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# 호흡기내과 의사를 위한 Respiratory Review of 2025

## Chronic Obstructive Pulmonary Disease

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# Contents

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- 1. Risk factors**
- 2. Assessment and Diagnosis**
- 3. Treatment**



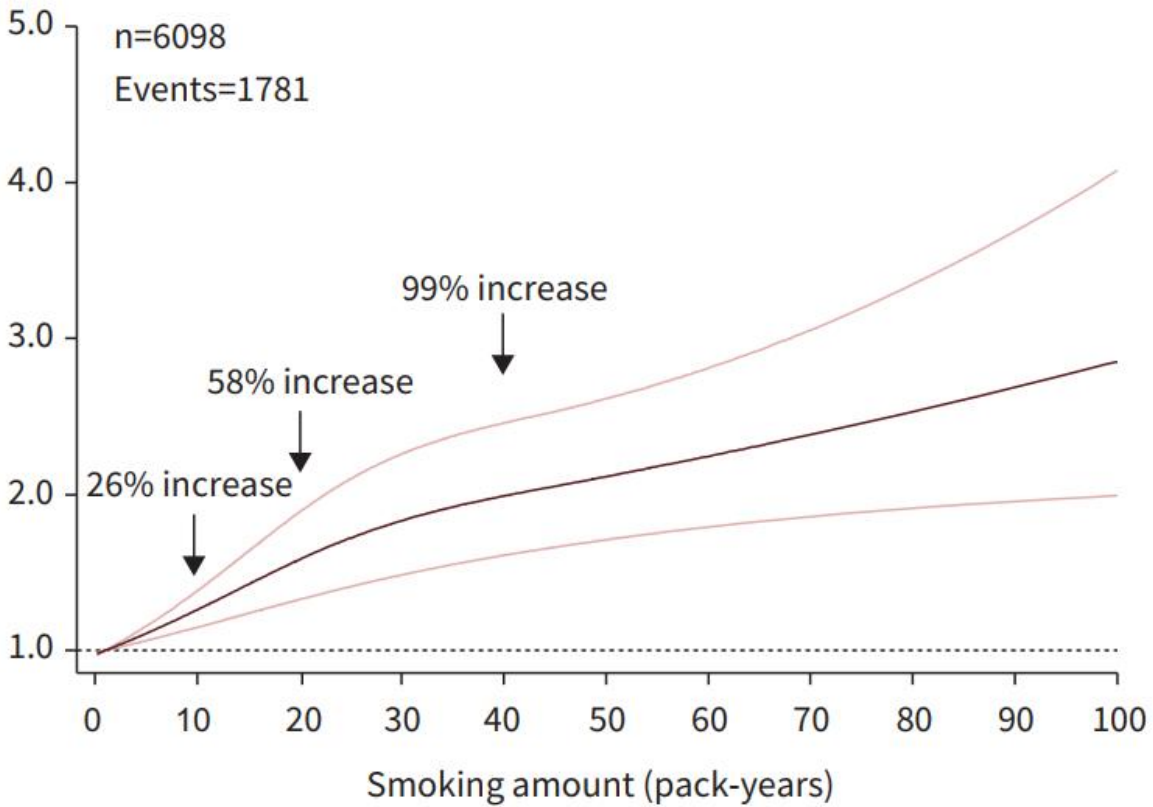
# Low smoking exposure and development and prognosis of COPD over four decades: a population-based cohort study

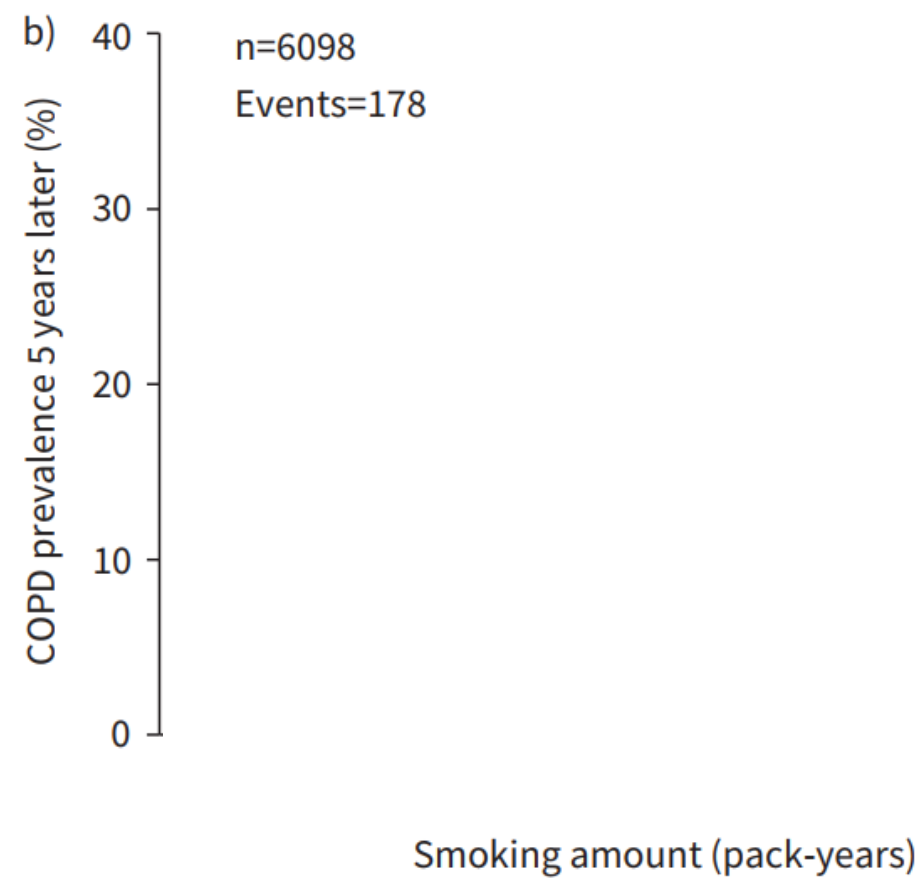
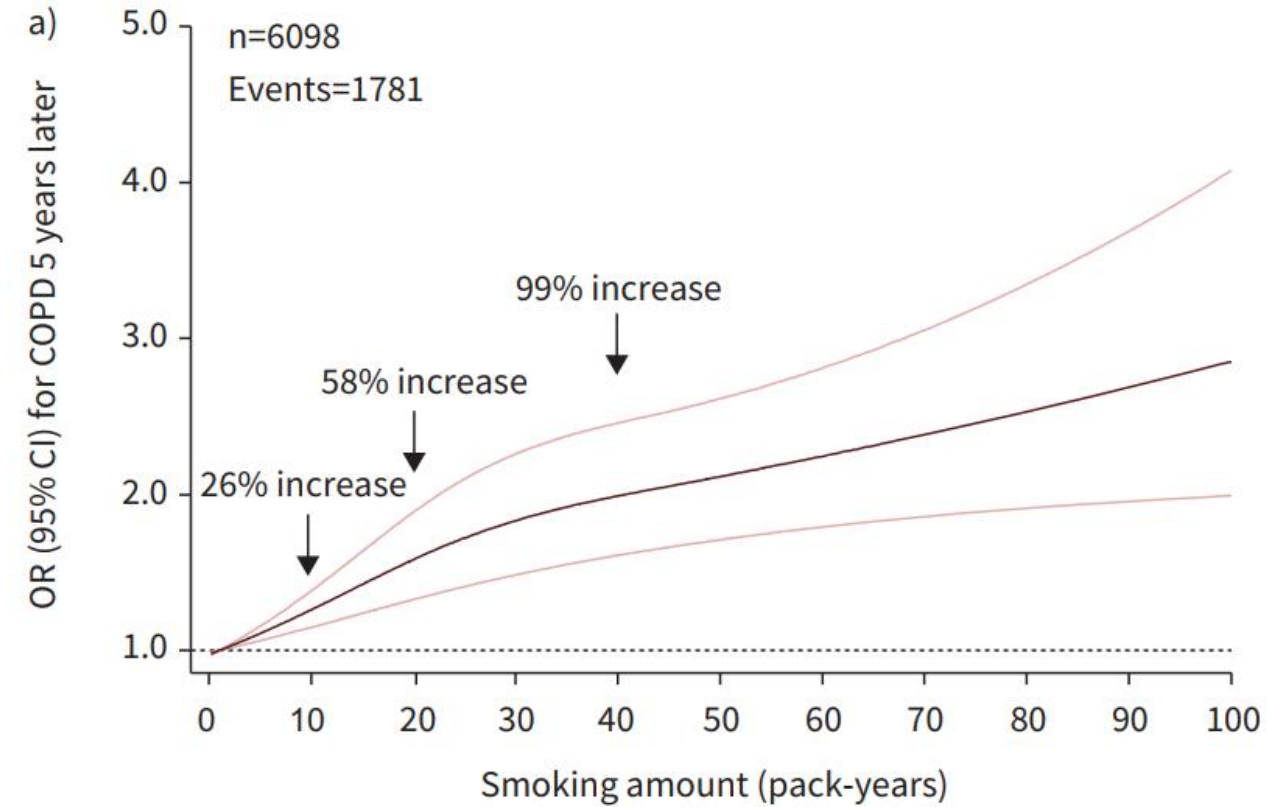
Yunus Çolak <sup>1,2</sup>, Anders Løkke <sup>3,4</sup>, Jacob L. Marott <sup>5</sup>, Peter Lange<sup>1,2,5,6</sup>, Jørgen Vestbo <sup>7</sup>,  
Børge G. Nordestgaard <sup>2,5,8</sup> and Shoaib Afzal<sup>2,8</sup>



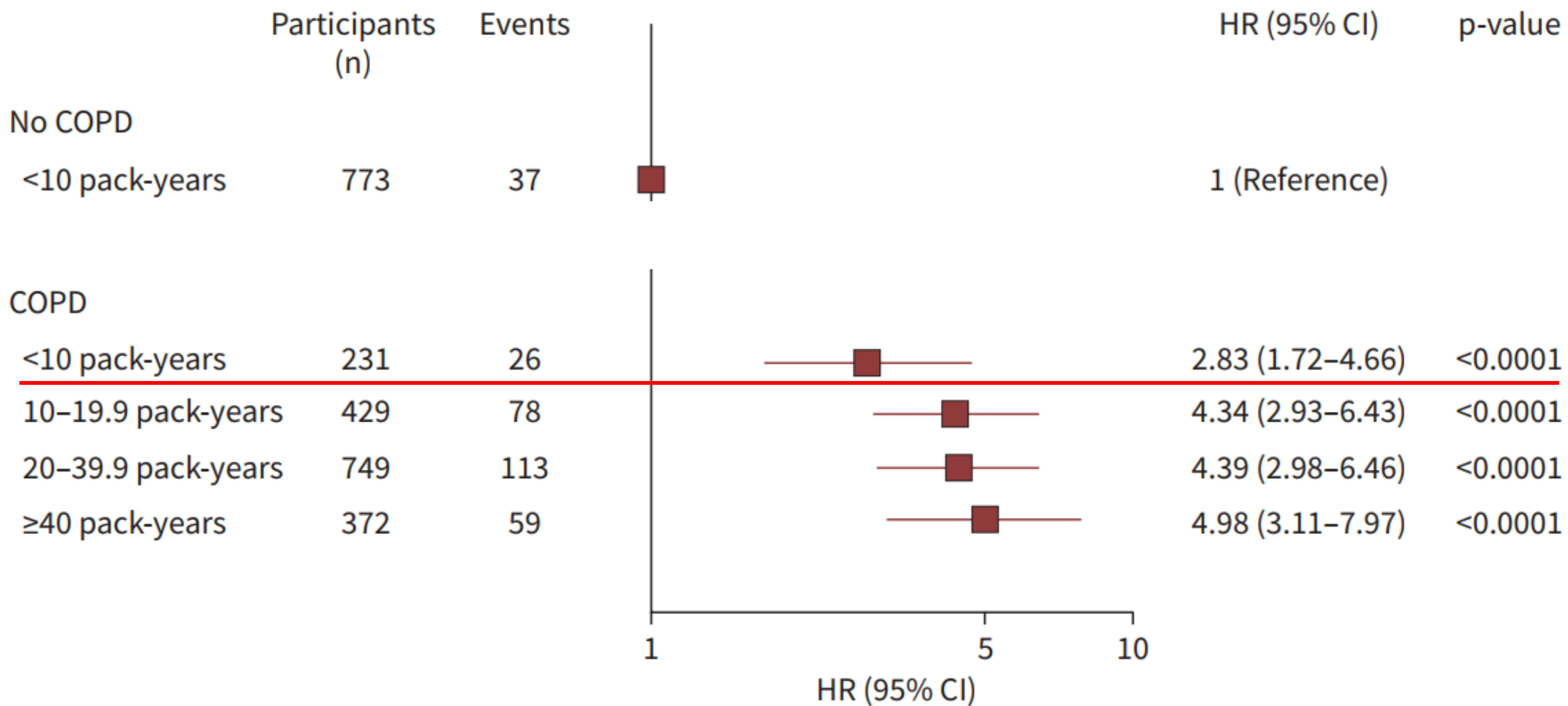
a)

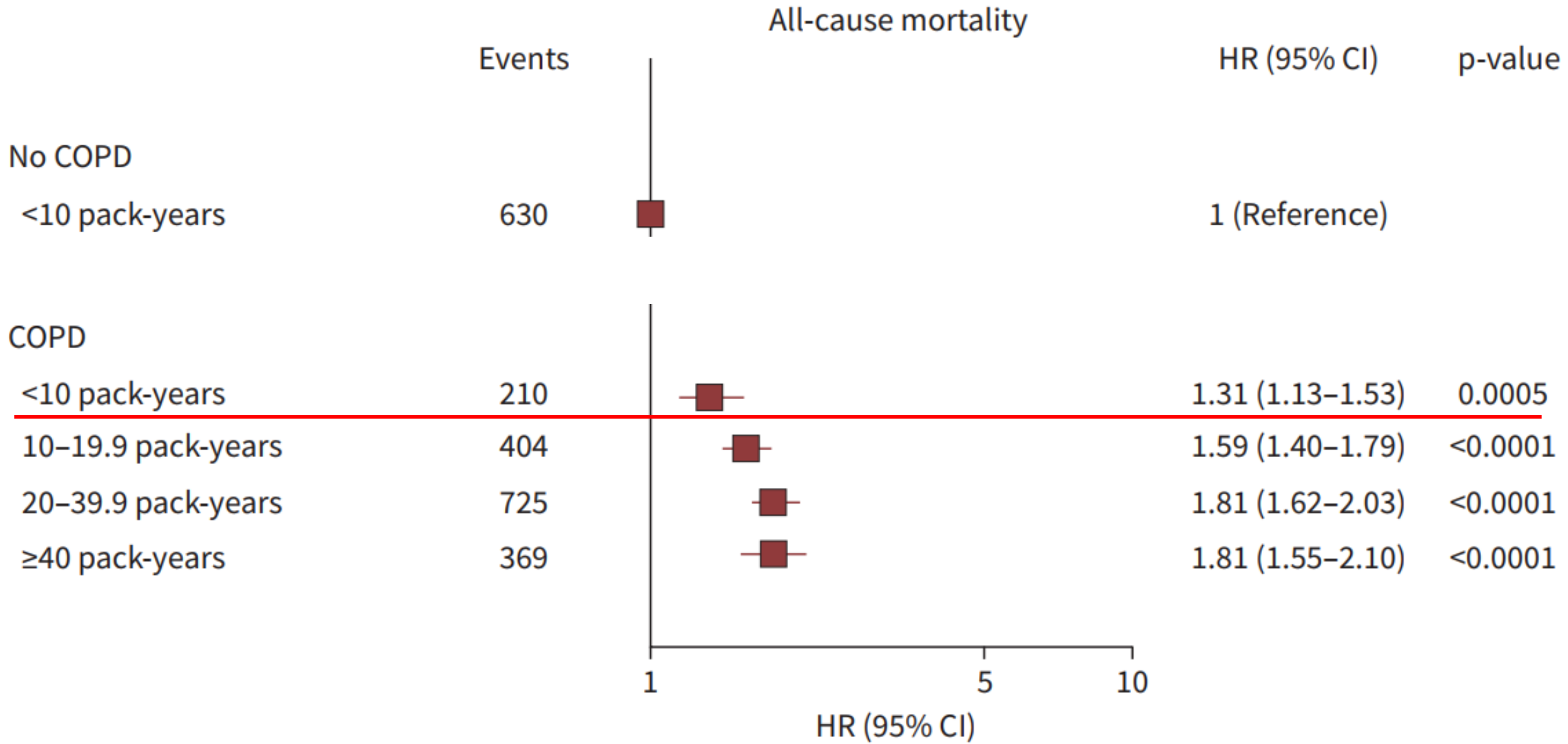
OR (95% CI) for COPD 5 years later



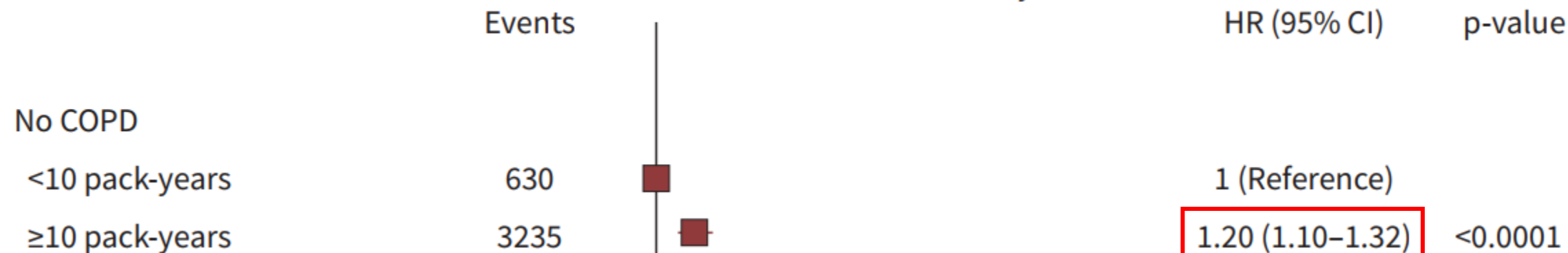
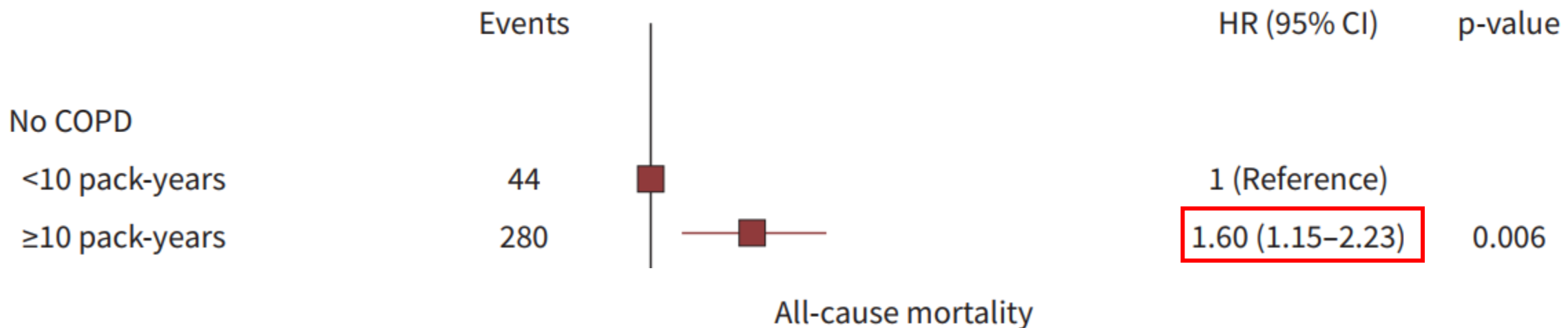
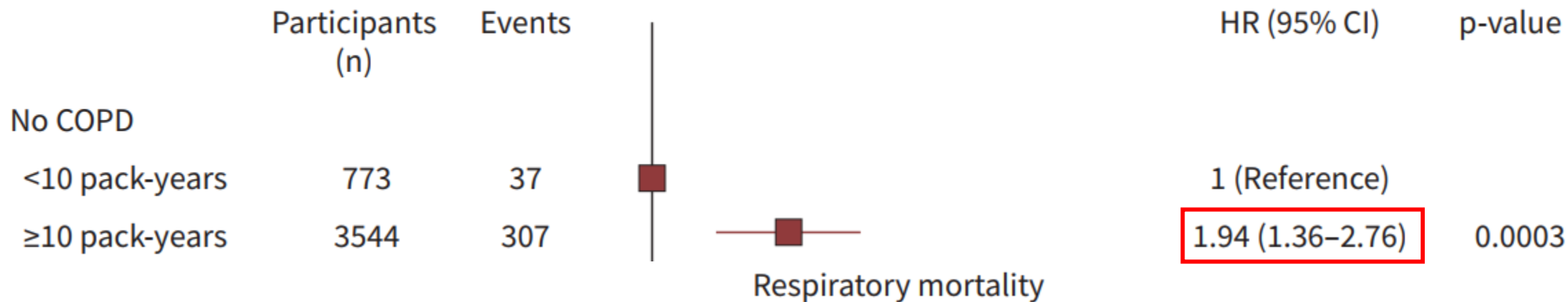


