

Redefining COPD: Etiotypes and Disease drivers

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Contents

- Definition
- Etiotypes; proportions
- Controversies
- Diagnosis

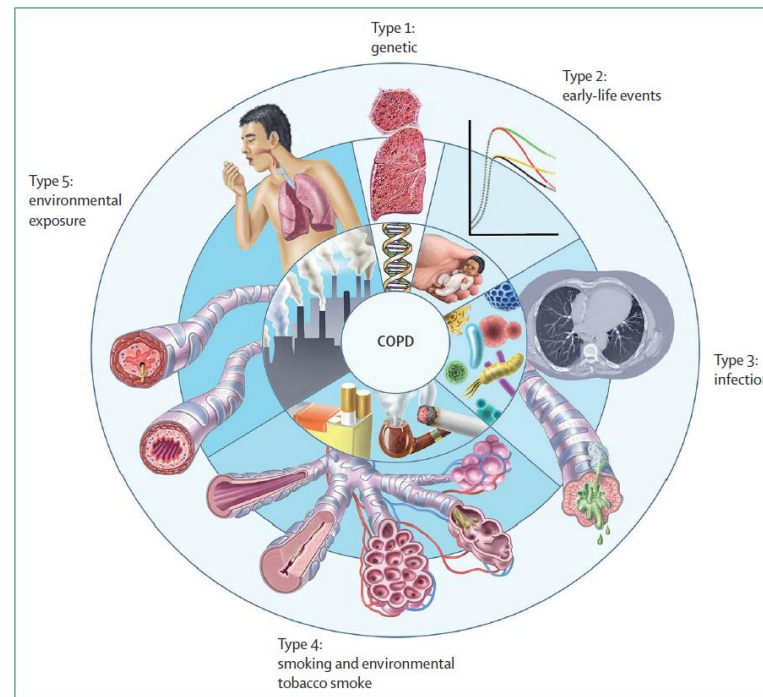
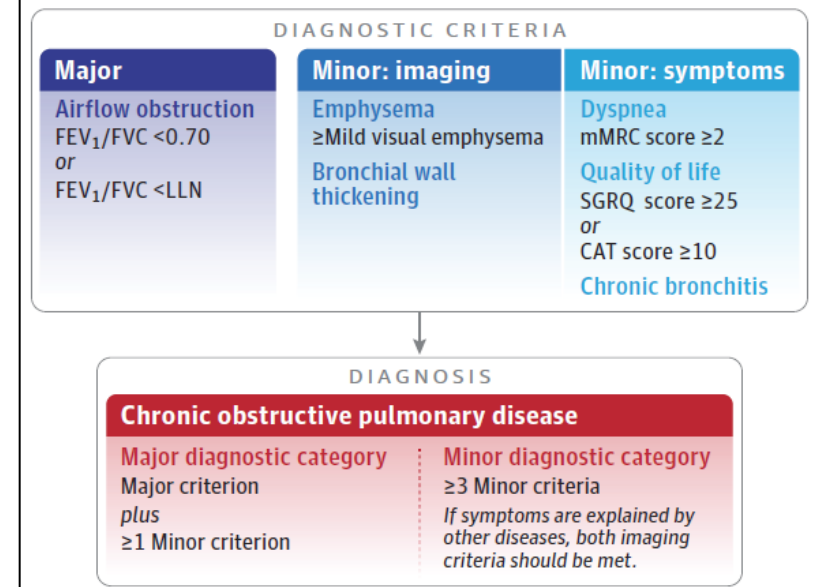


Figure 6: Proposed classification of COPD according to major risk factors

Figure 1. Diagnostic Schema for Chronic Obstructive Pulmonary Disease (COPD) Using Major and Minor Criteria



Stolz D et al. *Lancet*. 2022 Sep 17;400(10356):921-972.

JAMA. 2025 May 18:e257358

Changes to major components of COPD definition

	Definition
2011~2016	COPD is a common, preventable and treatable disease that is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in airways and the lungs to noxious particles or gases.
2017~2019	COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.
2020~2022	COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors, including abnormal lung development.
2023~2025	COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.

Changes to major components of COPD definition

Year	2011–2016	2017–2019	2020–2022	2023–2025
Symptoms		Persistent respiratory symptoms	Persistent respiratory symptoms	Chronic respiratory symptoms (dyspnea, cough, sputum and/or exacerbations)
Exposure	Noxious particles or gases	Noxious particles or gases	Noxious particles or gases	Not included in the definition, but various etiologies were separately mentioned.
Pathology	Chronic inflammatory response in airway and the lungs	Airway and/or alveolar abnormalities	Airway and/or alveolar abnormalities	Abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema)
Physiology	Persistent AFL	Persistent AFL	Persistent AFL	Persistent, often progressive airway obstruction

COPD: chronic obstructive pulmonary disease; AFL: airflow limitation.

정의 – 2024 COPD 진료지침

- 기도나 폐포의 이상(기관지염, 세기관지염, 폐기종)으로 인해 공기의 흐름(기류)이 제한되며 이로 인해 만성적인 호흡기 증상(숨참, 기침, 가래)을 보이는 폐의 질환이다.
- 기도와 폐포의 이상은 다양한 원인에 의해 생기며, 기류의 제한은 지속적이고 꾸준히 진행될 수 있다.

Causes and Risk Factors

- COPD results from gene(G)-environment(E) interactions occurring over the lifetime(T) of the individual (***GETomics***) that can damage the lungs and/or alter their normal development/aging processes.

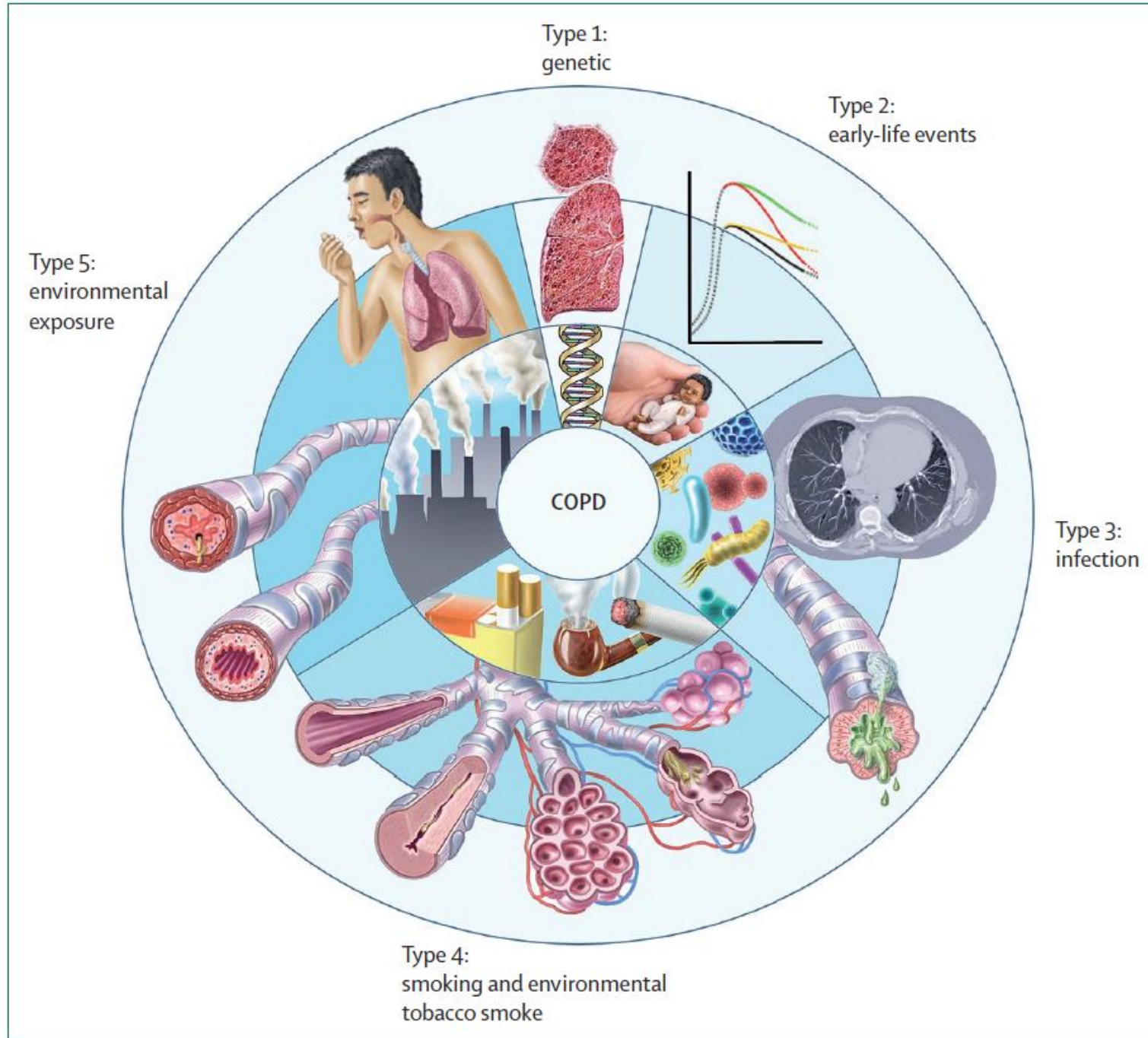


Figure 6: Proposed classification of COPD according to major risk factors

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)	<ul style="list-style-type: none"> • Exposure to tobacco smoke, including <i>in utero</i> 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, HIV-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)

Panel: Classification of COPD by the Lancet Commission on COPD

Type 1: genetically determined COPD

- 1.1 α_1 antitrypsin deficiency
- 1.2 Telomerase reverse transcriptase mutations
- 1.3 Other genetic variants

Type 2: COPD related to early-life events

- 2.1 Prematurity (chronic lung disease of prematurity, bronchopulmonary dysplasia)
- 2.2 Childhood asthma

Type 3: infection-related COPD

- 3.1 Childhood respiratory infections
- 3.2 Tuberculosis-associated COPD
- 3.3 HIV-associated COPD

Type 4: COPD related to smoking or vaping

- 4.1 Tobacco smoking
- 4.2 In-utero exposure to tobacco smoke
- 4.3 Passive smoking (childhood and adult)
- 4.4 Vaping or e-cigarette smoking
- 4.5 Cannabis smoking

Type 5: environmental exposure-related COPD

- 5.1 Exposure to indoor air pollutants
- 5.2 Outdoor air pollution and smog
- 5.3 Wildfire smoke
- 5.4 Occupational exposures (to vapours, gases, dusts, or fumes)

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- What is the proportion of each etiotype?

