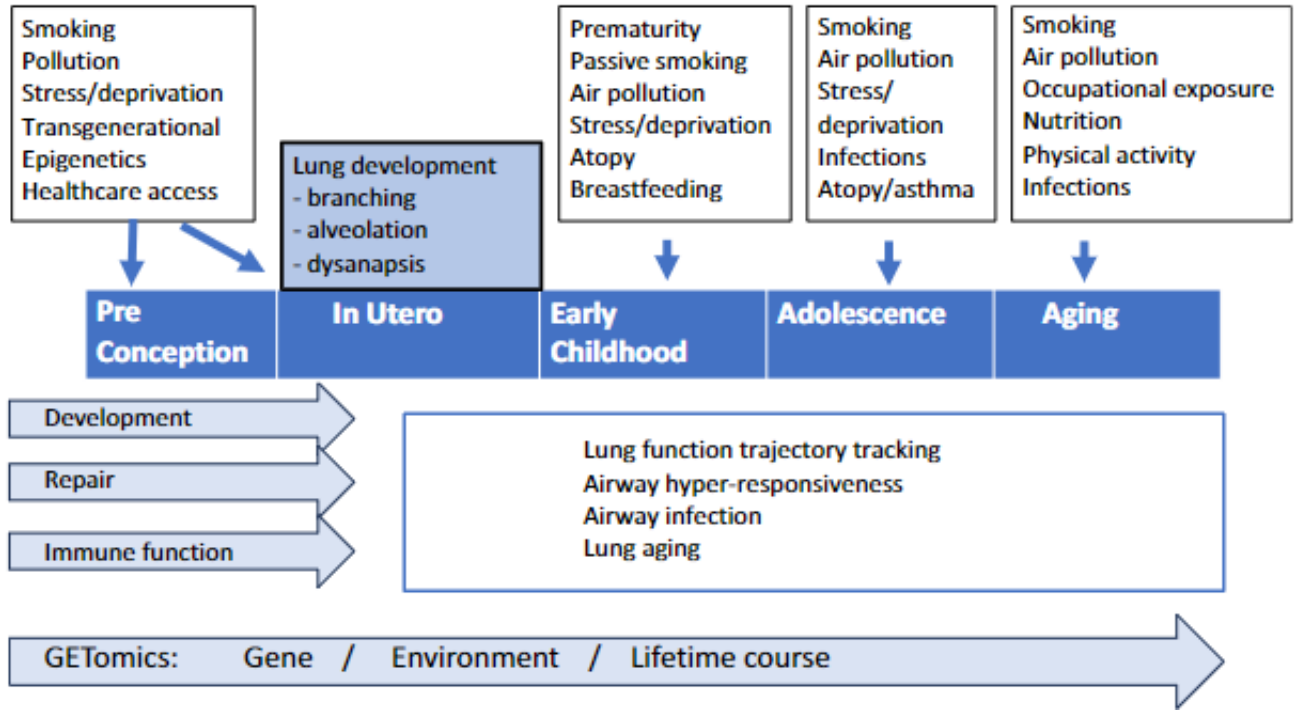
Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

Abnormal lung development





Lange P, NEJM 2015;373:111

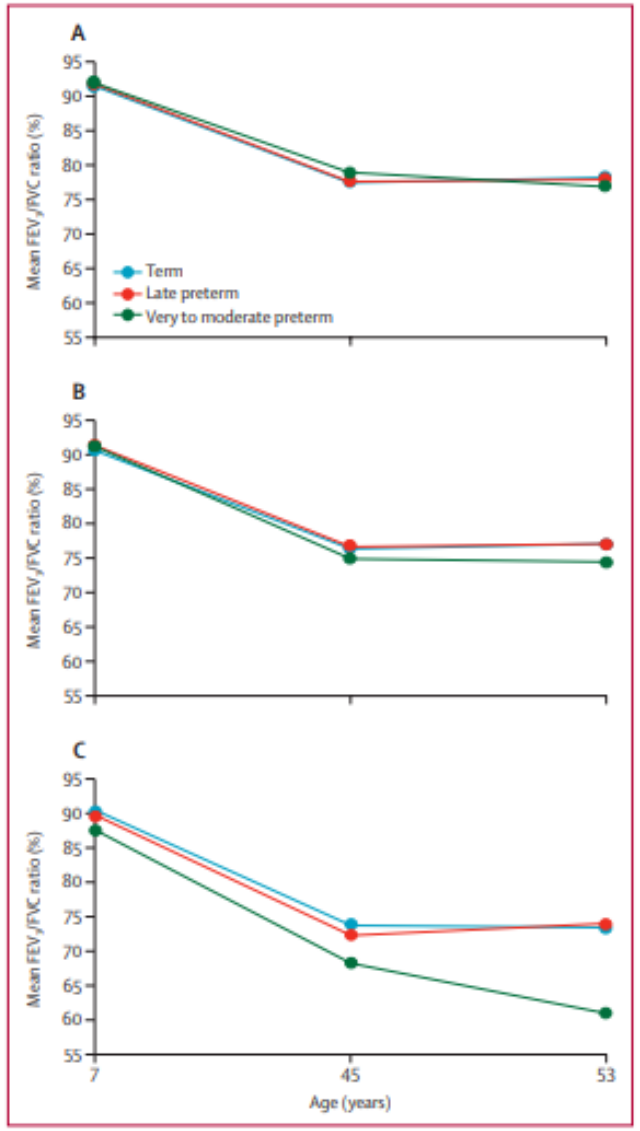
Hopkinson N, AJRCCM 2024;210:572

Pre-term birth:
Tasmanian cohort at age 53

	Term ≥37 weeks (n=1227)	Late preterm (34 weeks to <37 weeks; n=172)		Very to moderate preterm (28 weeks to <34 weeks; n=46)	
	Adjusted mean	Adjusted mean	Beta-coefficient or OR (95% CI)*	Adjusted mean	Beta-coefficient or OR (95% CI)*
Post-BD FEV_1/FVC ratio (%)	79·3	79·3	0·03 (–1·0 to 1·1)	76·5	–2·9 (–4·9 to –0·8)†
COPD (FEV_1/FVC ratio<LLN)	..	..	OR 1·3 (0·7 to 2·5)	..	OR 2·9 (1·1 to 7·7)‡
Post-BD FEV_1 (mL)	3274	3345	71 (–5·7 to 148)	3083	–190 (–339 to –40)‡
Post-BD FVC (mL)	4144	4231	87 (0·07 to 174)	4049	–92 (–262 to 76)
Post-BD $FEF_{25-75\%}$ (mL/s)	3243	3299	56 (–111 to 223)	2906	–339 (–664 to –14)‡
DLCO (mmol/min/kPa)	8·66	8·75	–0·16 (–0·50 to 0·19)	8·10	–0·55 (–0·97 to –0·13)†
Post FEV_1 decline 45–53 years, (mL per year)	–25·8	–26·9	–1·1 (–9·1 to 6·9)	–34·6	–8·7 (–25·1 to 7·6)
Post FVC decline 45–53 years, (mL per year)	–25·3	–22·9	2·4 (–8·1 to 13·0)	–23·7	1·6 (–19·0 to 23·0)
Post FEV_1/FVC ratio decline 45–53 years (% per year)	–0·13	–0·16	–0·03 (–0·17 to 0·11)	–0·34	–0·21 (–0·50 to 0·08)

Adjusted for sex, age, adult height, maternal age at birth, number of siblings, maternal and paternal smoking, and family socioeconomic status in early life. BD=bronchodilator. COPD=chronic obstructive pulmonary disease. DLCO=diffusing capacity for carbon monoxide. $FEF_{25-75\%}$=forced expiratory flow at 25–75% of FVC. FVC=forced vital capacity. LLN=lower limit of normal. OR=odds ratio. *Term birth is the reference group. †p<0·01. ‡p<0·05.