### Exacerbation



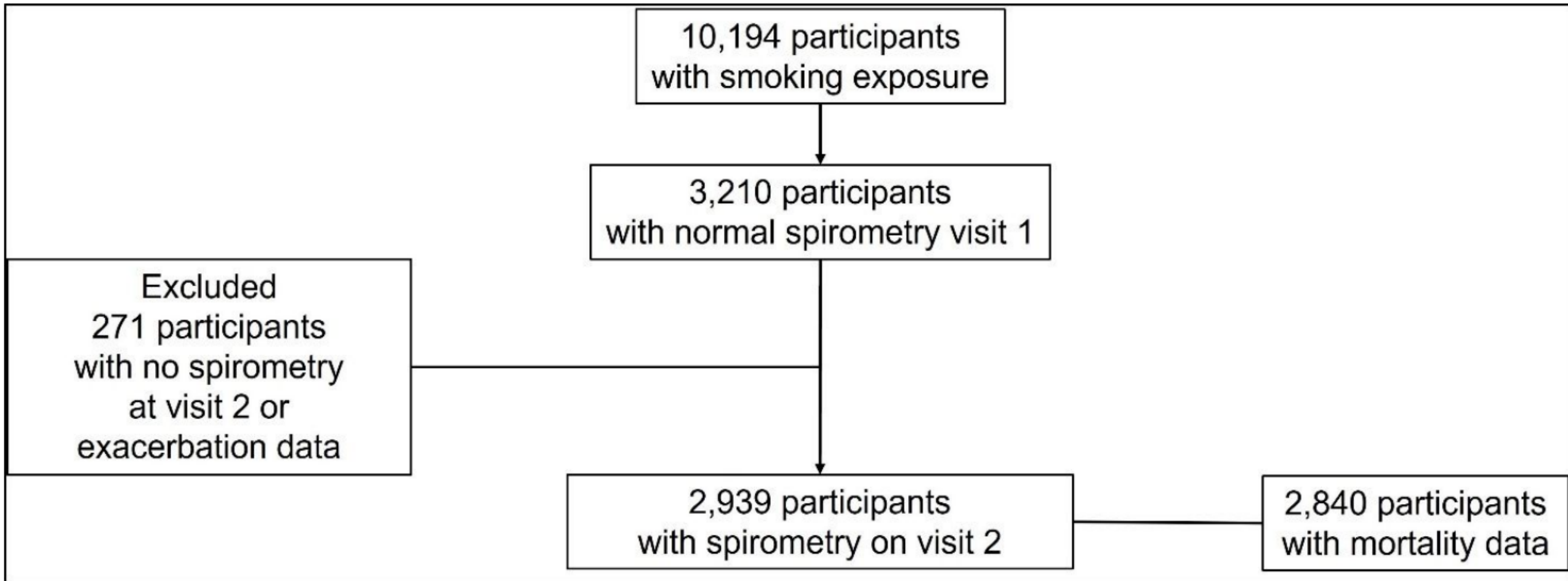


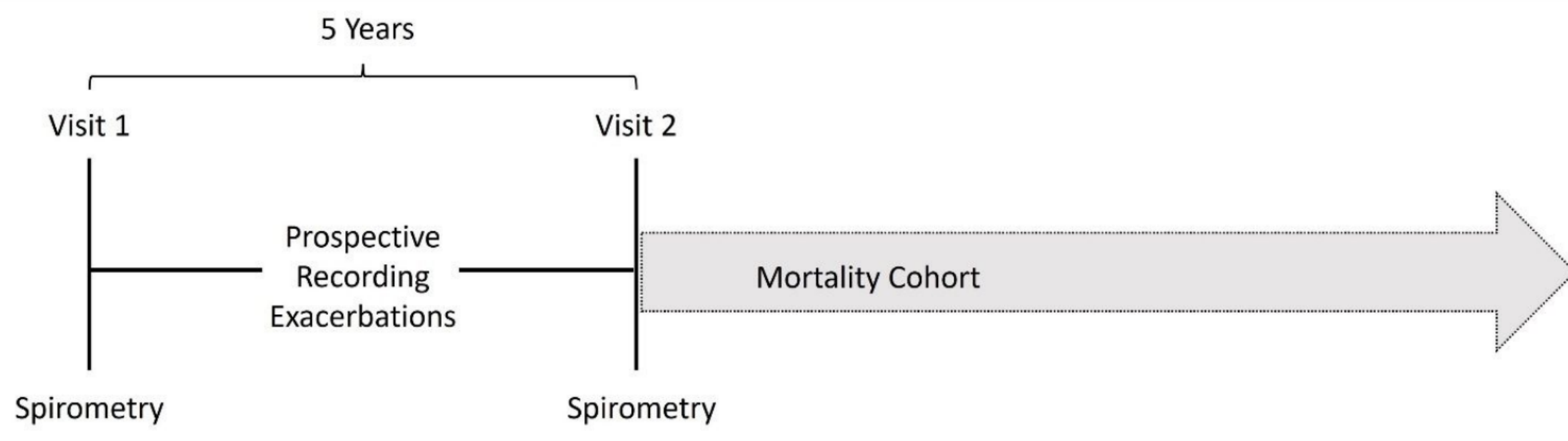
### Exacerbation



## **Respiratory Exacerbations and Lung Function Decline in People with Smoking History and Normal Spirometry**

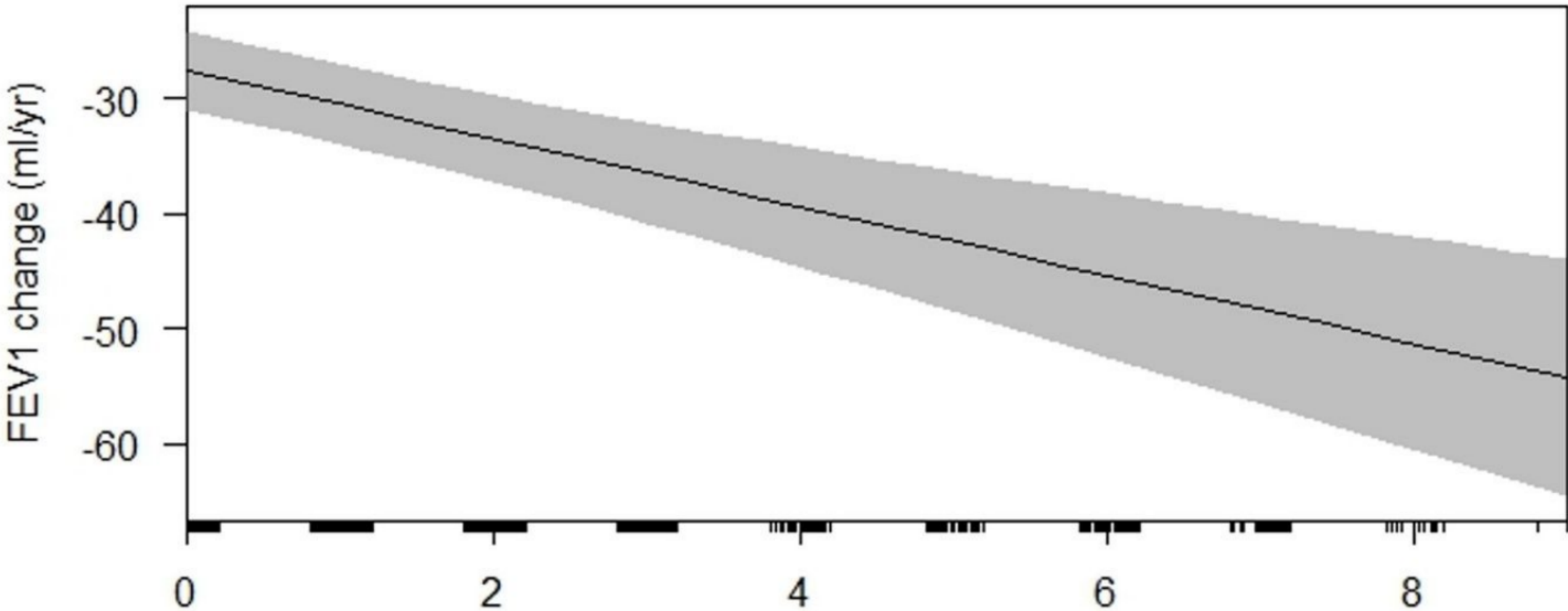
Spyridon Fortis, MD, PhD, MS,<sup>1,2</sup> Matthew Strand, PhD,<sup>3</sup> Surya P. Bhatt, MD, MSPH,<sup>4</sup> Patrick Ten Eyck, MS, PhD,<sup>5</sup> Linder Wendt, MS,<sup>5</sup> Trisha Parekh, DO, MSPH,<sup>6</sup> MeiLan K. Han, MD, MS,<sup>7</sup> John E. Hokanson, PhD,<sup>8</sup> Gregory Kinney, MPH, PhD,<sup>8</sup> Jeffrey L. Curtis, MD,<sup>7</sup> Russell P. Bowler, MD, PhD,<sup>9</sup> Emily S. Wan, MD, MPH,<sup>10,11</sup> Ken M. Kunisaki, MD, MS,<sup>12</sup> Chris H. Wendt, MD,<sup>12</sup> Elizabeth Regan, MD, PhD,<sup>13</sup> Mark Dransfield, MD,<sup>4,14</sup> James D. Crapo, MD,<sup>9</sup> Edwin K. Silverman, MD,<sup>11</sup> Alejandro P. Comellas, MD<sup>2</sup> on behalf of COPDGene investigators.



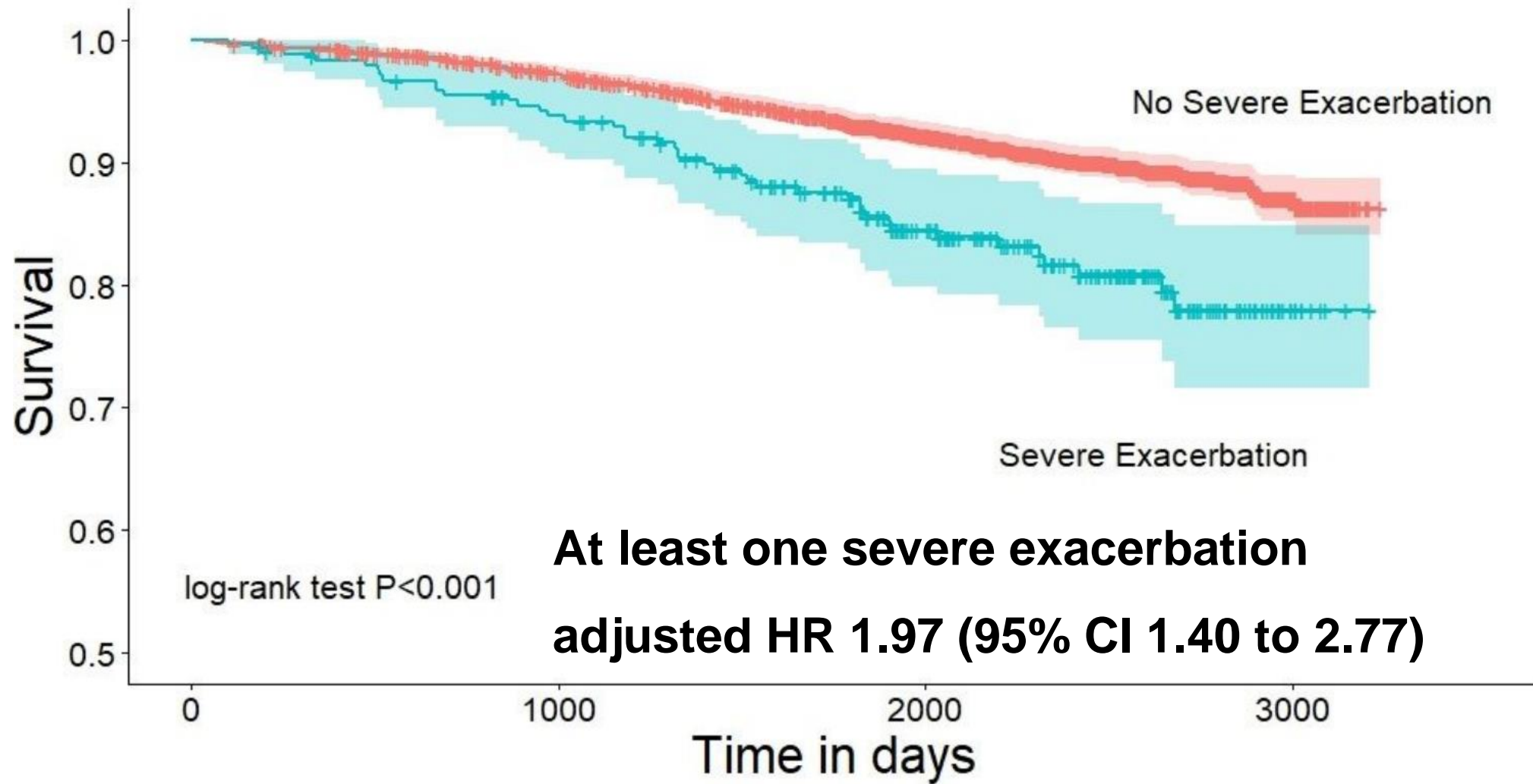


	No exacerbations	Exacerbation	P value
<b>n</b>	2,252	687	
<b>Age, y</b>	59.36 (8.65%)	59.48 (8.45%)	0.75
<b>Female, n (%)</b>	1056 (46.9%)	443 (64.5%)	<0.001
<b>Black, n (%)</b>	575 (25.5%)	156 (22.7%)	0.147
<b>Body mass index</b>	28.86 ± 5.58	30.35 ± 6.11	<0.001
<b>Pack-years</b>	38.15 ± 20.95	39.83 ± 25.23	0.079
<b>Current smoking, n (%)</b>	1020 (45.3%)	304 (44.3%)	0.66
<b>Chronic bronchitis, n (%)</b>	191 (8.5%)	123 (17.9%)	<0.001
<b>Asthma, n (%)</b>	202 (9.0%)	151 (22.0%)	<0.001
<b>mMRC≥2, n (%)</b>	381 (16.9%)	227 (33.1%)	<0.001
<b>Wheezing, n (%)</b>	894 (39.7%)	428 (62.3%)	<0.001
<b>Wheezing last 12 months, n (%)</b>	572 (25.5%)	327 (47.8%)	<0.001
<b>ICS, n (%)</b>	29 (1.3%)	38 (5.6%)	<0.001
<b>ICS and LABA, n (%)</b>	54 (2.4%)	81 (11.9%)	<0.001
<b>LAMA, n (%)</b>	37 (1.7%)	45 (6.7%)	<0.001
<b>Post-bronchodilator FEV<sub>1</sub>, L</b>	2.83 ± 0.68	2.60 ± 0.66	<0.001
<b>Post-bronchodilator FVC, L</b>	3.68 ± 0.90	3.40 ± 0.87	<0.001
<b>Post-bronchodilator FEV<sub>1</sub>/FVC</b>	0.77 ± 0.06	0.77 ± 0.06	0.16
<b>Post-bronchodilator FEV<sub>1</sub> z score</b>	-0.21 ± 0.85	-0.36 ± 0.85	<0.001
<b>Post-bronchodilator FVC z score</b>	-0.08 ± 0.89	-0.18 ± 0.90	0.008
<b>Post-bronchodilator FEV<sub>1</sub>/FVC z score</b>	-0.23 ± 0.82	-0.32 ± 0.82	0.008
<b>Post-bronchodilator FVC&lt;LLN, n (%)</b>	44 (2.0%)	19 (2.8%)	0.26
<b>Bronchodilator responsiveness, n (%)</b>	172 (7.7%)	66 (9.7%)	0.115
<b>Pi10, mm</b>	1.98 ± 0.42	2.05 ± 0.44	<0.001
<b>% Emphysema</b>	2.51 ± 3.17	2.54 ± 3.25	0.81
<b>% Gas trapping</b>	11.50 ± 9.01	11.36 ± 8.63	0.74
<b>Change in FEV<sub>1</sub> between Visit 1 and 2 (ml/y)</b>	-39.79 ± 47.16	-44.62 ± 50.01	0.021

**23.4%**



	<b>Decline in spirometric values between visit 1 and 2</b>		
	<b>FEV<sub>1</sub> ml/y (95%CI)</b>	<b>FVC ml/y (95%CI)</b>	<b>FEV<sub>1</sub>/FVC (95%CI)</b>
<b>Severe exacerbation</b>	14.6 (8.56, 20.6)	12.5 (4.4, 20.6)	0.002 (0.001, 0.004)



Number at risk

	0	1000	2000	3000
No Severe Exacerbation	2594	2445	1973	129
Severe Exacerbation	246	222	147	9

Time in days

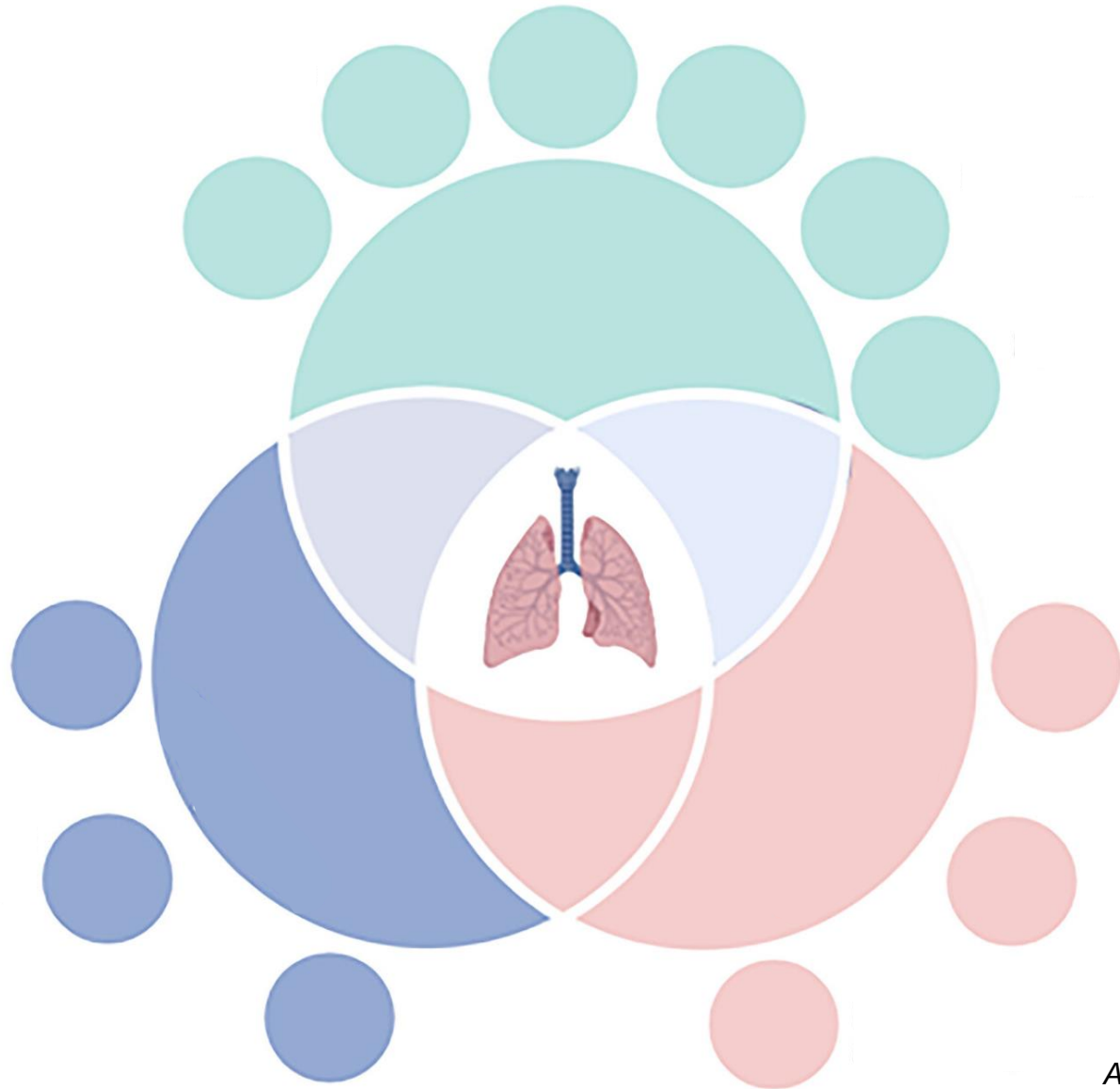
## Susceptible Young Adults and Development of Chronic Obstructive Pulmonary Disease Later in Life

Yunus Çolak<sup>1,2,4</sup>, Peter Lange<sup>1,2,4,5</sup>, Jørgen Vestbo<sup>6</sup>, Børge G. Nordestgaard<sup>2,3,4</sup>, and Shoaib Afzal<sup>2,3,4</sup>

<sup>1</sup>Department of Respiratory Medicine, <sup>2</sup>The Copenhagen General Population Study, and <sup>3</sup>Department of Clinical Biochemistry, Copenhagen University Hospital – Herlev and Gentofte, Copenhagen, Denmark; <sup>4</sup>Department of Clinical Medicine, Faculty of Health and Medical Sciences, and <sup>5</sup>Department of Public Health, Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark; and <sup>6</sup>Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom

# Pre-COPD

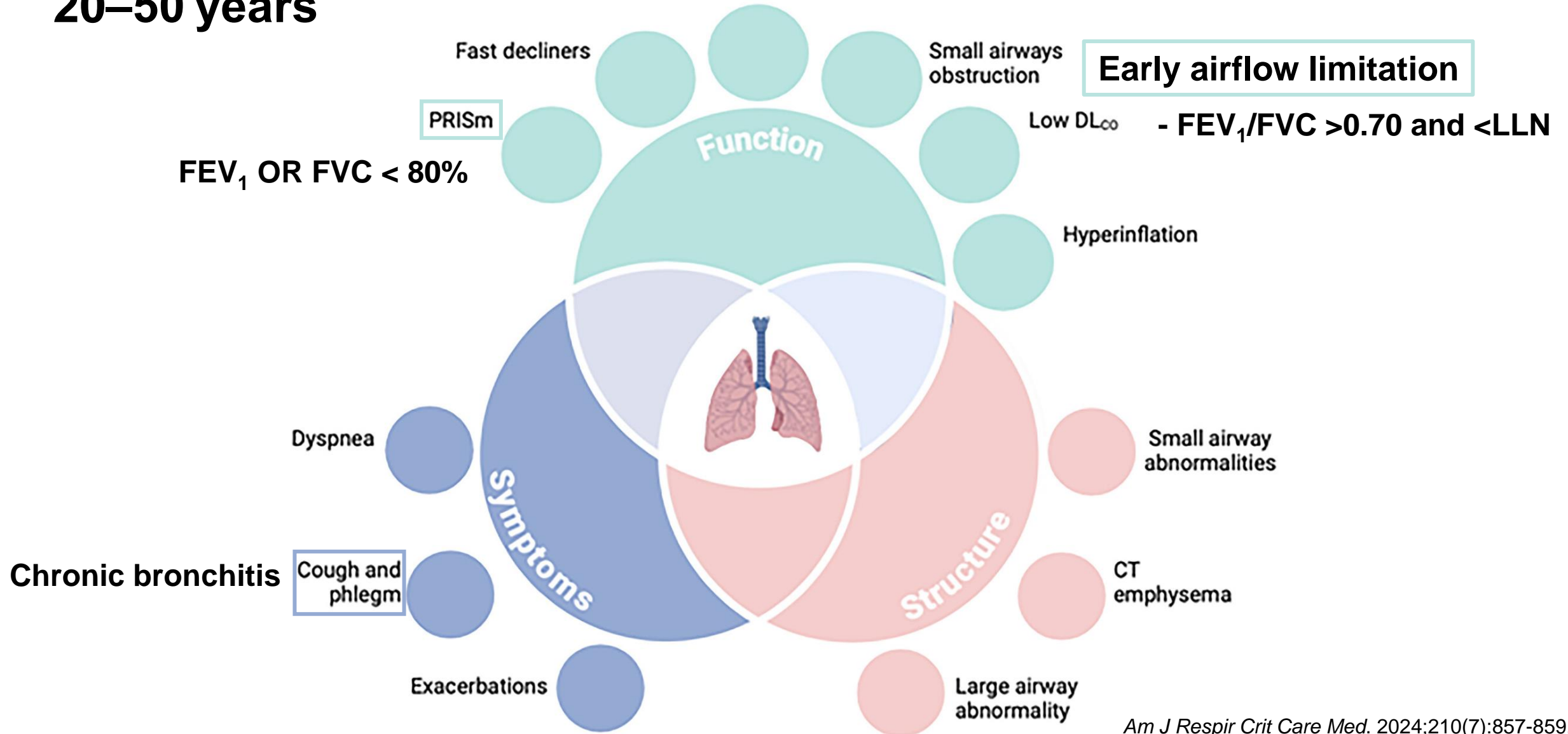
$FEV_1/FVC > 0.7$



# Pre-COPD

$FEV_1/FVC > 0.7$

20–50 years



# **Copenhagen General Population Study (CGPS)**

2003, *10 year*

*N = 5,497*

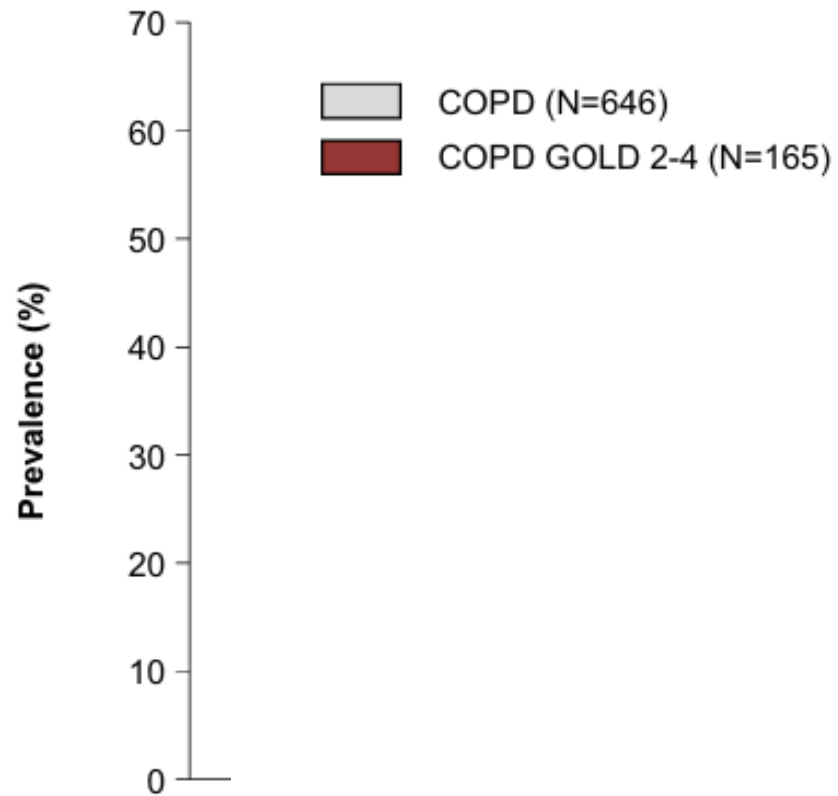
# **Copenhagen City Heart Study (CCHS)**

1976–1978, 1981-1983, 1991-1994, 2001-2004

*N = 2,609*

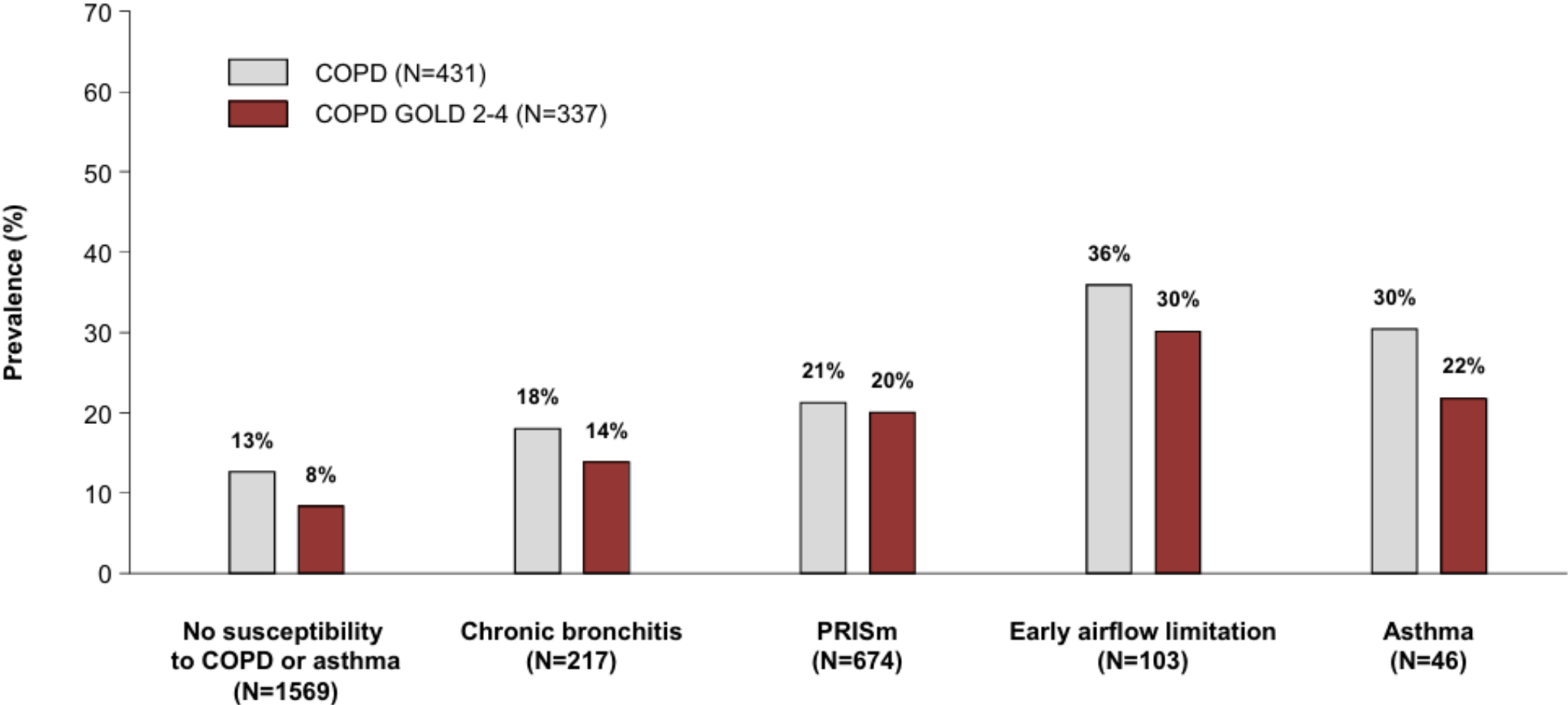
# The Copenhagen General Population Study