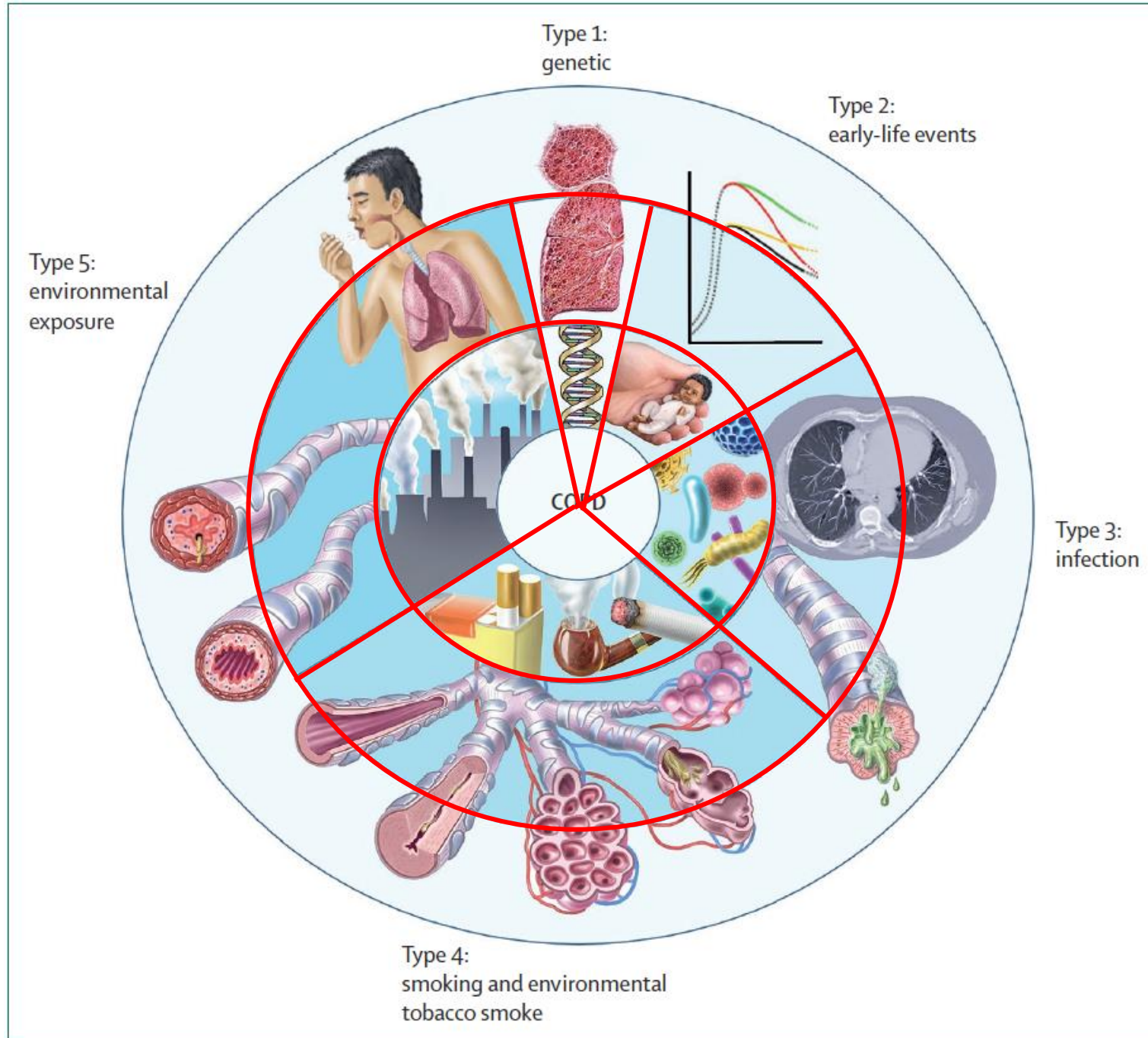


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- What is the proportion of each etiology?
- Deficiencies in α_1 antitrypsin are noted in 1–2% of white patients with COPD.
- TERT mutation - predominantly found in women and in 1% of patients with severe early onset COPD.

- COPDGene
 - ≥ 10 pack-year cigarette smoking history with and without COPD
- SPIROMICs
 - Subjects with current or former history of tobacco use (≥ 20 pack-year)
- ECLIPSE
 - smoking history of ≥ 10 pack-yrs
- Hokkaido COPD Cohort
 - smoking history of at least 10 pack-years.
- CanCOLD, KOCOSS
 - A history of smoking is not mandatory.

Original Research



Application of the Lancet Commission COPD classification to COPD Cohort Population in South Korea

Hyonsoo Joo^a, Hyoung Kyu Yoon^b, Yong Il Hwang^c, Sang Hyuk Kim^d, Soo-Jung Um^e,
Won-Yeon Lee^f, Ki-Suck Jung^c, Kwang Ha Yoo^g, Woo Jin Kim^h, Chin Kook Rhee^{i,*}

Open Access Full Text Article

ORIGINAL RESEARCH

COPD Risk Factor Profiles in General Population and Referred Patients: Potential Etiotypes