Table 2: **Adjusted associations between prematurity and post-bronchodilator lung function and COPD in middle age**



Never smoking

Former smoking

Current smoking

Bui D et al., Lancet Respir Med 2022

COPD Etiotypes

Proposed Taxonomy (Etiotypes) for COPD

Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

The future is “non-smoking”

- Monitoring the Future Study
- U.S. 12th graders

Daily use	1992	2002	2012	2022
Cigarettes	17.2%	16.9%	9.3%	1.6%

https://monitoringthefuture.org

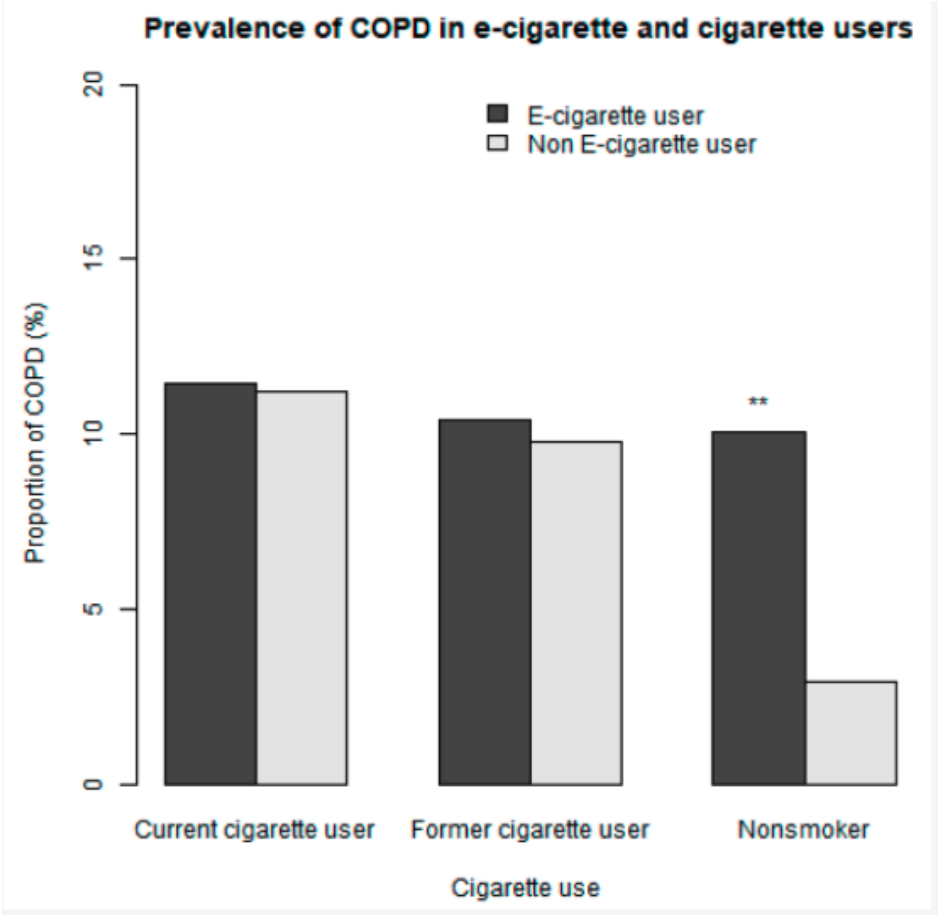
The future is “non-smoking”

- Monitoring the Future Study
- U.S. 12th graders

Daily use	1992	2002	2012	2022
Cigarettes	17.2%	16.9%	9.3%	1.6%
Marijuana	1.9%	6.0%	6.5%	6.3%
Vaping nicotine	--	--	--	6.2%
Vaping marijuana	--	--	--	2.1%

https://monitoringthefuture.org

Vaping



Smoking and vaping status	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Dual users	5.97 (5.51, 6.47)	4.39 (3.98, 4.85)
Current smokers	5.79 (5.53, 6.05)	3.80 (3.58, 4.02)
Current vapers who were ex-smokers	3.66 (3.14, 4.27)	3.24 (2.78, 3.78)
Current vapers who never smoked	0.71 (0.53, 0.96)	1.47 (1.01, 2.12)
Ex-smokers	3.99 (3.83, 4.16)	2.56 (2.43, 2.69)
Never users	Reference	Reference

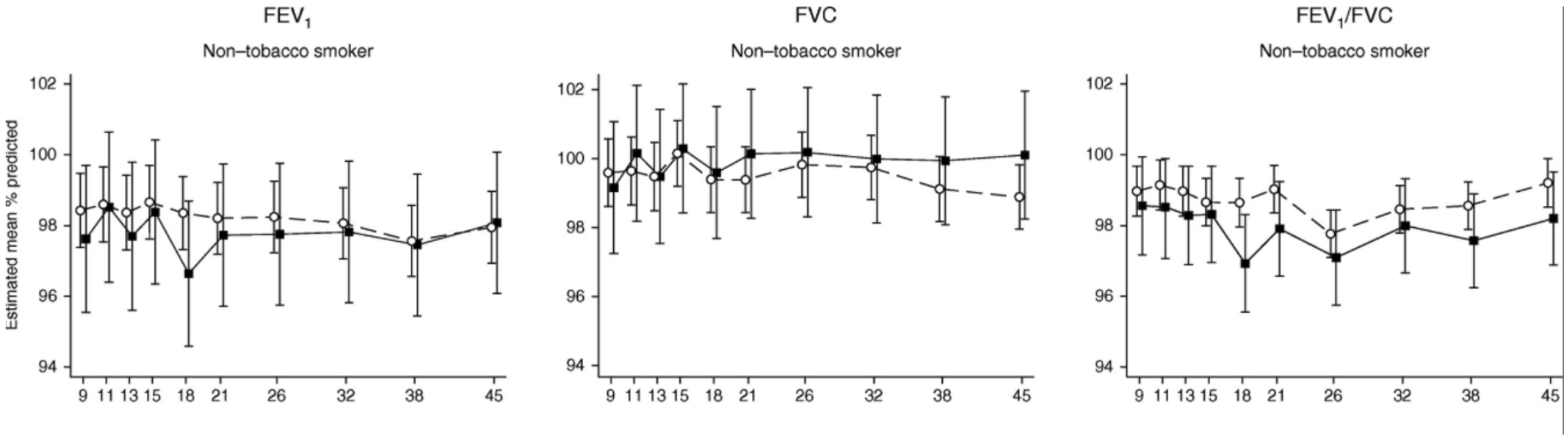
Limitations:
Self-report of COPD
Cross sectional

Perez MF, Int j Environ Res Public Health 2019;16:3938. Xie Z, Nicotine Tob Res 2020;22:1155

Cannabis

- Chronic cough and sputum
- Redued FEV1/FVC
  - Elevated FVC, TLC
- “Bong Lung”

Radiopaedia.org



Hancox RJ, AJRCCM 2022;205:1179

COPD Etiotypes

Proposed Taxonomy (Etiotypes) for COPD

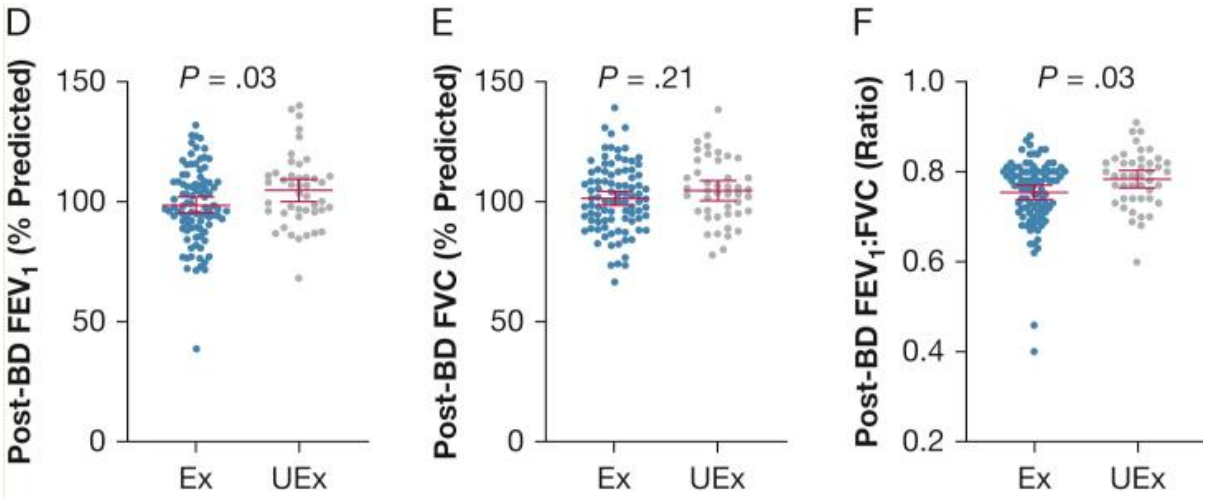
Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