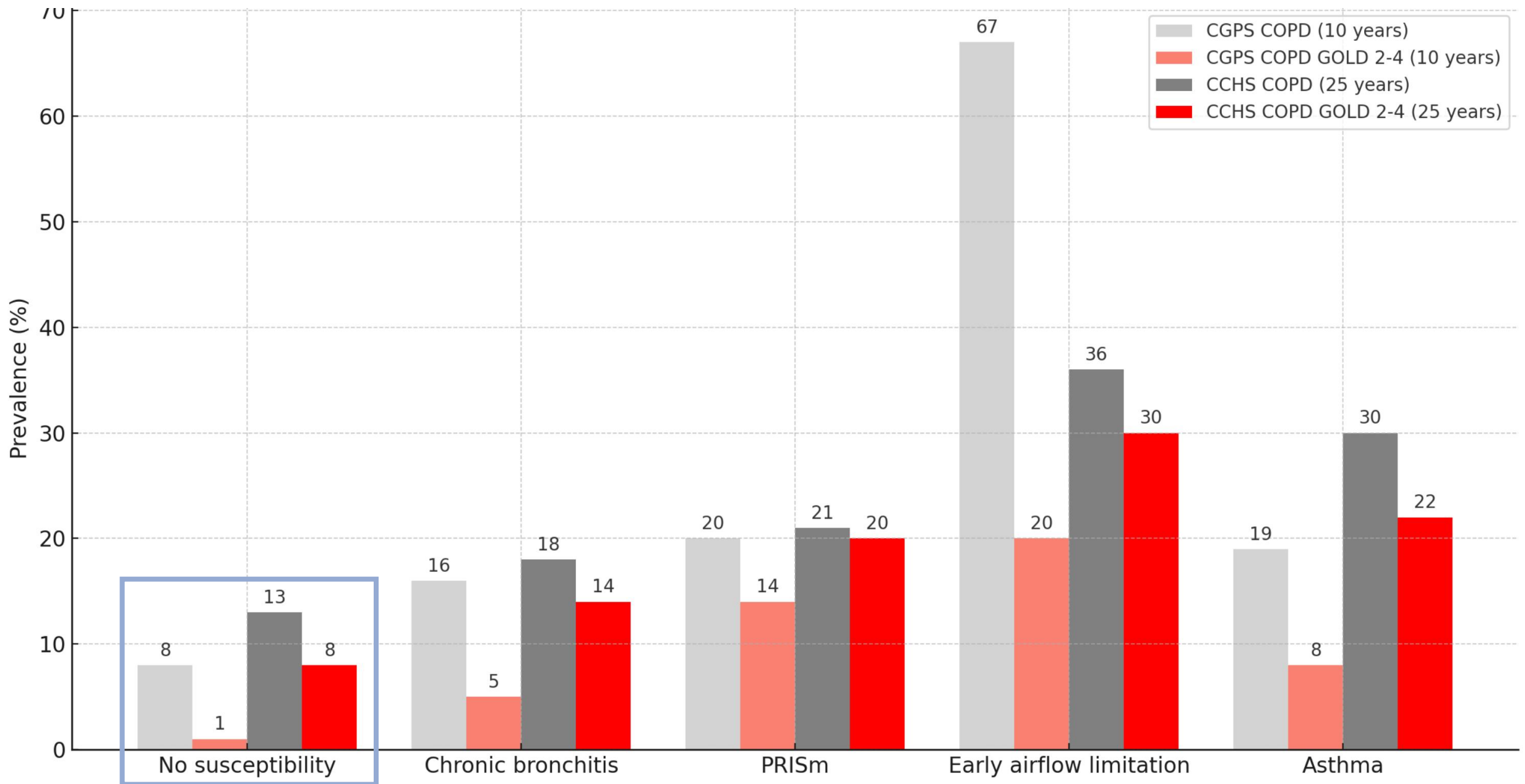
## Prevalence of COPD at final examination 10 years later



# The Copenhagen City Heart Study

## Prevalence of COPD at final examination 25 years later



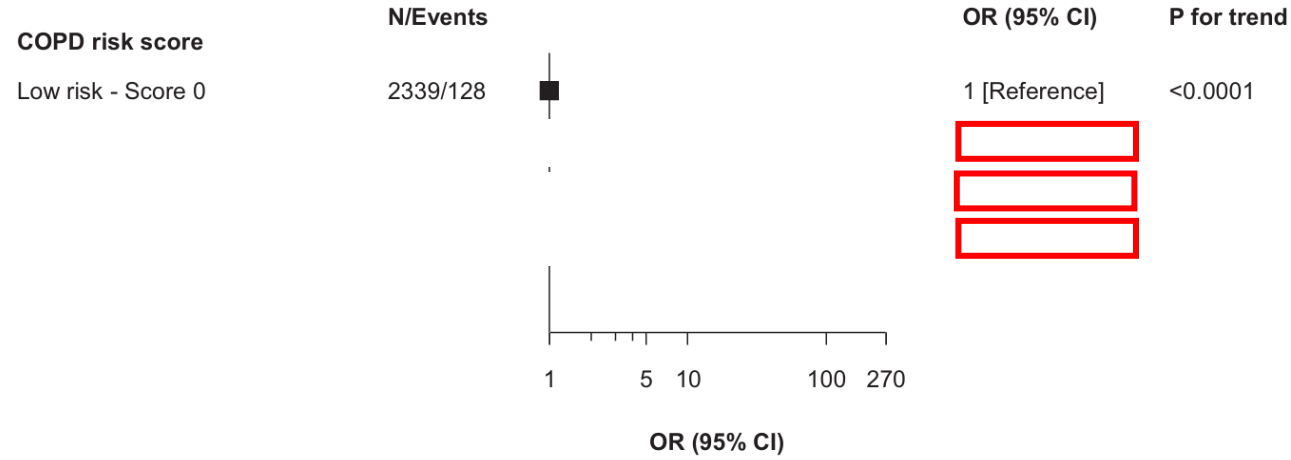


**Table 2.** Risk Factors Used for Calculating COPD Risk Score in Individuals without Airflow Limitation

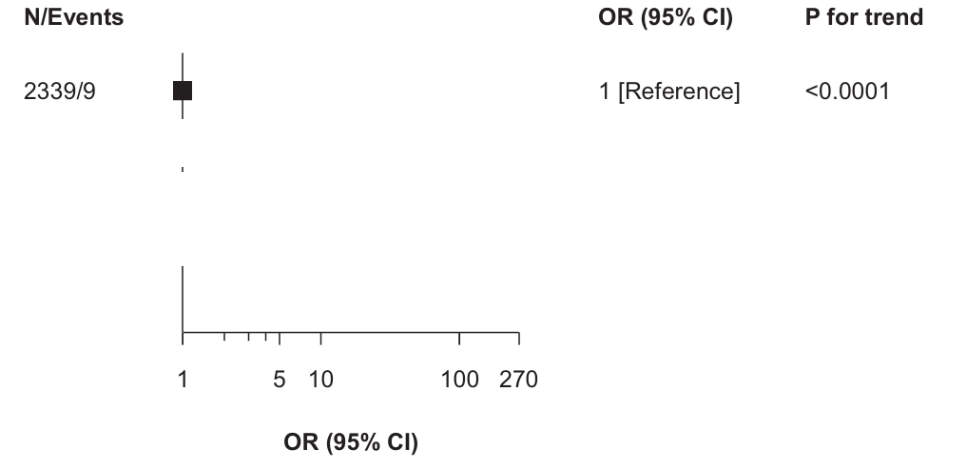
Risk Factors	Point on COPD Risk Score	
	0	1
Susceptibility to COPD	—	—
Chronic bronchitis	No	Yes
FEV <sub>1</sub> and FVC, % predicted	≥80	<80
FEV <sub>1</sub> /FVC	≥LLN	<LLN
Active smoking history	No	Yes
Asthma	No	Yes
Risk Management	COPD Risk Score	
Low	0	
Intermediate	1	
High	2	
Very high	≥3	

# The Copenhagen General Population Study

## COPD at final examination 10 years later

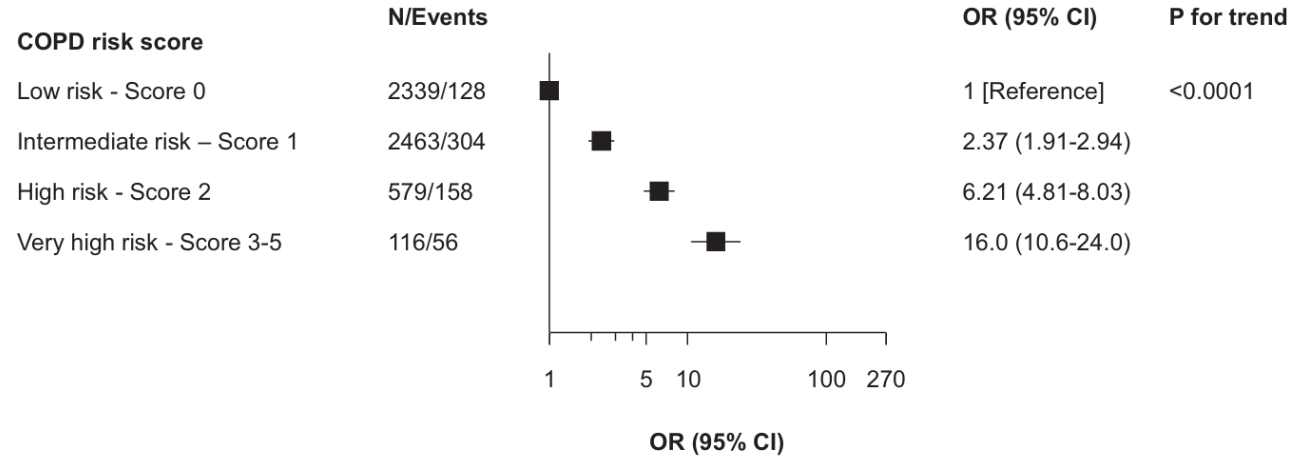


## COPD GOLD 2-4 at final examination 10 years later

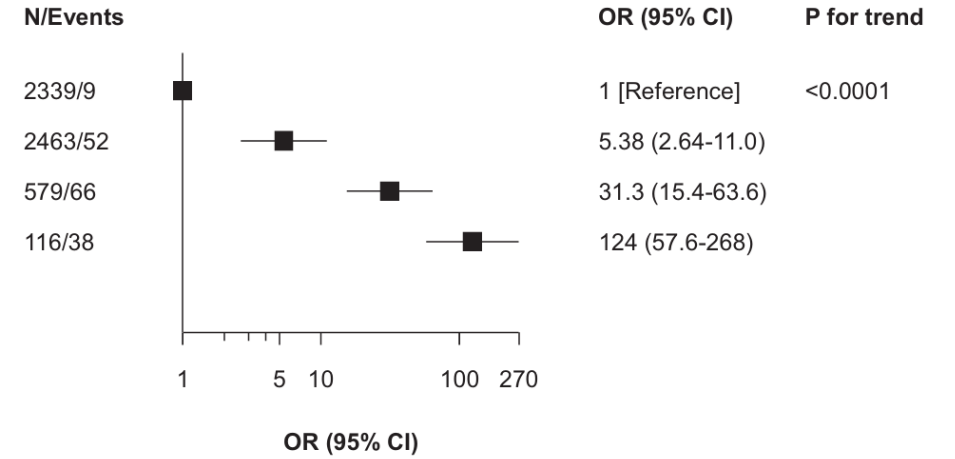


# The Copenhagen General Population Study

## COPD at final examination 10 years later

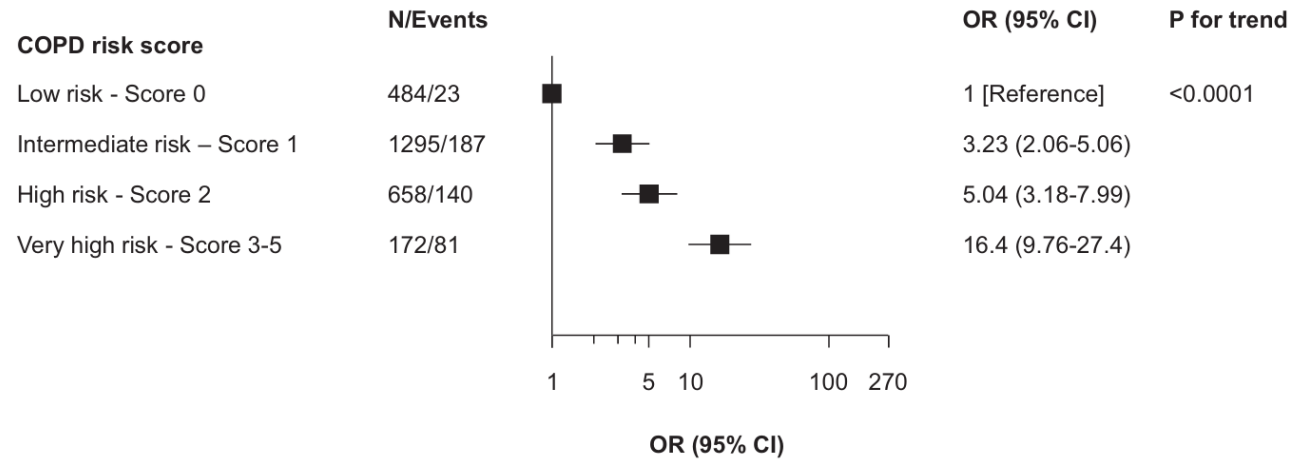


## COPD GOLD 2-4 at final examination 10 years later

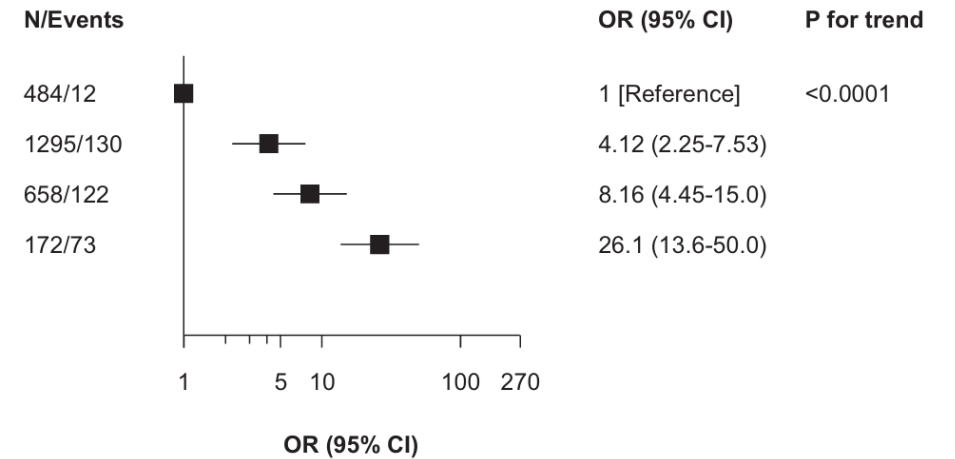


# The Copenhagen City Heart Study

## COPD at final examination 25 years later



## COPD GOLD 2-4 at final examination 25 years later



1. Risk factors

**2. Assessment and Diagnosis**

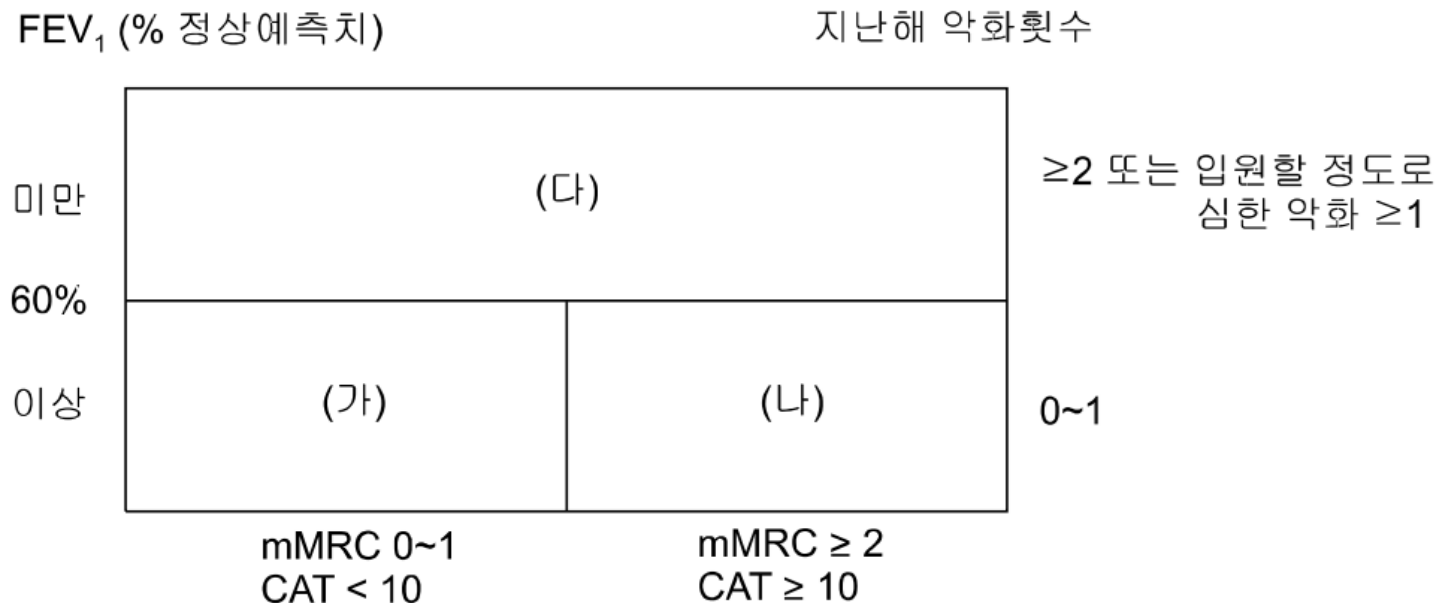
3. Treatment

대한결핵 및 호흡기학회

# COPD 진료지침

2024 개정

# 2018 지침



	FEV <sub>1</sub> ≥ 60% pred. and 0~1 exacerbation/year		FEV <sub>1</sub> < 60% pred. or ≥2 exacerbation/year or history of AE COPD* related admission (다군)
	mMRC 0~1 or CAT < 10 (가군)	mMRC ≥ 2 or CAT ≥ 10 (나군)	
	Short-acting beta2-agonist as required		
First choice	SABA as needed	LABA or LAMA      or      LABA + LAMA	LABA + LAMA

# 2024 지침

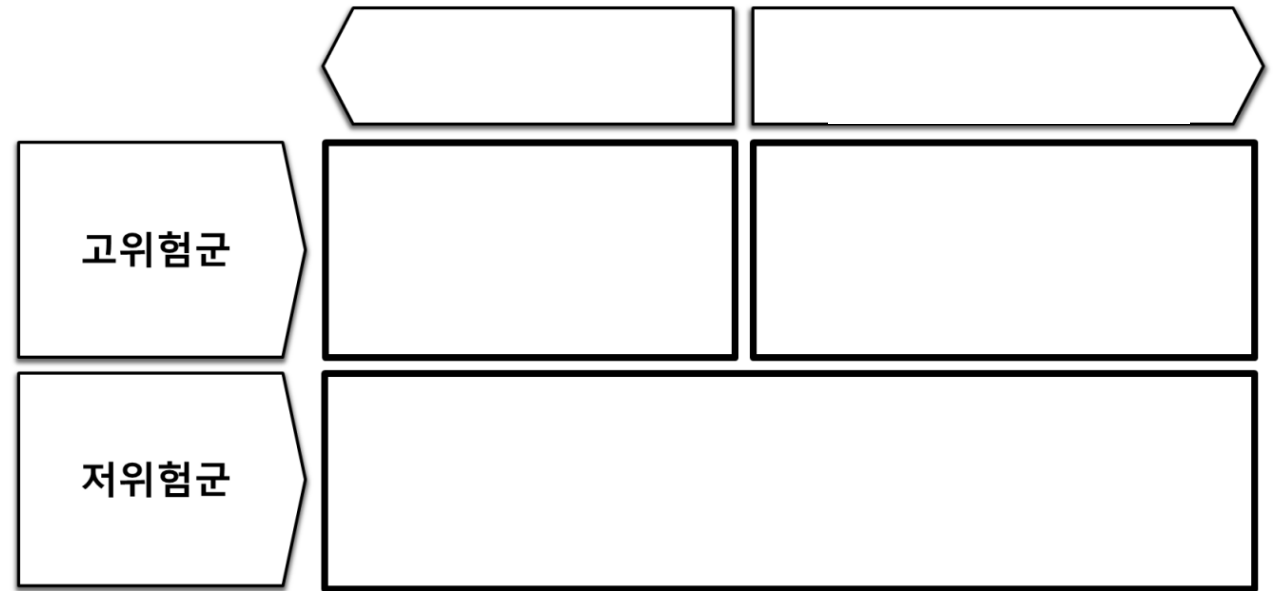
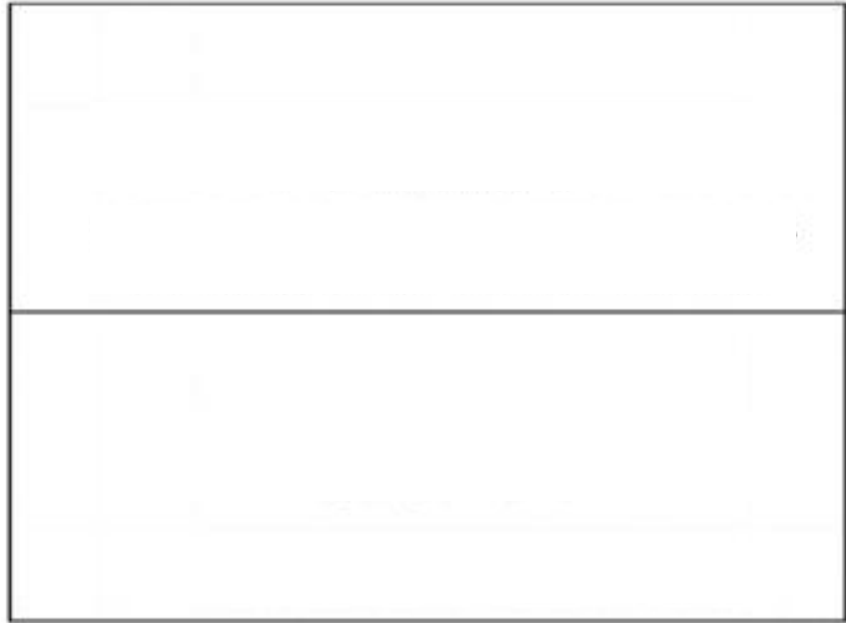