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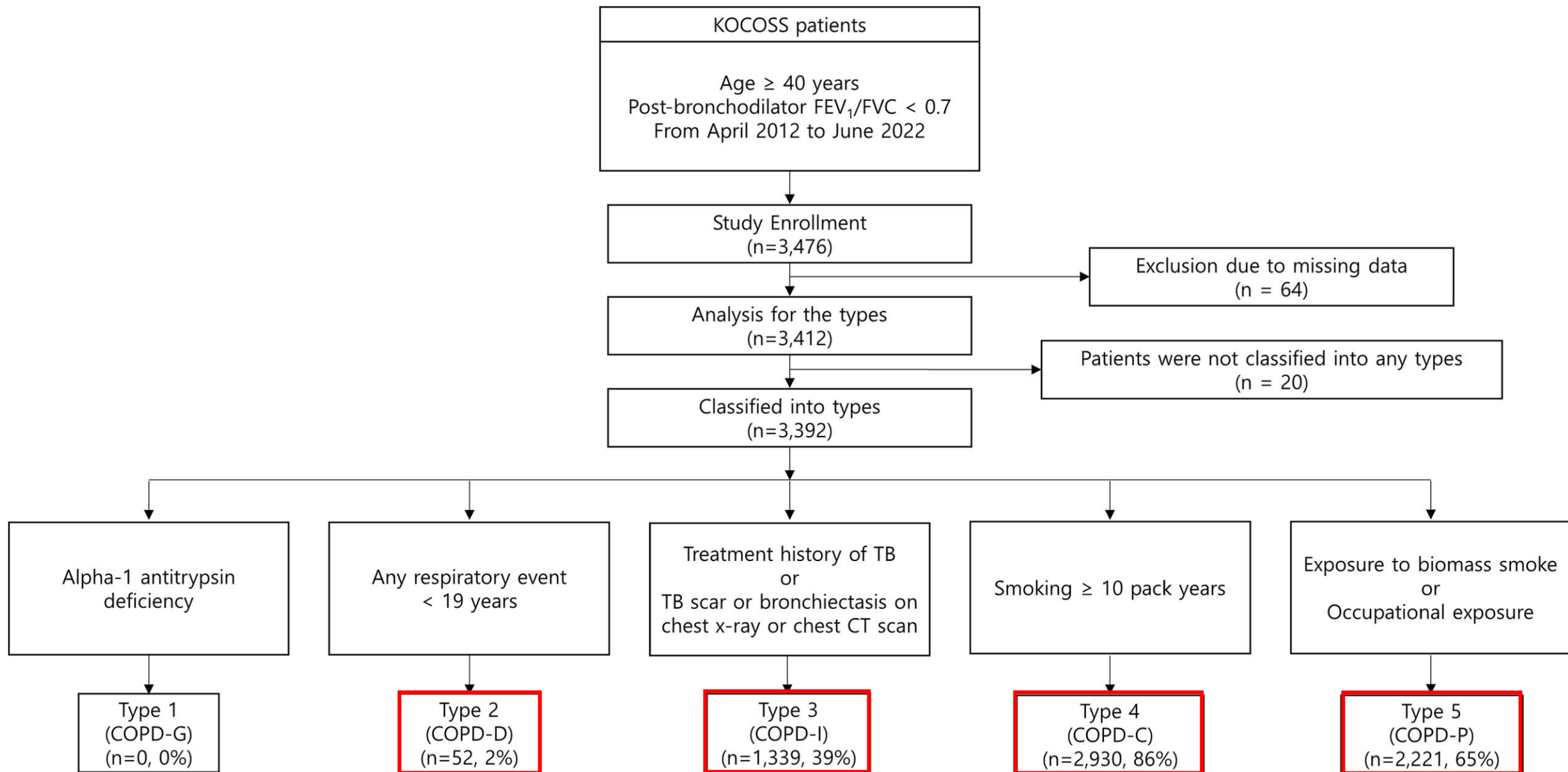
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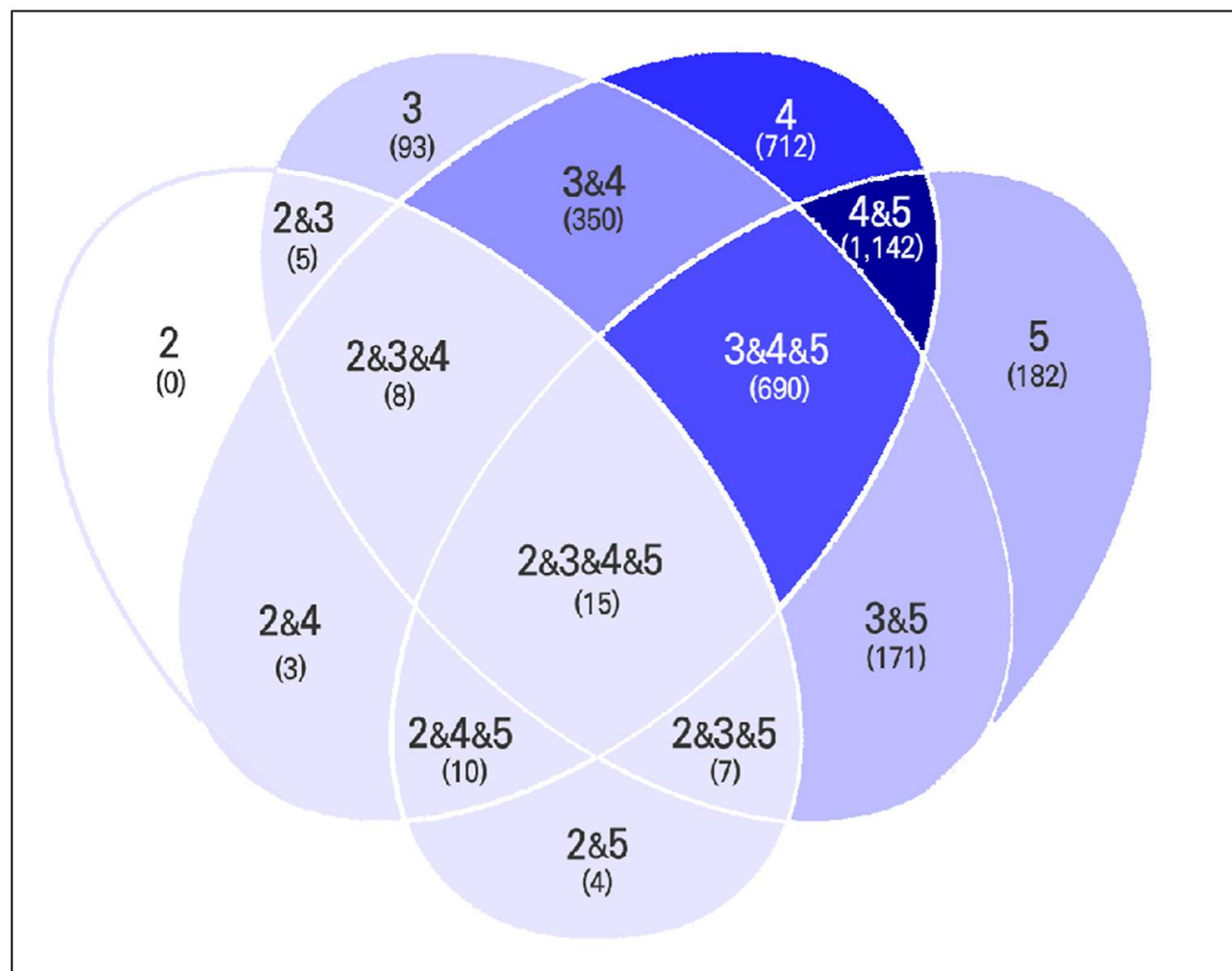
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Comparison of characteristics among non-overlapping patients with COPD according to the new classification.

	Type 3 (COPD-I) only (N = 93)	Type 4 (COPD-C) only (n = 712)	Type 5 (COPD-P) only (n = 182)	P-value
Age, years	65.61 ± 9.81	68.43 ± 8.20	69.53 ± 8.64	0.001
Sex, M	52 (56 %)	690 (97 %)	126 (69 %)	0.000
BMI, kg/m ²	23.79 ± 3.96	23.23 ± 3.43	23.80 ± 3.40	0.074
Never smoker, %	71 (76 %)	0 (0 %)	89 (49 %)	<0.001
Ex-smoker, %	15 (16 %)	502 (71 %)	56 (31 %)	<0.001
Current smoker, %	7 (8 %)	210 (30 %)	37 (20 %)	<0.001
Pack-years	0.83 ± 2.09	43.43 ± 24.18	1.60 ± 2.99	<0.001
COPD grades				
GOLD 1	12 (13 %)	106 (15 %)	24 (13 %)	0.770
GOLD 2	40 (43 %)	369 (52 %)	102 (56 %)	0.123
GOLD 3	34 (37 %)	193 (27 %)	50 (27 %)	0.159
GOLD 4	7 (8 %)	44 (6 %)	6 (3 %)	0.247

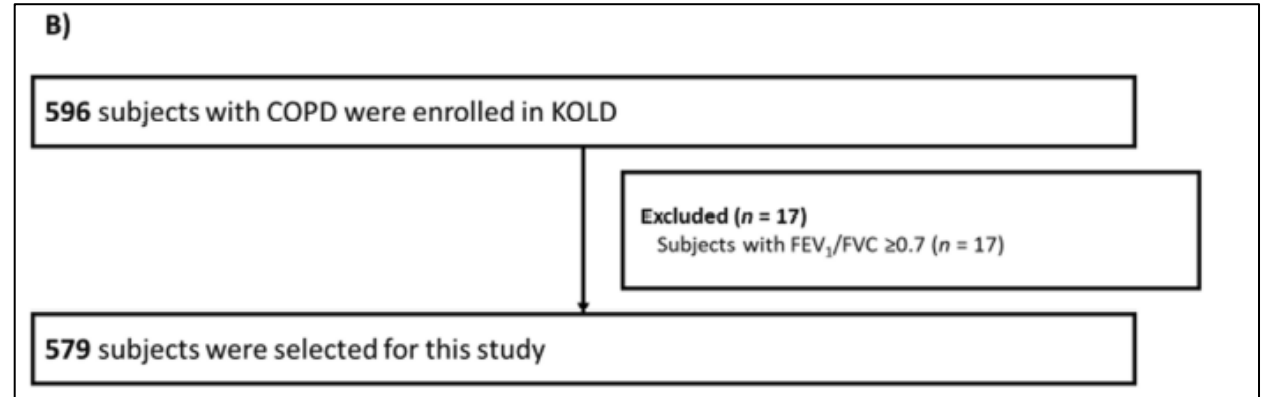
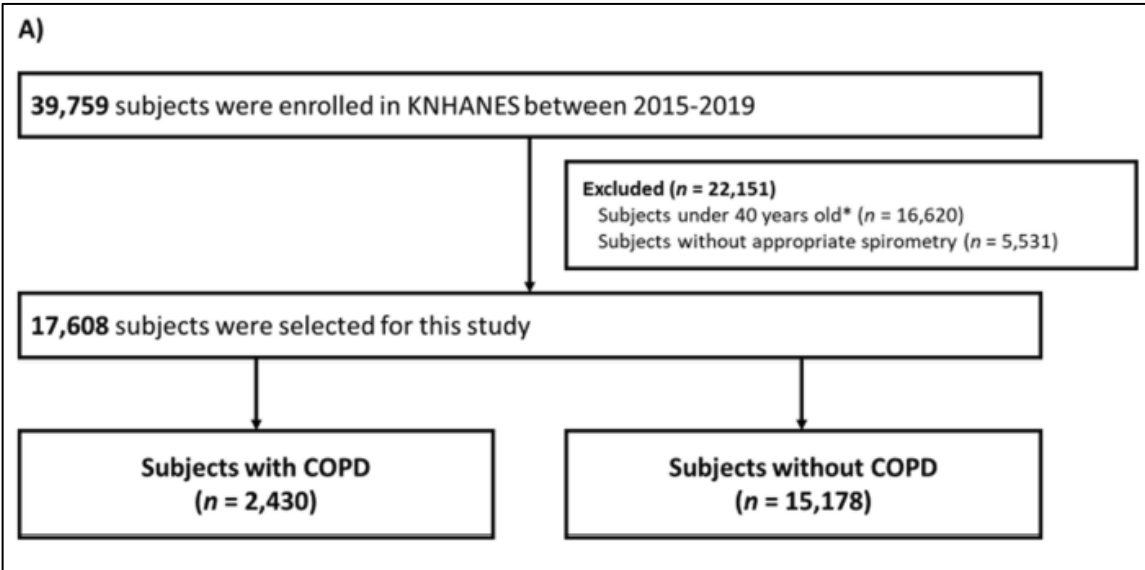
Acute exacerbation rates and frequency of non-overlapping COPD during prospective follow-up according to the new classification.