Occupational exposures

Secondhand smoke:
flight attendants - pre/post 2000



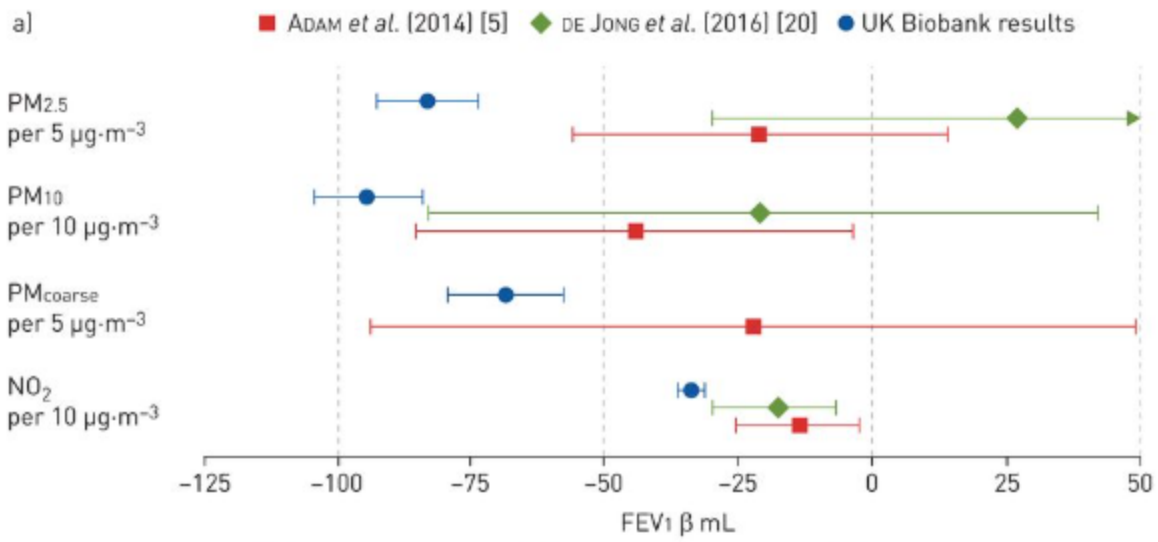
VGDF: vapors, gases, dusts, fumes
COPDGene study

Diaz del Valle, Chest 2022

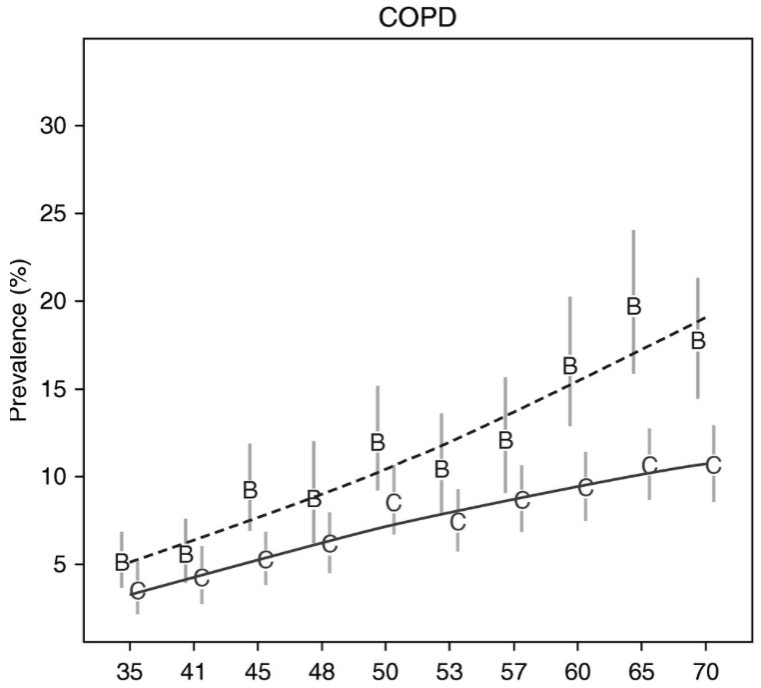
Van Koeverden, COPD 2015

Air pollution

Outdoor



Indoor biomass cooking - LMICs



Chronic bronchitis
Airway thickening on chest CT

Doiron D, ERJ 2019;54:1802140. Siddharthan T, AJRCCM 2018:197:611. Yang IA, Lancet Respir Med 2022;10:497

COPD Etiotypes

Proposed Taxonomy (Etiotypes) for COPD

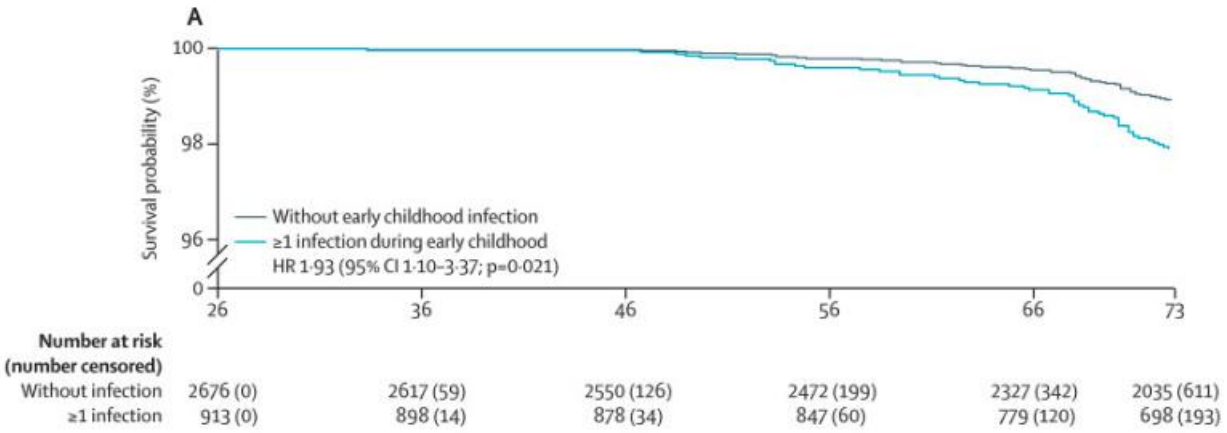
Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