그림 3-3. 안정 시 COPD의 초기 약물 치료

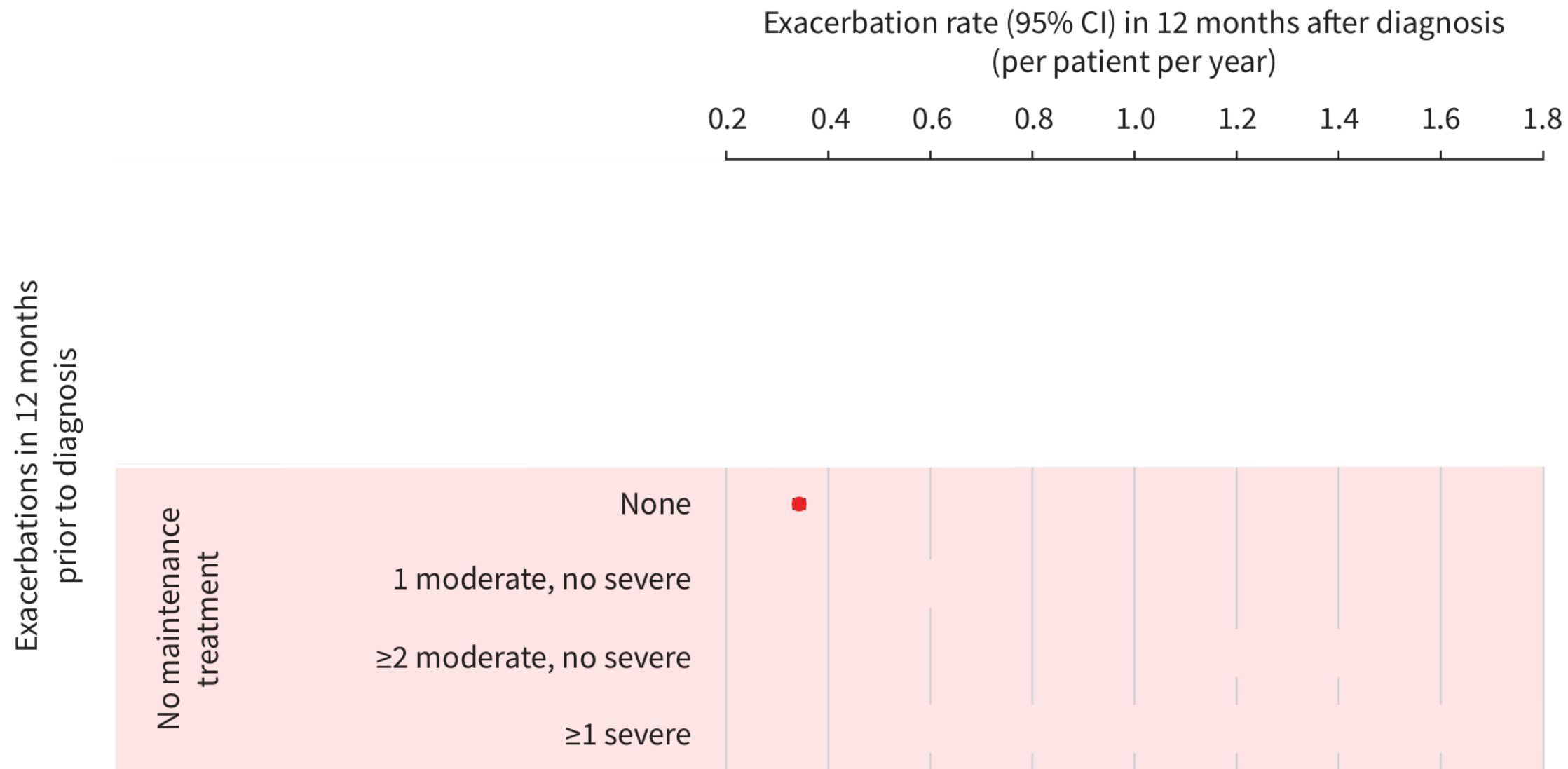


# Exacerbation history and blood eosinophil count prior to diagnosis of COPD and risk of subsequent exacerbations

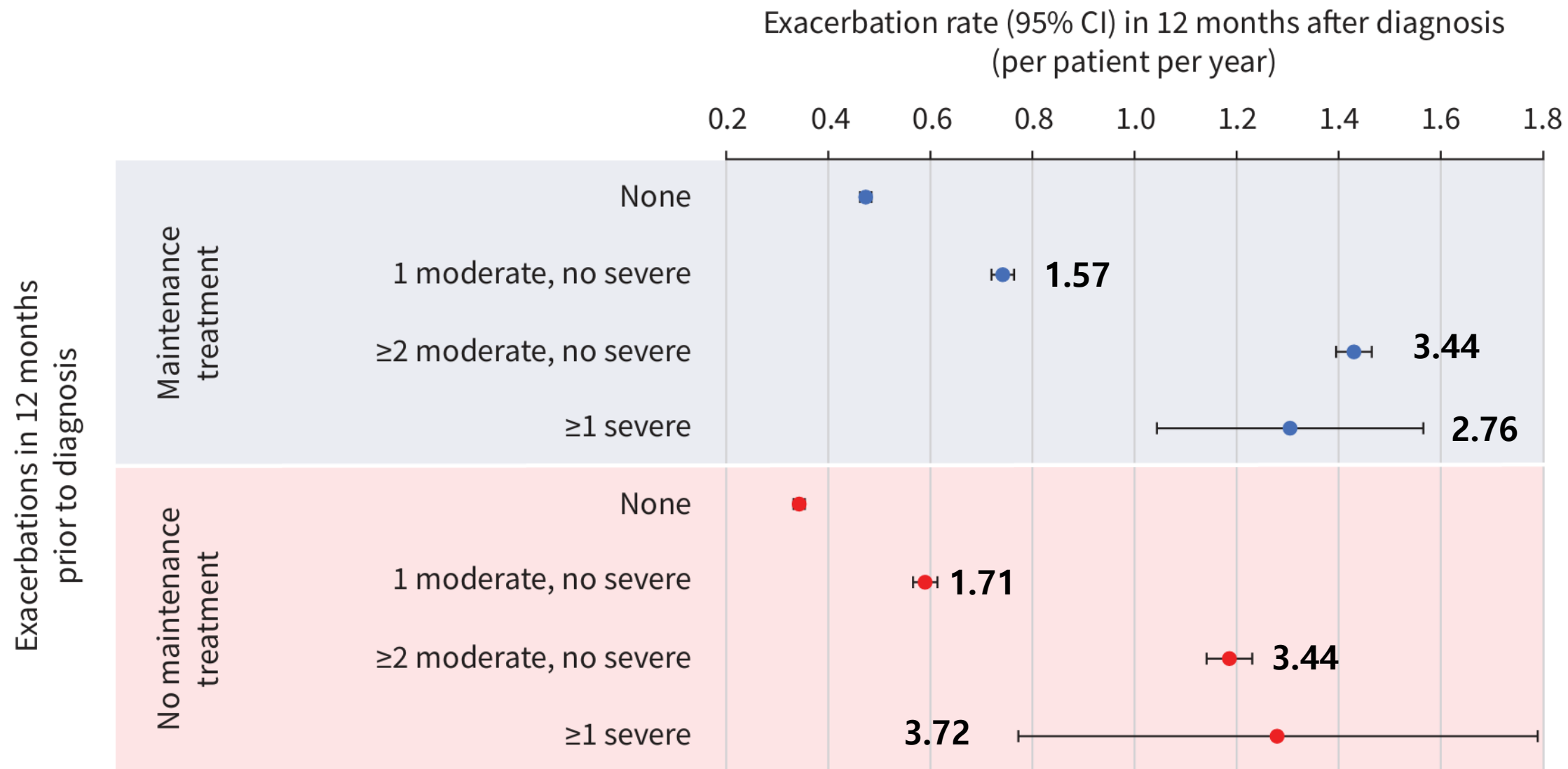
David M.G. Halpin <sup>1,2</sup>, Heath Healey<sup>3</sup>, Derek Skinner<sup>3</sup>, Victoria Carter<sup>3</sup>, Rachel Pullen<sup>2</sup>  
and David Price <sup>2,3,4</sup>

<sup>1</sup>University of Exeter Medical School, College of Medicine and Health, University of Exeter, Exeter, UK. <sup>2</sup>Observational and Pragmatic Research Institute, Singapore, Singapore. <sup>3</sup>Optimum Patient Care, Cambridge, UK. <sup>4</sup>Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK.





**FIGURE 2** Rates of moderate or severe exacerbations in the 12 months after diagnosis with 95% confidence intervals, according to exacerbation history in the 12 months prior to diagnosis and whether maintenance therapy was started.



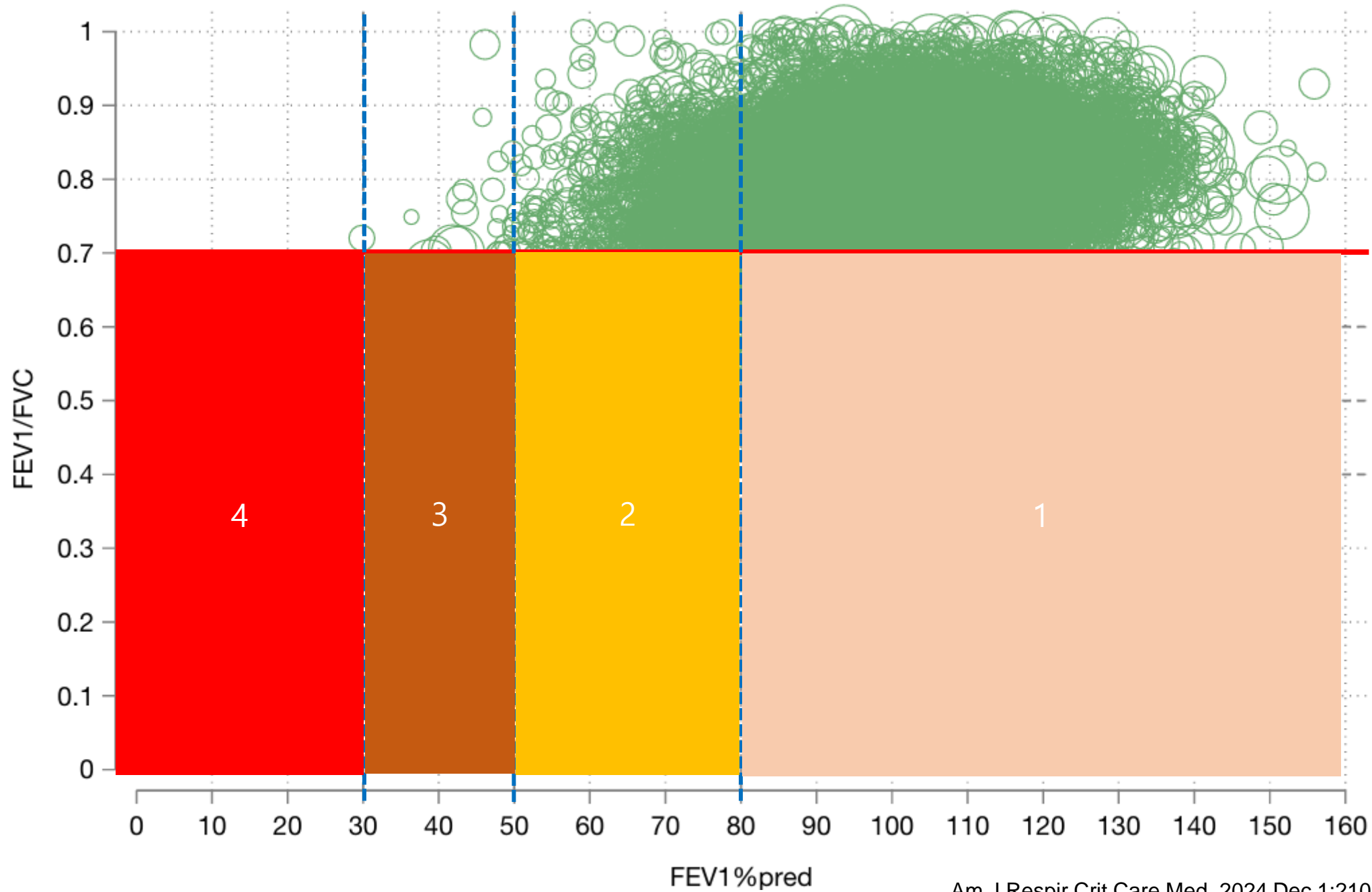
**FIGURE 2** Rates of moderate or severe exacerbations in the 12 months after diagnosis with 95% confidence intervals, according to exacerbation history in the 12 months prior to diagnosis and whether maintenance therapy was started.

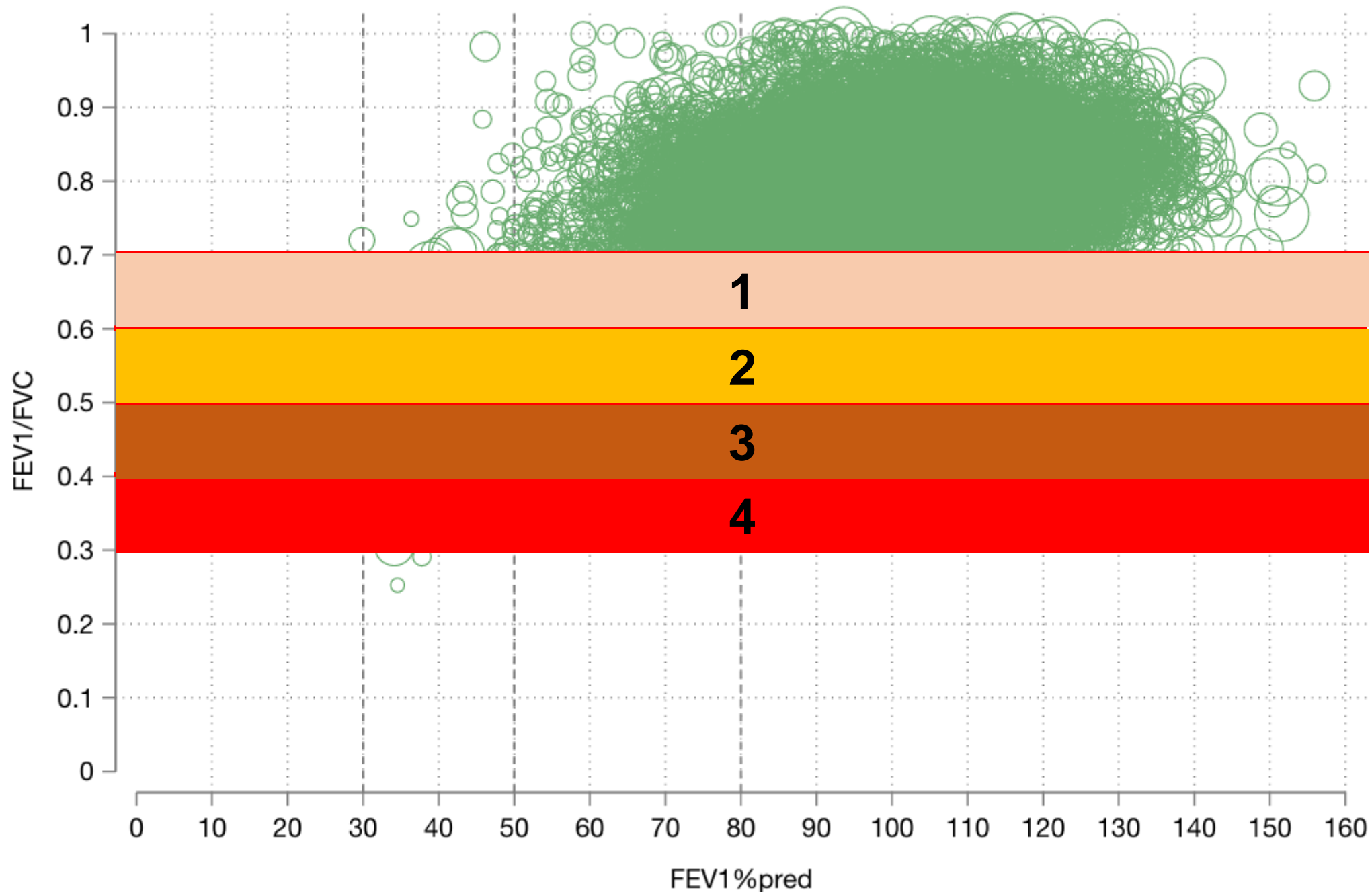
## Rate of moderate and severe exacerbations in the 12 months following diagnosis

Prior Exacerbation	BEC	Exacerbation Rate (No Tx)	Exacerbation Rate (Tx)
<b>None</b>	All	0.47	
<b>1 moderate, no severe</b>	<100	0.5	0.69
	100-300	0.56	0.73
	>300	0.67	0.82
<b>≥2 moderate, no severe</b>	<100	1.13	1.51
	100-300	1.08	1.37
	>300	1.34	1.58
<b>≥1 severe</b>	<100	NC	0.6
	100-300	0.94	1.16
	>300	1.13	1.7

# **FEV<sub>1</sub>/FVC Severity Stages for Chronic Obstructive Pulmonary Disease**

Surya P. Bhatt<sup>1,2</sup>, Arie Nakhmani<sup>1,3</sup>, Spyridon Fortis<sup>4</sup>, Matthew J. Strand<sup>5</sup>, Edwin K. Silverman<sup>6</sup>, Frank C. Sciurba<sup>7\*</sup>, and Sandeep Bodduluri<sup>1,2\*</sup>





## FEV<sub>1</sub>/FVC Severity Stages for Chronic Obstructive Pulmonary Disease

Surya P. Bhatt<sup>1,2</sup>, Arie Nakhmani<sup>1,3</sup>, Spyridon Fortis<sup>4</sup>, Matthew J. Strand<sup>5</sup>, Edwin K. Silverman<sup>6</sup>, Frank C. Scirba<sup>7\*</sup>, and Sandeep Bodduluri<sup>1,2\*</sup>

**Table 1.** Comparison of All-cause Mortality by Severity Stage

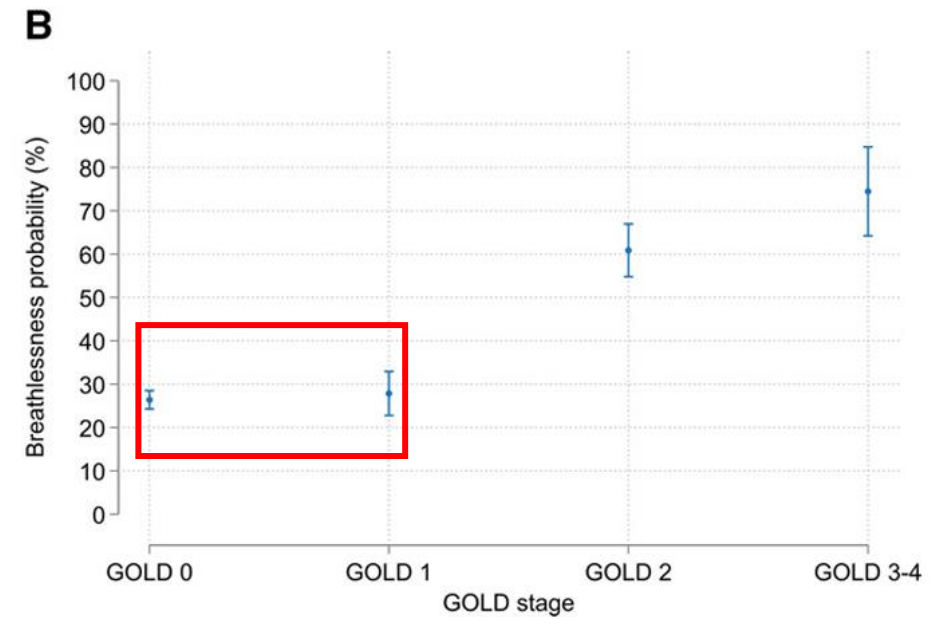
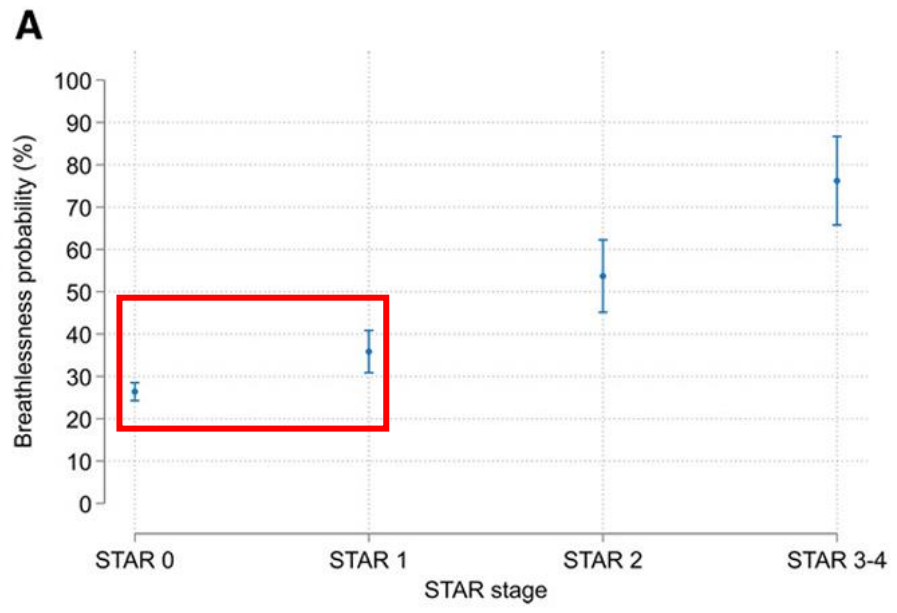
Stage	COPDGene				Pittsburgh			
	Unadjusted HR (95% CI)		Adjusted HR* (95% CI)		Unadjusted HR (95% CI)		Adjusted HR* (95% CI)	
	GOLD	STAR	GOLD	STAR	GOLD	STAR	GOLD	STAR
1	1.11 <sup>†</sup> (0.91–1.35)	1.47 (1.29–1.68)	0.95 <sup>†</sup> (0.78–1.17)	1.34 (1.66–1.53)	1.28* (0.89–1.84)	1.64 (1.22–2.19)	1.02 <sup>†</sup> (0.71–1.48)	1.49 (1.11–1.99)
2	2.09 (1.86–2.35)	2.52 (2.19–2.89)	1.77 (1.57–1.99)	2.15 (1.87–2.48)	2.43 (1.89–3.13)	2.76 (2.10–3.63)	2.18 (1.69–2.80)	2.40 (1.82–3.16)
3	4.20 (3.75–4.72)	3.92 (3.44–4.47)	3.42 (3.05–3.87)	3.25 (2.84–3.73)	4.38 (3.41–5.63)	3.32 (2.53–4.35)	3.98 (3.09–5.12)	3.09 (2.35–4.06)
4	9.41 (8.32–10.64)	6.89 (6.17–7.70)	7.92 (6.98–8.98)	5.79 (5.15–6.51)	7.73 (6.02–9.94)	6.32 (4.98–8.02)	7.32 (7.67–9.44)	5.65 (4.43–7.19)

# **Severity of Airflow Obstruction Based on FEV<sub>1</sub>/FVC Versus FEV<sub>1</sub> Percent Predicted in the General U.S. Population**

Helena Backman<sup>1</sup>, Lowie E. G. W. Vanfleteren<sup>2,3</sup>, David M. Mannino<sup>4,5</sup>, and Magnus Ekström<sup>6</sup>

**Table 1.** Participant Characteristics

Characteristics	Men	Women	All
<i>n</i>	7,093	7,030	14,123
Female, <i>n</i> (%)	0 (0)	7,030 (100)	7,030 (50.3)
Age, mean (SD)	44.9 (17.2)	45.3 (17.0)	45.1 (17.1)
Weight, kg, mean (SD)	87.2 (20.5)	76.1 (20.7)	81.7 (21.4)
Height, cm, mean (SD)	174.7 (7.7)	161.2 (7.1)	168.0 (10.1)
Body mass index, kg/m <sup>2</sup> , mean (SD)	28.5 (6.1)	29.3 (7.5)	28.9 (6.8)
<i>n</i> (%)			
<18.5	84 (1.0)	154 (2.4)	238 (1.7)
18.5 to <25	2,009 (27.5)	2,091 (33.4)	4,100 (30.4)
25 to <30	2,645 (38.4)	2,006 (28.6)	4,651 (33.5)
≥30	2,355 (33.1)	2,779 (35.6)	5,134 (34.4)
Smoking status, <i>n</i> (%)			
Never	3,085 (47.0)	4,214 (58.9)	7,299 (53.0)
Former	1,793 (25.1)	1,206 (19.8)	2,999 (22.4)
Current	1,772 (23.6)	1,258 (18.1)	3,030 (20.9)
Missing	443 (4.2)	352 (3.2)	795 (3.7)
Asthma, <i>n</i> (%)	392 (5.7)	657 (9.3)	1,049 (7.5)
Diabetes mellitus, <i>n</i> (%)	717 (7.4)	690 (7.1)	1,407 (7.2)
Hypertension, <i>n</i> (%)	2,090 (26.9)	2,143 (26.6)	4,233 (26.7)
Heart failure, <i>n</i> (%)	150 (1.6)	100 (1.2)	250 (1.4)
Ischemic heart disease, <i>n</i> (%)	380 (4.3)	172 (1.8)	552 (3.1)
FEV <sub>1</sub> /FVC, mean (SD)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)
FEV <sub>1</sub> /FVC < 0.70, <i>n</i> (%)	980 (13.2)	541 (8.5)	1,521 (10.8)
FEV <sub>1</sub> , L, mean (SD)	3.6 (0.9)	2.6 (0.7)	3.1 (0.9)
FEV <sub>1</sub> %pred, mean (SD)	97.9 (16.7)	98.1 (16.7)	98.0 (16.7)
FVC (L), mean (SD)	4.6 (1.0)	3.3 (0.7)	3.9 (1.1)
STAR stage, <i>n</i> (%)			
0	6,113 (86.8)	6,489 (91.5)	12,602 (89.2)
1	748 (10.3)	411 (6.6)	1,159 (8.4)
2	155 (1.9)	96 (1.4)	251 (1.6)
3	55 (0.9)	28 (0.4)	83 (0.6)
4	22 (0.2)	6 (0.1)	28 (0.2)
GOLD stage, <i>n</i> (%)			
0	6,113 (86.8)	6,489 (91.5)	12,602 (89.2)
1	574 (8.6)	256 (4.5)	830 (6.6)
2	355 (4.1)	237 (3.4)	592 (3.7)
3	49 (0.5)	46 (0.5)	95 (0.5)
4	2 (0.0)	2 (0.0)	4 (<0.1)
Breathlessness, mMRC score ≥1, only available for ages ≥40yr, <i>n</i> (%)	1,062 (24.9)	1,491 (32.8)	2,553 (29.0)
Deaths, <i>n</i> (%)	668 (7.2)	432 (4.6)	1,100 (5.9)
Follow-up time in years, median (interquartile range)	9.8 (8.2–11.2)	9.8 (8.3–11.2)	9.8 (8.3–11.2)



**GOLD 1**  
93.2% → STAR 1  
6.7% → STAR 2  
0.1% → STAR 3+

**GOLD 2**  
59.1% → STAR 1  
28.4% → STAR 2  
12.5% → STAR 3+

**GOLD 3+**  
16.9% → STAR 1  
23.2% → STAR 2  
59.8% → STAR 3+



**STAR 1**

**STAR 2**

**STAR 3+**

# Reclassification of Airflow Limitation: A STAR with a GOLD Lining

Classification based on STAR & FEV <sub>1</sub> % pred	n	a) RRR (95% CI) for breathlessness		c) HR (95% CI) for mortality	
		Unadjusted	Adjusted	Unadjusted	Adjusted
1. Preserved ratio impaired spirometry (PRISm) (FEV <sub>1</sub> /FVC ≥0.70 & FEV <sub>1</sub> <80%pred)	859	2.15 (1.72 to 2.67)	1.62 (1.29 to 2.05)	2.98 (2.33 to 63.80)	2.47 (1.94 to 3.15)
<i>Matching stage 1</i>					
2. STAR 1 & GOLD 1 (FEV <sub>1</sub> /FVC ≥0.60 to <0.70 & FEV <sub>1</sub> ≥80%pred)	686	1.10 (0.82 to 1.48)	1.33 (0.96 to 1.76)	1.89 (1.51 to 2.37)	1.15 (0.92 to 1.43)
<i>Reclassification to more severe stage</i>					
3. STAR 1 & GOLD 2-4 (FEV <sub>1</sub> /FVC ≥0.60 to <0.70 & FEV <sub>1</sub> <80%pred)	348	4.45 (3.17 to 6.25)	4.38 (3.09 to 6.20)	3.95 (2.99 to 5.21)	2.59 (1.96 to 3.41)
<i>Reclassification to less severe stage</i>					
4. STAR 2-4 & GOLD 1 (FEV <sub>1</sub> /FVC<0.60 & FEV <sub>1</sub> ≥80%pred)	58	1.99 (0.94 to 4.18)	2.59 (1.27 to 5.29)	4.78 (2.40 to 9.51)	1.76 (0.83 to 3.73)
<i>Matching stages 2-4</i>					
5. STAR 2-4 & GOLD 2-4 (FEV <sub>1</sub> /FVC<0.60 & FEV <sub>1</sub> <80%pred)	282	5.74 (4.07 to 8.09)	7.16 (4.85 to 10.55)	5.02 (3.78 to 6.68)	2.81 (2.12 to 3.74)
Measure of model classification		Correctly classified: 70.4%	Correctly classified: 71.2%	C = 0.63 (0.62 to 0.65)	C = 0.75 (0.74 to 0.77)



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# Respiratory Medicine

journal homepage: [www.elsevier.com/locate/rmed](http://www.elsevier.com/locate/rmed)