	Type 3 (COPD-I) only (n = 41)	Type 4 (COPD-C) only (n = 296)	Type 5 (COPD-P) only (n = 86)	P-value
Moderate exacerbation over 1 year				
Rate	15 (37 %)	115 (39 %)	26 (30 %)	0.345
Mean number	0.73 ± 1.23	0.88 ± 1.64	0.60 ± 1.27	0.336
Severe exacerbation over 1 year				
Rate	6 (15 %)	22 (7 %)	2 (2 %)	0.038
Mean number	0.24 ± 0.73	0.11 ± 0.49	0.02 ± 0.15	0.048

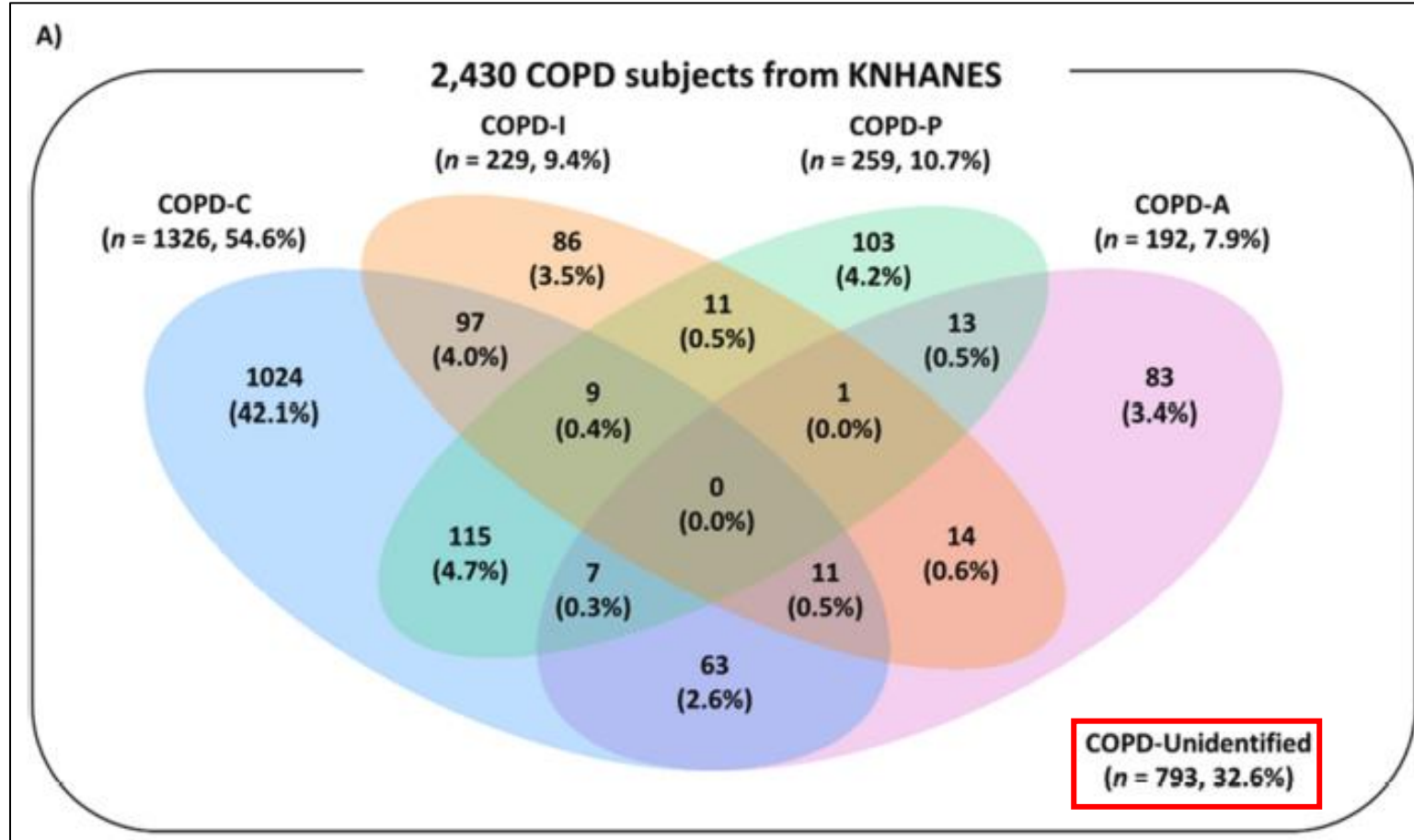
COPD Risk Factor Profiles in General Population and Referred Patients: Potential Etiotypes

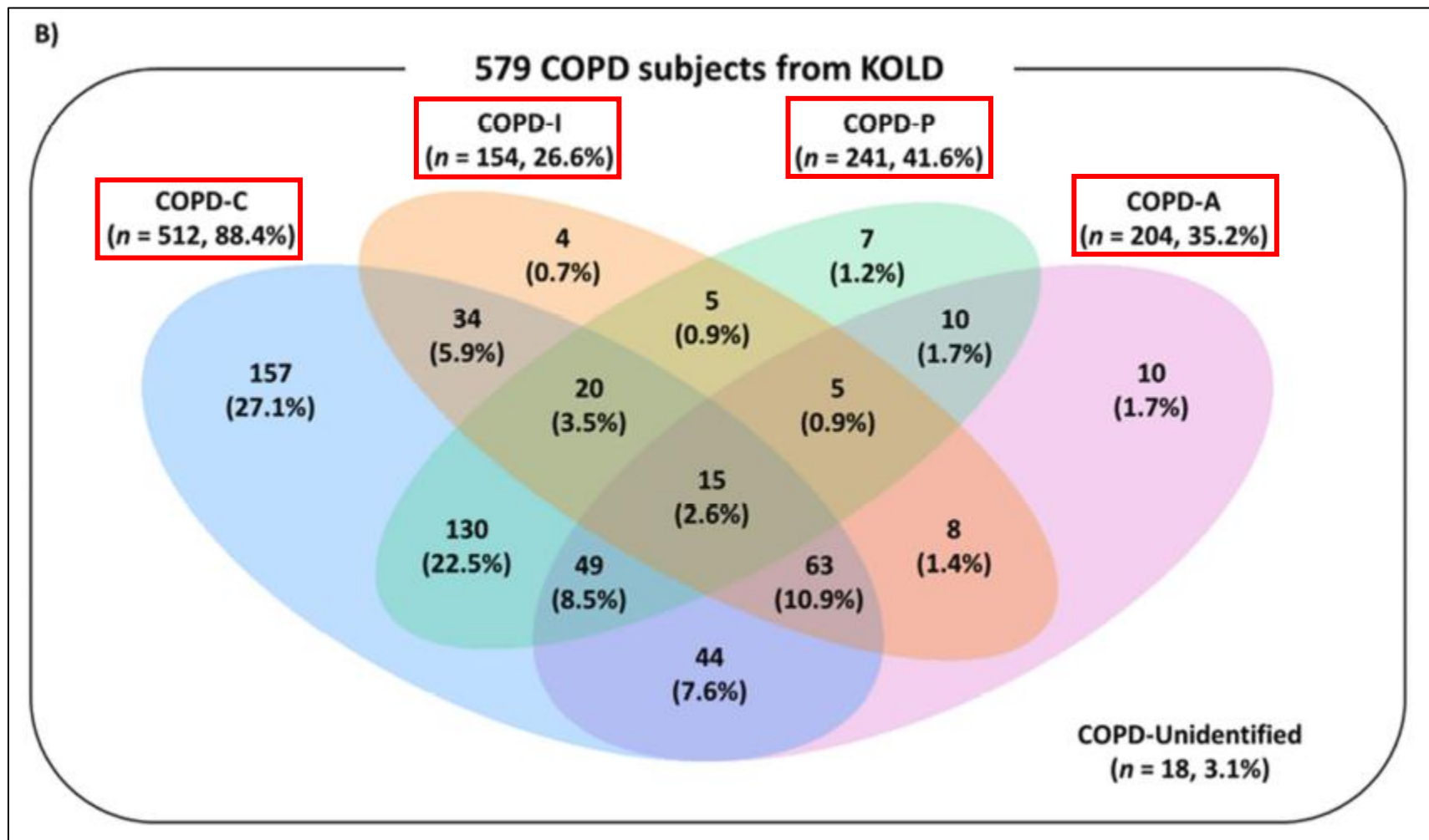
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- Risk factors**
- C (cigarette smoking)
 - I (infection)
 - P (pollution)
 - A (asthma)
 - U (unidentified)





asthma (A) by a history of asthma with physician diagnosis.