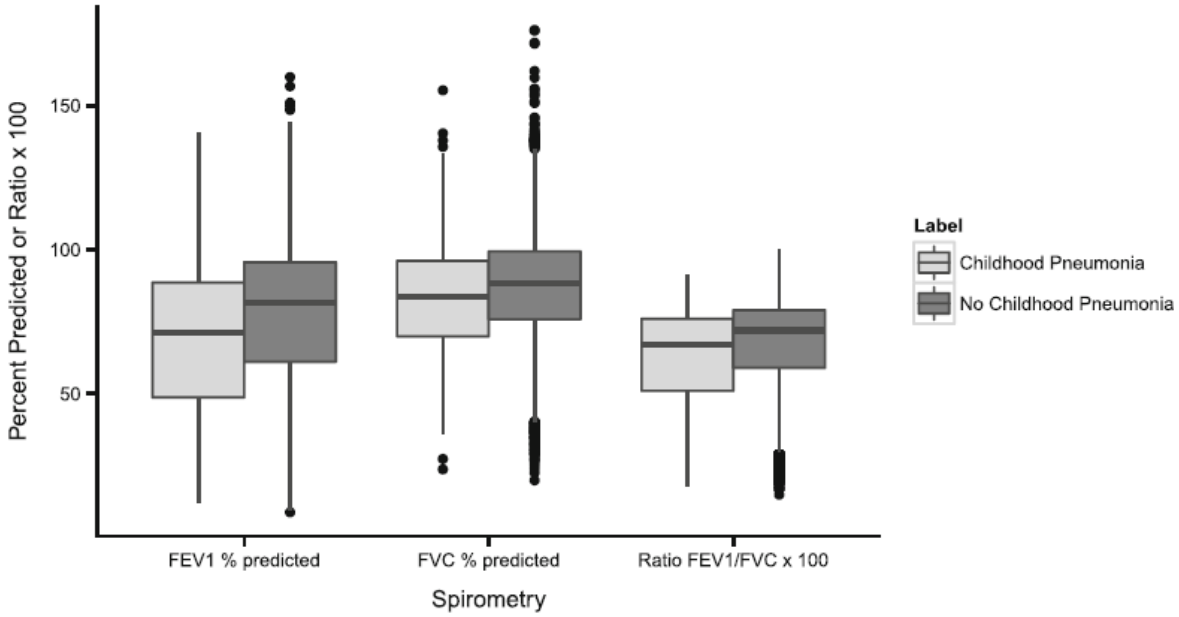
Childhood pneumonia

UK 1946 birth cohort



Allinson JP, Lancet 2023; 401:1183

COPDGene study



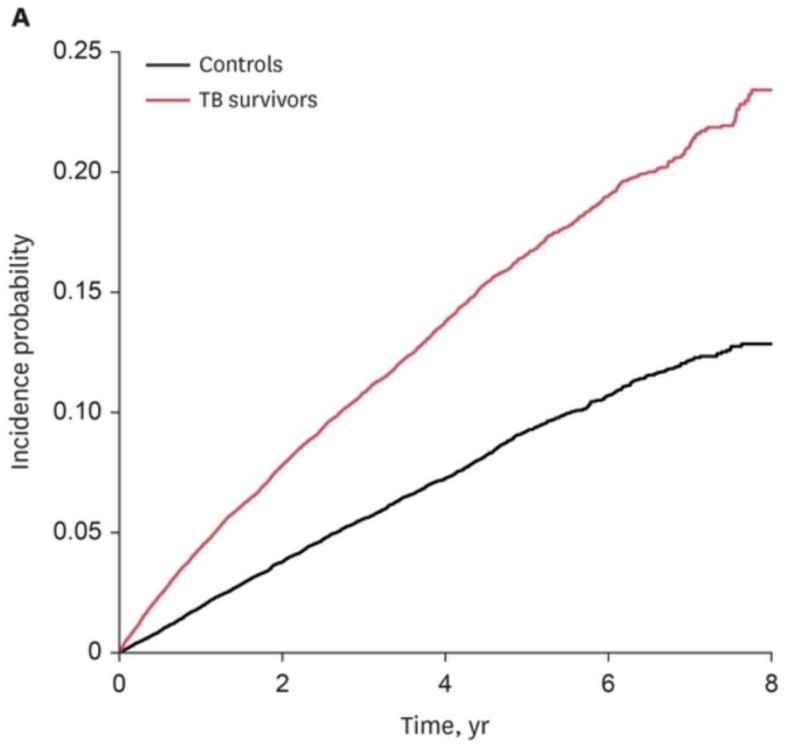
Childhood pneumonia: OR 1.40

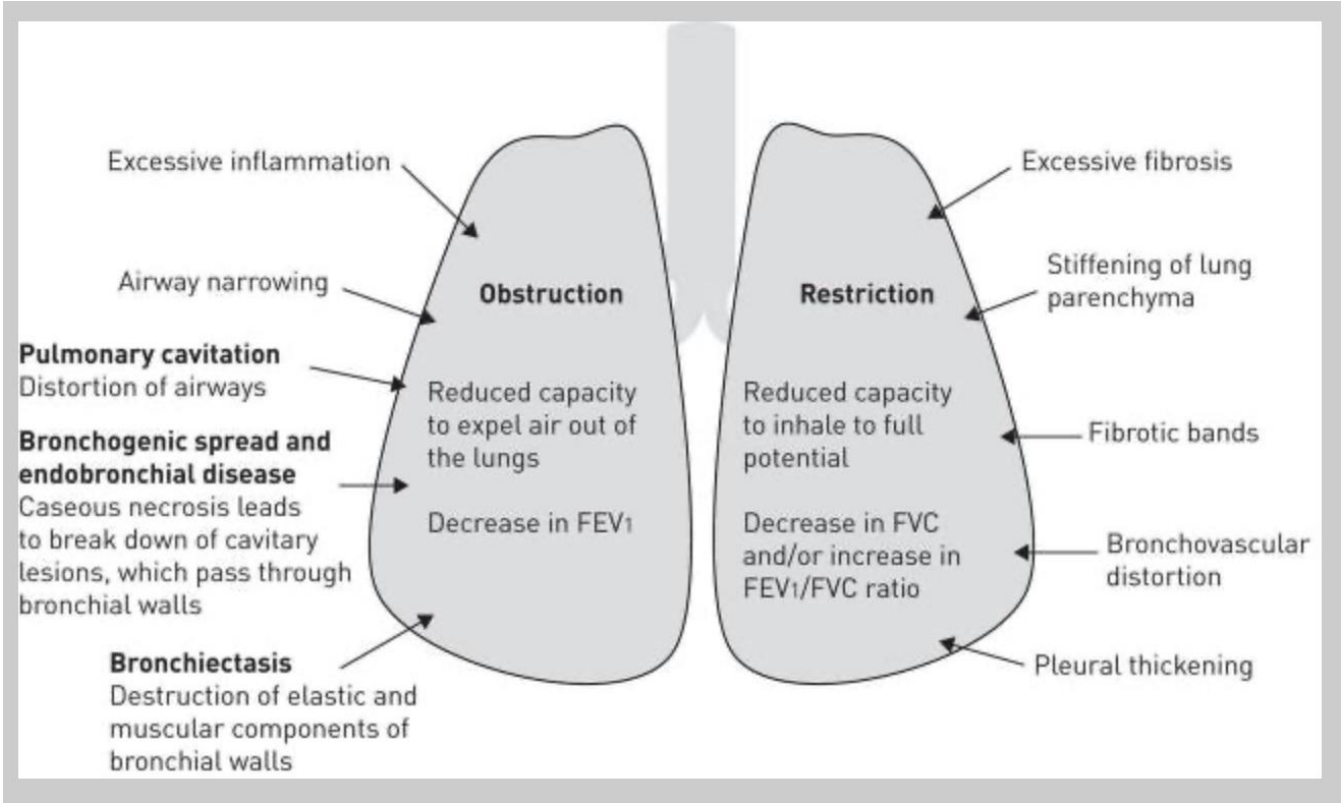
Childhood pneumonia + asthma: OR 1.85

Hayden L, Resp Res 2015;16:115

Prior Tuberculosis

Korean National Health Insurance Database



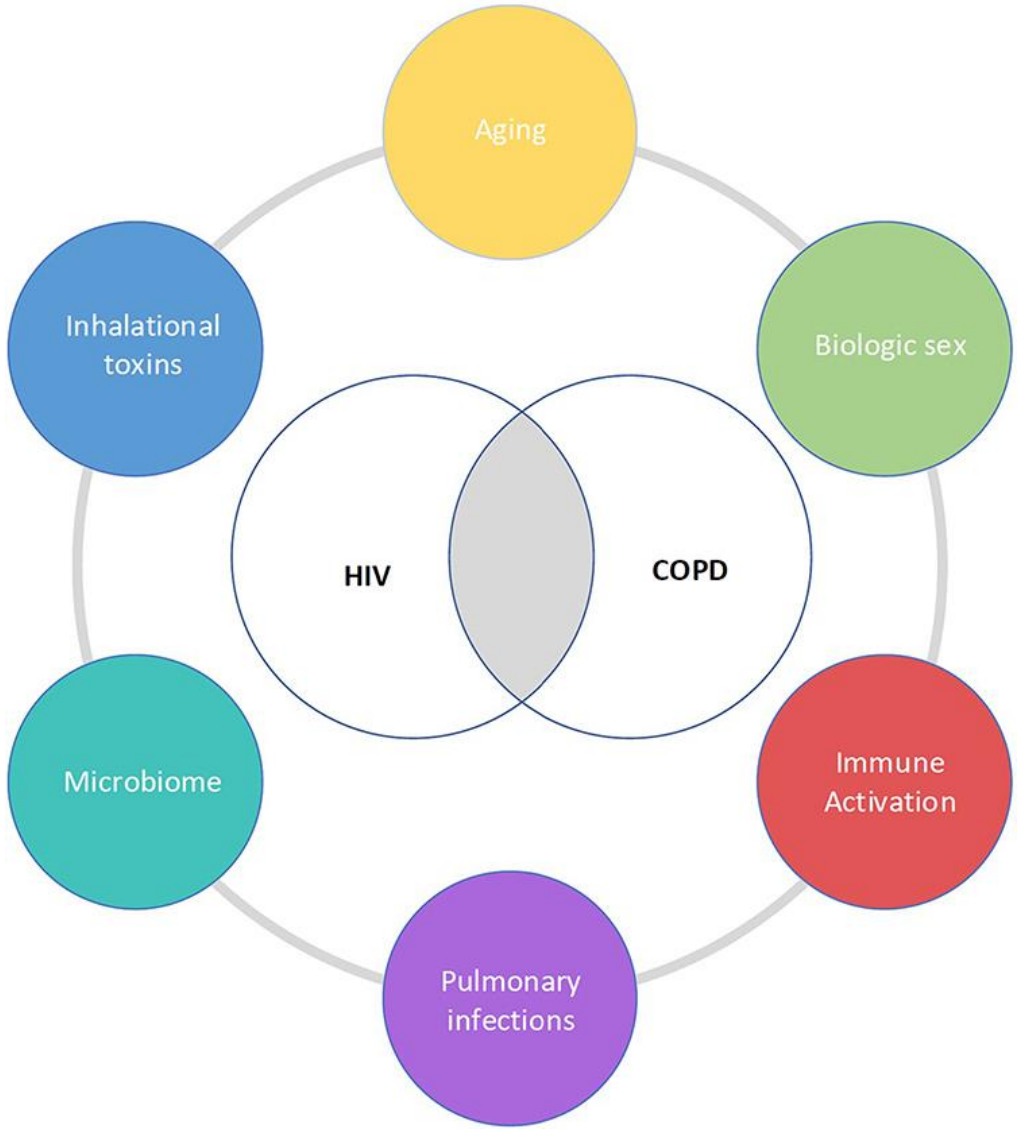


Kim T, J Korean Med Soc 2024

Ravimohan R, Eur Respir Rev 2018

COPD and HIV

- In N. America, 3-40% in ART era
  - Higher prevalence in CT studies
  - <10% in sub-Saharan Africa
- Association with lower CD4
  - Not with Viral Load
  - Clinical trial of ART did not change lung function decline
- Reduced DLCO
- Inhaled corticosteroids
  - Risk of pneumonia, TB
  - CYP3A4 inhibitors, e.g. ritonavir



Byanova KL, Int J COPD 2023. Byankova KL, Expert Rev Respir Med 2021
Kunisaki K, Lancet Respir Med 2016. Konstantinidis, Nat Rev Dis Primers 2023

COPD Etiotypes

Proposed Taxonomy (Etiotypes) for COPD

Table 1.1

