호흡기내과의사를 위한 Respiratory Review of 2017 - COPD

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[Original Research **Asthma**]

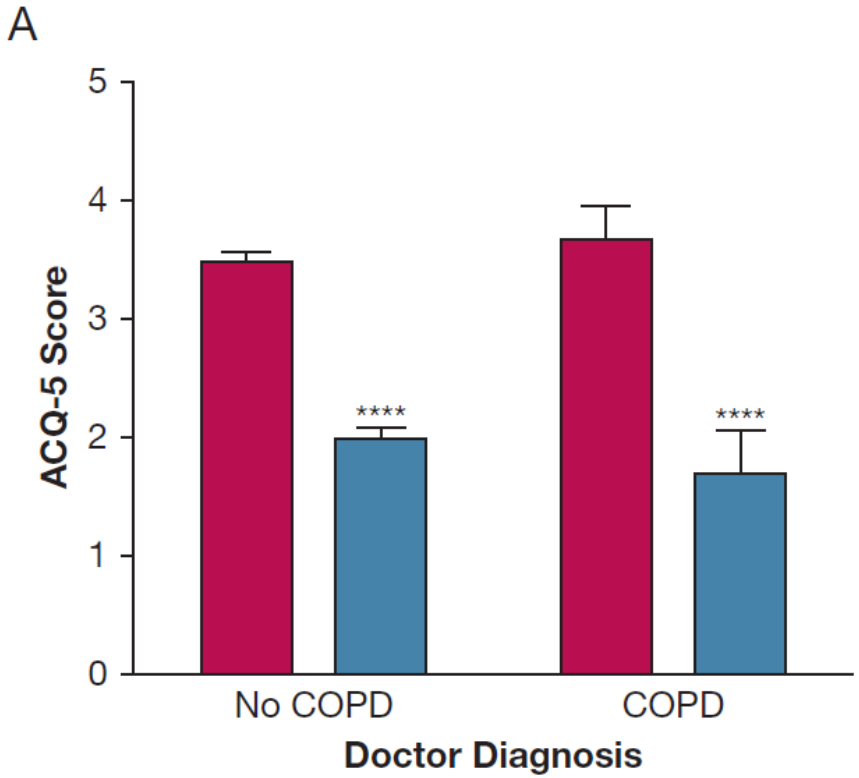
CHEST

Omalizumab Treatment Response in a Population With Severe Allergic Asthma and Overlapping COPD

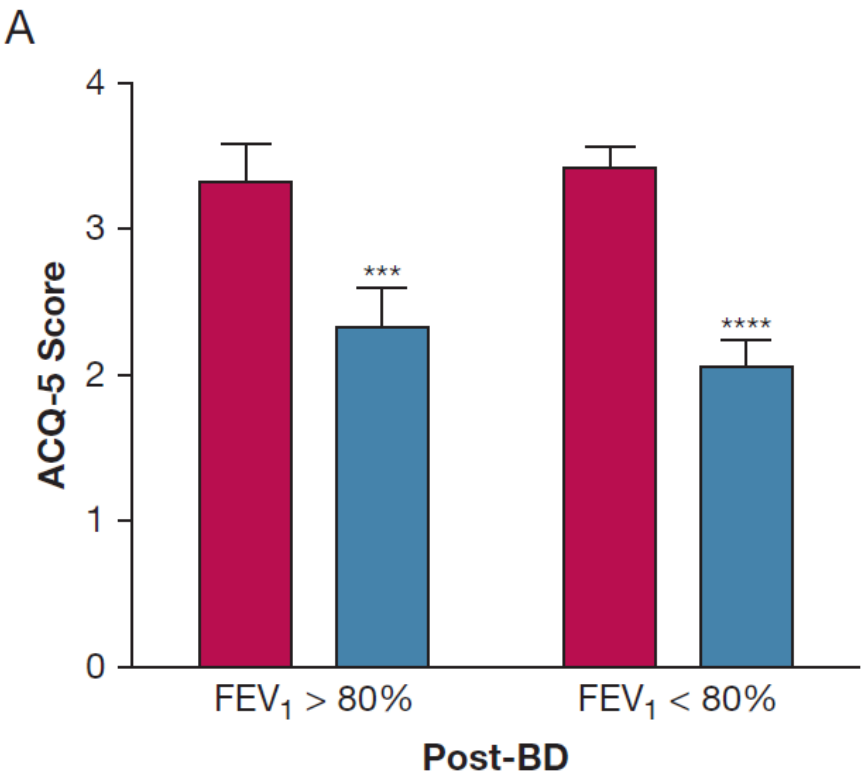
Steven Maltby, PhD; Peter G. Gibson, MBBS; Heather Powell, MMedSc; and Vanessa M. McDonald, PhD, B Nurs, RN

- Data from the Australian Xolair Registry
- Compare Tx responses in ACO with severe asthma only
- Assessed at baseline & after 6m Tx

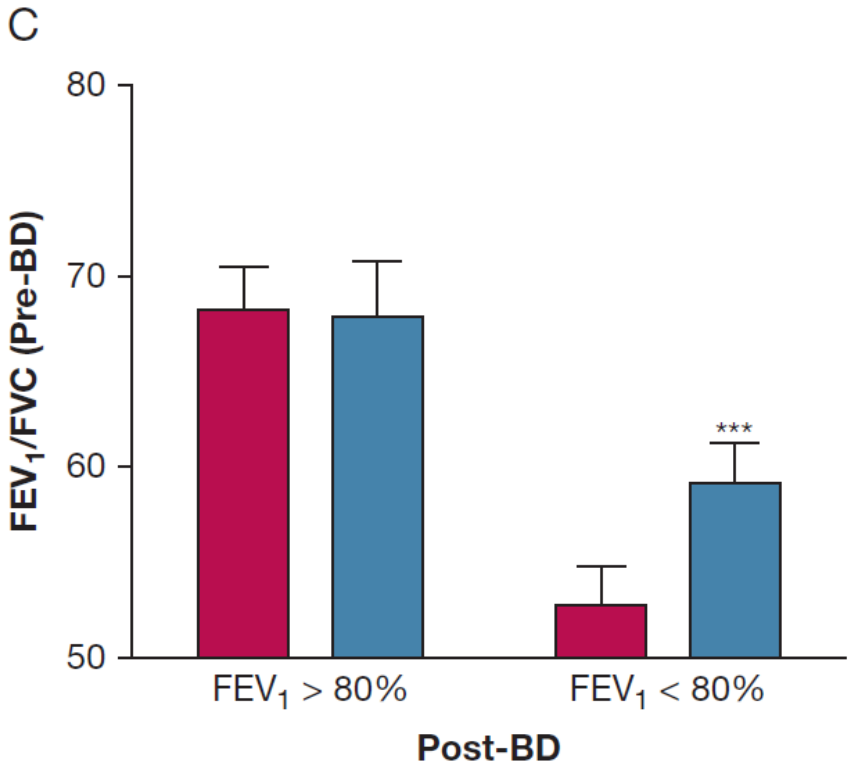
Chest. 2017;151(1):78-89.



Chest. 2017;151(1):78-89.

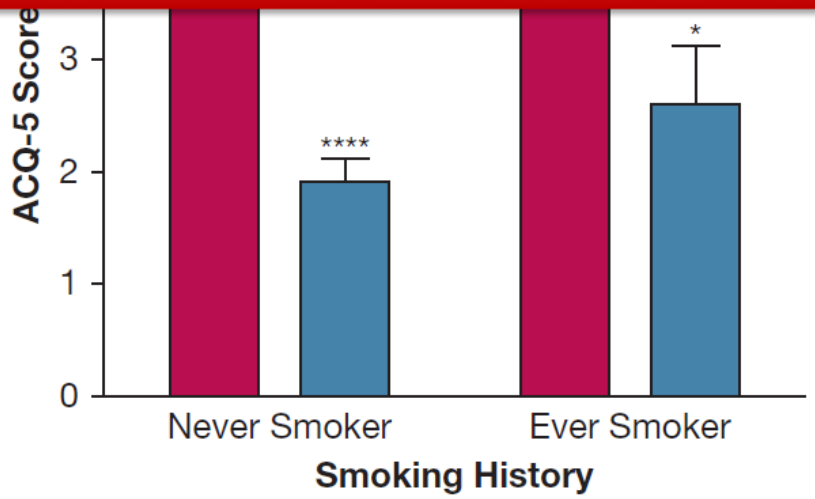


Chest. 2017;151(1):78-89.



Chest. 2017;151(1):78-89.

- **Conclusion**
- Omalizumab improves asthma control and QOL in ACO.