Comparison of proportions

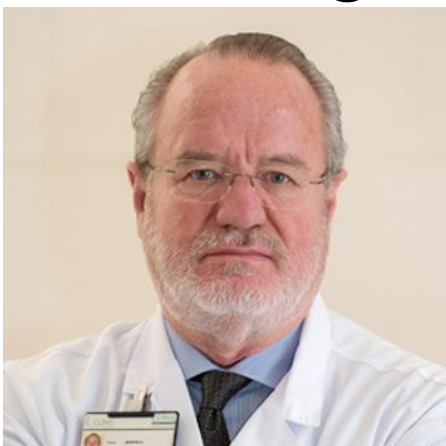
	KOCOSS	KOLD
Type 2 : COPD - D	5.2% (n=52)	
: COPD - A		35.2% (n=204)
Type 3 : COPD - I	39% (n=1,339)	26.6% (n=154)
Type 4 : COPD - C	86% (n=2,930)	88.4% (n=512)
Type 5 : COPD - P	65% (n=2,221)	41.6% (n=241)

PRO/CON debate

Etiotypes in COPD: a pro/con debate



- PRO (Alvar Agusti) / CON (Marc Miravittles)



Towards the elimination of chronic obstructive pulmonary disease: a *Lancet* Commission



Pro



- The 2024 GOLD document states that COPD is “a heterogeneous lung condition that results from gene(G)-environment(E) interactions occurring over the lifetime(T) of the individual(**GETomics**) that can damage the lungs and/or alter their normal development/aging processes”.
- Following this statement, GOLD proposes the existence of several etiotypes.

Pro



- Importantly, GOLD explicitly states that “this proposal has relatively little impact on current clinical practice, other than illuminating this so-far ignored aspect of COPD, but it is of the utmost importance to highlight the need to explore current and future therapies in these other etiologies of COPD”.

Con



- The continuous and endless use of new terms to try to define the heterogeneity of COPD only creates more and more confusion to clinicians. (COPD의 이질성을 정의하기 위해 계속해서 새로운 용어들을 사용하는 것은 결국 임상 의들에게 더 많은 혼란만을 초래합니다.)
- 이러한 혼란의 근본적인 원인은, COPD라는 용어가 만성 기류 제한(CAL, Chronic Airflow Limitation)의 동의어처럼 사용되고 있기 때문입니다.
- 그러나 CAL은 질병도 아니고 증후군도 아닙니다. 이는 단순히 진단 검사를 통해 얻어진 생리학적 정의이며, 호흡기 증상이 있으면서 흡연이나 유사한 유해물질에 노출된 성인에게서 질병(COPD 등)을 진단하는 데 참고될 수 있는 수치일 뿐입니다.

Con



- 그럼에도 불구하고, 역학 연구에서는 기관지 확장제 투여 후 FEV_1/FVC 가 0.7 미만(Lower Limit of Normal 이하 포함)인 경우, 증상이나 노출 이력이 없어도 모두 COPD로 분류하는 경우가 많습니다.
- 하지만 단순히 $FEV_1/FVC < 0.7$ 이라는 수치가 과연 질병을 의미하는 것인가?
- 그건 경우에 따라 다릅니다. 이 수치는 다양한 질병의 결과일 수 있습니다 — 예를 들어 천식, 기관지확장증, 결핵 후유증 등. 혹은 노인에서는 정상 생리적 현상일 수도 있습니다

Con



- 선진국에서 발생하는 전체 CAL의 약 70% 이상은 흡연이 병인으로 잘 알려져 있습니다.
- 그러므로 우리는 COPD를 흡연에 의해 유발된 CAL, 즉 흡연에 의한 기류 제한과 그에 수반되는 증상 및 징후를 가진 질환으로 정의하고, 다른 원인으로 생긴 CAL은 각기 다른 이름을 붙여야 합니다.
- 하지만 Lancet Commission과 GOLD 2023/2024 문서는 이와 반대로 "COPD의 병인형(etiotypes)"이라는 개념을 제안하며, 다양한 형태의 COPD들을 구분하자고 합니다.
- 그러나 이 용어 자체가 혼란을 일으킵니다. 왜냐하면 질병을 가장 잘 정의하는 것은 원래 병인(etiology)이기 때문입니다.
- 병인이 다르면 다른 질병으로 간주되어야 하는 것이 타당합니다.

Con



- 예를 들어, GOLD나 Lancet에서 말하는 “COPD-A”(즉, 천식 병력이 있는 COPD)는 사실 그 자체가 천식입니다.
- 어릴 때 중증 천식을 앓았던 사람이 성인기에 기류 제한을 보이게 되더라도, 그것은 단지 병이 변한 것이 아니라 여전히 천식인 것이며, COPD-A라는 새로운 이름으로 부르는 것은 오히려 천식을 COPD로 잘못 치료하게 만들 위험이 있습니다.
- 또 다른 예는 “COPD-I”입니다. 예를 들어 결핵이나 소아기 감염 이후 생긴 기류 제한은 그 병인이 전혀 다르며, 이런 사람들에게 COPD 치료가 효과가 있는지도 확실치 않습니다. 병태생리나 예후가 COPD-C와 같은지도 불확실합니다. 오히려 “결핵 관련 CAL”처럼 명확한 이름을 붙이는 것이 낫습니다.

Con



- 병인형 개념이 도입된 목적 중 하나는 비흡연자 COPD에 대한 인식을 높이기 위함이었지만 선진국의 역학 연구에 따르면 COPD(혹은 CAL)의 약 25%는 비흡연자에서 발생한다고 하지만, 중요한 점은 나머지 75%는 여전히 흡연이 원인이라는 사실입니다.
- 중증 COPD의 대부분은 흡연자에게서 나타납니다.
- 또 비흡연자 COPD는 장기 예후도 나쁘지 않거나 오히려 정상인보다 좋을 수도 있습니다. 그럼에도 비흡연자 CAL에 대한 연구는 분명 필요하지만, 공중보건에 실질적인 영향을 주려면 흡연 관련 COPD 연구에 더 큰 투자가 필요합니다.
- 새로운 임상적 가치를 더하지 않는다면, 단지 새로운 단어를 만들 이유는 없습니다.

Conclusion

- Pro - 흡연 관련 COPD를 넘어서는 영역까지 연구의 범위를 확장해야 한다는 필요성을 강조
 - ✓ 모든 형태의 CAL을 COPD라는 이름 아래 포함시키고, 그 안에서 다양한 병인형을 구분하자
- Con - 새로운 임상적 가치를 더하지 않는다면, 단지 새로운 단어를 만들 이유는 없음
 - ✓ COPD라는 용어를 흡연과 관련된 가장 흔한 CAL 형태에 한정하고, 나머지 형태는 각기 독립된 질환으로 분리하자
- 어떤 접근이 환자들에게 더 도움이 될지?
 - Time will tell.

Proposed Etiotypes for Chronic Obstructive Pulmonary Disease: Controversial Issues

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Controversial Issues 1: Bronchiectasis with Airflow Limitation

Controversial Issues 2: COPD Due to Infection

Controversial Issues 3: COPD Due to Environmental Exposure

Bronchiectasis with airflow limitation

- Bronchiectasis은 전통적으로 COPD와 다른 독립된 질환으로 간주됨.
- 하지만 COPD 환자 중 상당수가 CT에서 기관지확장증을 보이며, 기관지확장증 환자 중에서도 폐쇄성 패턴이 흔함.
- 병리학적으로 COPD는 주로 소기도 및 폐포 손상, 기관지확장증은 기관지의 확장 및 염증이 특징.
- 치료 접근법이 다르며, 기관지확장증에서는 airway clearance가 핵심이고, COPD에서는 Bronchodilator가 중심.
- 이에 따라 GOLD는 기관지확장증을 COPD의 etiotype이 아닌 comorbidity으로 분류할 것을 권장.

Bronchiectasis with airflow limitation

- Lancet commission에서 Bronchiectasis에 대한 많은 언급은 없었지만

Tuberculosis-associated COPD

Tuberculosis remains a major health problem in many countries. There is a strong association between a history of tuberculosis and the development of COPD in non-smoking patients.⁹¹ Despite successful treatment of tuberculosis, impaired lung function often persists.⁹² The risk of airflow limitation in patients with a history of tuberculosis is more than twice that in patients with no history of tuberculosis. The chronic inflammatory response and long-term tuberculosis-associated structural alterations, such as airway remodelling with scar formation, stenosis, and bronchiectasis, are the pathological basis for the development of COPD.

- Bronchiectasis가 COPD 발달에 기초가 된다고 언급한 부분이 있었습니다.