Original Research

## The role of FEV<sub>1</sub>/FVC in the prediction of acute exacerbation of COPD

Jong Geol Jang<sup>a,1</sup>, Youlim Kim<sup>b,1</sup>, Sun Hye Shin<sup>c</sup>, Kyung Hoon Min<sup>d</sup>, Ki Suck Jung<sup>e</sup>,  
Yu-il Kim<sup>f</sup>, Shinhee Park<sup>g</sup>, Joo Ock Na<sup>h</sup>, Hyun Lee<sup>i,\*\*,2</sup>, Kwang Ha Yoo<sup>b,\*,2</sup>



\* OR (95% CI)

P value

**Any exacerbation**

FEV1 $\geq$ 50% and FEV1/FVC $\geq$ 50	reference	●	
FEV1 $\geq$ 50% and FEV1/FVC < 50	1.23 (0.90, 1.68)	●	0.001
FEV1 < 50% and FEV1/FVC $\geq$ 50	2.42 (1.57, 3.74)	●	0.069
FEV1 < 50% and FEV1/FVC < 50	3.58 (2.74, 4.66)	●	<0.001

**Moderate to severe exacerbation**

FEV1 $\geq$ 50% and FEV1/FVC $\geq$ 50	reference	●	
FEV1 $\geq$ 50% and FEV1/FVC < 50	1.28 (0.93, 1.76)	●	0.012
FEV1 < 50% and FEV1/FVC $\geq$ 50	2.42 (1.56, 3.74)	●	0.041
FEV1 < 50% and FEV1/FVC < 50	2.94 (2.25, 3.83)	●	<0.001

**Severe exacerbation**

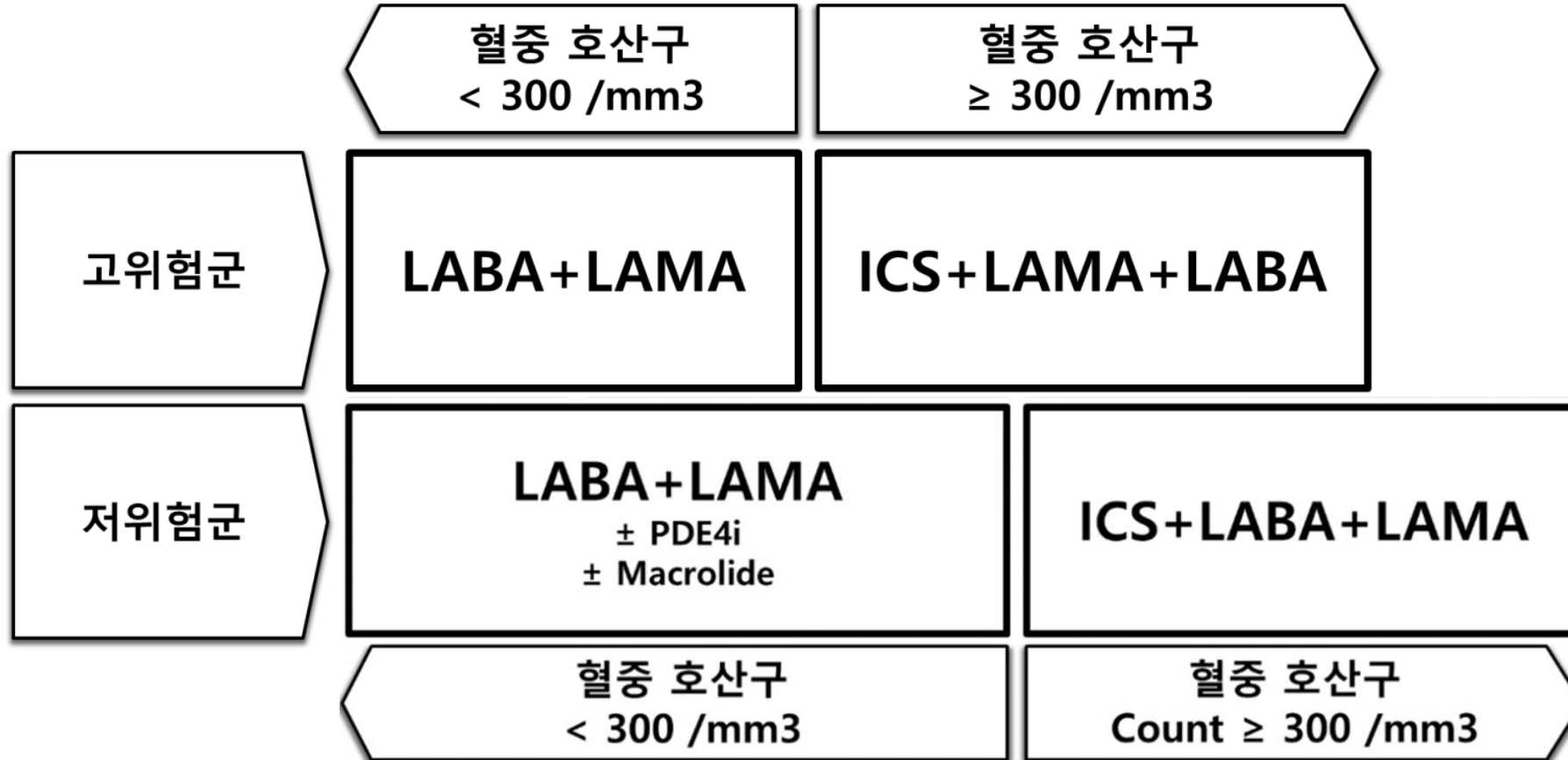
FEV1 $\geq$ 50% and FEV1/FVC $\geq$ 50	reference	●	
FEV1 $\geq$ 50% and FEV1/FVC < 50	1.14 (0.59, 2.22)	●	0.011
FEV1 < 50% and FEV1/FVC $\geq$ 50	3.12 (1.59, 6.16)	●	0.086
FEV1 < 50% and FEV1/FVC < 50	5.16 (3.34, 7.97)	●	<0.001



1. Risk factors
2. Assessment and Diagnosis
- 3. Treatment**

# COPD 진료지침 2024 개정

## 악화 후 치료



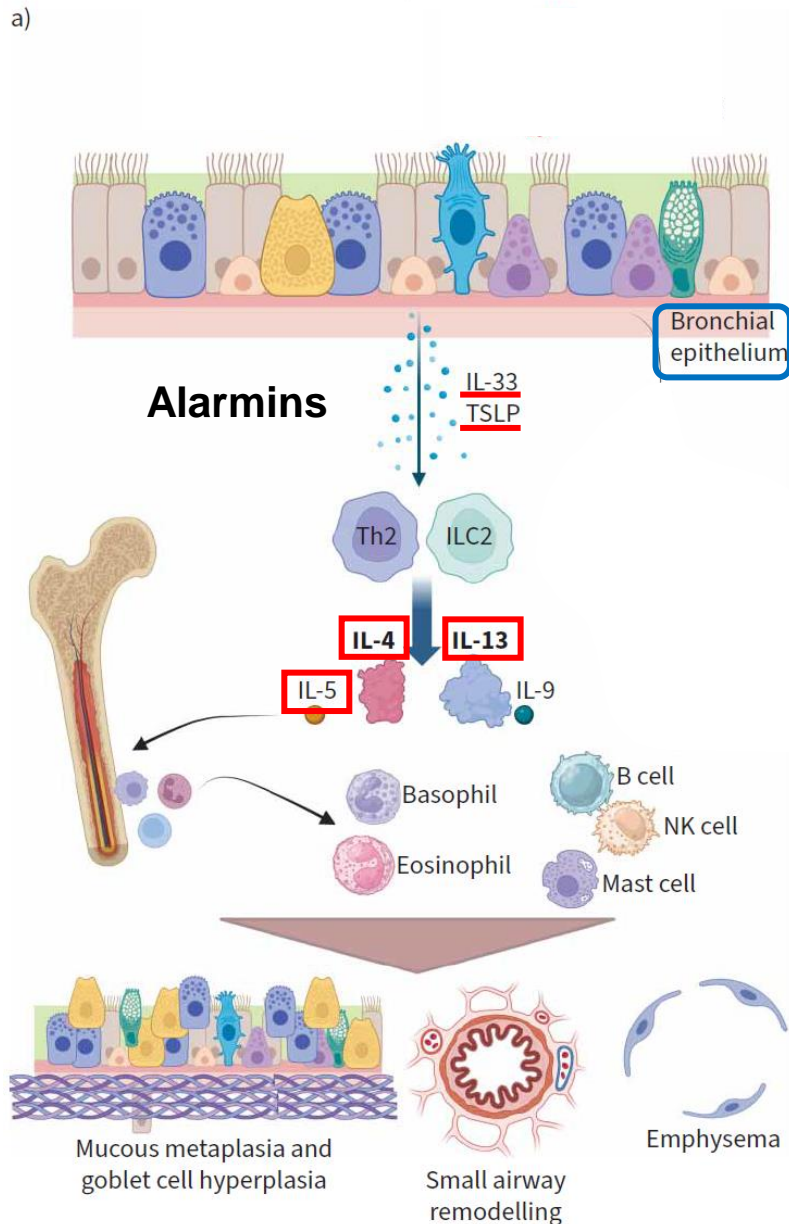
# COPD 진료지침 2024 개정

## 악화 후 치료

	혈중 호산구 < 100 /mm <sup>3</sup>	100 ≤ 혈중 호산구 < 300 /mm <sup>3</sup>	혈중 호산구 ≥ 300 /mm <sup>3</sup>
고위험군			—
저위험군	LABA+LAMA ± PDE4i ± Macrolide		ICS+LABA+LAMA
	혈중 호산구 < 300 /mm <sup>3</sup>		혈중 호산구 Count ≥ 300 /mm <sup>3</sup>

# Biologics in COPD

a)



# Biologics in COPD

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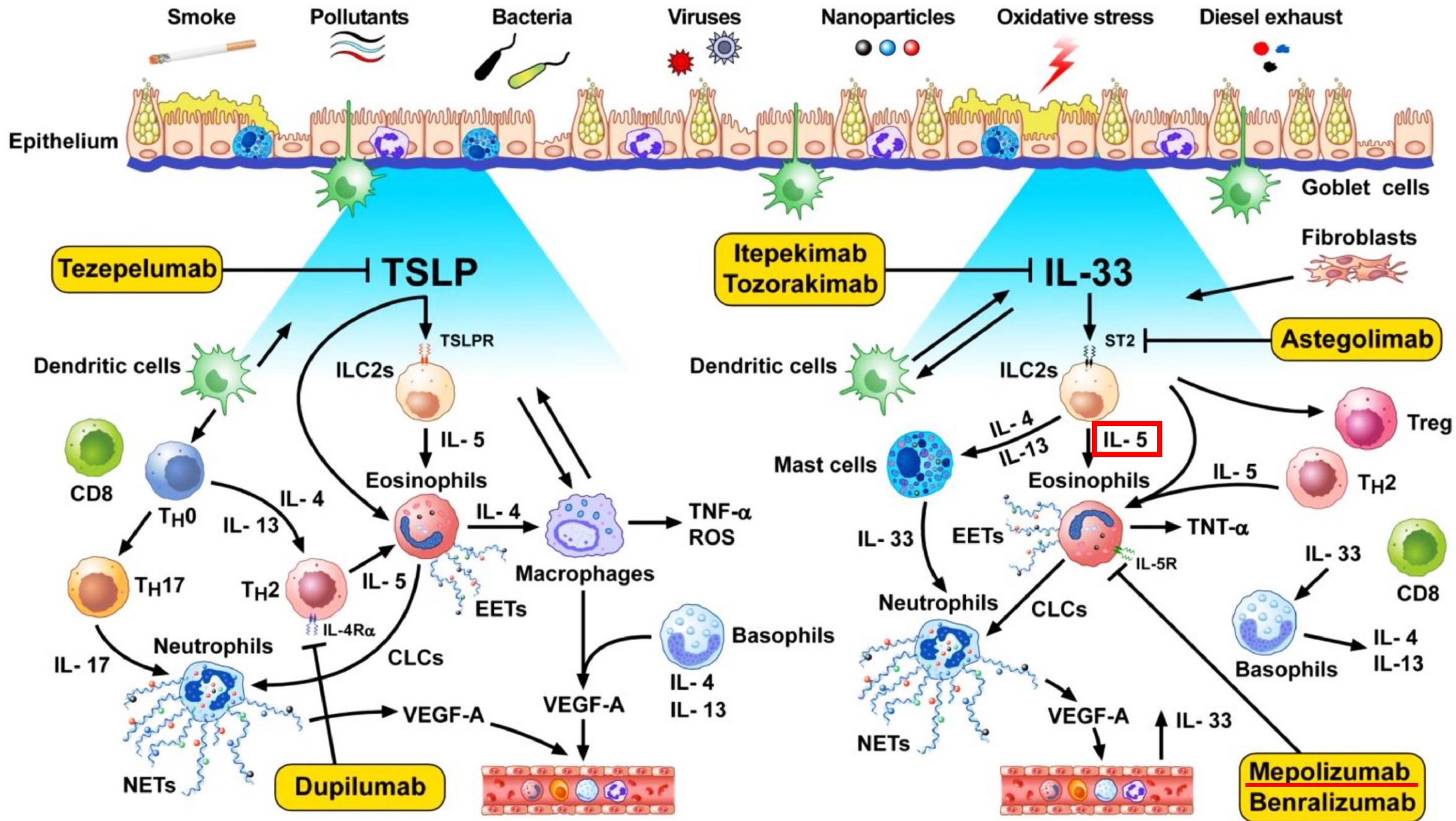
2017

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## **Mepolizumab**

-METREX

-METREO



# Biologics in COPD

2017

## Mepolizumab

-METREX

-METREO

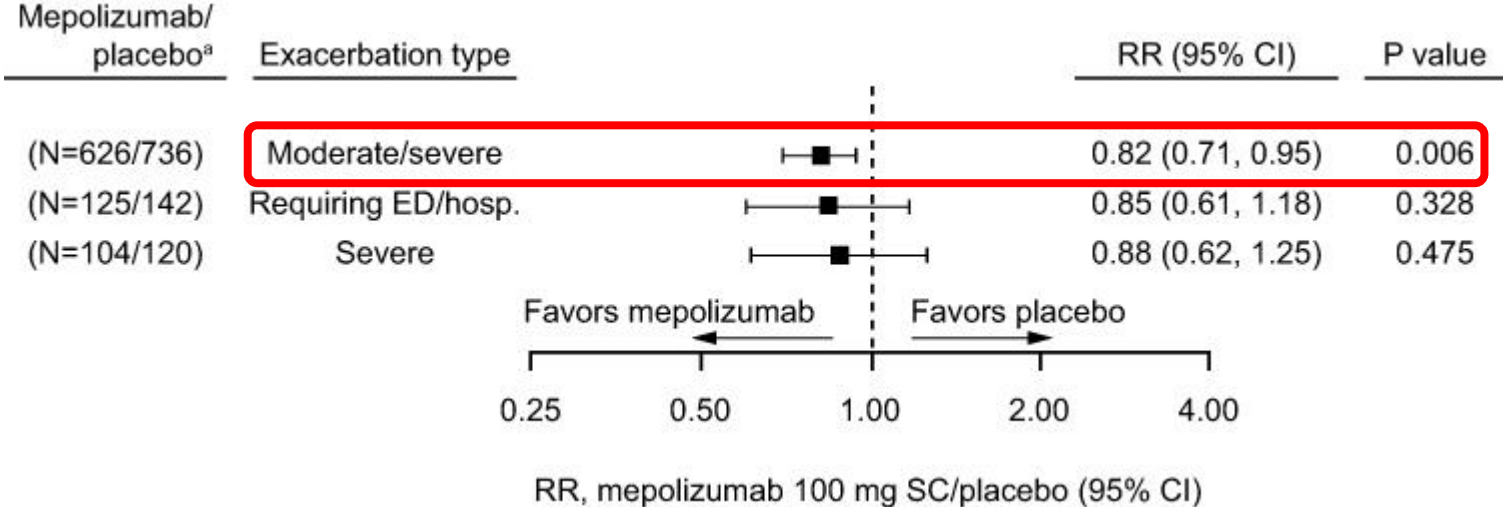
Target	Inhibitor	Study	Asthma Exclusions	Blood Eosinophils	Results
<i>IL-5</i>	Mepolizumab, 100 mg Q4W	Ph3 METREX	Excluded patients with current asthma in current/former smokers and history of asthma in nonsmokers	No cutoff; stratification by blood eosinophil	Completed Primary endpoint: annual rate of moderate or severe exacerbations Results: reduced exacerbations in those with highest baseline blood eosinophils (23)
	Mepolizumab, 100 mg Q4W, 300 mg Q4W	Ph3 METREO	Excluded patients with current asthma in current/former smokers and history of asthma in nonsmokers	$\geq 150$ cells/ $\mu$ l at screening or $\geq 300$ cells/ $\mu$ l in past year	Completed Primary endpoint: annual rate of moderate or severe exacerbations Results: primary and secondary endpoint results were not significant (23)
	Mepolizumab, 100 mg Q4W	Ph3 MATINEE	Excluded patients with current diagnosis or history of asthma	$\geq 300$ cells/ $\mu$ l at screening and documented historical $\geq 150$ / $\mu$ l within 12 mo to 1 mo before screening or visit 1	Estimated primary completion: July 2023 Primary endpoint: annualized rate of moderate* or severe† exacerbations <a href="https://clinicaltrials.gov/ct2/show/NCT04133909">https://clinicaltrials.gov/ct2/show/NCT04133909</a>

# Biologics in COPD

2017

## Mepolizumab

-METREX  
-METREO

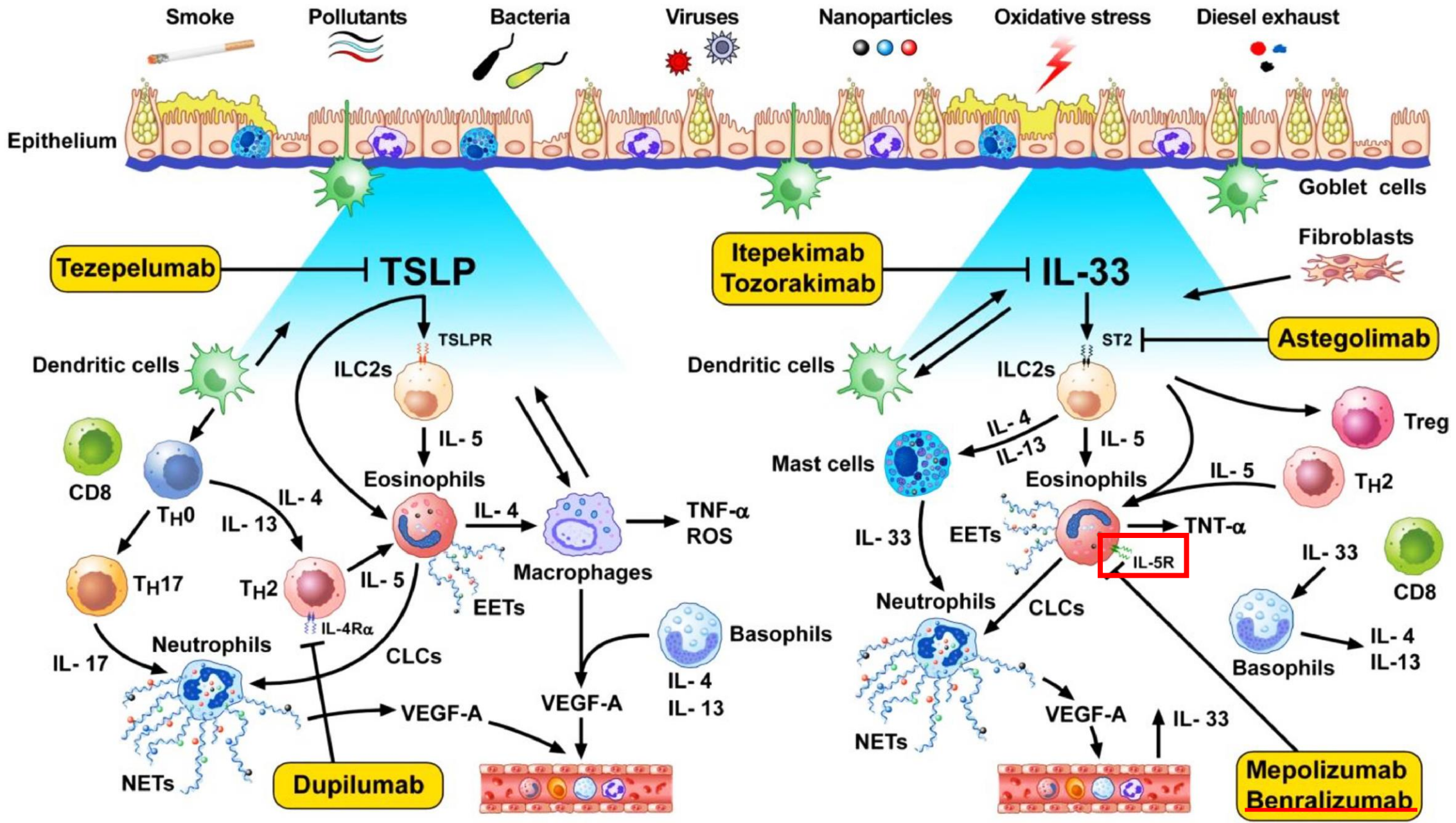


**METREO**  
Intention-to-Treat Population

Mepolizumab, 300 mg (N=225)	Placebo (N=226)
-----------------------------------	--------------------

Primary end point: moderate or severe exacerbations

Mean annual rate — events/yr†	1.40	1.71	1.49	1.52	1.19	1.27	1.49
Rate ratio vs. placebo (95% CI)	0.82 (0.68 to 0.98)	—	0.98 (0.85 to 1.12)	—	0.80 (0.65 to 0.98)	0.86 (0.70 to 1.05)	—
Adjusted P value	0.04	—	>0.99	—	0.07	0.14	—



# Biologics in COPD

2017

2019

**Mepolizumab**

- METREX
- METREO

**Benalizumab**

- GALATHEA
- TERRANOVA

*IL-5R $\alpha$*

Benralizumab, 30 mg Q4W/Q8W, 100 mg Q4W/Q8W      Ph3 GALATHEA

Benralizumab, 10 mg Q4W/Q8W, 30 mg Q4W/Q8W, 100 mg Q4W/Q8W      Ph3 TERRANOVA

Excluded patients with asthma as a primary or main diagnosis according to GINA guidelines or other

Stratification by blood eosinophils; cap for blood eosinophil counts

Completed  
 Primary endpoint: annualized COPD exacerbation  
 Rate ratio in patients with baseline blood eosinophil counts >220 cells/ $\mu$ l  
 Results: no reduction in annualized exacerbation rate ratios vs. placebo (24)

Excluded patients with asthma as a primary diagnosis according to GINA guidelines or other

Stratification by blood eosinophils; cap for blood eosinophil counts

Completed  
 Primary endpoint: annualized COPD exacerbation  
 Rate ratio in patients with baseline blood eosinophil counts >220 cells/ $\mu$ l  
 Results: no reduction in annualized exacerbation rate ratios vs. placebo (24)

Benralizumab, 100 mg Q4W (first three doses) and Q8W      Ph3 RESOLUTE

Excluded patients with current diagnosis or history of asthma or asthma/COPD overlap, excluding resolved childhood asthma

$\geq$ 300 cells/ $\mu$ l at screening and documented historical  $\geq$ 150/ $\mu$ l within 52 wk of enrollment

Estimated primary completion: March 2024  
 Primary endpoint: annualized rate of moderate\* or severe<sup>†</sup> exacerbations  
<https://clinicaltrials.gov/ct2/show/NCT04052624>