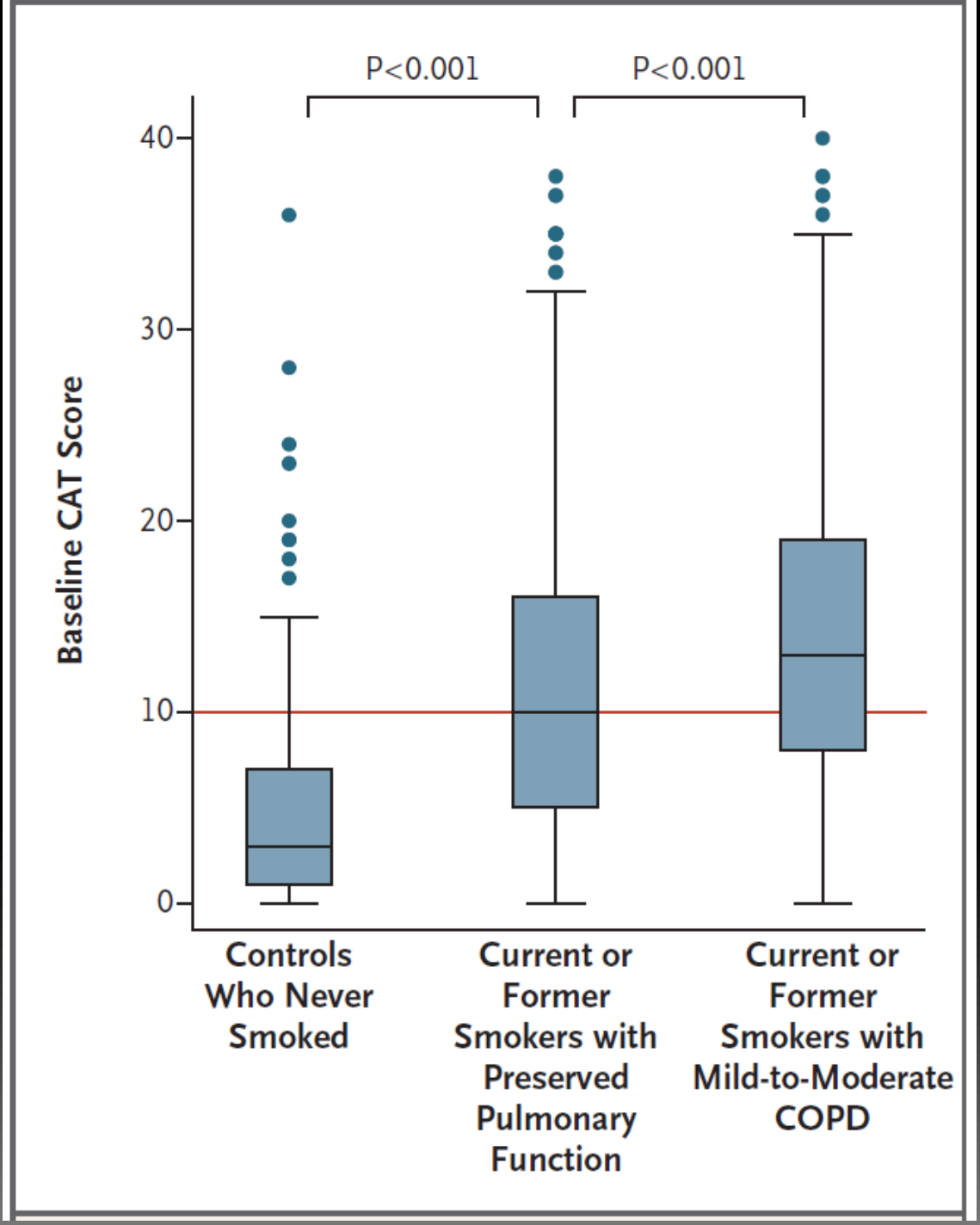
Chest. 2017;151(1):78-89.

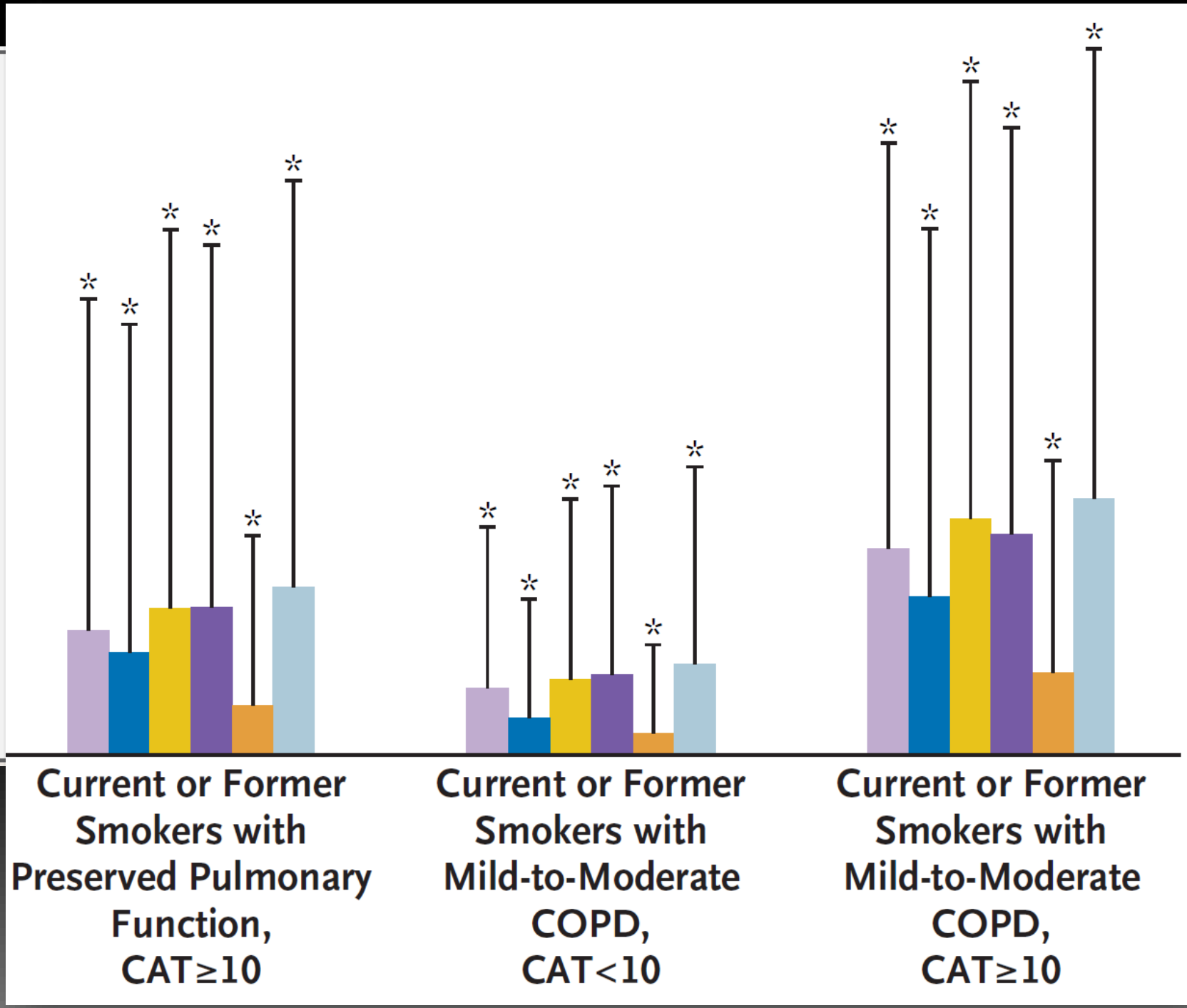
Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function

Prescott G. Woodruff, M.D., R. Graham Barr, M.D., Dr.P.H., Eugene Bleecker, M.D., Stephanie A. Christenson, M.D., David Couper, Ph.D., Jeffrey L. Curtis, M.D., Natalia A. Gouskova, Ph.D., Nadia N. Hansel, M.D., Eric A. Hoffman, Ph.D., Richard E. Kanner, M.D., Eric Kleerup, M.D., Stephen C. Lazarus, M.D., Fernando J. Martinez, M.D., Robert Paine, III, M.D., Stephen Rennard, M.D., Donald P. Tashkin, M.D., and MeiLan K. Han, M.D., for the SPIROMICS Research Group*

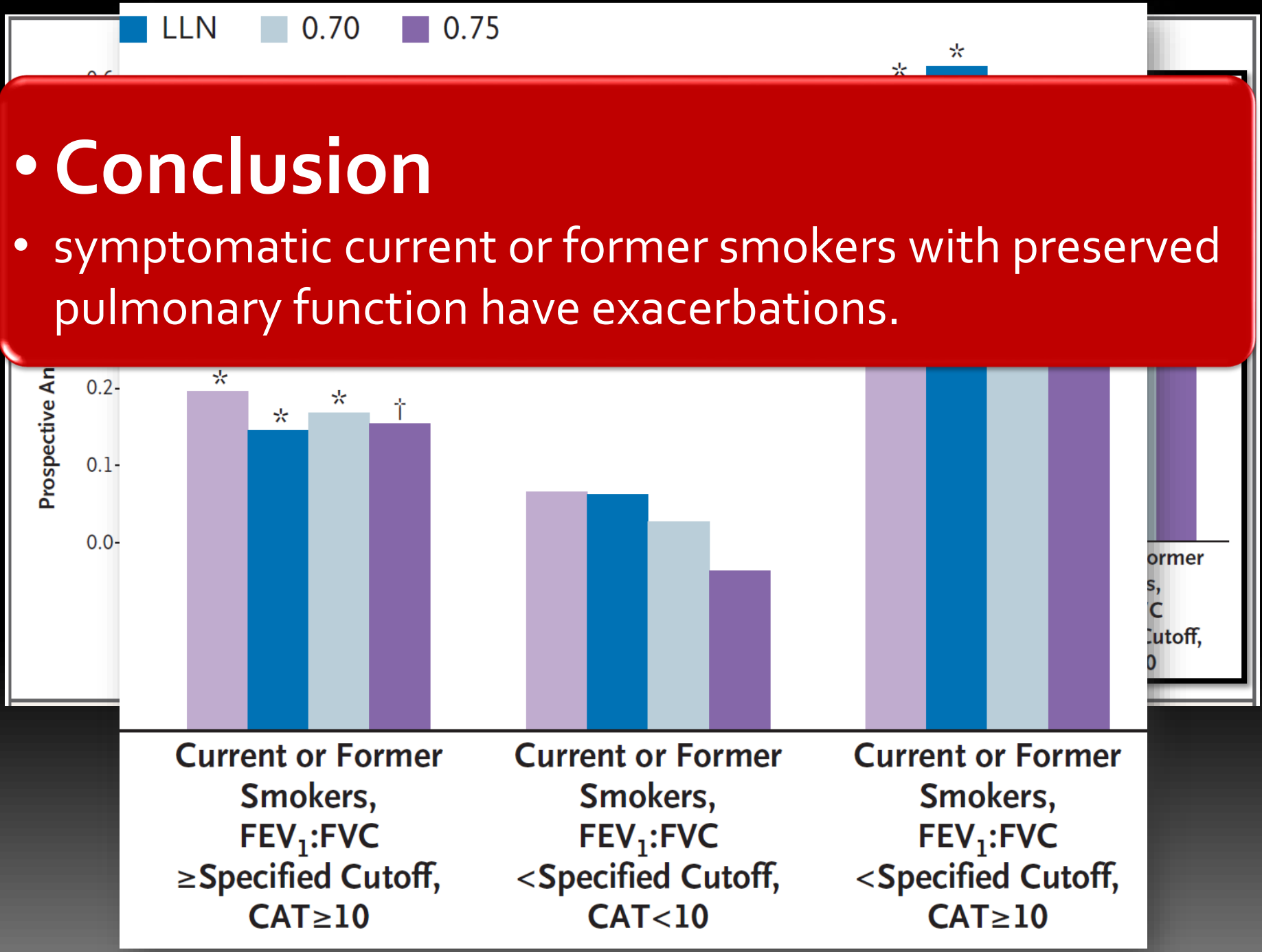
- SPIROMICS cohort
- Current or former smokers
- Preserved pulmonary function
- FEV1/FVC ≥ 0.7
- FVC above the LLN