COPD due to infection

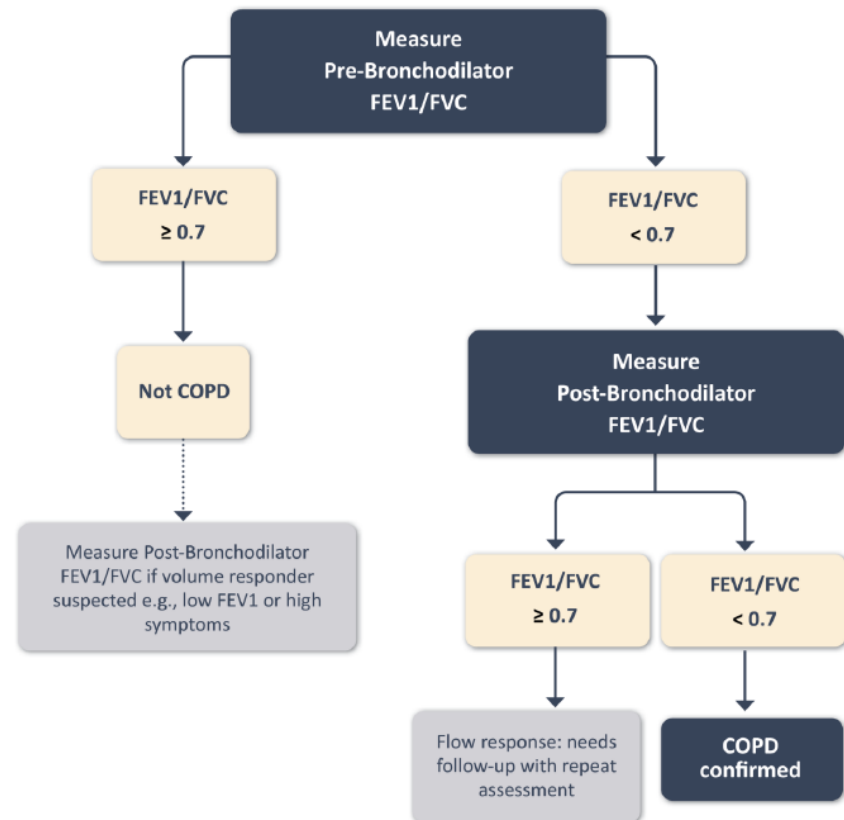
- 폐결핵(TB), 소아 감염, HIV 등은 비흡연성 COPD의 주요 원인으로, GOLD 2023에서 COPD-I로 제안됨.
- 폐결핵 앓은 이후 COPD 발생 위험이 2.6배 이상 증가하고, FEV₁ 감소 속도도 빠름.
- 기관지확장제 치료가 폐기능 개선과 사망률 감소에 효과가 있음.
- COPD-I (Type3)에서 기류 제한은 COPD와 유사할 수 있으나, 근본적인 병인과 예후, 치료가 달라 독립적 분류 필요성 있음.

Diagnosis of COPD

A diagnosis of COPD should be **considered** in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease (**Figure 2.1**) but **forced spirometry** that demonstrates the presence of a post-bronchodilator FEV1/FVC < 0.7 is **mandatory** to establish the diagnosis of COPD.⁽⁴⁶⁾

Pre- and Post- Bronchodilator Spirometry

Figure 2.6



Role of Spirometry in COPD

Figure 2.7

- **Diagnosis**
- **Assessment of severity of airflow obstruction (for prognosis)**
- **Follow-up assessment**
 - Therapeutic decisions
 - Pharmacological in selected circumstances (e.g., discrepancy between spirometry and level of symptoms)
 - Consider alternative diagnoses when symptoms are disproportionate to degree of airflow obstruction
 - Non-pharmacological (e.g., interventional procedures)
- **Identification of rapid decline**

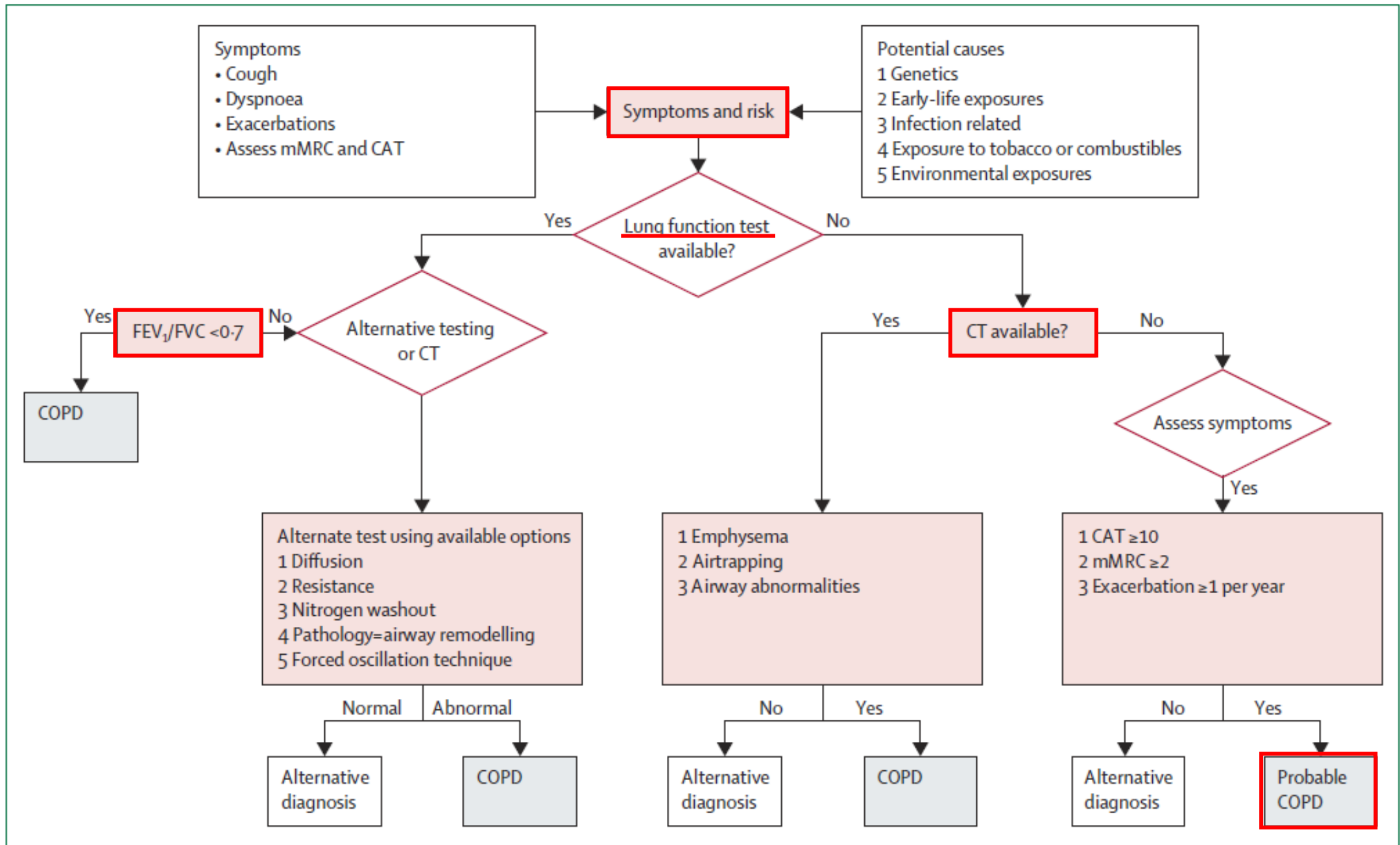


Figure 11: Proposed diagnostic algorithm for COPD

B84 DIAGNOSIS OF COPD: A PRO CON DEBATE

Assembly on Clinical Problems

2:15 P.M. - 3:45 P.M.

Target Audience

Physicians, nurse practitioners, physician assistants, respiratory therapists, researchers

Objectives

At the conclusion of this session, the participant will be able to:

- learn about the impact of using the lower limit of normal versus the fixed 0.70 cutoff for FEV1/FVC, their strengths and limitations, and practical considerations for clinical practice
- appreciate the implications of restricting diagnosis of COPD to spirometric impairment versus expanding diagnosis beyond spirometry to include imaging and symptoms
- gain new knowledge of the definition of Pre-COPD, and its pros and cons

2:15 Pro: COPD Should Be Diagnosed Using the Lower Limit of Normal for Airflow Obstruction

2:29 Con: COPD Should Be Diagnosed Using the Fixed FEV1/FVC Ratio for Airflow Obstruction

2:48 Pro: COPD Should Be Diagnosed on the Basis of Spirometric Airflow Obstruction

3:00 Con: The Diagnosis of COPD Should Extend Beyond Spirometric Airflow Obstruction

3:17 Pro: Pre-COPD Is Real and Will Impact Clinical Practice

3:29 Con: Pre-COPD Is A Premature Concept

The slide content is as follows:

- It is time to redefine the O
- We have new, perhaps more sensitive (and available?), tools
- It is a new era of COPD pharmacotherapy
- We need to broaden (and simplify) our definitions

- It is the O in COPD
- Obstructed spirometry is the cornerstone of COPD diagnosis
- Spirometric obstruction is included in almost all clinical COPD trials

Logos at the bottom of the slide include the Center for Lung Health and Althim Health (The academic core of Althim Health).