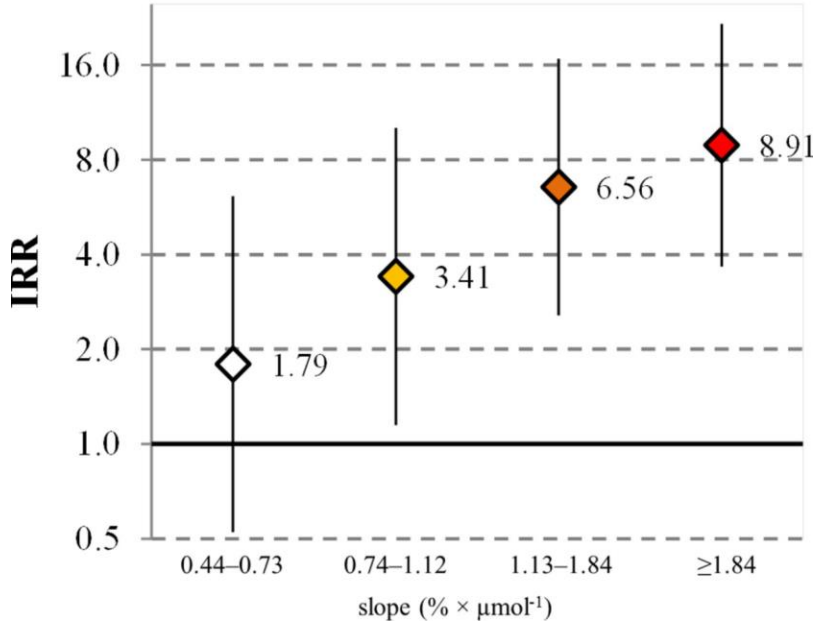
Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

Asthma and COPD: The Dutch hypothesis

- Orie 1961
- Common host factors for asthma and COPD
  - Airway hyperreponsiveness
  - Atopy
- “Chronic non-specific lung disease”
- British hypothesis: Fletcher 1959
  - Recurrent bronchial infections

Incidence of COPD (median 9 yr)



Marcon A, Thorax 2018; 73:825

Asthma-COPD overlap is common

Country/region	Criteria	% of COPD
Spain	Self-report of MD diagnosis	17%
Italy	Self-report of MD diagnosis	25-33%
Latin America	Self-report of MD diagnosis Wheeze + BDR	23% 15%
Finland	Hospital discharges	16%
Korea	Health insurance database	55%
Maryland, USA	Medicaid database	43%
Worldwide (NOVELTY study*)	MD diagnosis	26%

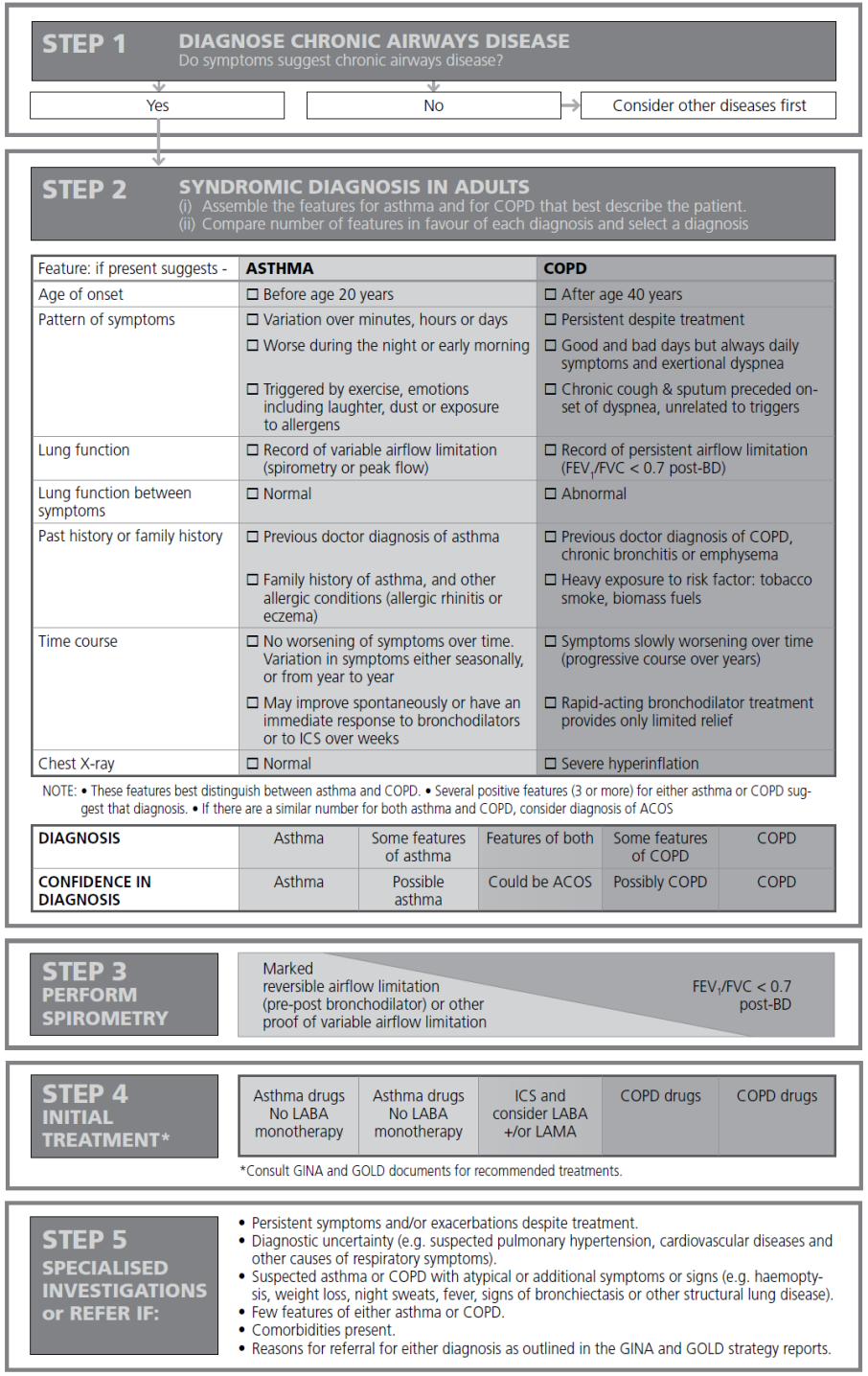
Miravitlles, Resp Med 2013;107:1053, deMarco, PLOS ONE 2013;8:e62985, Talamo, Chest 2007;131:60, Menezes, Chest 2014;145:297, Andersen, Clin Respir J 2013;7:342, Rhee, COPD 2014;11:163, Shaya, Chest 2008;134:14, *Reddel, ERJ 2021;58:2003927