N Engl J Med. 2016;374(19):1811-1821.


P<0.001
P<0.001
40
30
20
10
0
Baseline CAT Score
Controls Who Never Smoked
Current or Former Smokers with Preserved Pulmonary Function
Current or Former Smokers with Mild-to-Moderate COPD


Prospective Annualized Exacerbation Rate
Current or Former Smokers with Preserved Pulmonary Function, CAT≥10
Current or Former Smokers with Mild-to-Moderate COPD, CAT<10
Current or Former Smokers with Mild-to-Moderate COPD, CAT≥10

- **Conclusion**
- symptomatic current or former smokers with preserved pulmonary function have exacerbations.

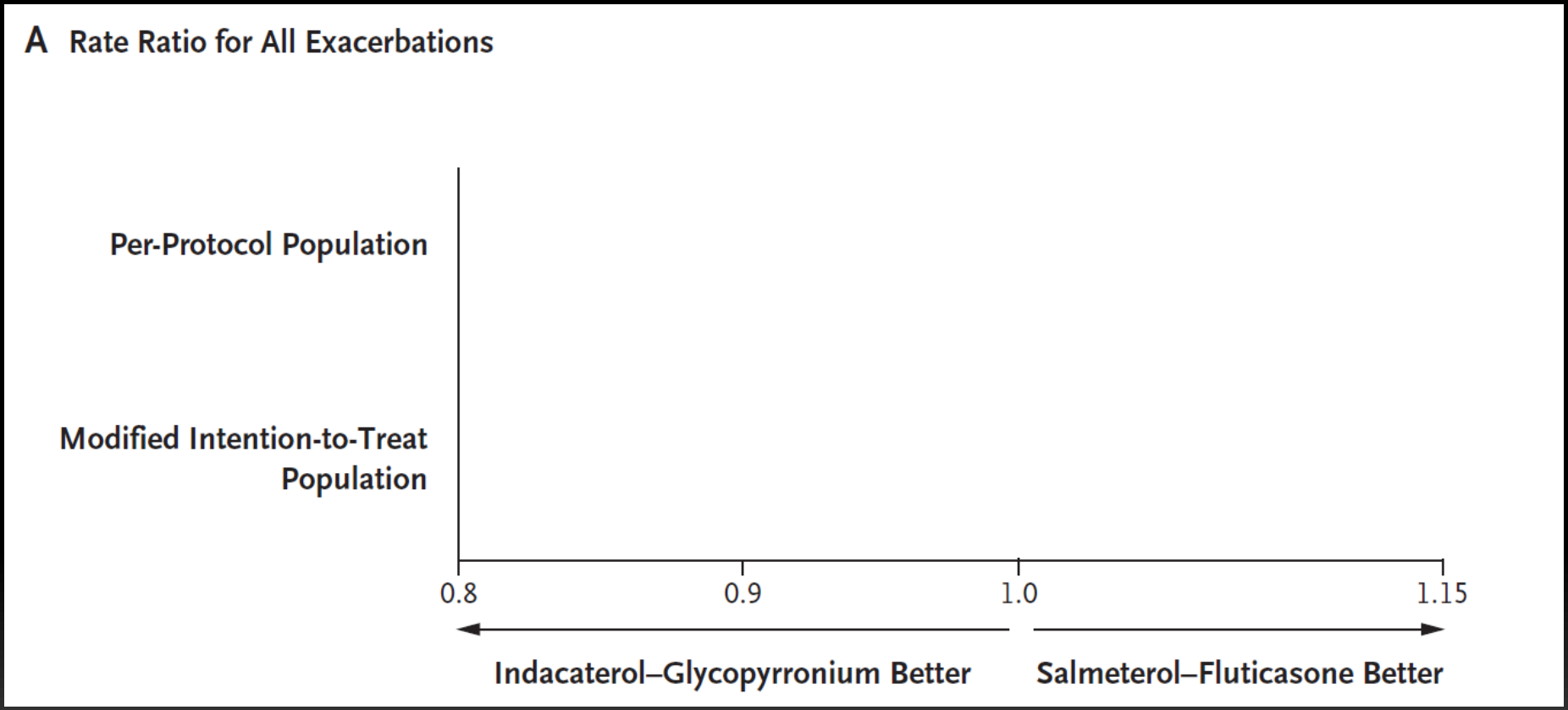


Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

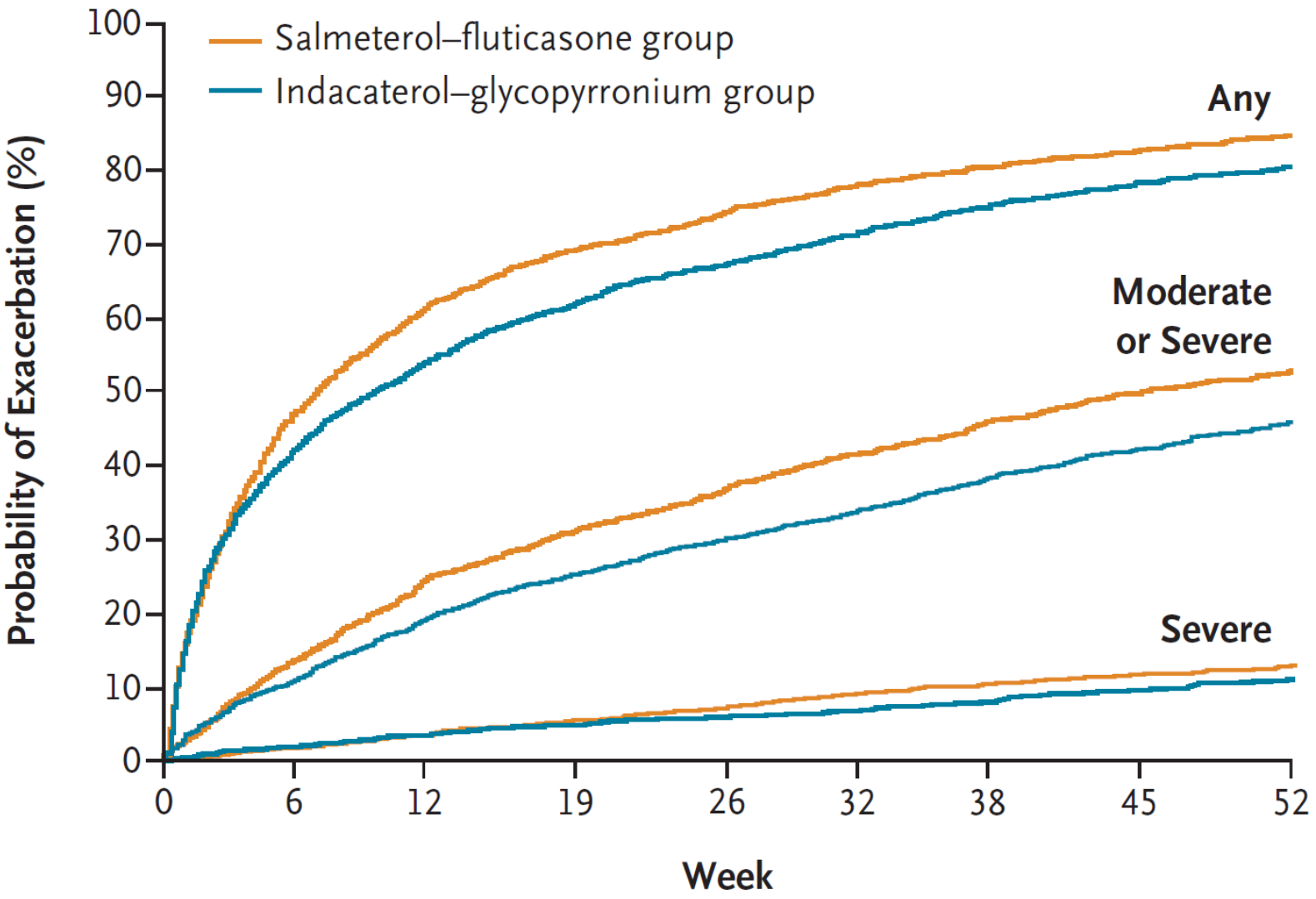
Jadwiga A. Wedzicha, M.D., Donald Banerji, M.D., Kenneth R. Chapman, M.D., Jørgen Vestbo, M.D., D.M.Sc., Nicolas Roche, M.D., R. Timothy Ayers, M.Sc., Chau Thach, Ph.D., Robert Fogel, M.D., Francesco Patalano, M.D., and Claus F. Vogelmeier, M.D., for the FLAME Investigators*

- 52 weeks
- mMRC ≥ 2
- FEV1 25% ~ 60%
- At least one exacerbation/yr

N Engl J Med. 2016;374(23):2222-2234.