A Multidimensional Diagnostic Approach for Chronic Obstructive Pulmonary Disease

COPDGene 2025 Diagnosis Working Group and CanCOLD Investigators

Figure 1. Diagnostic Schema for Chronic Obstructive Pulmonary Disease (COPD) Using Major and Minor Criteria

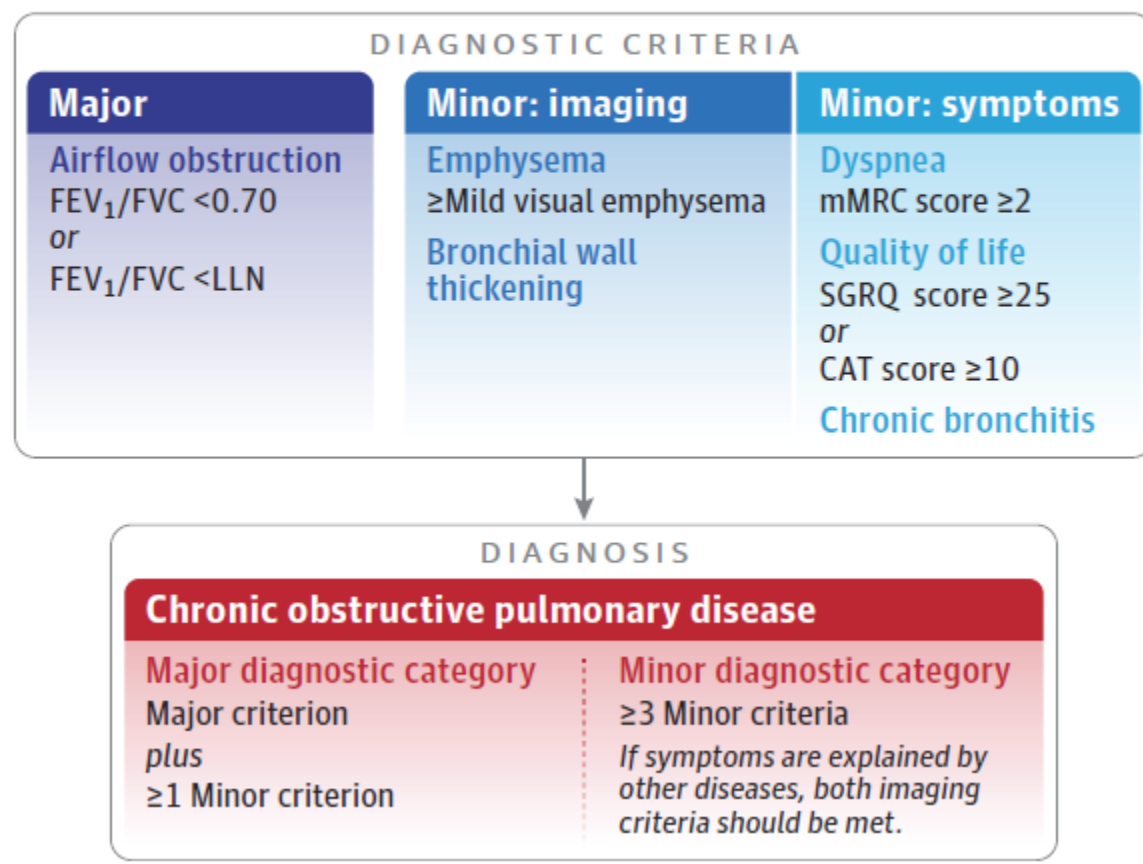


Figure 2. Reclassification of Participants by New Diagnostic Schema by Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage

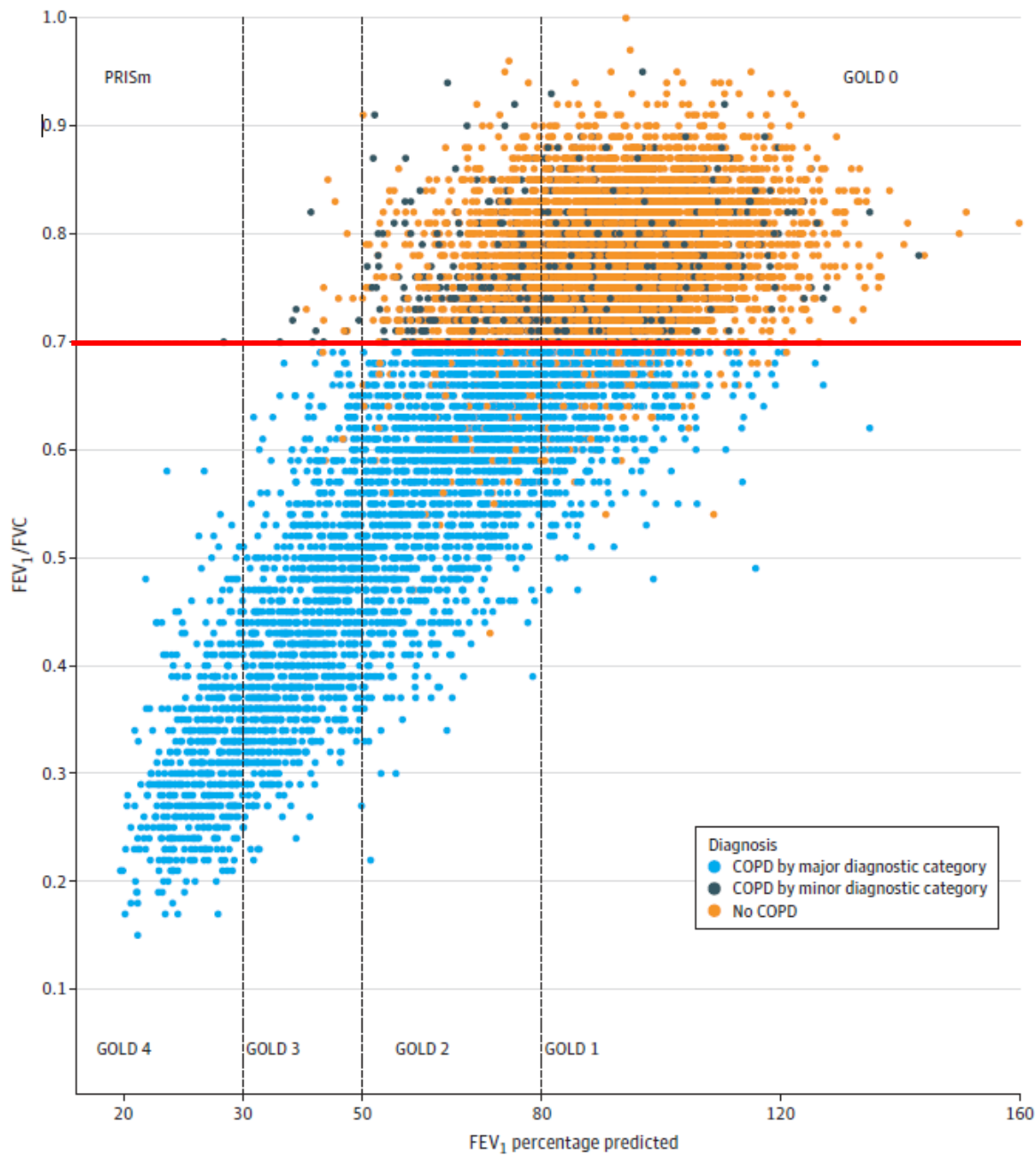
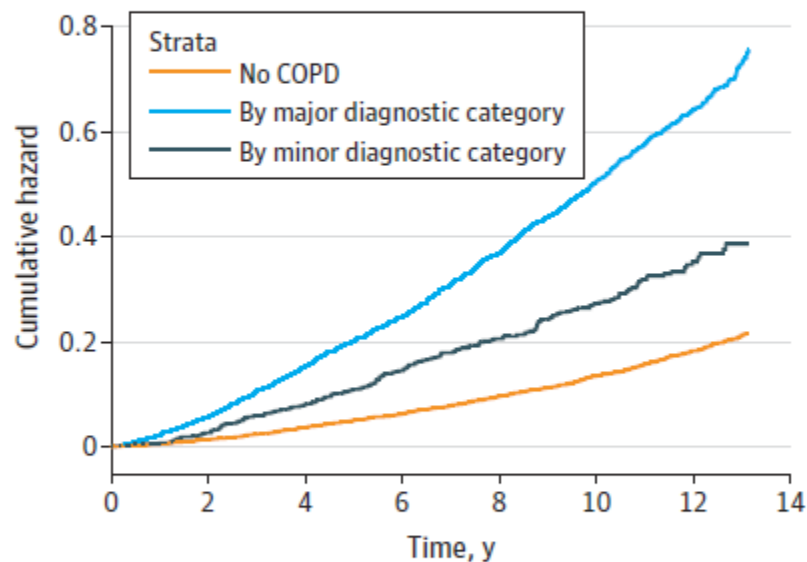


Figure 3. Associations Between Clinical Outcomes and Chronic Obstructive Pulmonary Disease (COPD) Status by New Diagnostic Schema in Genetic Epidemiology of COPD

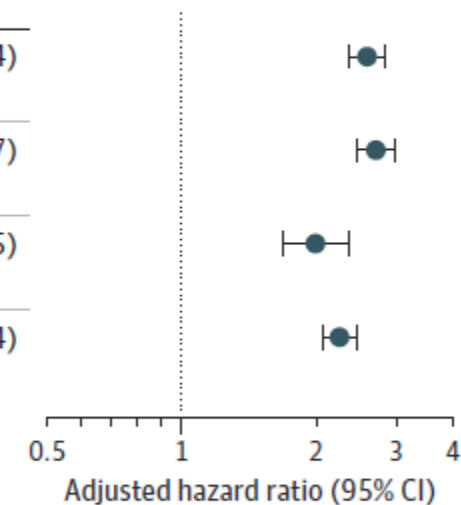
A Multivariable cumulative hazards plot of all-cause mortality by COPD category