# Biologics in COPD

2017

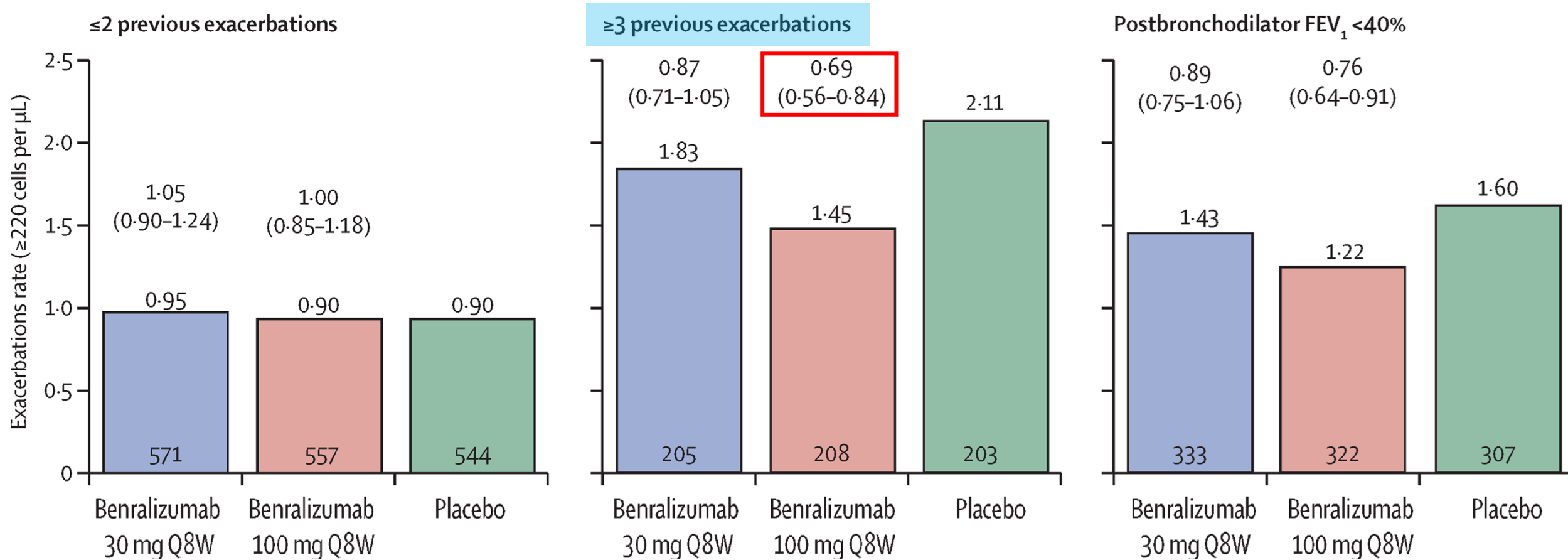
2019

**Mepolizumab**  
-METREX  
-METREO

**Benalizumab**  
-GALATHEA  
-TERRANOVA

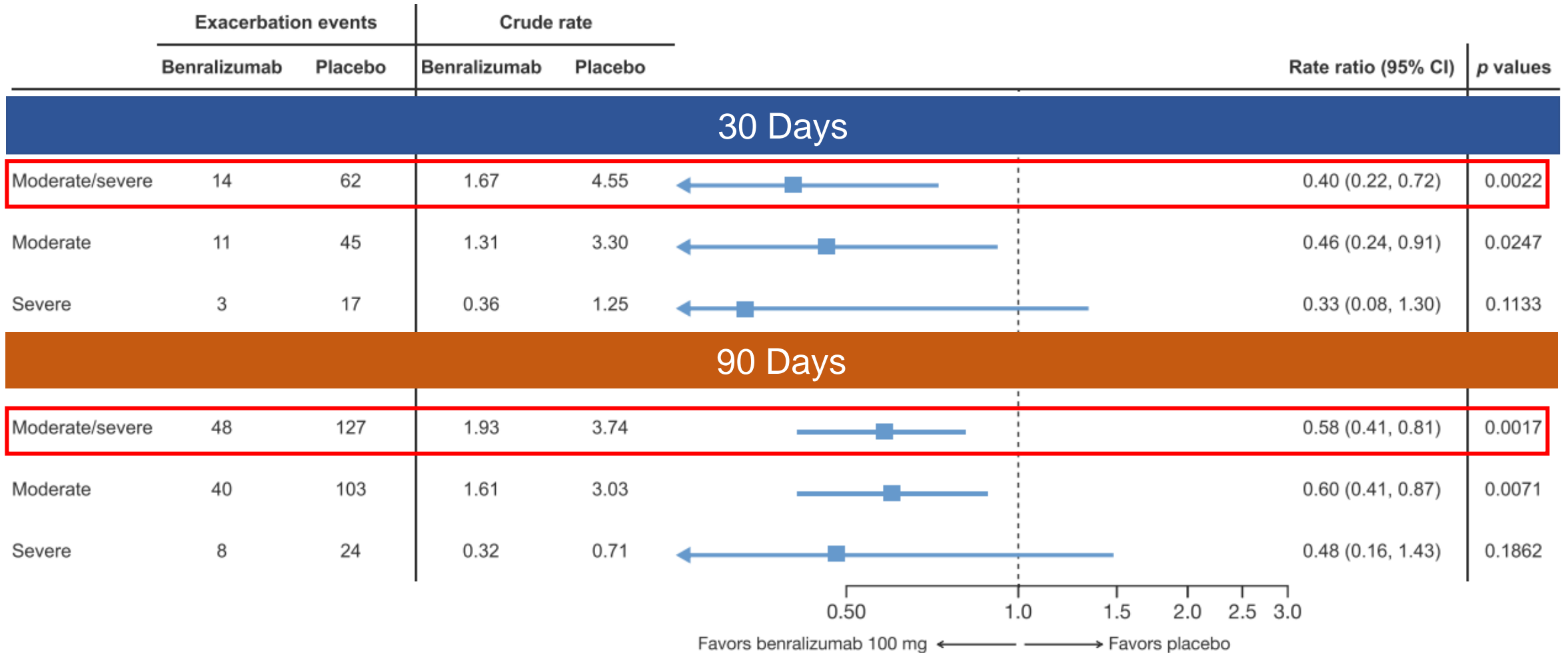
End Point	GALATHEA			TERRANOVA			
	Benralizumab, 30 mg (N=382)	Benralizumab, 100 mg (N=379)	Placebo (N=359)	Benralizumab, 10 mg (N=377)	Benralizumab, 30 mg (N=394)	Benralizumab, 100 mg (N=386)	Placebo (N=388)
Exacerbations							
Estimated annual rate (95% CI) — exacerbations/yr	1.19 (1.04–1.36)	1.03 (0.90–1.19)	1.24 (1.08–1.42)	0.99 (0.87–1.13)	1.21 (1.08–1.37)	1.09 (0.96–1.23)	1.17 (1.04–1.32)
Rate ratio, benralizumab vs. placebo (95% CI)†	0.96 (0.80–1.15)	0.83 (0.69–1.00)	—	0.85 (0.71–1.01)	1.04 (0.88–1.23)	0.93 (0.78–1.10)	—
Unadjusted P value	0.65	0.05	—	0.06	0.66	0.40	—
Severe exacerbations							
Estimated annual rate (95% CI) — exacerbations/yr	0.25 (0.19–0.33)	0.12 (0.08–0.17)	0.21 (0.15–0.28)	0.18 (0.14–0.25)	0.22 (0.17–0.28)	0.17 (0.13–0.22)	0.25 (0.19–0.32)
Rate ratio, benralizumab vs. placebo (95% CI)‡	1.20 (0.80–1.80)	0.57 (0.36–0.91)	—	0.75 (0.51–1.11)	0.88 (0.61–1.27)	0.68 (0.46–1.00)	—

# Blood EOS $\geq 220$ cells/ $\mu$ L



# ≥3 COPD exacerbations and Blood EOS ≥ 300 cells/μL

## Recurrent COPD exacerbations within 30 and 90 days



# Treating eosinophilic exacerbations of asthma and COPD with benralizumab (ABRA): a double-blind, double-dummy, active placebo-controlled randomised trial



*Sanjay Ramakrishnan, Richard E K Russell, Hafiz R Mahmood, Karolina Krassowska, James Melhorn, Christine Mwasuku, Ian D Pavord, Laura Bermejo-Sanchez, Imran Howell, Mahdi Mahdi, Stefan Peterson, Thomas Bengtsson, Mona Bafadhel*



At the time of an acute exacerbation of asthma or COPD:  $\geq 300$ cell/uL

G1: **PD** 30mg qd for 5 days + 100mg **benralizumab** (52)

G2: 100mg **benralizumab** (53)

G3: **PD** 30mg qd for 5 days (53)

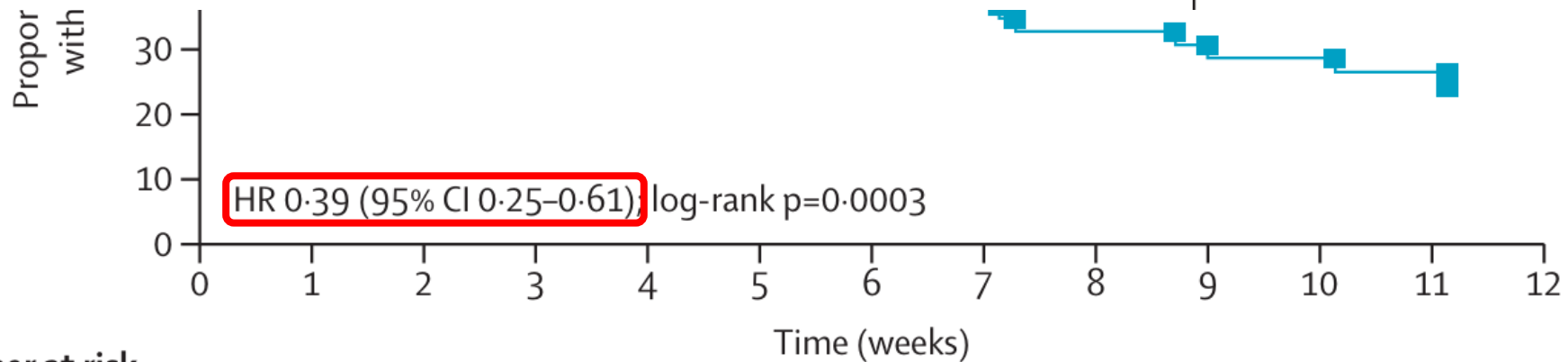
# Primary Outcome: Treatment Failure within 90 days

Treatment Failure: death, admission, re-treatment

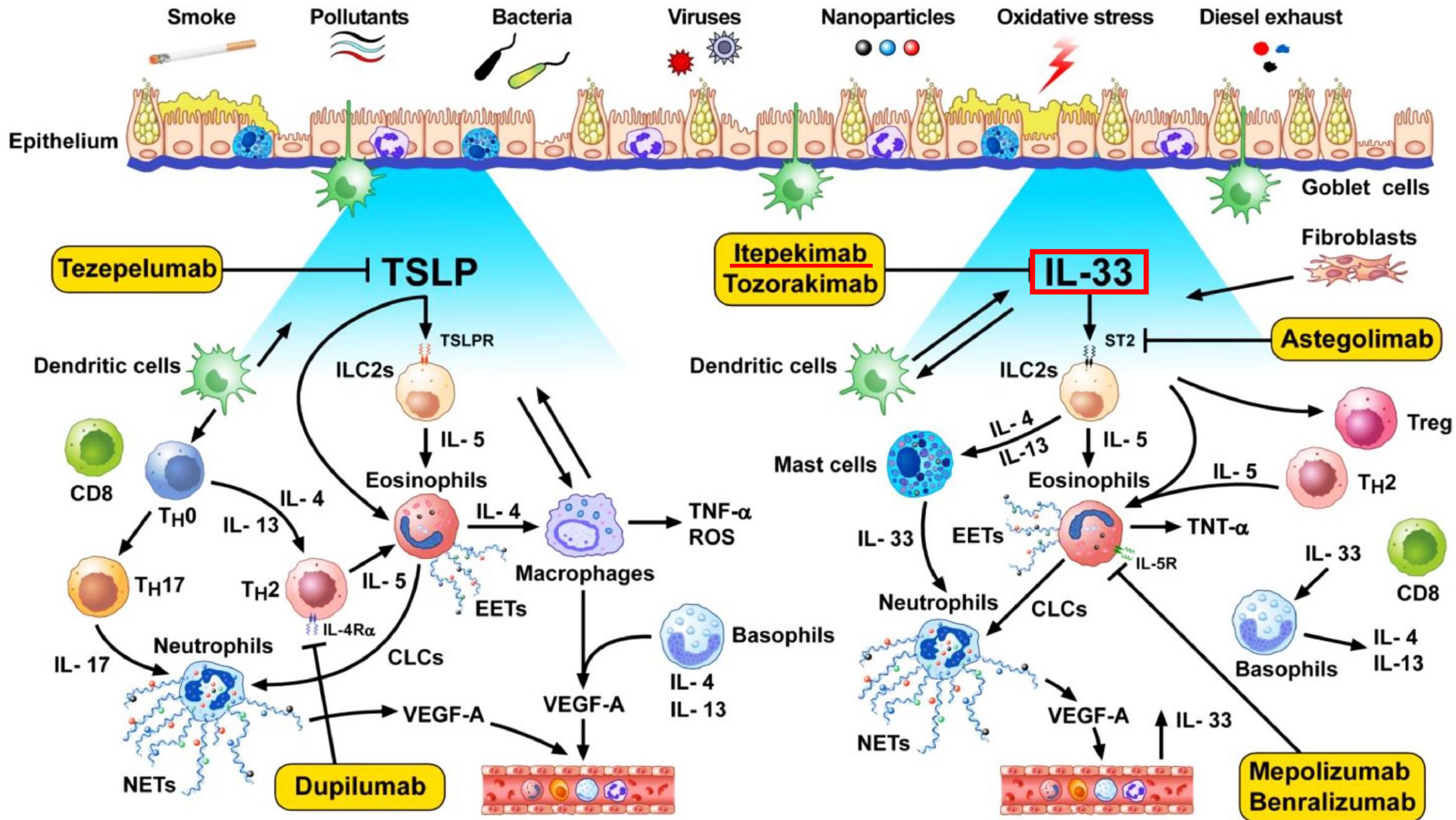


Adjudicated diagnosis

Adjudicated diagnosis	Pooled-BENRA group	PRED group	Hazard Ratio (95% CI)	p-value
Asthma	23/53 (43.4%)	25/35 (71.4%)	0.44 (0.25-0.78)	0.0037
COPD	19/36 (52.8%)	10/13 (76.9%)	0.43 (0.20-0.93)	0.027
Asthma and COPD	5/14 (35.7%)	3/5 (60.0%)	0.69 (0.16-2.91)	0.611



	0	1	2	3	4	5	6	7	8	9	10	11	12
<b>Number at risk</b>													
Pooled-BENRA group	105	98	86	79	79	72	68	66	65	61	59	55	49
PRED group	53	46	41	33	28	24	22	20	16	15	14	12	11



# Biologics in COPD

2017	2019	2021	
<b>Mepolizumab -IL-5</b>	<b>Benalizumab -IL-5R</b>	<b>Itepekimab -IL-33</b>	
<i>IL-33</i>	<u>Itepekimab, Q2W</u>	Ph2	Excluded patients with asthma No cutoff
	Itepekimab, Q2W, Q4W in former smokers	Ph3 AERIFY-1	Excluded patients with current diagnosis or history of asthma No cutoff
	Itepekimab, Q2W in current and former smokers, Q4W in former smokers	Ph3 AERIFY-2	Excluded patients with current diagnosis or history of asthma No cutoff
	MEDI3506, NR	Ph2 FRONTIER-4	Excluded patients with asthma No cutoff

Completed  
 Primary endpoint: annualized rate of moderate to severe acute exacerbations of chronic obstructive pulmonary disease  
 Results: reduced exacerbations and improved lung function in subgroup of former smokers (37)  
 Estimated primary completion: December 2023  
 Primary endpoint: annualized rate of acute moderate\* or severe† exacerbations  
<https://clinicaltrials.gov/ct2/show/NCT04701983>  
 Estimated primary completion: February 2024  
 Primary endpoint: annualized rate of acute moderate\* or severe† exacerbations in former smokers  
<https://clinicaltrials.gov/ct2/show/NCT04751487>  
 Estimated primary completion: March 2023  
 Primary endpoint: change from baseline to Week 12 in prebronchodilator FEV<sub>1</sub>  
<https://clinicaltrials.gov/ct2/show/NCT04631016>

# Biologics in COPD

2017

2019

2021

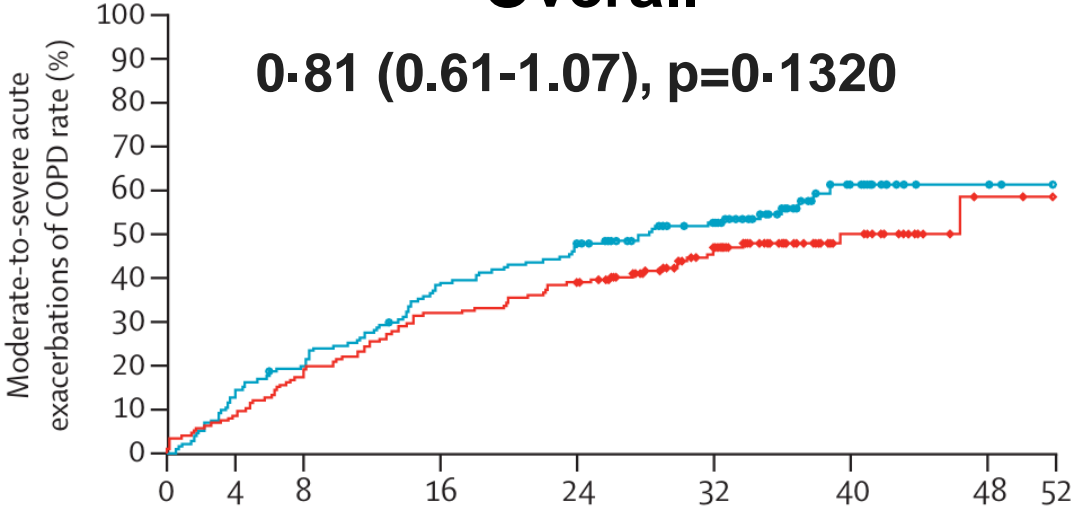
Mepolizumab  
-IL-5  
-METREX  
-METREO

Benalizumab  
-IL-5R  
-GALATHEA  
-TERRANOVA

Itepekimab  
-IL-33

## Overall

0.81 (0.61-1.07), p=0.1320

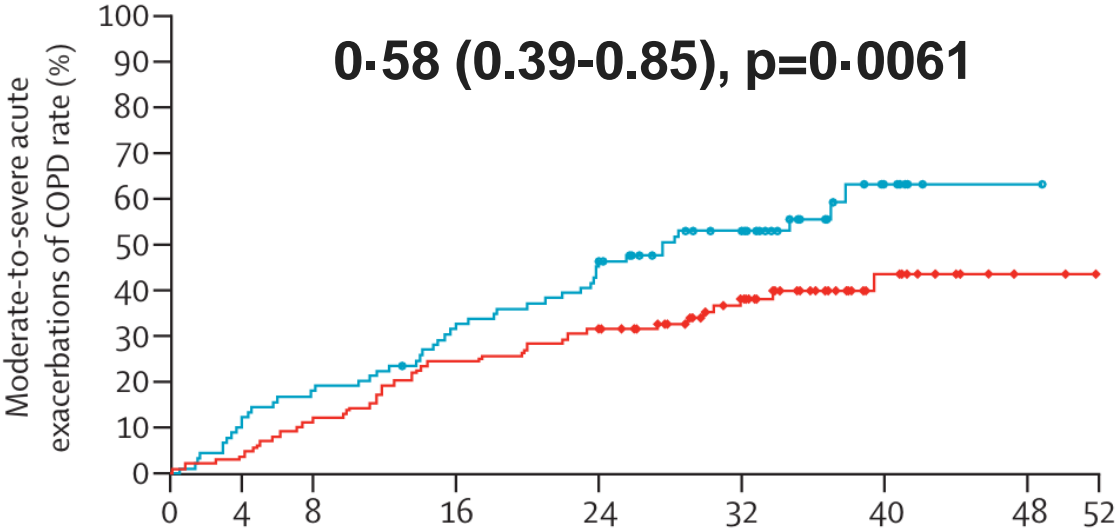


Number of patients  
at risk

Placebo	171	149	136	104	89	64	16	3	0
Itepekimab	172	157	142	117	105	69	22	4	0

## Former Smoker

0.58 (0.39-0.85), p=0.0061



Number of patients  
at risk

Placebo	89	80	73	60	48	30	7	1	0
Itepekimab	98	94	87	74	67	44	15	4	0

# Biologics in COPD

2017

2019

2021

## Mepolizumab -IL-5

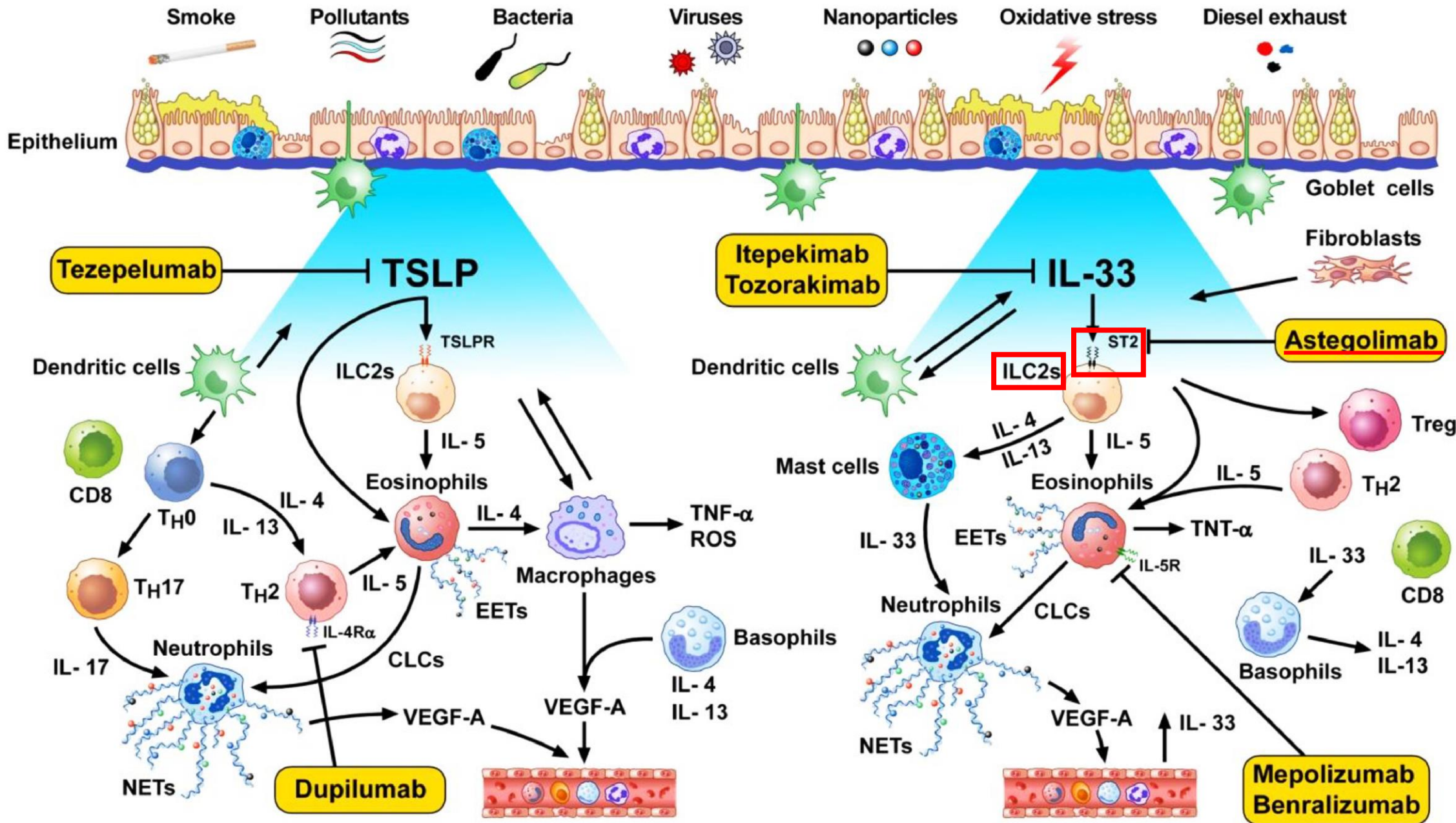
## Benalizumab -IL-5R

## Itepekimab -IL-33

2017	2019	2021
<i>IL-33</i>	Itepekimab, Q2W	Ph2
	Itepekimab, Q2W, Q4W in former smokers	Ph3 AERIFY-1
	Itepekimab, Q2W in current and former smokers, Q4W in former smokers	Ph3 AERIFY-2
MEDI3506, NR	Ph2 FRONTIER-4	

Excluded patients with asthma	No cutoff
Excluded patients with current diagnosis or history of asthma	No cutoff
Excluded patients with current diagnosis or history of asthma	No cutoff
Excluded patients with asthma	No cutoff

Completed  
 Primary endpoint: annualized rate of moderate to severe acute exacerbations of chronic obstructive pulmonary disease  
 Results: reduced exacerbations and improved lung function in subgroup of former smokers (37)  
 Estimated primary completion: December 2023  
 Primary endpoint: annualized rate of acute moderate\* or severe<sup>†</sup> exacerbations  
<https://clinicaltrials.gov/ct2/show/NCT04701983>  
 Estimated primary completion: February 2024  
 Primary endpoint: annualized rate of acute moderate\* or severe<sup>†</sup> exacerbations in former smokers  
<https://clinicaltrials.gov/ct2/show/NCT04751487>  
 Estimated primary completion: March 2023  
 Primary endpoint: change from baseline to Week 12 in prebronchodilator FEV<sub>1</sub>  
<https://clinicaltrials.gov/ct2/show/NCT04631016>