A Rate Ratio for All Exacerbations
Per-Protocol Population
Modified Intention-to-Treat Population
0.8
0.9
1.0
1.15
Indacaterol–Glycopyrronium Better
Salmeterol–Fluticasone Better

B Time to First Exacerbation



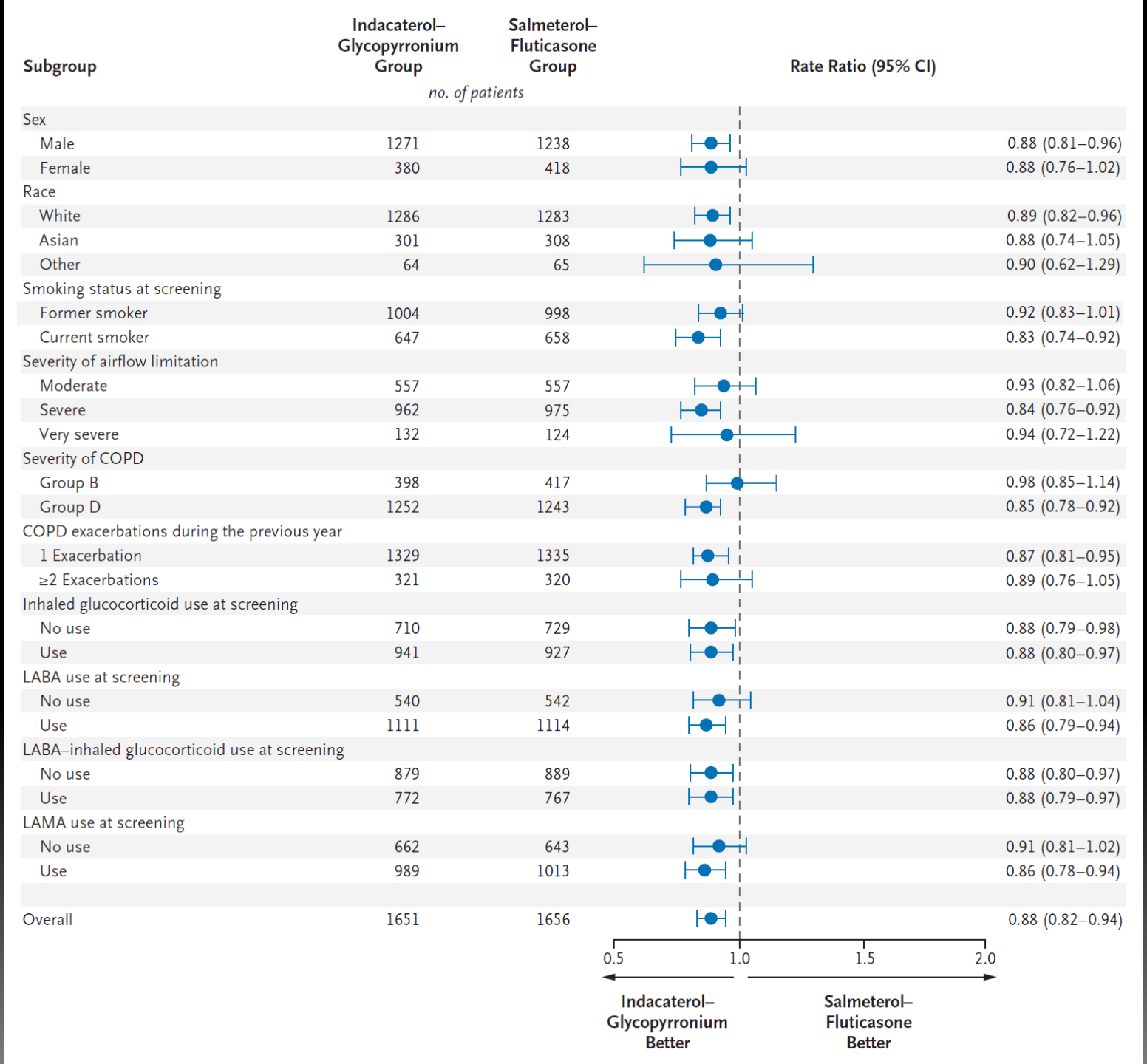

Subgroup
Indacaterol–Glycopyrronium Group
Salmeterol–Fluticasone Group
Rate Ratio (95% CI)
no. of patients
Sex
Male 1271 1238 0.88 (0.81–0.96)
Female 380 418 0.88 (0.76–1.02)
Race
White 1286 1283 0.89 (0.82–0.96)
Asian 301 308 0.88 (0.74–1.05)
Other 64 65 0.90 (0.62–1.29)
Smoking status at screening
Former smoker 1004 998 0.92 (0.83–1.01)
Current smoker 647 658 0.83 (0.74–0.92)
Severity of airflow limitation
Moderate 557 557 0.93 (0.82–1.06)
Severe 962 975 0.84 (0.76–0.92)
Very severe 132 124 0.94 (0.72–1.22)
Severity of COPD
Group B 398 417 0.98 (0.85–1.14)
Group D 1252 1243 0.85 (0.78–0.92)
COPD exacerbations during the previous year
1 Exacerbation 1329 1335 0.87 (0.81–0.95)
≥2 Exacerbations 321 320 0.89 (0.76–1.05)
Inhaled glucocorticoid use at screening
No use 710 729 0.88 (0.79–0.98)
Use 941 927 0.88 (0.80–0.97)
LABA use at screening
No use 540 542 0.91 (0.81–1.04)
Use 1111 1114 0.86 (0.79–0.94)
LABA–inhaled glucocorticoid use at screening
No use 879 889 0.88 (0.80–0.97)
Use 772 767 0.88 (0.79–0.97)
LAMA use at screening
No use 662 643 0.91 (0.81–1.02)
Use 989 1013 0.86 (0.78–0.94)
Overall 1651 1656 0.88 (0.82–0.94)
0.5
1.0
1.5
2.0
Indacaterol–Glycopyrronium Better
Salmeterol–Fluticasone Better

Table 2. Adverse Events and Serious Adverse Events.*

	Indacaterol	Salmeterol
Bacterial upper respiratory tract infection	125 (7.4)	168 (10.0)
Lower respiratory tract infection	82 (4.9)	98 (5.8)
Upper respiratory tract infection‡	81 (4.8)	83 (4.9)
Pneumonia	53 (3.2)	80 (4.8)
Cough	50 (3.0)	51 (3.0)
Dyspnea	49 (2.9)	51 (3.0)
Influenza	35 (2.1)	56 (3.3)
Oral candidiasis	20 (1.2)	71 (4.2)
Serious adverse event§	308 (18.4)	334 (19.9)
Death	24 (1.4)	24 (1.4)
Patients who discontinued because of adverse event	126 (7.5)	143 (8.5)
Patients who discontinued because of serious adverse event	85 (5.1)	87 (5.2)
Patients who discontinued because of nonserious adverse event	49 (2.9)	70 (4.2)