GLOBAL INITIATIVE FOR ASTHMA

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE

Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS)

www.ginasthma.org
www.goldcopd.org
2014



STEP 1 DIAGNOSE CHRONIC AIRWAYS DISEASE
Do symptoms suggest chronic airways disease?

Yes → **STEP 2**

No → Consider other diseases first

STEP 2 SYNDROMIC DIAGNOSIS IN ADULTS
(i) Assemble the features for asthma and for COPD that best describe the patient.
(ii) Compare number of features in favour of each diagnosis and select a diagnosis

Feature: if present suggests -	ASTHMA	COPD
Age of onset	☐ Before age 20 years	☐ After age 40 years
Pattern of symptoms	☐ Variation over minutes, hours or days ☐ Worse during the night or early morning ☐ Triggered by exercise, emotions including laughter, dust or exposure to allergens	☐ Persistent despite treatment ☐ Good and bad days but always daily symptoms and exertional dyspnea ☐ Chronic cough & sputum preceded onset of dyspnea, unrelated to triggers
Lung function	☐ Record of variable airflow limitation (spirometry or peak flow)	☐ Record of persistent airflow limitation ($FEV_1/FVC < 0.7$ post-BD)
Lung function between symptoms	☐ Normal	☐ Abnormal
Past history or family history	☐ Previous doctor diagnosis of asthma ☐ Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	☐ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema ☐ Heavy exposure to risk factor: tobacco smoke, biomass fuels
Time course	☐ No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year ☐ May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	☐ Symptoms slowly worsening over time (progressive course over years) ☐ Rapid-acting bronchodilator treatment provides only limited relief
Chest X-ray	☐ Normal	☐ Severe hyperinflation

NOTE: • These features best distinguish between asthma and COPD. • Several positive features (3 or more) for either asthma or COPD suggest that diagnosis. • If there are a similar number for both asthma and COPD, consider diagnosis of ACOS

DIAGNOSIS	Asthma	Some features of asthma	Features of both	Some features of COPD	COPD
CONFIDENCE IN DIAGNOSIS	Asthma	Possible asthma	Could be ACOS	Possibly COPD	COPD

STEP 3 PERFORM SPIROMETRY

Marked reversible airflow limitation (pre-post bronchodilator) or other proof of variable airflow limitation

$FEV_1/FVC < 0.7$ post-BD

STEP 4 INITIAL TREATMENT*

Asthma drugs No LABA monotherapy	Asthma drugs No LABA monotherapy	ICS and consider LABA +/or LAMA	COPD drugs	COPD drugs

*Consult GINA and GOLD documents for recommended treatments.

STEP 5 SPECIALISED INVESTIGATIONS or REFER IF:

- Persistent symptoms and/or exacerbations despite treatment.
- Diagnostic uncertainty (e.g. suspected pulmonary hypertension, cardiovascular diseases and other causes of respiratory symptoms).
- Suspected asthma or COPD with atypical or additional symptoms or signs (e.g. haemoptysis, weight loss, night sweats, fever, signs of bronchiectasis or other structural lung disease).
- Few features of either asthma or COPD.
- Comorbidities present.
- Reasons for referral for either diagnosis as outlined in the GINA and GOLD strategy reports.

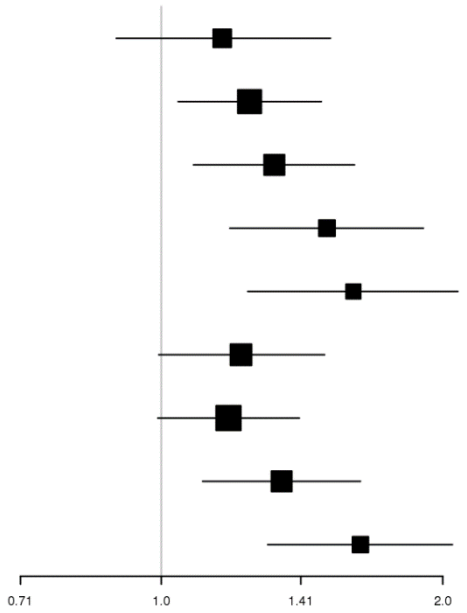
Asthma-COPD Overlap: Expert consensus

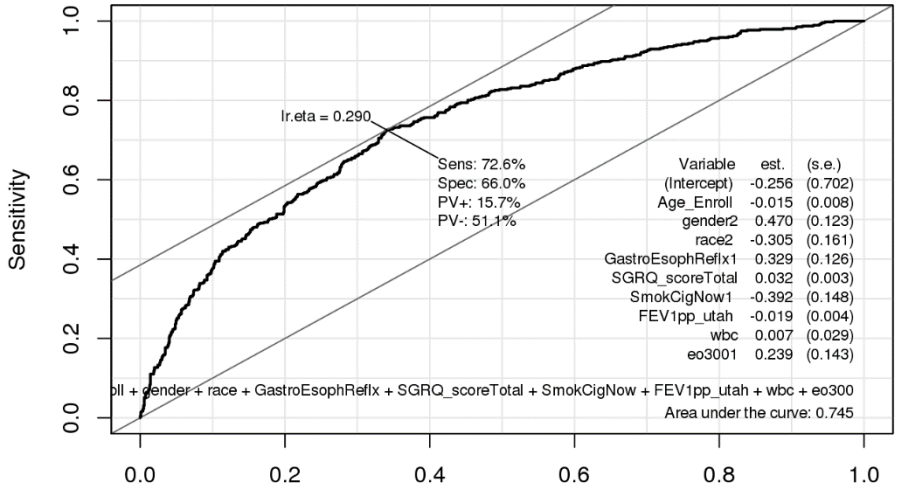
Major (all three should be present)	**Minor** (at least one)
1. Persistent airflow limitation (post-bronchodilator FEV_1/FVC <0.70 or LLN) in individuals 40 years of age or older; LLN is preferred	1. Documented history of atopy or allergic rhinitis
2. At least 10 pack-years of tobacco smoking OR equivalent indoor or outdoor air pollution exposure (*e.g.* biomass)	2. BDR of FEV_1 ≥200 mL and 12% from baseline values on 2 or more visits
3. Documented history of asthma before 40 years of age OR BDR of >400 mL in FEV_1	3. Peripheral blood eosinophil count of ≥300 cells·uL^{-1}