# Biologics in COPD

2017

2019

2021

2021

Mepolizumab

-IL-5

-METREX

-METREO

Benalizumab

-IL-5R

-GALATHEA

-TERRANOVA

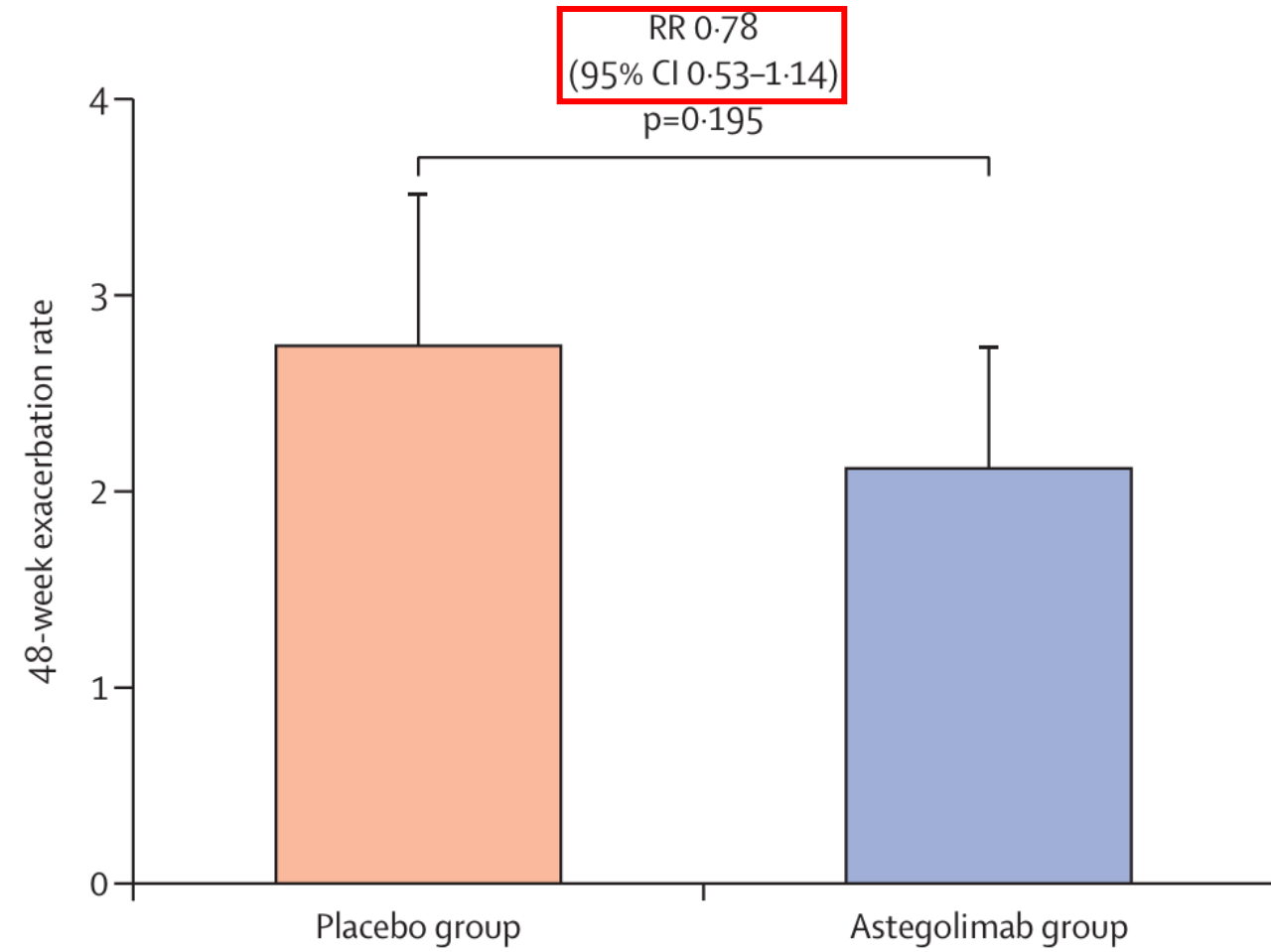
Itepekimab

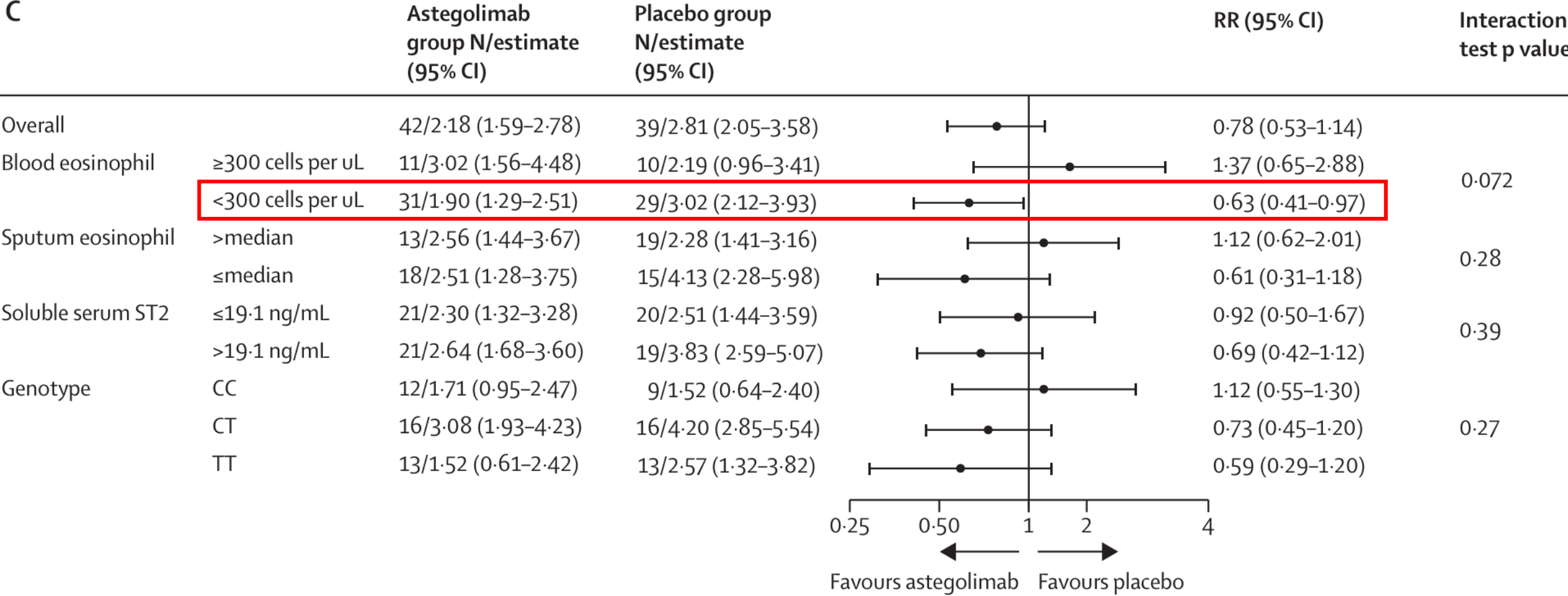
-IL-33

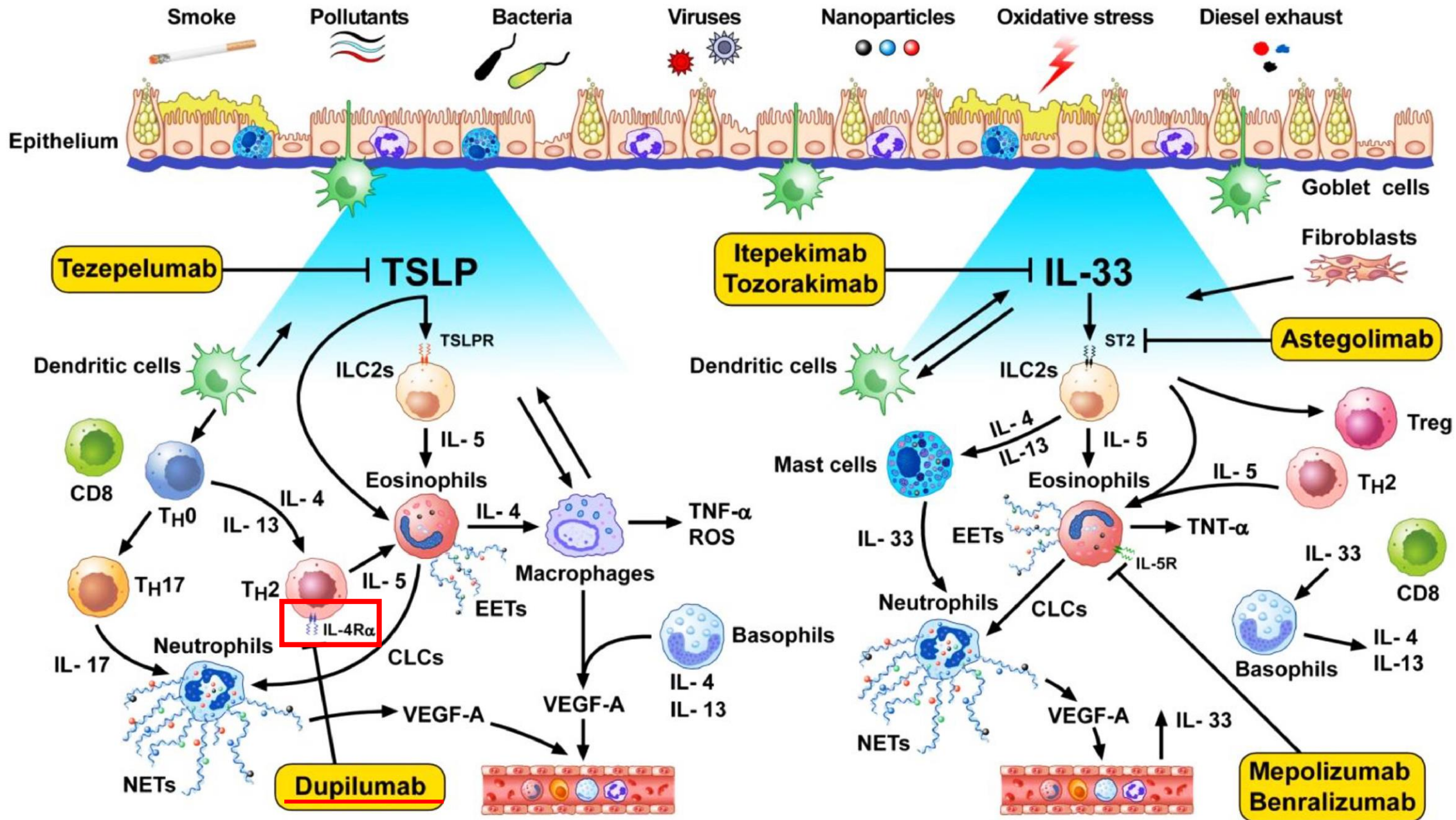
Astegolimab

-ST2(IL-33R)

Target	Inhibitor	Study	Asthma Exclusions	Blood Eosinophils	Results
ST-2 (IL-33R)	Astegolimab, 490 mg Q4W	Ph2a COPD-ST2OP	Excluded patients with known respiratory disorders other than COPD	No cutoff	Completed Primary endpoint: frequency of moderate to severe exacerbations Results: no reduction in exacerbation rates in the ITT population (86)
	Astegolimab, Q2W or Q4W, dose NR	Ph2b	Excluded patients with asthma	No cutoff	Estimated primary completion: May 2024 Primary endpoint: annualized rate of moderate and severe COPD exacerbations



**C**



# Biologics in COPD

2017

2019

2021

2022

2023

Mepolizumab  
-IL-5  
-METREX  
-METREO

Benalizumab  
-IL-5R  
-GALATHEA  
-TERRANOVA

Itepekimab  
-IL-33

Astegolimab  
-ST2(IL-33R)

Dupilumab  
-IL 4/13R

Target	Inhibitor	Study	Asthma Exclusions	Blood Eosinophils	Results
<i>IL-4R<math>\alpha</math></i>	Dupilumab, Q2W	<u>Ph3 BOREAS</u>	Excluded patients with current diagnosis or history of asthma	$\geq 300$ cells/ $\mu$ l at visit 1	Completed Primary endpoint: annualized rate of moderate* or severe† exacerbations <a href="https://clinicaltrials.gov/ct2/show/NCT03930732">https://clinicaltrials.gov/ct2/show/NCT03930732</a>
	Dupilumab, Q2W	<u>Ph3 NOTUS</u>	Excluded patients with current diagnosis or history of asthma	$\geq 300$ cells/ $\mu$ l at visit 1	Estimated primary completion: April 2024 Primary endpoint: annualized rate of moderate* or severe† exacerbations <a href="https://clinicaltrials.gov/ct2/show/NCT04456673">https://clinicaltrials.gov/ct2/show/NCT04456673</a>

# Biologics in COPD

2017

2019

2021

2021

2023

Mepolizumab

Benalizumab

Itepekimab

Astegolimab

Dupilumab

-IL-5

-IL-5R

-IL-33

-ST2(IL-33R)

-IL 4/13R

-METREX

-GALATHEA

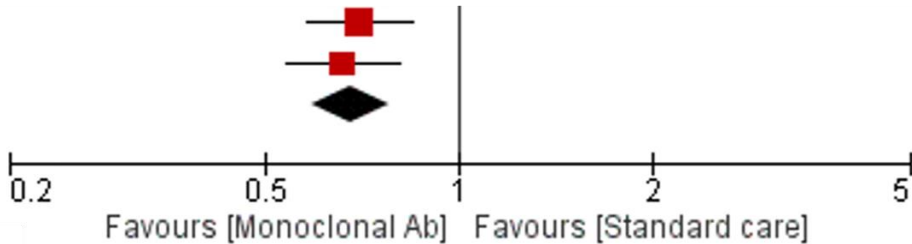
-METREO

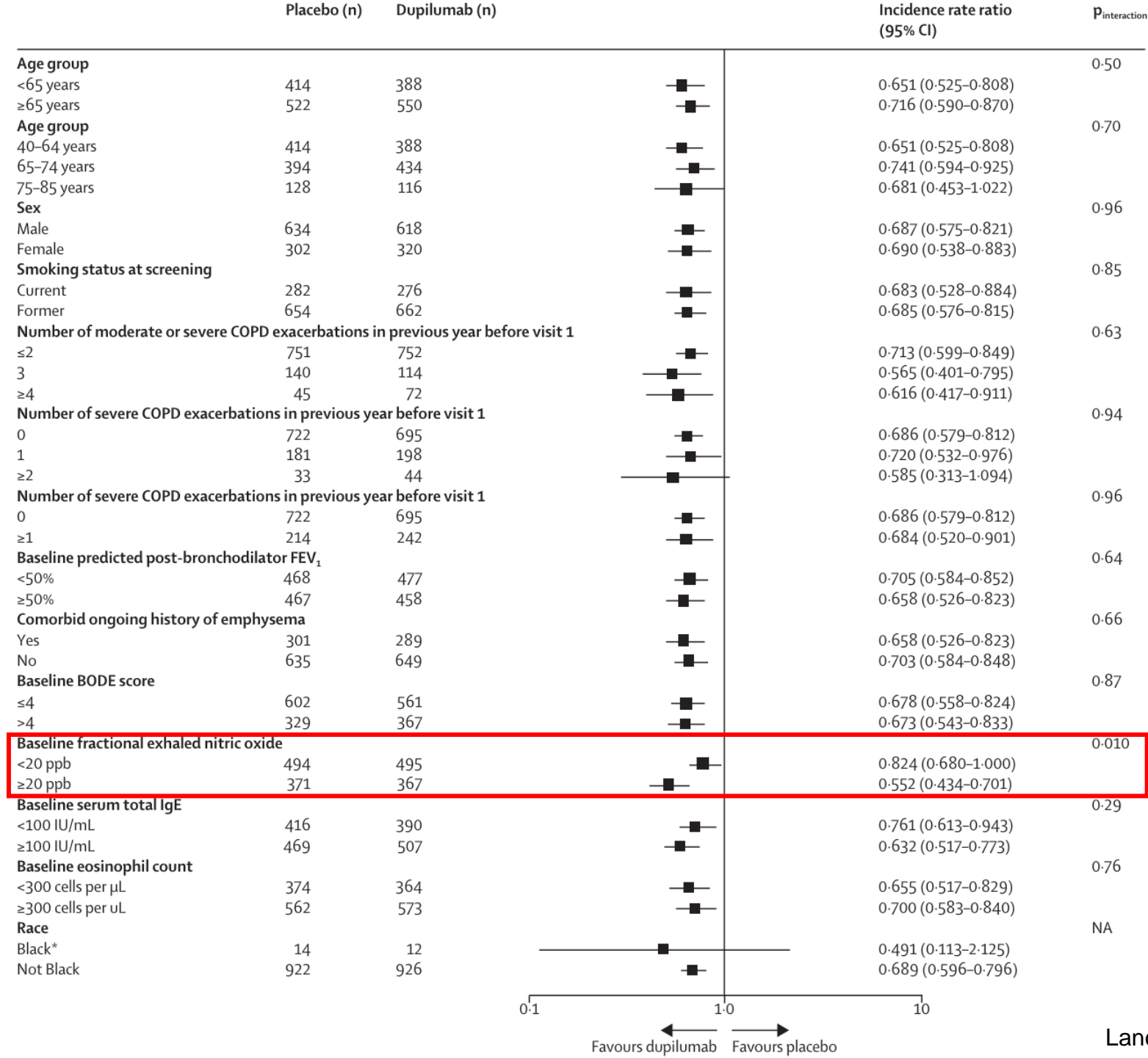
-TERRANOVA

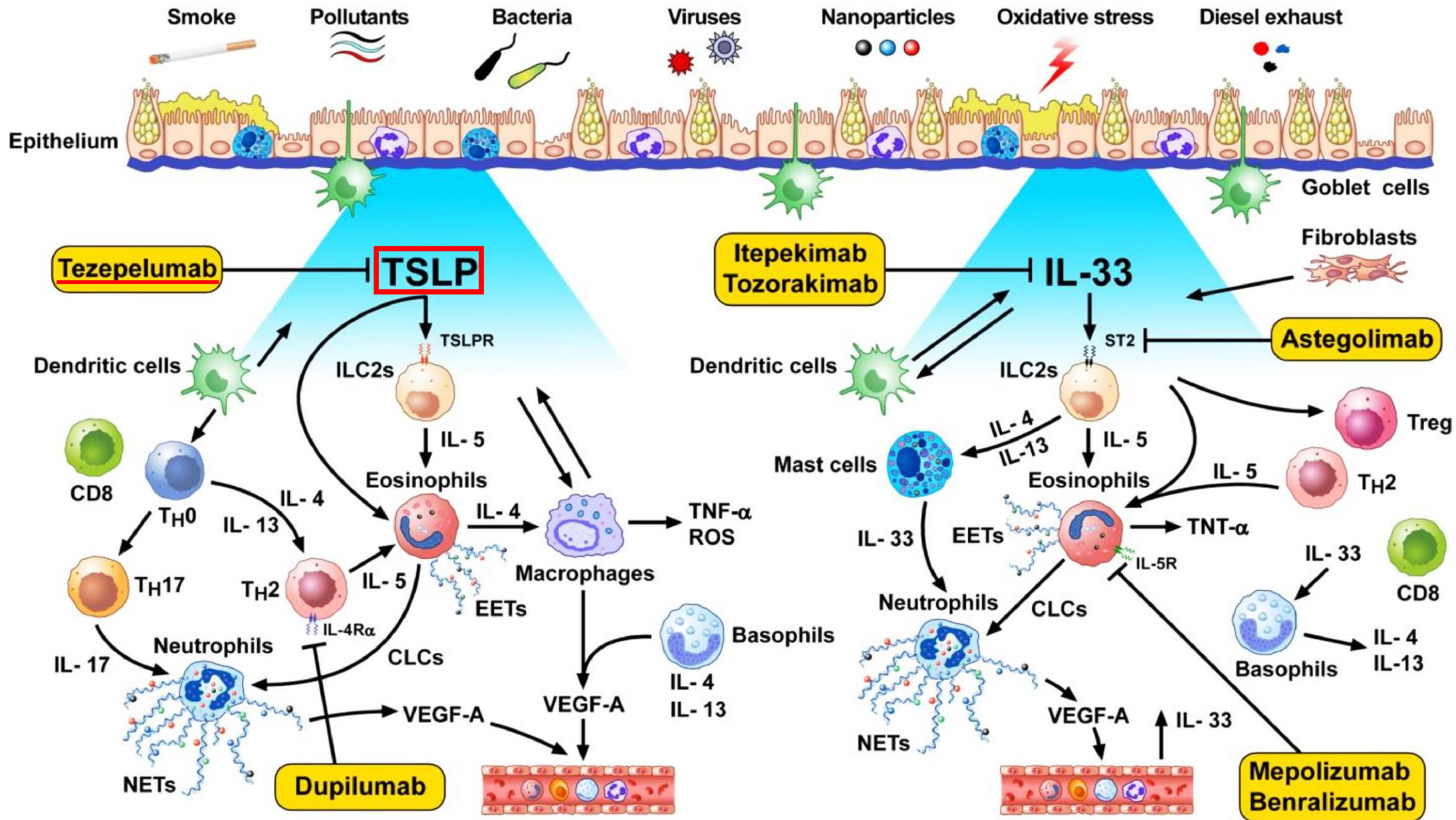
BOREAS 2023	-0.3567	0.0959	468	471	53.3%
NOTUS 2024	-0.4155	0.1024	470	465	46.7%
<b>Subtotal (95% CI)</b>			<b>938</b>	<b>936</b>	<b>100.0%</b>

0.70 [0.58, 0.84]
0.66 [0.54, 0.81]
<b>0.68 [0.59, 0.78]</b>

Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 0.18, df = 1 (P = 0.68); I<sup>2</sup> = 0%  
 Test for overall effect: Z = 5.49 (P < 0.00001)







# Biologics in COPD

2017	2019	2021	2021	2023	2024
Mepolizumab -IL-5 -METREX -METREO	Benalizumab -IL-5R -GALATHEA -TERRANOVA	Itepekimab -IL-33	Astegolimab -ST2(IL-33R)	Dupilumab -IL 4/13R	<b>Tezepelumab</b> <b>-TSLP</b>

Target	Inhibitor	Study	Asthma Exclusions	Blood Eosinophils	Results
<i>TSLP</i>	Tezepelumab, Q4W, dose NR	Ph2 COURSE	Excluded patients with asthma	No cutoff	Estimated primary completion: February 2023 Primary endpoint: moderate or severe COPD exacerbation rate ratio (tezepelumab vs. placebo) <a href="https://clinicaltrials.gov/ct2/show/NCT04039113">https://clinicaltrials.gov/ct2/show/NCT04039113</a>

# Efficacy and safety of tezepelumab versus placebo in adults with moderate to very severe chronic obstructive pulmonary disease (COURSE): a randomised, placebo-controlled, phase 2a trial



*Dave Singh, Christopher E Brightling, Klaus F Rabe, MeiLan K Han, Stephanie A Christenson, M Bradley Drummond, Alberto Papi, Ian D Pavord, Nestor A Molfino, Gun Almqvist, Ales Kotalik, Åsa Hellqvist, Monika Gołqbek, Navreet S Sindhvani, Sandhia S Ponnarambil, on behalf of the COURSE study investigators\**

Patients/rate

Rate ratio (95% CI)

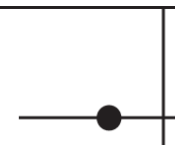
Tezepelumab group (n=165)    Placebo group (n=168)

Moderate or severe COPD exacerbations

Overall

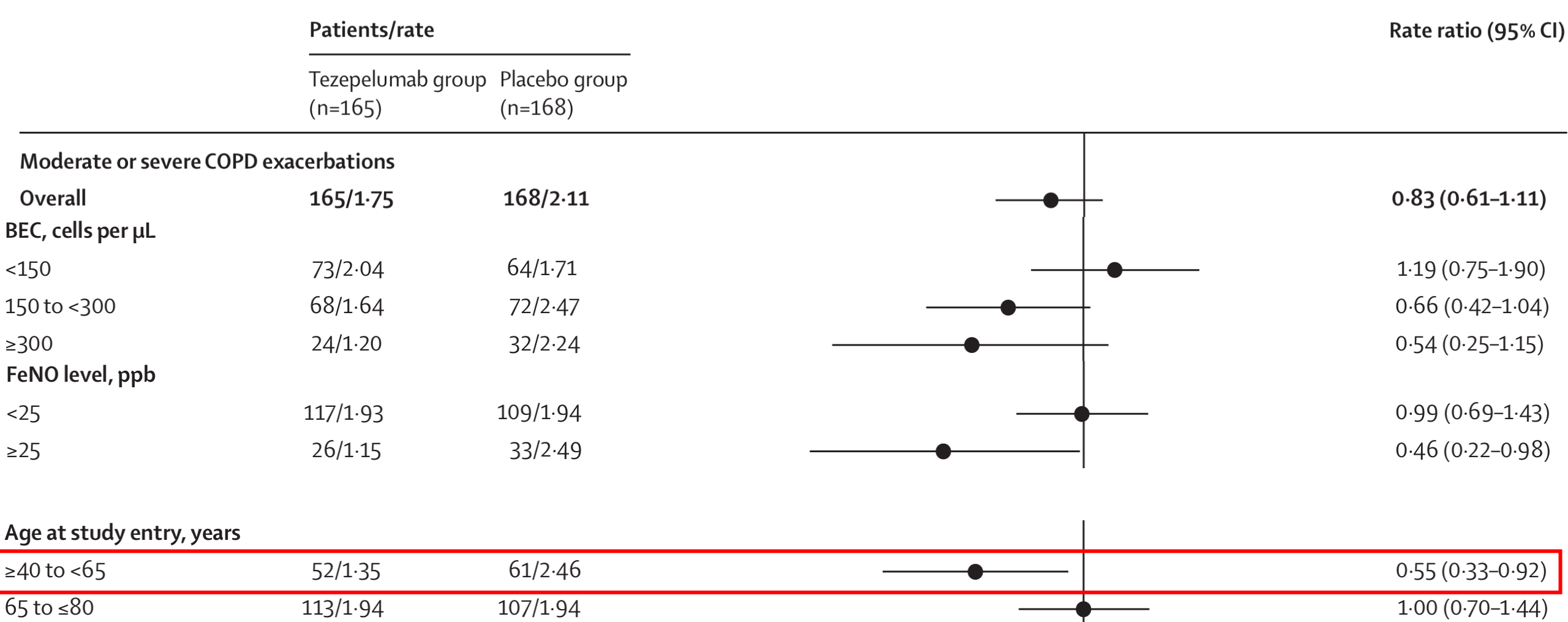
165/1.75

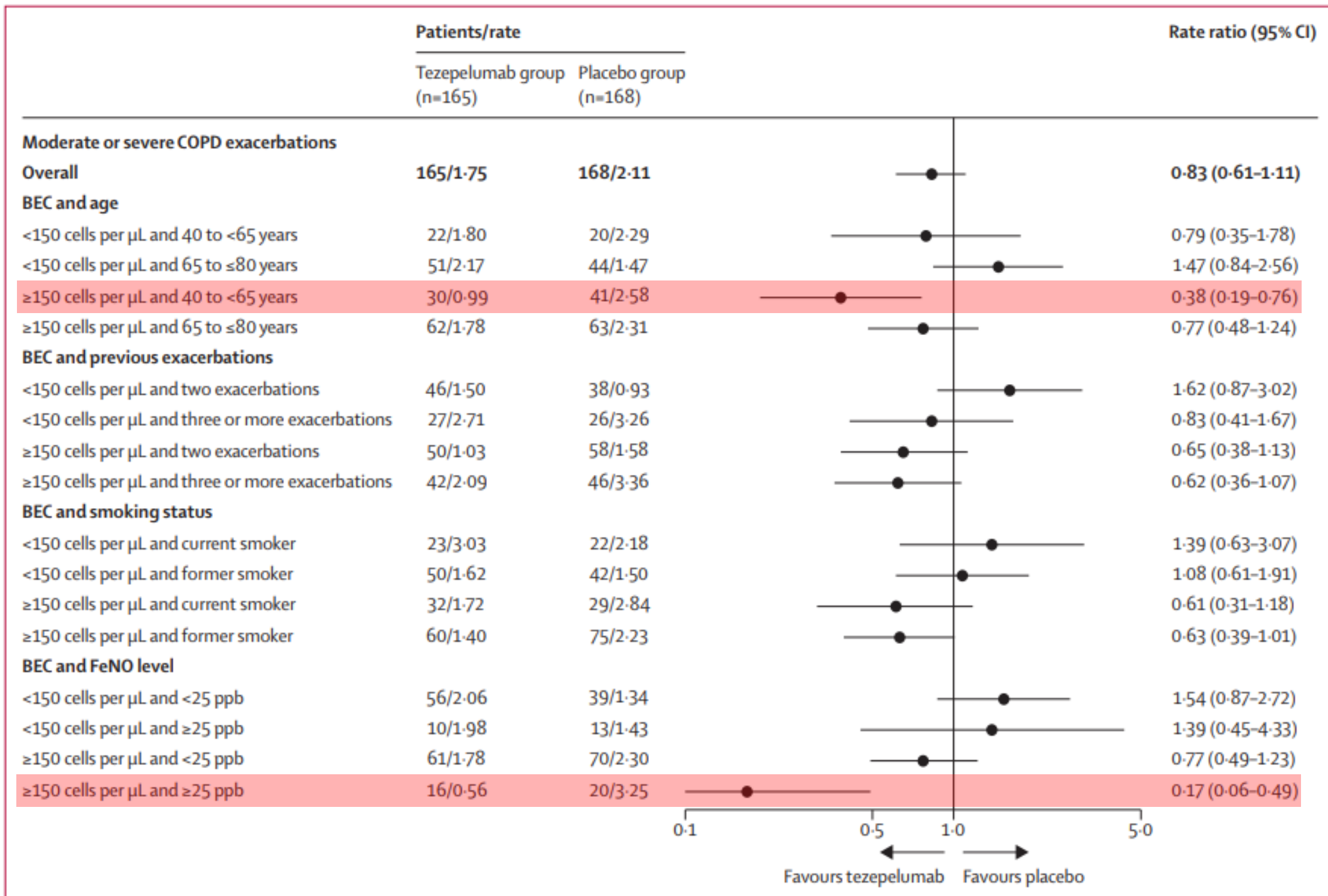
168/2.11



0.83 (0.61-1.11)