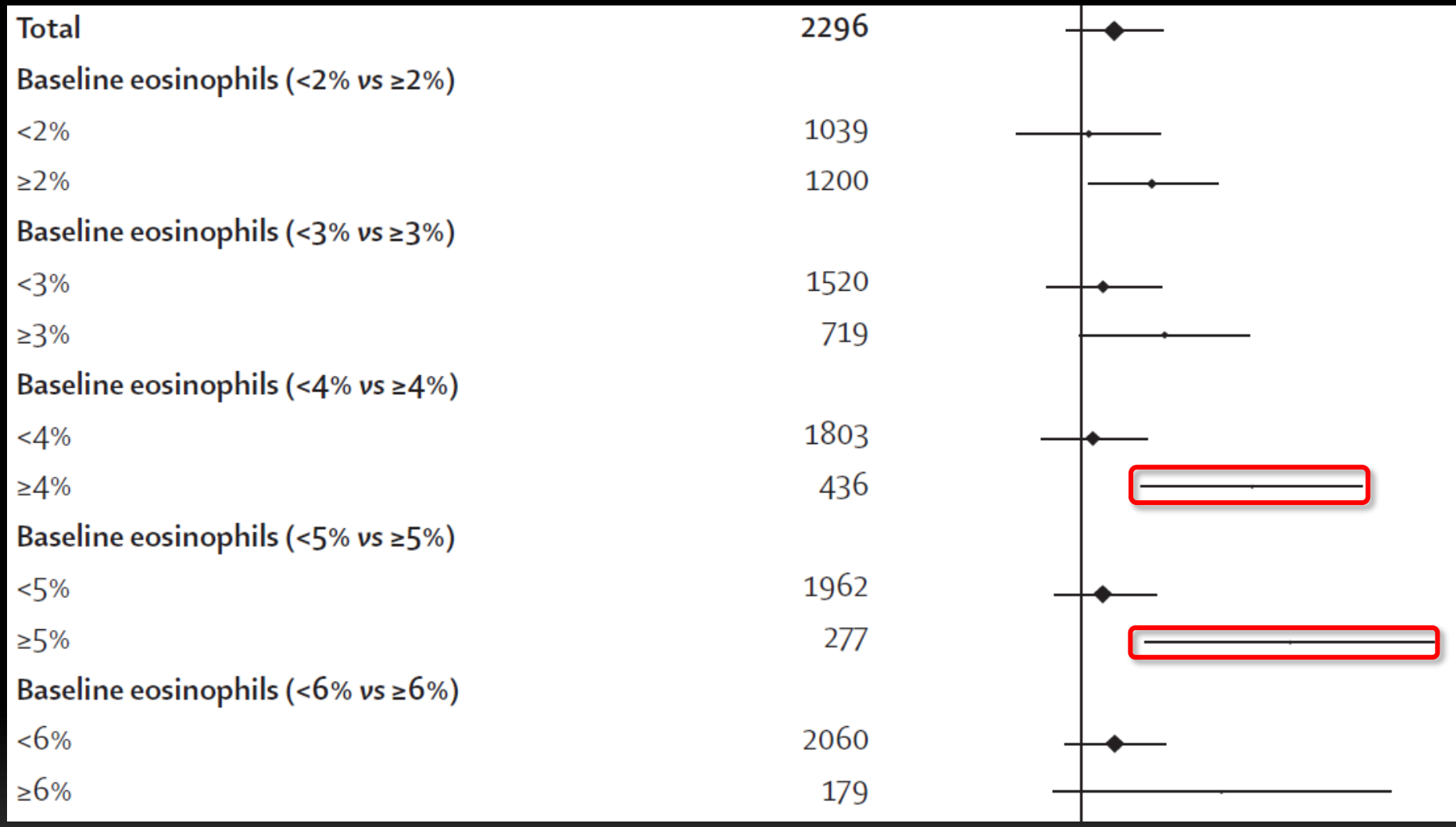
- **Conclusion**
- Indacaterol–glycopyrronium was more effective than salmeterol–fluticasone in preventing COPD exacerbations

Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial

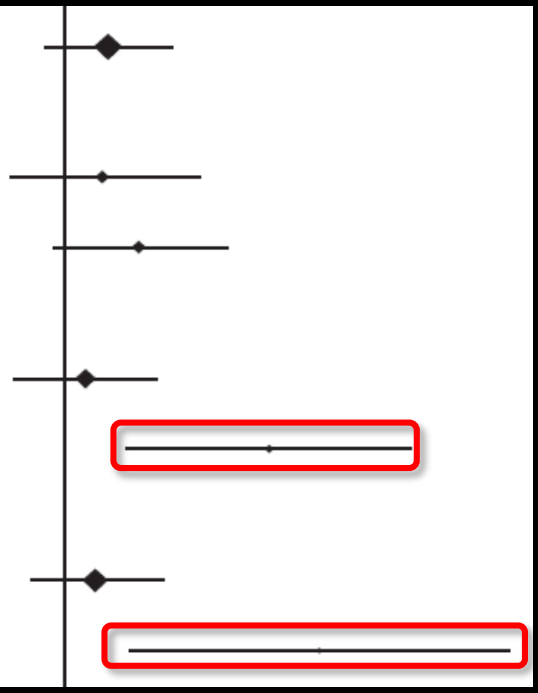
Henrik Watz, Kay Tetzlaff, Emiel F M Wouters, Anne Kirsten, Helgo Magnussen, Roberto Rodriguez-Roisin, Claus Vogelmeier, Leonardo M Fabbri, Pascal Chanez, Ronald Dahl, Bernd Disse, Helen Finnigan, Peter M A Calverley

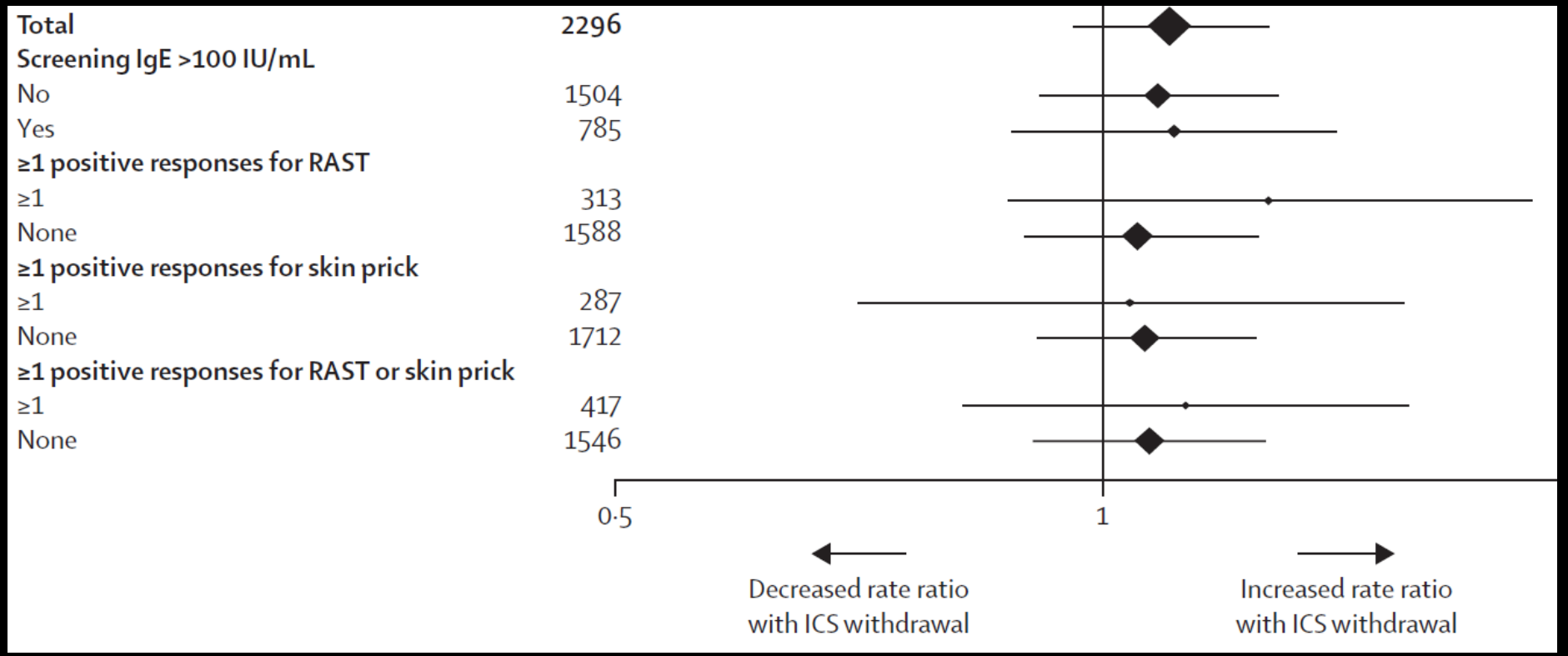
- Post-hoc analysis of WISDOM study
- Compare rate of exacerbations and time to exacerbation outcomes
- On the basis of blood eosinophil subgroups

Lancet Respir Med. 2016;4(5):390-398.


Total
2296
Baseline eosinophils (<2% vs ≥2%)
<2%
1039
≥2%
1200
Baseline eosinophils (<3% vs ≥3%)
<3%
1520
≥3%
719
Baseline eosinophils (<4% vs ≥4%)
<4%
1803
≥4%
436
Baseline eosinophils (<5% vs ≥5%)
<5%
1962
≥5%
277
Baseline eosinophils (<6% vs ≥6%)
<6%
2060
≥6%
179

Total	2296
Baseline eosinophils (<150 cells per µL *vs* ≥150 cells per µL)	
<150 cells per µL	1067
≥150 cells per µL	1172
Baseline eosinophils (<300 cells per µL *vs* ≥300 cells per µL)	
<300 cells per µL	1791
≥300 cells per µL	448
Baseline eosinophils (<400 cells per µL *vs* ≥400 cells per µL)	
<400 cells per µL	1992
≥400 cells per µL	247




Total
2296
Screening IgE >100 IU/mL
No
1504
Yes
785
≥1 positive responses for RAST
≥1
313
None
1588
≥1 positive responses for skin prick
≥1
287
None
1712
≥1 positive responses for RAST or skin prick
≥1
417
None
1546
0·5
1
Decreased rate ratio with ICS withdrawal
Increased rate ratio with ICS withdrawal