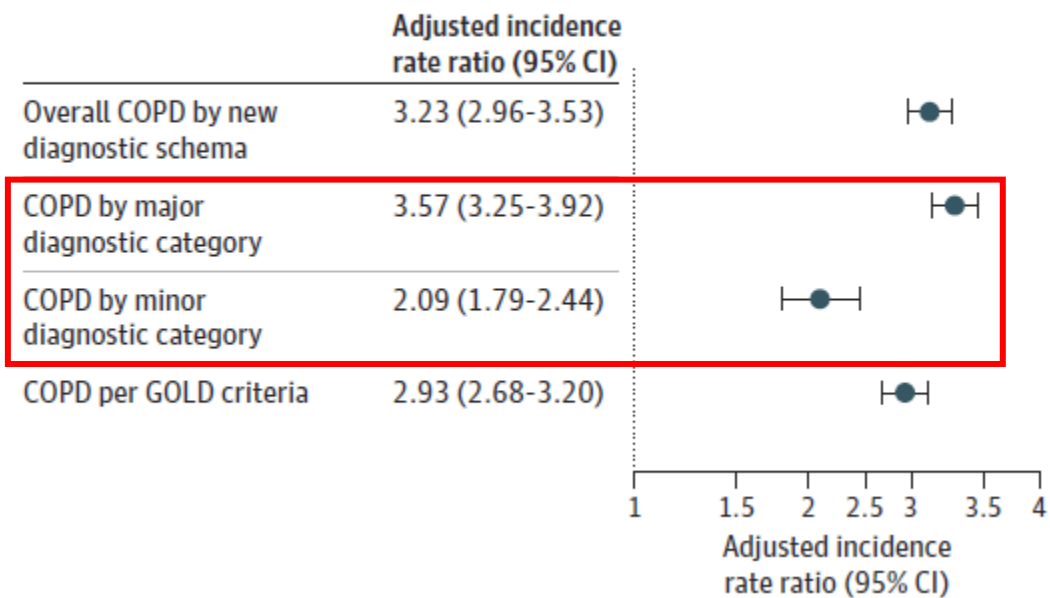
No. at risk	0	2	4	6	8	10	12	14
No COPD	4721	4183	3986	3612	3276	2932	1820	
By major diagnostic category	3884	3495	3100	2626	2160	1763	1015	
By minor diagnostic category	811	670	598	517	423	354	201	

B Adjusted hazard ratio for all-cause mortality by COPD category

	Adjusted hazard ratio (95% CI)
Overall COPD by new diagnostic schema	2.58 (2.35-2.84)
COPD by major diagnostic category	2.70 (2.45-2.97)
COPD by minor diagnostic category	1.98 (1.67-2.35)
COPD per GOLD criteria	2.24 (2.05-2.44)



C Adjusted incidence rate ratio for exacerbations



D Adjusted annualized change in FEV₁

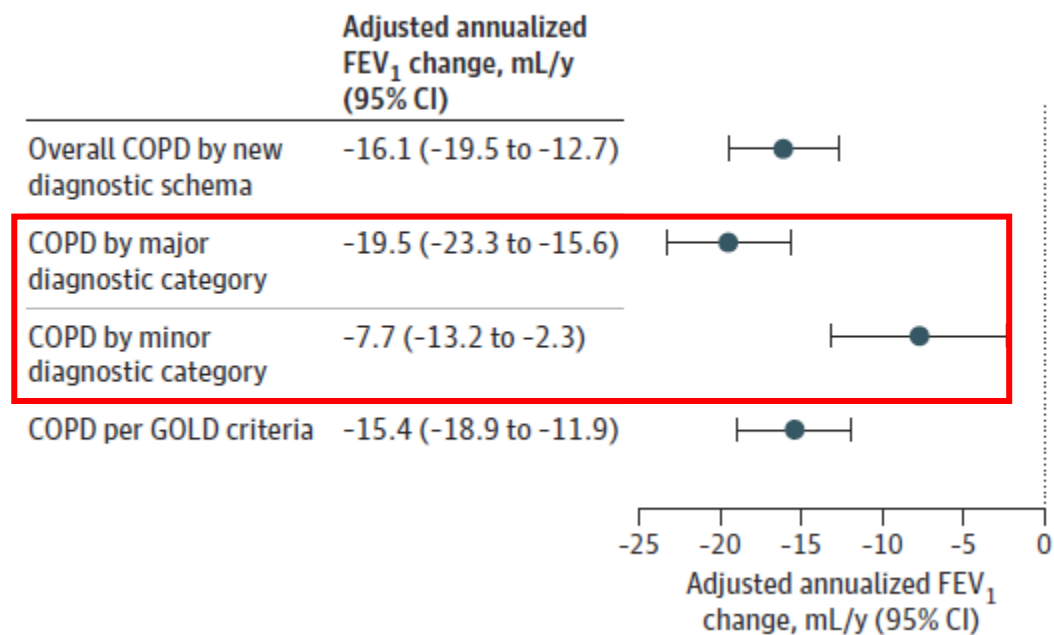
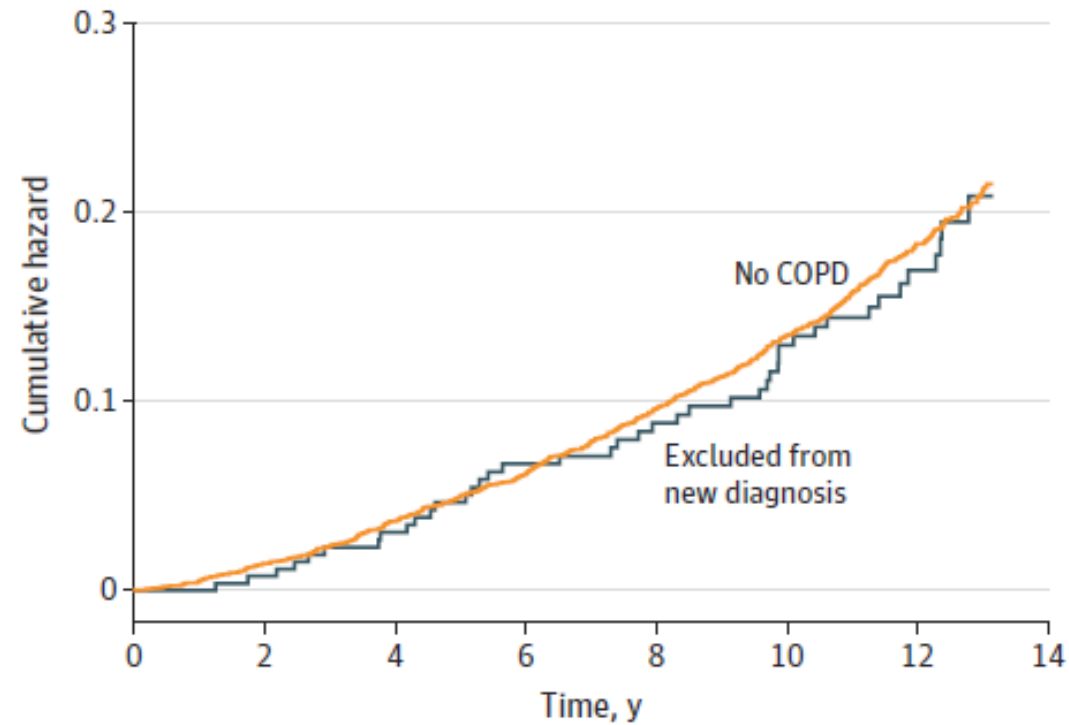


Figure 4. Associations Between the Category Excluded From Chronic Obstructive Pulmonary Disease (COPD) Diagnosis and Clinical Outcomes in the Genetic Epidemiology of COPD Study^a



No. at risk		0	2	4	6	8	10	12	14
No COPD		4439	3920	3731	3370	3048	2721	1682	
Excluded from new diagnosis		282	263	255	242	228	211	138	

Conclusion

- Using the new COPD diagnostic schema, compared with individuals classified as not having COPD, those with a new diagnosis of COPD had greater all-cause and respiratory-specific mortality, more frequent exacerbations, and faster FEV₁ decline.
- This new COPD diagnostic schema integrates multidimensional assessments to include additional individuals with high respiratory morbidity and to exclude individuals with air flow obstruction who do not have respiratory symptoms or evidence of structural lung disease

Summary

- Definition - heterogeneous lung condition
 - gene(G)-environment(E) interactions occurring over the lifetime(T) of the individual (GETomics)
- Etiotype - the proportion of each etiology?
 - 단일 병인형으로 분류된 환자는 28.4%에 불과
- Pro/Con - 모든 형태의 CAL을 COPD라는 이름 아래 포함시키고, 그 안에서 다양한 병인형을 구분하자/COPD라는 용어를 흡연과 관련된 가장 흔한 CAL 형태에 한정하고, 나머지 형태는 각기 독립된 질환으로 분리하자

Summary

Figure 1. Diagnostic Schema for Chronic Obstructive Pulmonary Disease (COPD) Using Major and Minor Criteria