	Patients/rate			Rate ratio (95% CI)
	Tezepelumab group (n=165)	Placebo group (n=168)		
<b>Moderate or severe COPD exacerbations</b>				
<b>Overall</b>	<b>165/1.75</b>	<b>168/2.11</b>		<b>0.83 (0.61-1.11)</b>
<b>BEC, cells per <math>\mu</math>L</b>				
<150	73/2.04	64/1.71		1.19 (0.75-1.90)
150 to <300	68/1.64	72/2.47		0.66 (0.42-1.04)
$\geq$ 300	24/1.20	32/2.24		0.54 (0.25-1.15)
<b>FeNO level, ppb</b>				
<25	117/1.93	109/1.94		0.99 (0.69-1.43)
$\geq$ 25	26/1.15	33/2.49		0.46 (0.22-0.98)

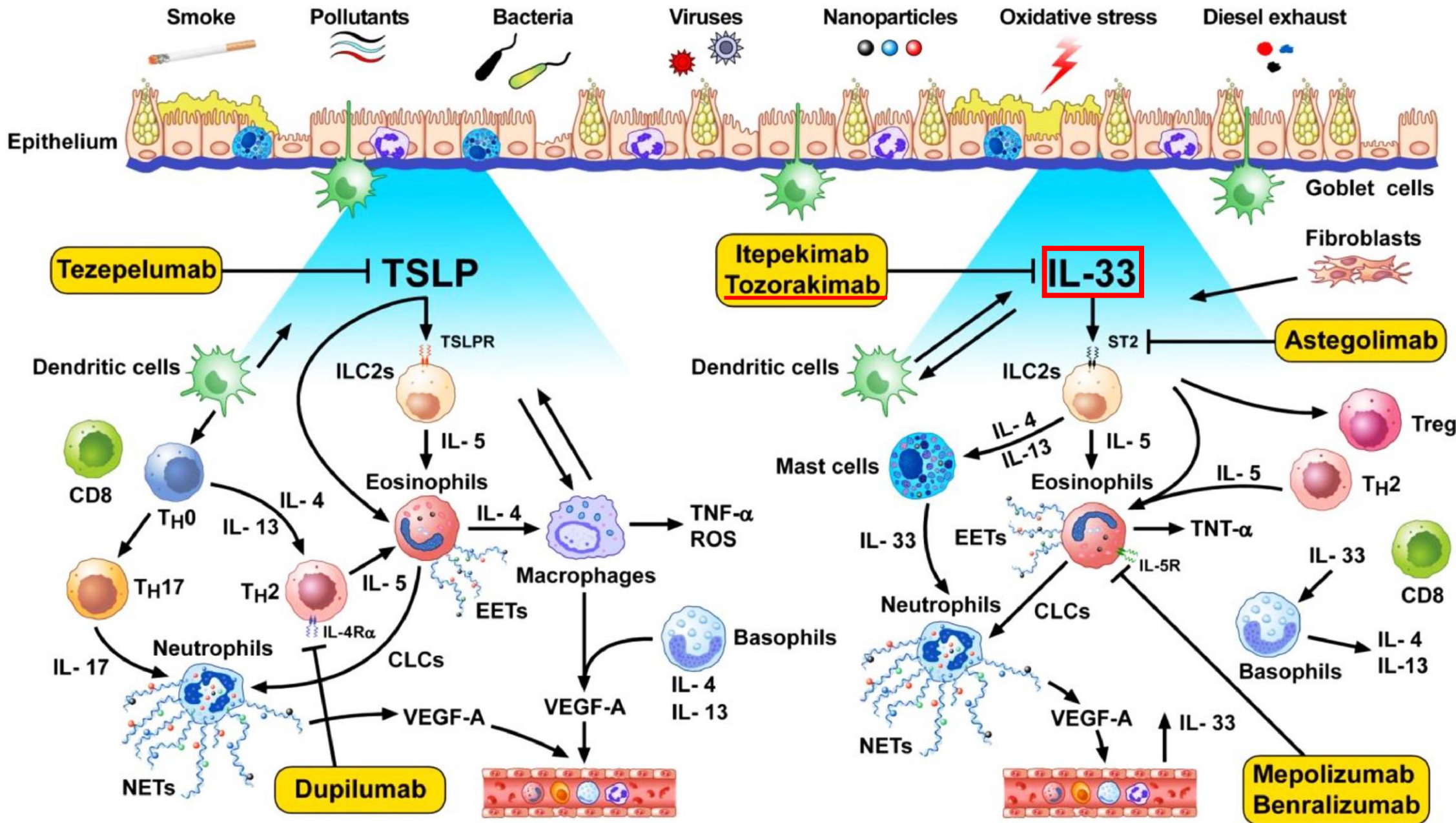




	Tezepelumab group (n=165)		Placebo group (n=168)		LS mean difference (95% CI)
	n	LS mean (SE)	n	LS mean (SE)	
<b>Pre-bronchodilator FEV<sub>1</sub>, L</b>					
Overall	163	0.026 (0.015)	166	-0.029 (0.015)	0.055 (0.014 to 0.096)
<b>Baseline BEC, cells per µL</b>					
<150	73	-0.002 (0.022)	63	-0.053 (0.023)	0.051 (-0.012 to 0.114)
150 to <300	66	0.010 (0.023)	72	-0.025 (0.022)	0.034 (-0.028 to 0.097)
≥300	24	0.160 (0.038)	31	0.013 (0.035)	0.146 (0.044 to 0.248)
<b>Baseline FeNO level, ppb</b>					
<25	117	0.009 (0.018)	107	-0.022 (0.019)	0.031 (-0.020 to 0.082)
≥25	25	0.118 (0.038)	33	0.000 (0.035)	0.118 (0.016 to 0.220)
<b>SGRQ total score</b>					
Overall	157	-4.80 (1.18)	156	-1.86 (1.19)	-2.93 (-6.23 to 0.36)
<b>Baseline BEC, cells per µL</b>					
<150	69	-1.91 (1.75)	60	-0.30 (1.89)	-1.62 (-6.69 to 3.45)
150 to <300	66	-6.05 (1.81)	69	-3.64 (1.75)	-2.41 (-7.36 to 2.55)
≥300	22	-10.22 (3.14)	27	-0.68 (3.01)	-9.53 (-18.11 to -0.96)
<b>Baseline FeNO level, ppb</b>					
<25	112	-4.46 (1.43)	102	-2.28 (1.49)	-2.18 (-6.24 to 1.88)
≥25	24	-7.23 (3.08)	29	-1.90 (2.87)	-5.33 (-13.56 to 2.91)

BEC=blood eosinophil count. FeNO=fractional exhaled nitric oxide. LS=least-squares. ppb=parts per billion. SGRQ=St George's Respiratory Questionnaire.

**Table 2: Change from baseline to week 52 in pre-bronchodilator FEV<sub>1</sub> and SGRQ total score in the overall population (secondary endpoint) and in prespecified patient subgroups by baseline BEC and FeNO level (full analysis set)**



# Biologics in COPD

2017

2019

2021

2021

2023

2024

2025

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**Mepolizumab**  
-IL-5  
-METREX  
-METREO

**Benalizumab**  
-IL-5R  
-GALATHEA  
-TERRANOVA

**Itepekimab**  
-IL-33

**Astegolimab**  
-ST2(IL-33R)

**Dupilumab**  
-IL 4/13R

**Tezepelumab**  
-TSLP

**Tozorakimab**  
-IL-33



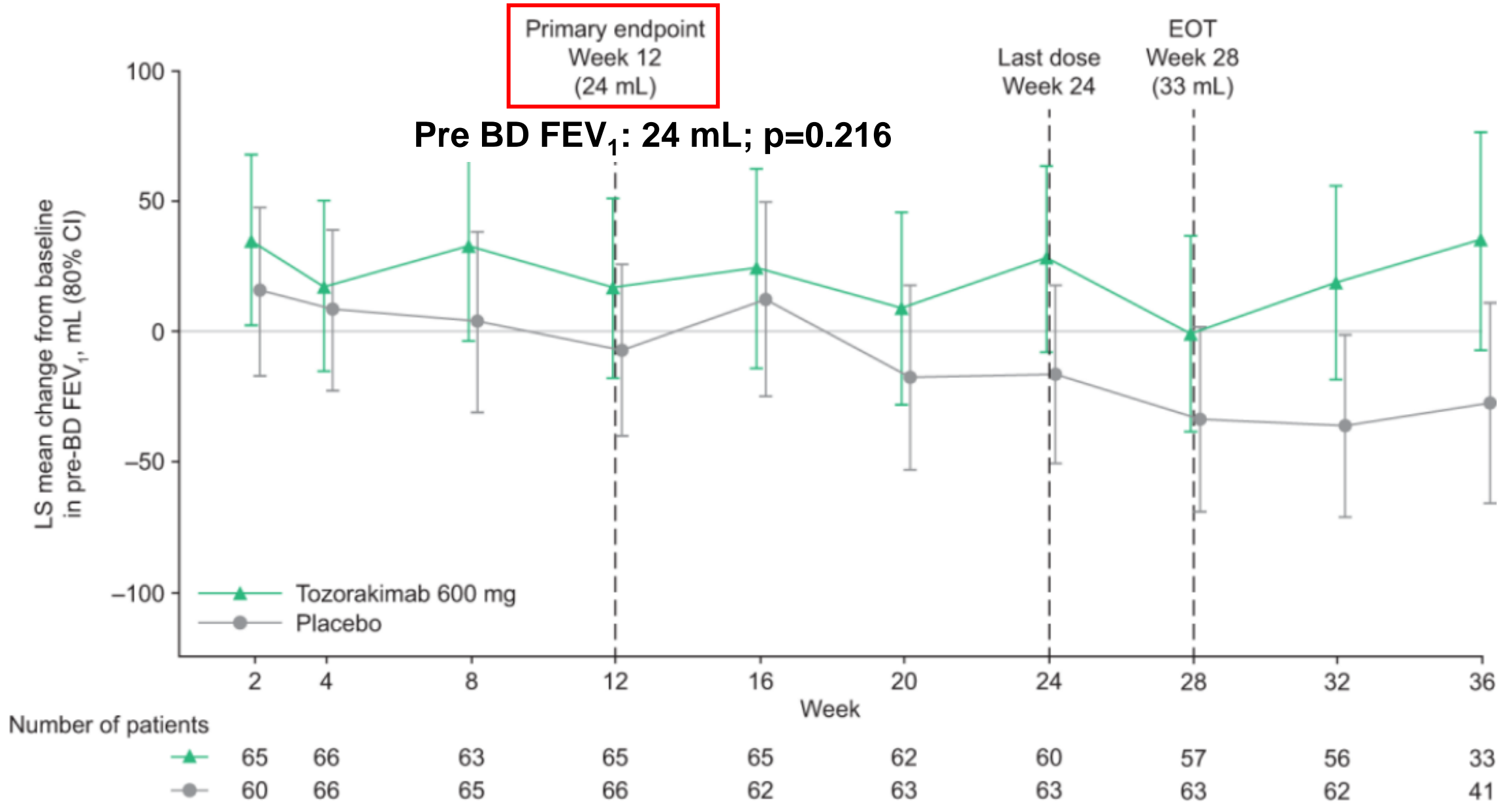
## Early View

Original Research Article

### **A phase 2a trial of the IL-33 mAb tozorakimab in patients with COPD: FRONTIER-4**

Dave Singh, Patricia Guller, Fred Reid, Sarah Doffman, Ulla Seppälä, Ioannis Psallidas, Rachel Moate, Rebecca Smith, Joanna Kiraga, Eulalia Jimenez, Dennis Brooks, Aoife Kelly, Lars H. Nordenmark, Muhammad Waqas Sadiq, Luis Mateos Caballero, Chris Kell, Maria G Belvisi, Hitesh Pandya

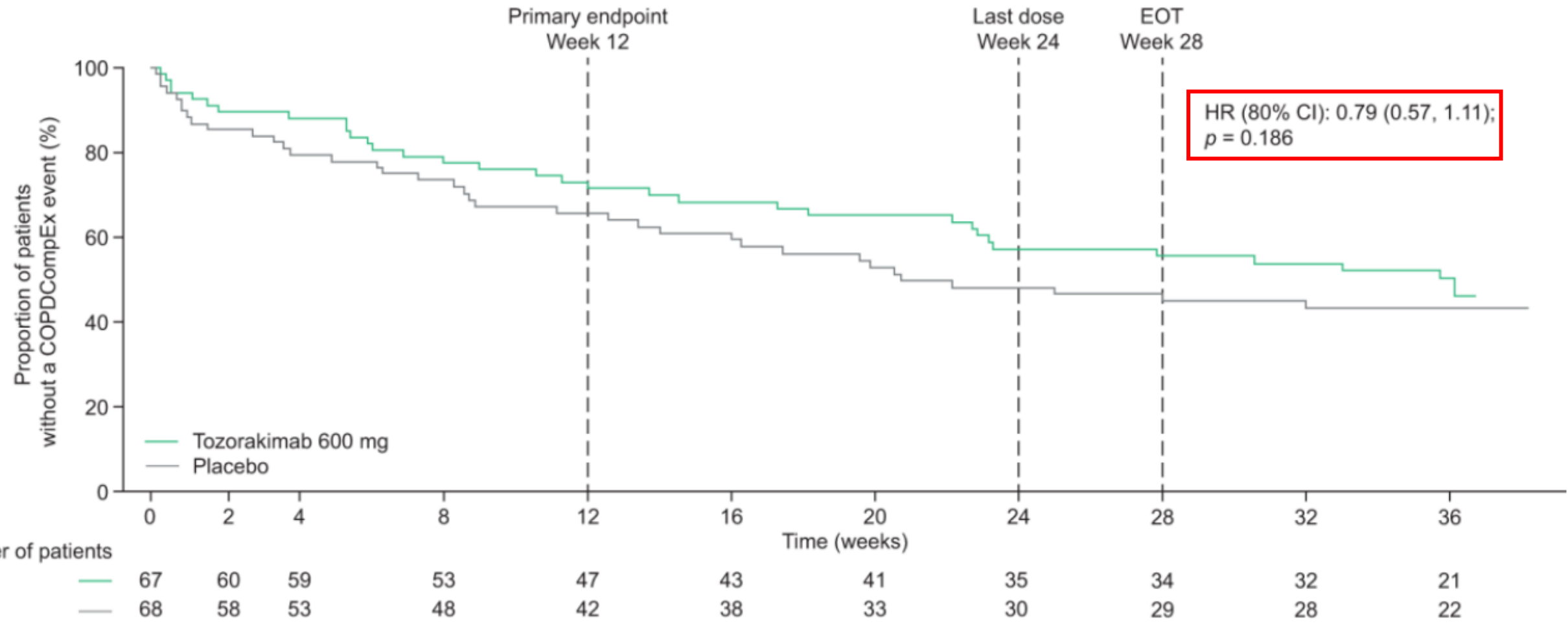
**FIGURE 2** Change in pre-BD FEV<sub>1</sub> in the ITT population.

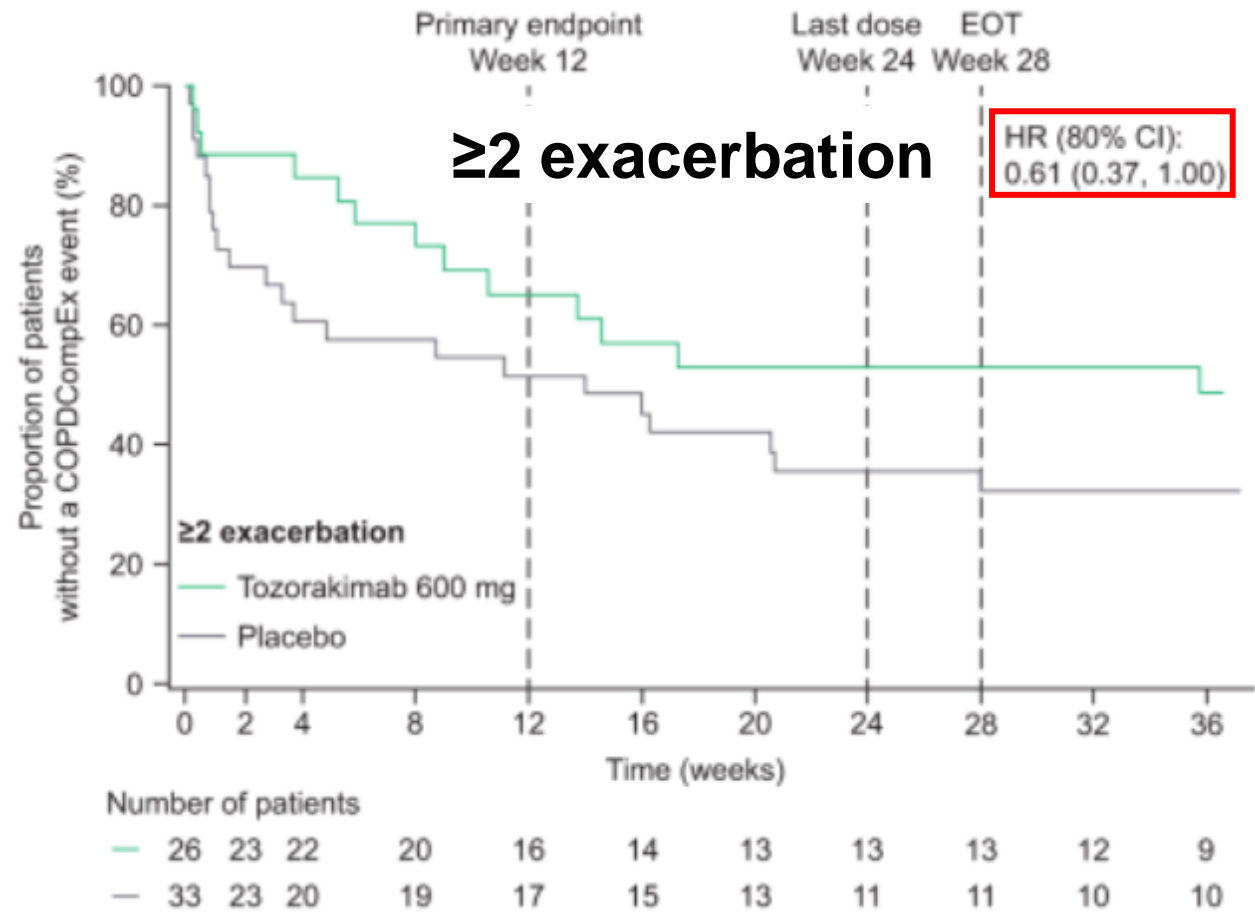
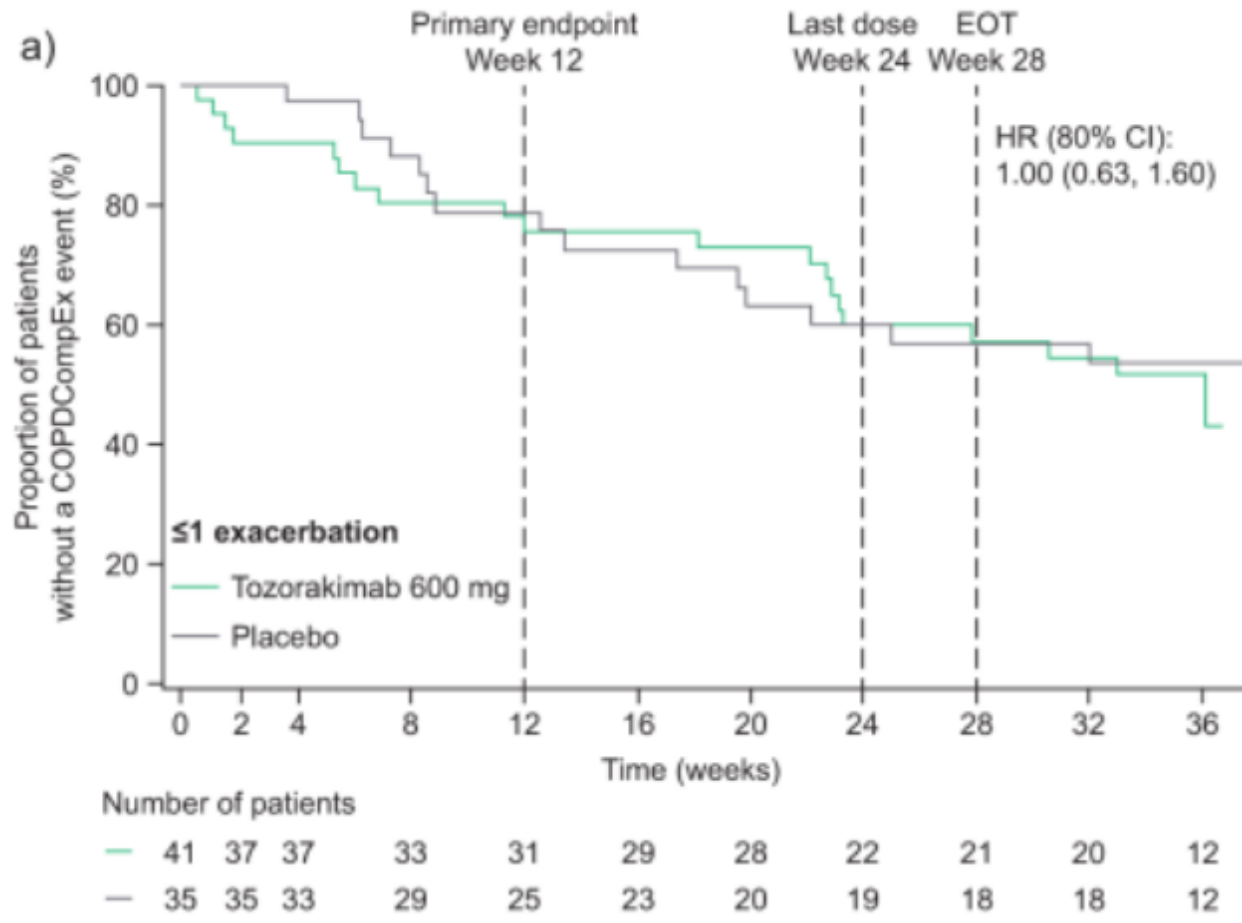


**SUPPLEMENTARY TABLE S1** Change in post-BD FEV<sub>1</sub> in the ITT population and in relevant subgroups

Subgroup	Treatment	Post-BD FEV <sub>1</sub>	
		LS mean change from baseline to week 28, mean (SE), mL	Difference vs placebo Mean (80% CI), mL <i>p</i> = 0.036
ITT population	Tozorakimab 600 mg (n=67)	21 (36)	70 (20, 120) <i>p</i> = 0.036
	Placebo (n=68)	-49 (33)	N/A
≥2 exacerbations in last 12 months	Tozorakimab 600mg (n=26)	54 (50)	121 (44, 198)
	Placebo (n=33)	-67 (44)	NA
≥2 moderate and/or ≥1 severe exacerbation in the 12 months before study enrolment	Tozorakimab 600 mg (n=29)	3 (60)	98 (25, 171)
	Placebo (n=36)	-95 (56)	N/A

**FIGURE 3** Kaplan–Meier plots of time-to-first COPDCompEx event in the ITT population.





# Summary

## Risk factor

Low smoking exposure

Smoker without COPD

Young adults with pre-COPD

## Assessment and Diagnosis

Exacerbation history prior to diagnosis of COPD

FEV<sub>1</sub>/FVC

# Biologics in COPD

2017	2019	2021	2021	2023	2024	2025
<b>Mepolizumab</b> <b>-IL-5</b> -METREX -METREO  <b>AE: X</b> <b>Subgroup</b> -bEOS	<b>Benalizumab</b> <b>-IL-5R</b> -GALATHEA -TERRANOVA  <b>AE: X</b> <b>Subgroup</b> -bEOS/≥3 AE -at Severe AE	<b>Itepekimab</b> <b>-IL-33</b>  <b>AE: X</b> <b>Subgroup</b> -Former	<b>Astegolimab</b> <b>-ST2(IL-33R)</b>  <b>AE: X</b> <b>Subgroup</b> -low bEOS	<b>Dupilumab</b> <b>-IL 4/13R</b> <b>-BOREAS</b> <b>-NOTUS</b>  <b>AE: O</b> <b>Subgroup</b> -high FeNO	<b>Tezepelumab</b> <b>-TSLP</b>  <b>AE: X</b> <b>Subgroup</b> -40-65 yrs -High FeNO	<b>Tozorakimab</b> <b>-IL-33</b>  <b>Pre-BD FEV1: X</b> <b>Subgroup</b> - ≥2 AE