- **Conclusion**
- High blood eosinophil – risk for AE after withdrawal ICS

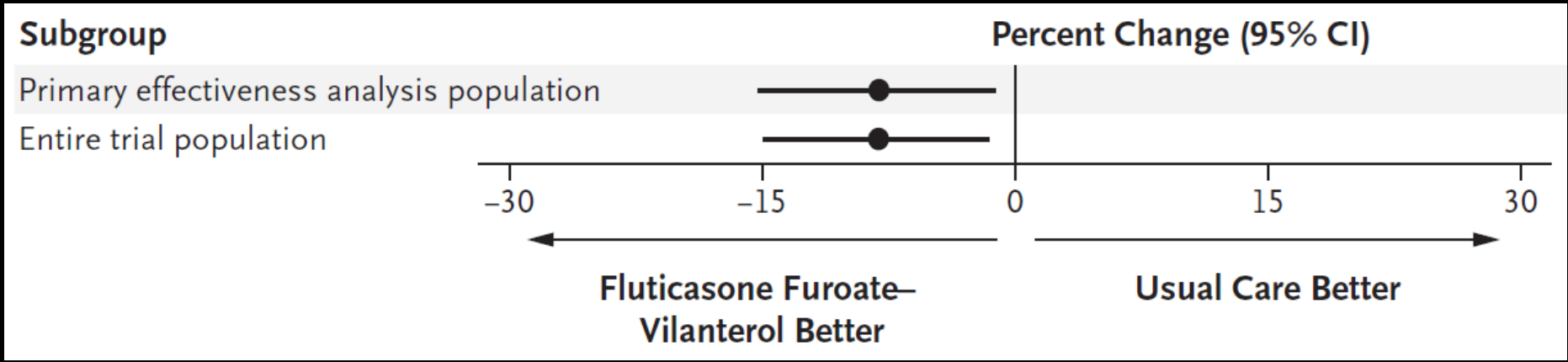
	n	Hazard ratio (95% CI)	p value
<4% eosinophils	1766	1·087 (0·938–1·259)	0·27
≥4% eosinophils	433	1·516 (1·099–2·091)	0·011
<5% eosinophils	1924	1·114 (0·967–1·283)	0·13
≥5% eosinophils	275	1·667 (1·085–2·561)	0·020
<6% eosinophils	2022	1·143 (0·995–1·314)	0·059
≥6% eosinophils	177	1·321 (0·806–2·165)	0·27
<150 cells per µL	1043	1·161 (0·955–1·411)	0·14
≥150 cells per µL	1156	1·144 (0·953–1·375)	0·15
<300 cells per µL	1754	1·079 (0·930–1·251)	0·31

Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice

Jørgen Vestbo, D.M.Sc., David Leather, M.B., Ch.B., Nawar Diar Bakerly, M.D., John New, M.B., B.S., J. Martin Gibson, Ph.D., Sheila McCorkindale, M.B., Ch.B., Susan Collier, M.B., Ch.B., Jodie Crawford, M.Sc., Lucy Frith, M.Sc., Catherine Harvey, D.Phil., Henrik Svedsater, Ph.D., and Ashley Woodcock, M.D., for the Salford Lung Study Investigators*

- Pragmatic RCT
- Fluticasone/Vilanterol vs usual care
- Documented diagnosis of COPD
- One or more COPD exacerbations in previous 3 years
- No restrictions regarding smoking history or spirometric values

N Engl J Med. 2016;375(13):1253-1260.


Subgroup
Percent Change (95% CI)
Primary effectiveness analysis population
Entire trial population
–30
–15
0
15
30
Fluticasone Furoate–Vilanterol Better
Usual Care Better

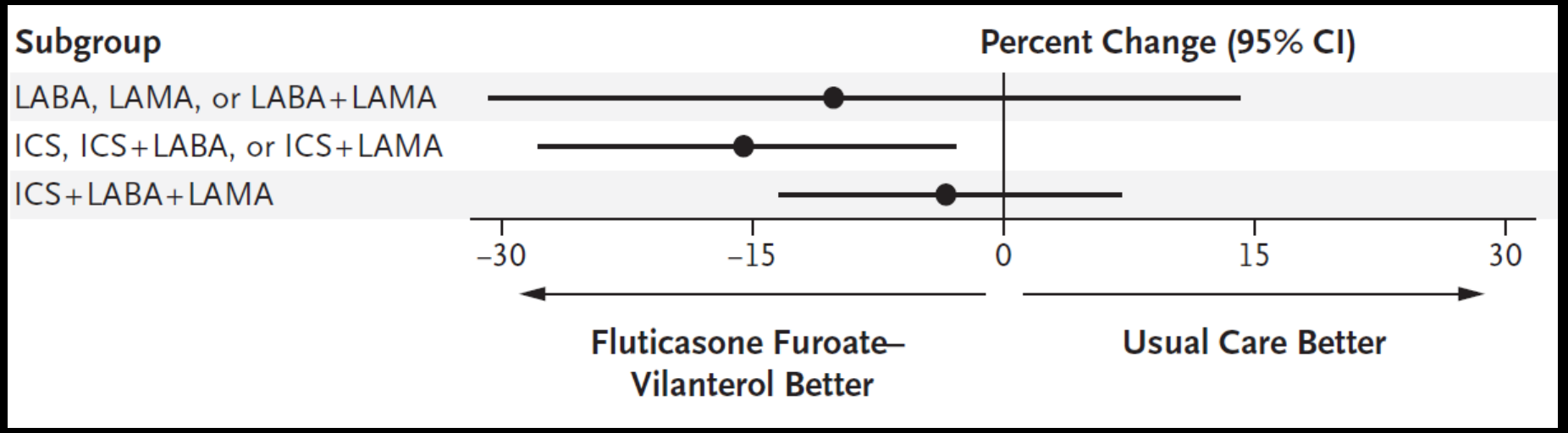

Subgroup
Percent Change (95% CI)
LABA, LAMA, or LABA+LAMA
ICS, ICS+LABA, or ICS+LAMA
ICS+LABA+LAMA
−30
−15
0
15
30
Fluticasone Furoate–Vilanterol Better
Usual Care Better

Table 2. Serious Adverse Events of Special Interest during Treatment

- **Conclusion**
- FF/VI is better than other ICSLABA in real world study

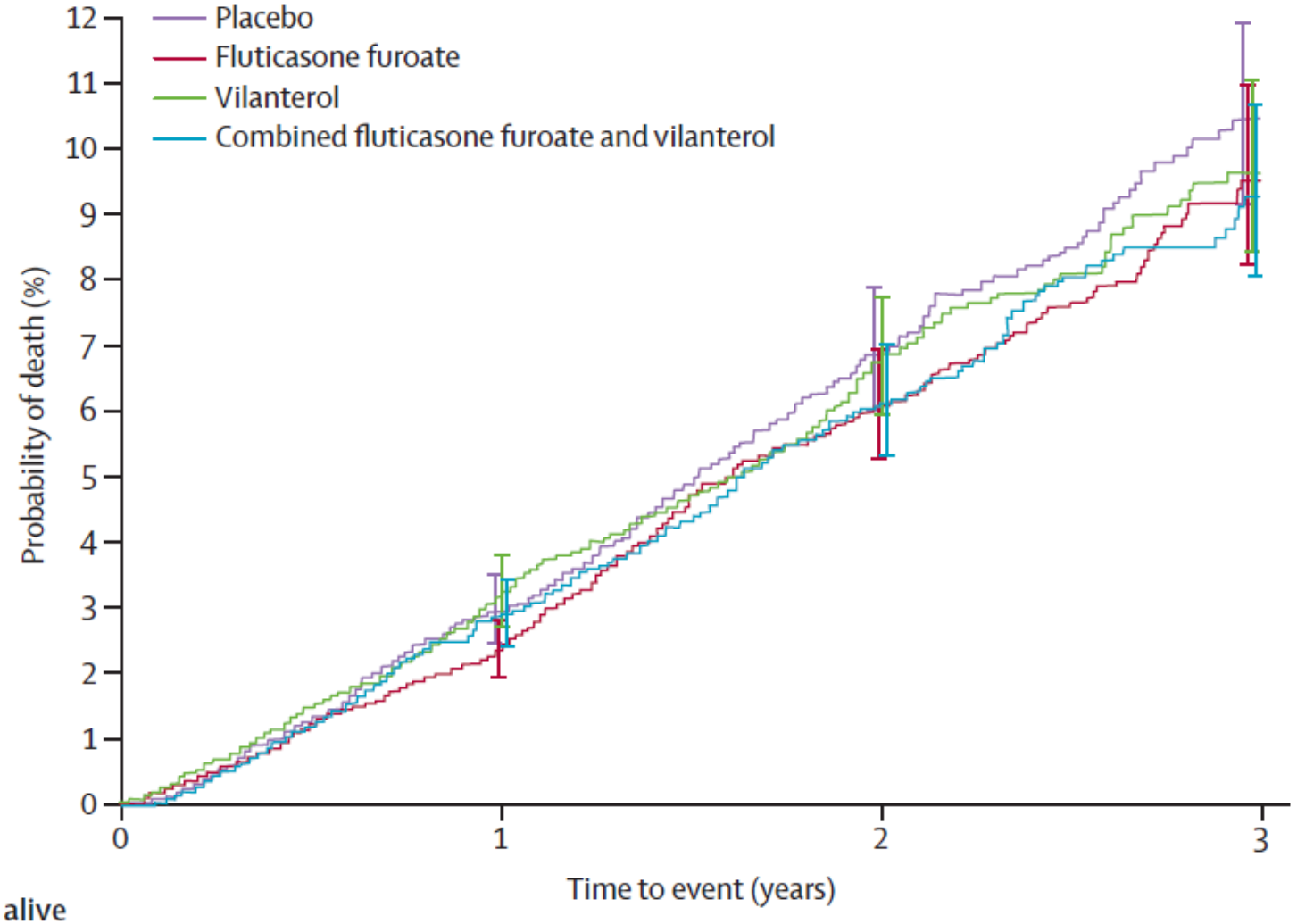
Any event	107 (8)	108 (8)
Cardiac arrhythmia	54 (4)	52 (4)
Cardiac failure	28 (2)	28 (2)
Cardiac ischemia	33 (2)	34 (2)
Hypertension	1 (<1)	0
Stroke	25 (2)	21 (2)
Pneumonia	83 (6)	94 (7)
Lower respiratory tract infection, excluding pneumonia	58 (4)	64 (5)

Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial

Jørgen Vestbo, Julie A Anderson, Robert D Brook, Peter M A Calverley, Bartolome R Celli, Courtney Crim, Fernando Martinez, Julie Yates, David E Newby, on behalf of the SUMMIT Investigators

- FEV1 50% ~ 70%
- Patients had to have a history, or be at increased risk, of cardiovascular disease

Lancet. 2016;387(10030):1817-1826.