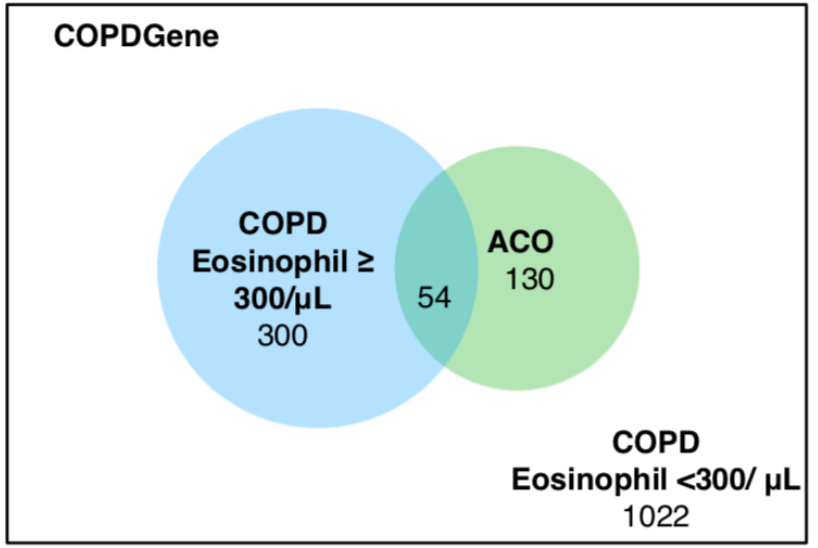
Sin DD, et al. ERJ 2016;48:664

Eosinophilic COPD and exacerbations

Eosinophil Cutoff	< n	≥ n	IRR
100 cells/uL	223	1330	1.162
200 cells/uL	814	739	1.243
300 cells/uL	1187	366	1.321
340 cells/uL	1350	203	1.504
400 cells/uL	1398	155	1.605
2 %	408	1145	1.217
3 %	859	694	1.18
4 %	1166	387	1.345
5 %	1334	219	1.633





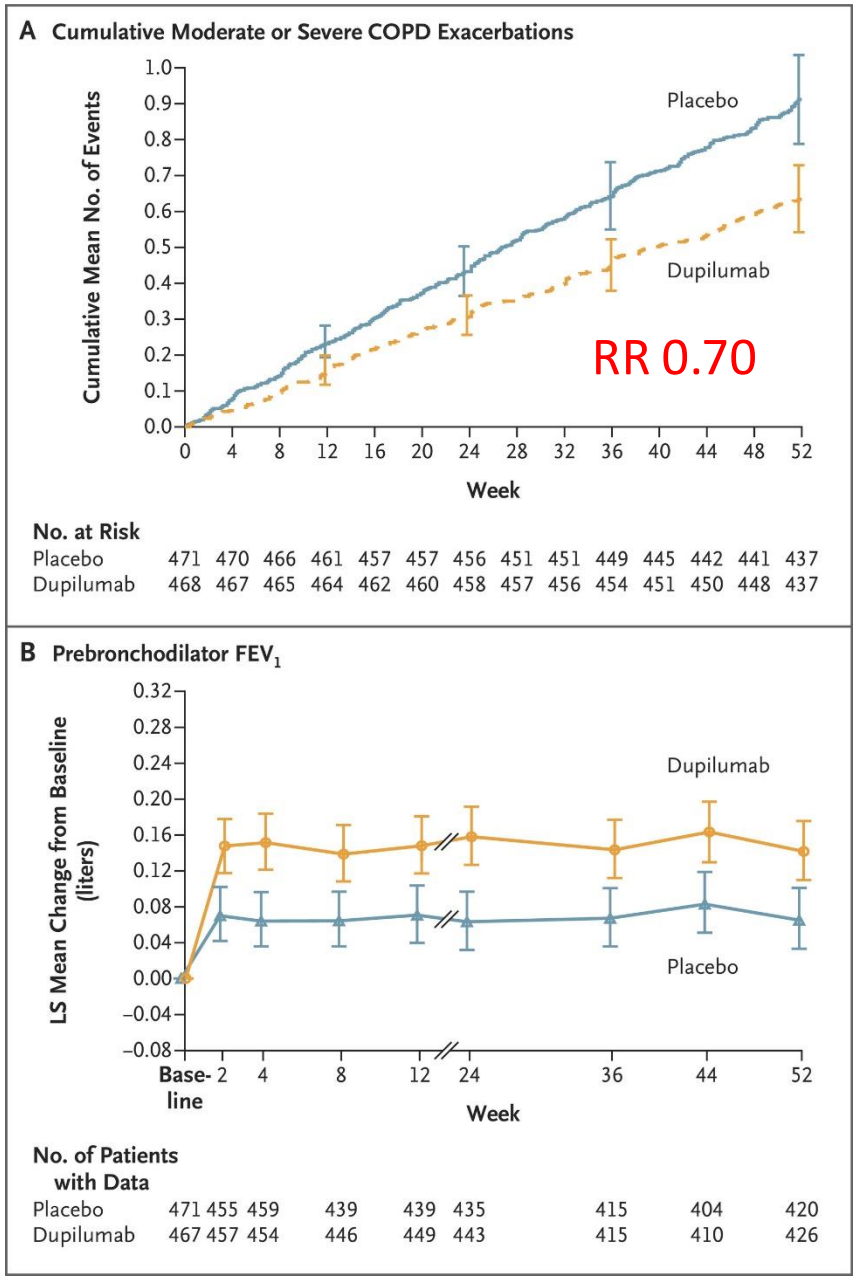


Yun JH, JACI 2018;141:2037

BOREAS trial: Dupilumab

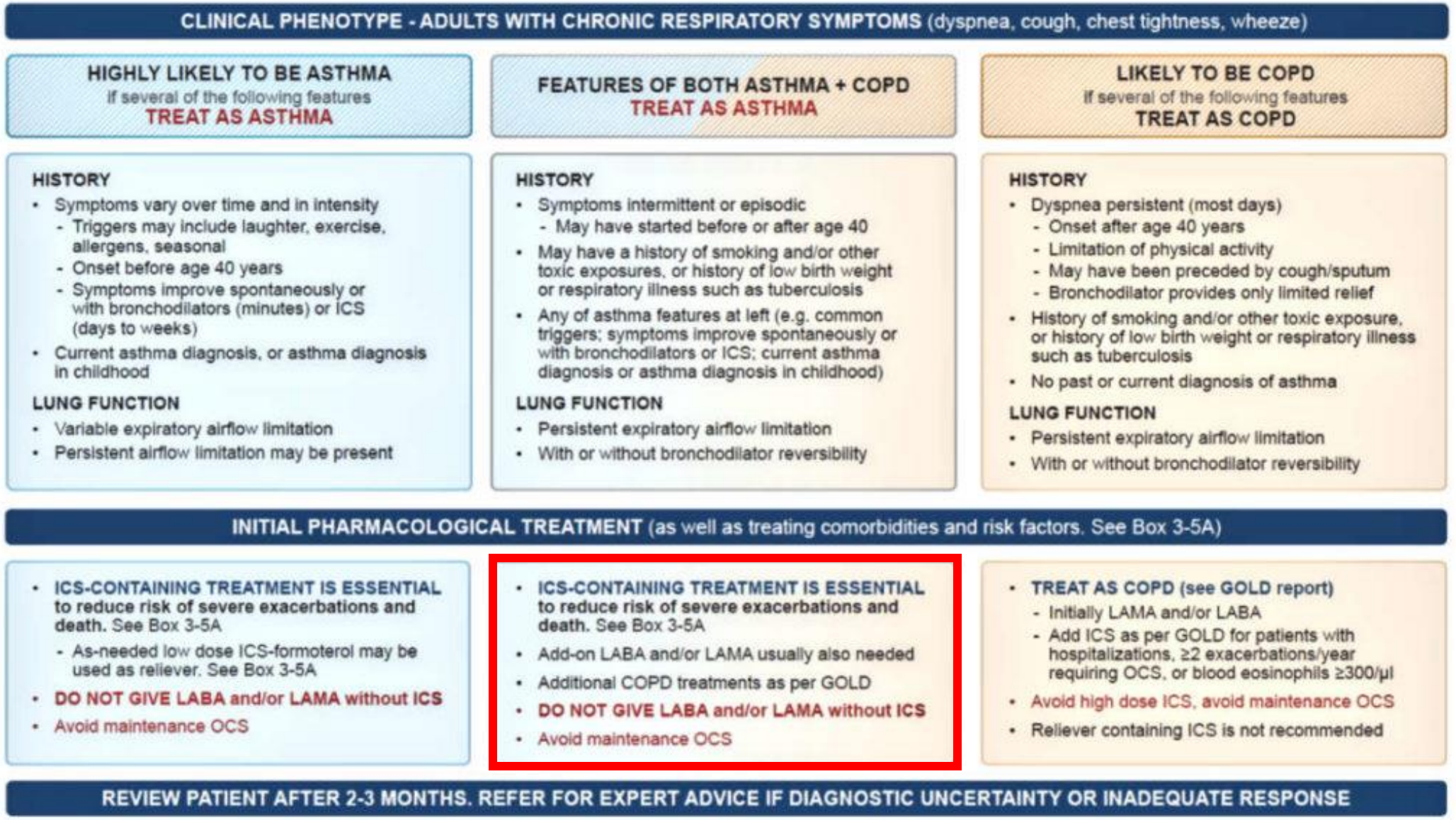
- Current/former smokers (N=939)
  - FEV1 30-80%
  - Blood eos ≥300
  - Exacerbation history
  - On LABA/LAMA/ICS
- Dupilumab 300mg sc q2wks vs. placebo
- Findings largely replicated in NOTUS trial