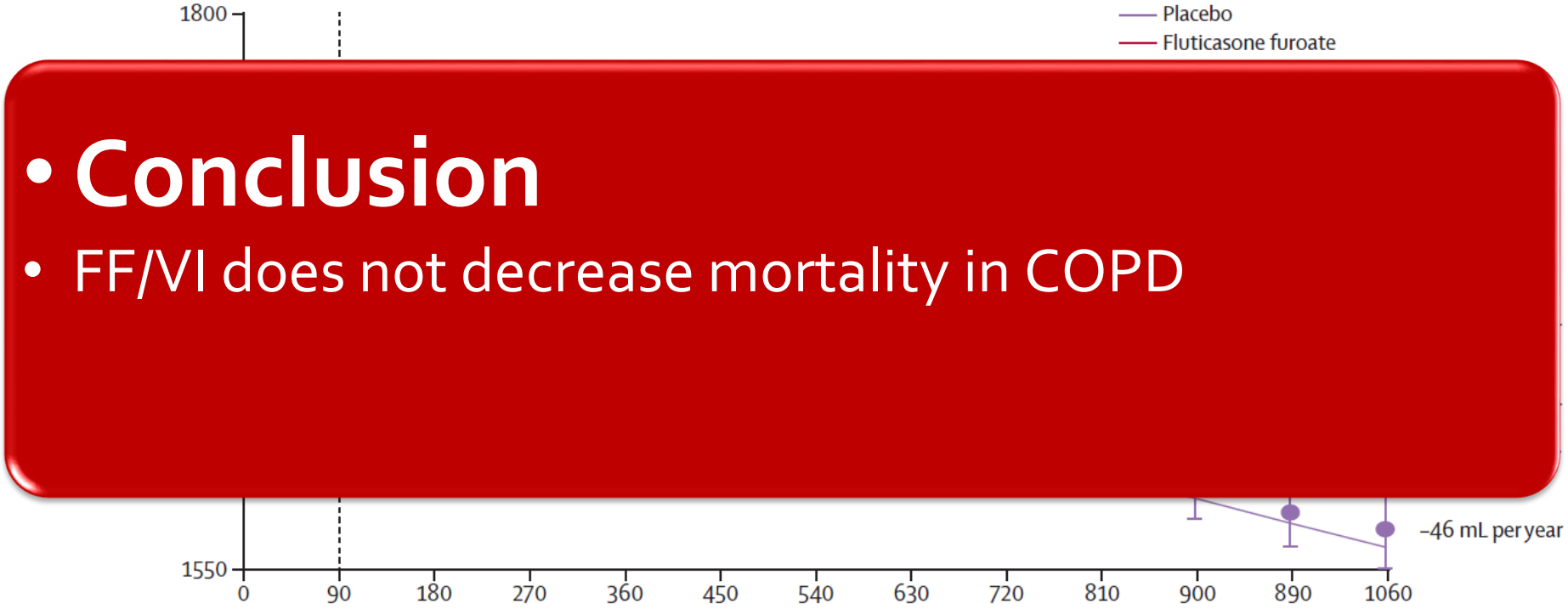


Number alive				
Placebo	4111	3465	1715	469
Fluticasone furoate	4135	3499	1734	490
Vilanterol	4118	3466	1734	486
Combined fluticasone furoate and vilanterol	4121	3484	1718	485

	Placebo (n=4111)	Fluticasone furoate (n=4135)	p value vs placebo	Vilanterol (n=4118)	p value vs placebo	Combination therapy (n=4121)	p value vs placebo
All-cause mortality	275 (6·7%)	251 (6·1%)	0·284*	265 (6·4%)	0·655*	246 (6·0%)	0·137
Cause-specific mortality							
Cardiovascular	122 (3·0%)	97 (2·3%)	..	118 (2·9%)	..	108 (2·6%)	..
Pulmonary	35 (0·9%)	34 (0·8%)	..	33 (0·8%)	..	35 (0·8%)	..
Cancer	62 (1·5%)	59 (1·4%)	..	61 (1·5%)	..	56 (1·4%)	..
Other	20 (0·5%)	21 (0·5%)	..	25 (0·6%)	..	22 (0·5%)	..
Unknown	36 (0·9%)	40 (1·0%)	..	28 (0·7%)	..	25 (0·6%)	..
Decline in post-bronchodilator FEV_1 (mL per year)	46 (2·5)	38 (2·4)	0·026*	47 (2·4)	0·654*	38 (2·4)	0·019*
First composite cardiovascular event	173 (4·2%)	161 (3·9%)	0·317*	180 (4·4%)	0·908*	174 (4·2%)	0·478*
Myocardial infarction	38 (0·9%)	45 (1·1%)	..	44 (1·1%)	..	46 (1·1%)	..
Unstable angina	26 (0·6%)	16 (0·4%)	..	22 (0·5%)	..	19 (0·5%)	..
Stroke	33 (0·8%)	33 (0·8%)	..	30 (0·7%)	..	31 (0·8%)	..
Transient ischaemic attack	8 (0·2%)	7 (0·2%)	..	12 (0·3%)	..	7 (0·2%)	..
Sudden death	62 (1·5%)	53 (1·3%)	..	62 (1·5%)	..	63 (1·5%)	..
Procedural death	1 (<0·1%)	1 (<0·1%)	..	0	..	0	..
Other cardiovascular death	5 (0·1%)	6 (0·1%)	..	10 (0·2%)	..	8 (0·2%)	..
Annual rate of moderate and severe exacerbations	0·35	0·31	0·004*	0·31	0·017*	0·25	<0·0001*
Annual rate of severe exacerbations	0·07	0·06	0·023*	0·06	0·013*	0·05	0·0004*

Data are n (%) or mean (SE). FEV_1=forced expiratory volume in 1 sec *All p values are versus placebo and are nominal for descriptive purposes only.

Table 3: Primary and secondary outcomes and exacerbations of chronic obstructive pulmonary disease



Number at visit													
Placebo	3800	3782	3563	3396	3279	2678	2197	1858	1498	1171	949	736	486
Fluticasone furoate	3879	3858	3688	3580	3452	2777	2311	1936	1569	1246	1001	792	528
Vilanterol	3866	3830	3658	3554	3438	2813	2347	1971	1612	1300	1043	831	542
Combined fluticasone furoate and vilanterol	3912	3883	3731	3610	3505	2864	2391	1997	1633	1290	1035	827	545