  Bhatt SP, NEJM 2024



Bhatt SP, NEJM 2023;389:205

Asthma + COPD Treatment: GINA



www.ginasthma.org

Limitations of etiotype framework

Proposed Taxonomy (Etiotypes) for COPD — Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, WHIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

- Single vs multiple etiologies
  - Interactions, esp. smoking
- Limited clinical impact

Example work-up of non-smoking COPD

- Early-life history
  - Birth
  - Childhood respiratory illness
  - Other developmental issues
- Exposure history
  - ETS
  - Vaping, marijuana smoking
  - Occupation
  - Indoor and outdoor environment
- Family history
  - Lung and liver disease
- PFTs
  - Spirometry pre/post-BD
  - Lung volumes, DLCO
- Chest CT scan
  - Inspiratory and expiratory
- Labs
  - AAT testing
  - Eosinophil count
  - Total and specific IgE
  - HIV

Example work-up of ~~non-smoking~~ COPD

- Early-life history
  - Birth
  - Childhood respiratory illness
  - Other developmental issues
- Exposure history
  - ETS
  - Vaping, marijuana smoking
  - Occupation
  - Indoor and outdoor environment
- Family history
  - Lung and liver disease
- PFTs
  - Spirometry pre/post-BD
  - Lung volumes, DLCO
- Chest CT scan
  - Inspiratory and expiratory
- Labs
  - AAT testing
  - Eosinophil count
  - Total and specific IgE
  - HIV

Comparing smoking vs non-smoking COPD

	COPD in ever-smokers	COPD in never-smokers
Typical age of onset	>40 years	>30 years
Sex	More males than females affected	Males and females affected equally, or more females than males affected (especially in LMICs)
Symptoms	More cough and dyspnoea (relatively less sputum production)	More cough (relatively less dyspnoea and sputum production)
Respiratory exacerbations	Frequent (and potentially severe)	Frequent (and potentially severe)
Comorbidities	Prevalent	Generally less prevalent
Risk of lung cancer	High	High
Lung physiology	More severe airflow obstruction; greater increase in RV/TLC (hyperinflation); increase in airway resistance; less small airways obstruction; reduced DLCO	Milder airflow obstruction; increase in RV/TLC (hyperinflation); greater increase in airway resistance; more small airways obstruction; normal DLCO
FEV_1 decline	Can be rapid	Usually normal
Lung CT imaging	Less air trapping due to small airways obstruction; more emphysema	More air trapping due to small airways obstruction; less emphysema
Sputum inflammatory cells	Greater increase in neutrophils	Increase in neutrophils; relatively greater increase in eosinophils
Pharmacological responses	Long-acting bronchodilators favoured over inhaled corticosteroids in terms of safety and effectiveness, especially among those with predominant emphysema	Not known

COPD=chronic obstructive pulmonary disease. DLCO=diffusing capacity of the lung for carbon monoxide. RV=residual volume. TLC=total lung capacity.

Table 2: **Clinical characteristics of COPD in never-smokers compared with ever-smokers**[13,28-30]

Yang IA,
Lancet Respir Med 2022

Avoid oversimplification

	COPD in ever-smokers	COPD in never-smokers
Typical age of onset	>40 years	>30 years
Sex	More males than females affected	Males and females affected equally, or more females than males affected (especially in LMICs)
Symptoms	More cough and dyspnoea (relatively less sputum production)	More cough (relatively less dyspnoea and sputum production)
Respiratory exacerbations	Frequent (and potentially severe)	Frequent (and potentially severe)
Comorbidities	Prevalent	Generally less prevalent
Risk of lung cancer	High	High
Lung physiology	More severe airflow obstruction; greater increase in RV/TLC (hyperinflation); increase in airway resistance; less small airways obstruction; reduced DLCO	Milder airflow obstruction; increase in RV/TLC (hyperinflation); greater increase in airway resistance; more small airways obstruction; normal DLCO
FEV_1 decline	Can be rapid	Usually normal
Lung CT imaging	Less air trapping due to small airways obstruction; more emphysema	More air trapping due to small airways obstruction; less emphysema
Sputum inflammatory cells	Greater increase in neutrophils	Increase in neutrophils; relatively greater increase in eosinophils
Pharmacological responses	Long-acting bronchodilators favoured over inhaled corticosteroids in terms of safety and effectiveness, especially among those with predominant emphysema	Not known

COPD=chronic obstructive pulmonary disease. DLCO=diffusing capacity of the lung for carbon monoxide. RV=residual volume. TLC=total lung capacity.

Table 2: **Clinical characteristics of COPD in never-smokers compared with ever-smokers**[13,28-30]

Yang IA,
Lancet Respir Med 2022

Back to the case

- PFTs
  - No BD response
  - TLC 118%, RV 168%
  - DLCO 66%
- CT chest: mild airway thickening
- AAT level: normal
- HIV: negative
- Eos 120, IgE 45
- Additional history: spina bifida occulta, neurogenic bladder
- Diagnosis: (presumed) developmental COPD
- Treatment?

Treatable traits: toward precision medicine of chronic airway diseases

Alvar Agusti[1], Elisabeth Bel[2], Mike Thomas[3], Claus Vogelmeier[4], Guy Brusselle[5,6], Stephen Holgate[7], Marc Humbert[8], Paul Jones[9], Peter G. Gibson[10], Jørgen Vestbo[11], Richard Beasley[12] and Ian D. Pavord[13]

ERJ 2016;47:359

- Pulmonary:
  - airflow limitation, eosinophilic inflammation, chronic bronchitis, chronic respiratory failure
- Extrapulmonary:
  - deconditioning, obesity, cachexia, sleep apnea, cardiovascular disease
- Behavior/lifestyle
  - smoking/exposures, side effects, adherence

Treatable traits in non-smoking COPD

Trait	Treatment
COPD symptoms	Bronchodilators (GOLD)
High exacerbation risk	Bronchodilators +/- ICS (GOLD) Azithromycin, Roflumilast
Occupational or environmental exposure	Limit exposure Respirator mask
AAT deficiency	Augmentation therapy
HIV	ART
Severe Asthma	LABA/ICS, LAMA, Biologics
Vaping and cannabis (?)	cessation

*Population level: prenatal care, TB case-finding, air quality regulations…

COPD beyond smoking: Summary

- Avoid generalizations – not one disease
- Multiple COPD etiologies
  - Often in combination with smoking
- Asthma, lung development, ETS, occupation, AAT deficiency, HIV
- Vaping? Marijuana?
- Diagnosis
  - Patient history
  - Lab testing, chest CT scan
- Treatable traits