- **Conclusion**
- FF/VI does not decrease mortality in COPD

ORIGINAL ARTICLE

Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease

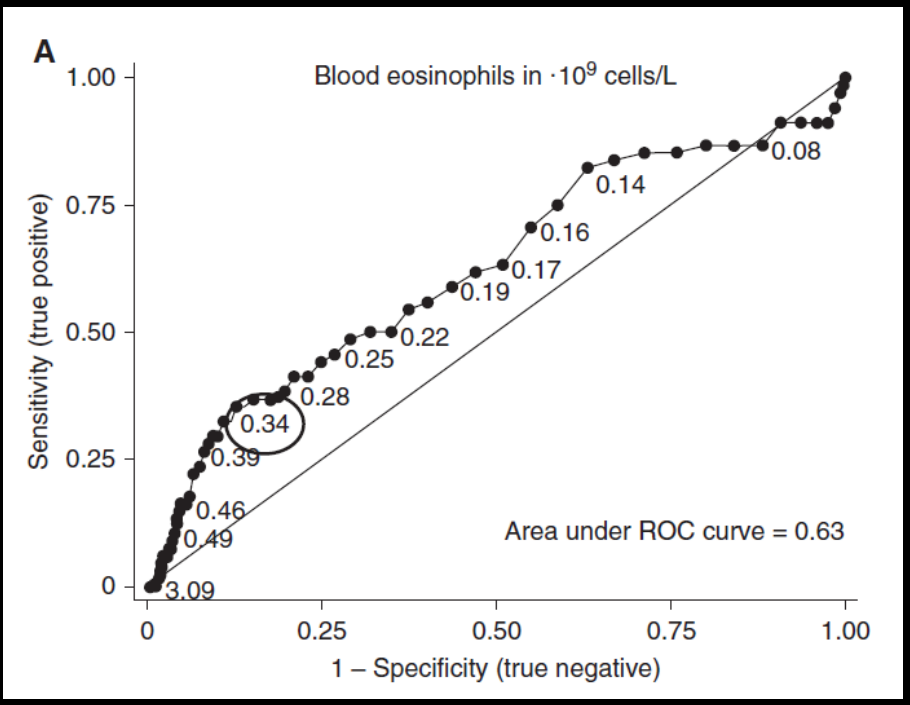
The Copenhagen General Population Study

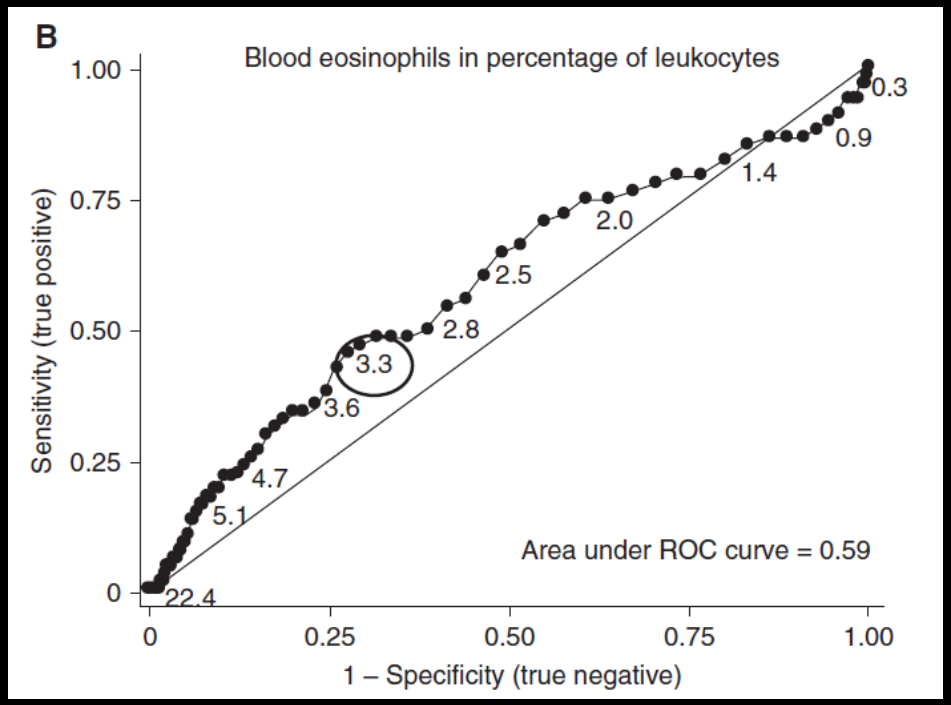
Signe Vedel-Krogh[1,2,3], Sune F. Nielsen[1,2,3], Peter Lange[3,4,5], Jørgen Vestbo[6], and Børge G. Nordestgaard[1,2,3]

- Copenhagen General Population Study
- 7,225 with COPD based on spirometry
- Recorded blood eosinophils at baseline and future COPD exacerbations longitudinally

Am J Respir Crit Care Med. 2016;193(9):965-974.

Am J Respir Crit Care Med. 2016;193(9):965-974.


A
Blood eosinophils in ·10^9 cells/L
Sensitivity (true positive)
1 – Specificity (true negative)
Area under ROC curve = 0.63
1.00
0.75
0.50
0.25
0
0
0.25
0.50
0.75
1.00
3.09
0.46
0.49
0.39
0.34
0.28
0.25
0.22
0.19
0.17
0.16
0.14
0.08

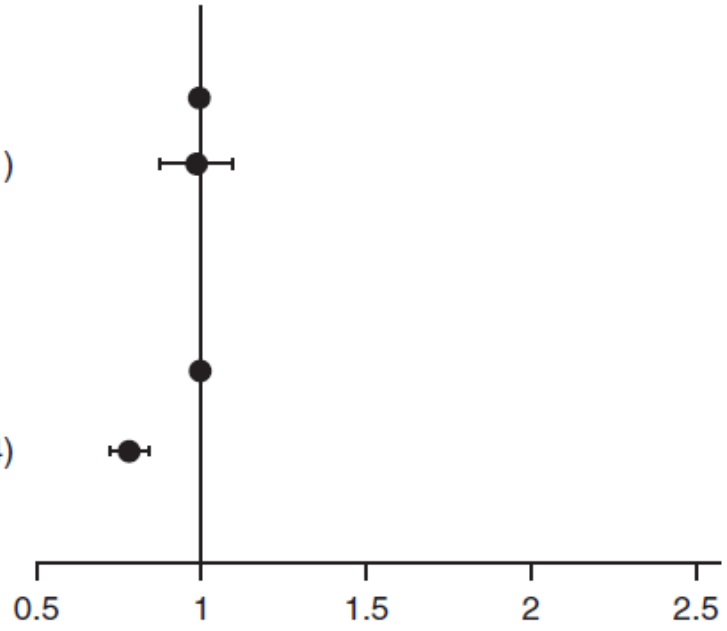

B
Blood eosinophils in percentage of leukocytes
Sensitivity (true positive)
1 – Specificity (true negative)
Area under ROC curve = 0.59
1.00
0.75
0.50
0.25
0
0
0.25
0.50
0.75
1.00
22.4
5.1
4.7
3.6
3.3
2.8
2.5
2.0
1.4
0.9
0.3

Clinical COPD Blood eosinophils	N/Events	Person years of follow-up	IRR (95% CI)

Am J Respir Crit Care Med. 2016;193(9):965-974.

COPD

Blood eosinophils	N/Events	Person years of follow-up	IRR (95% CI)
Severe exacerbations			
< 2% (ref.)	2,618/511	9,529	1.00
≥ 2%	4,607/928	16,816	0.99 (0.88–1.11)
Moderate exacerbations			
< 2%	2,618/1,207	9,529	1.00
≥ 2%	4,607/1,657	16,816	0.78 (0.72–0.84)



Am J Respir Crit Care Med. 2016;193(9):965-974.

Clinical COPD Risk of severe exacerbations	N/Events	Person years of follow-up	IRR (95% CI)

- **Conclusion**
- High blood E is risk factor for AE

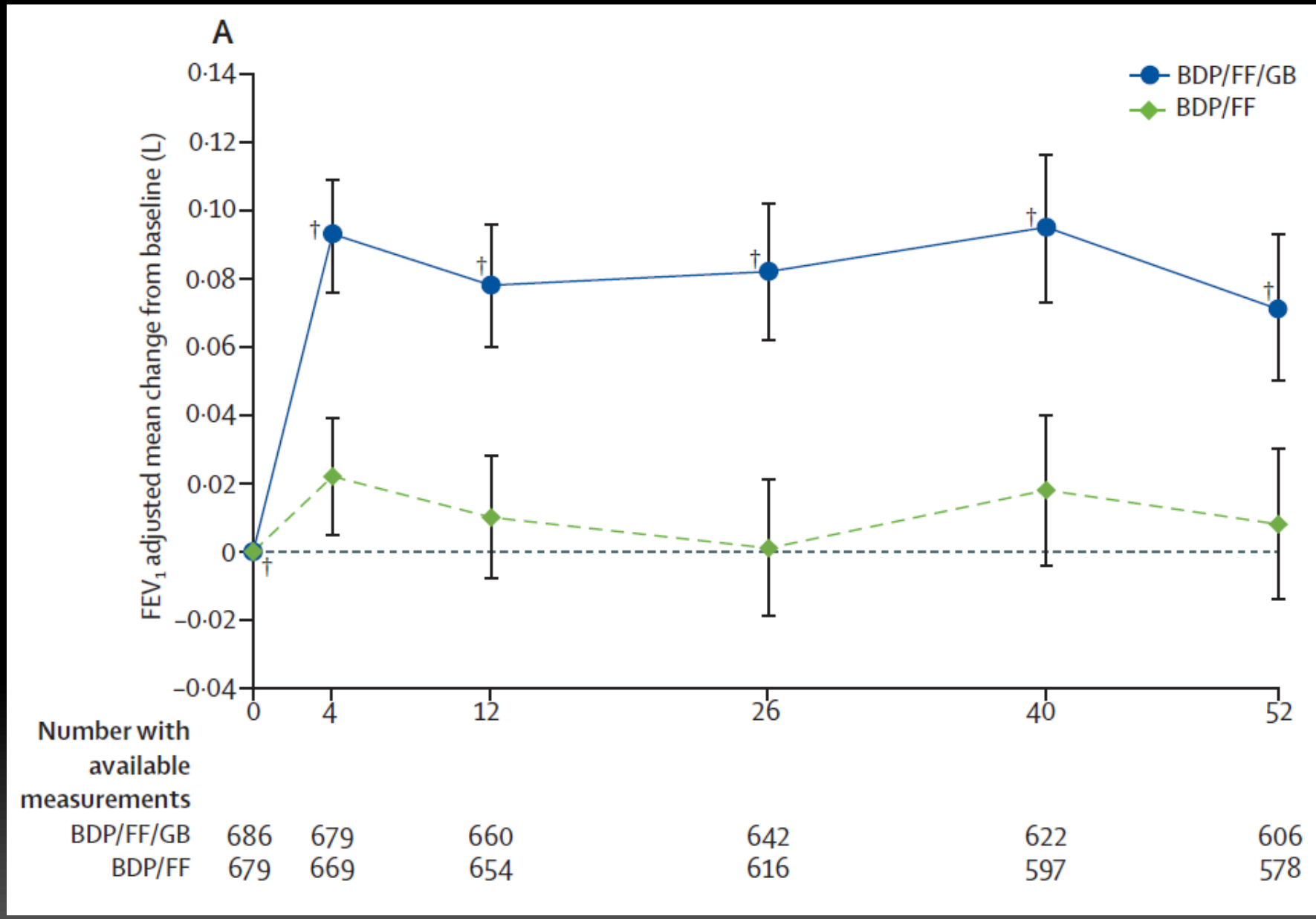
Am J Respir Crit Care Med. 2016;193(9):965-974.

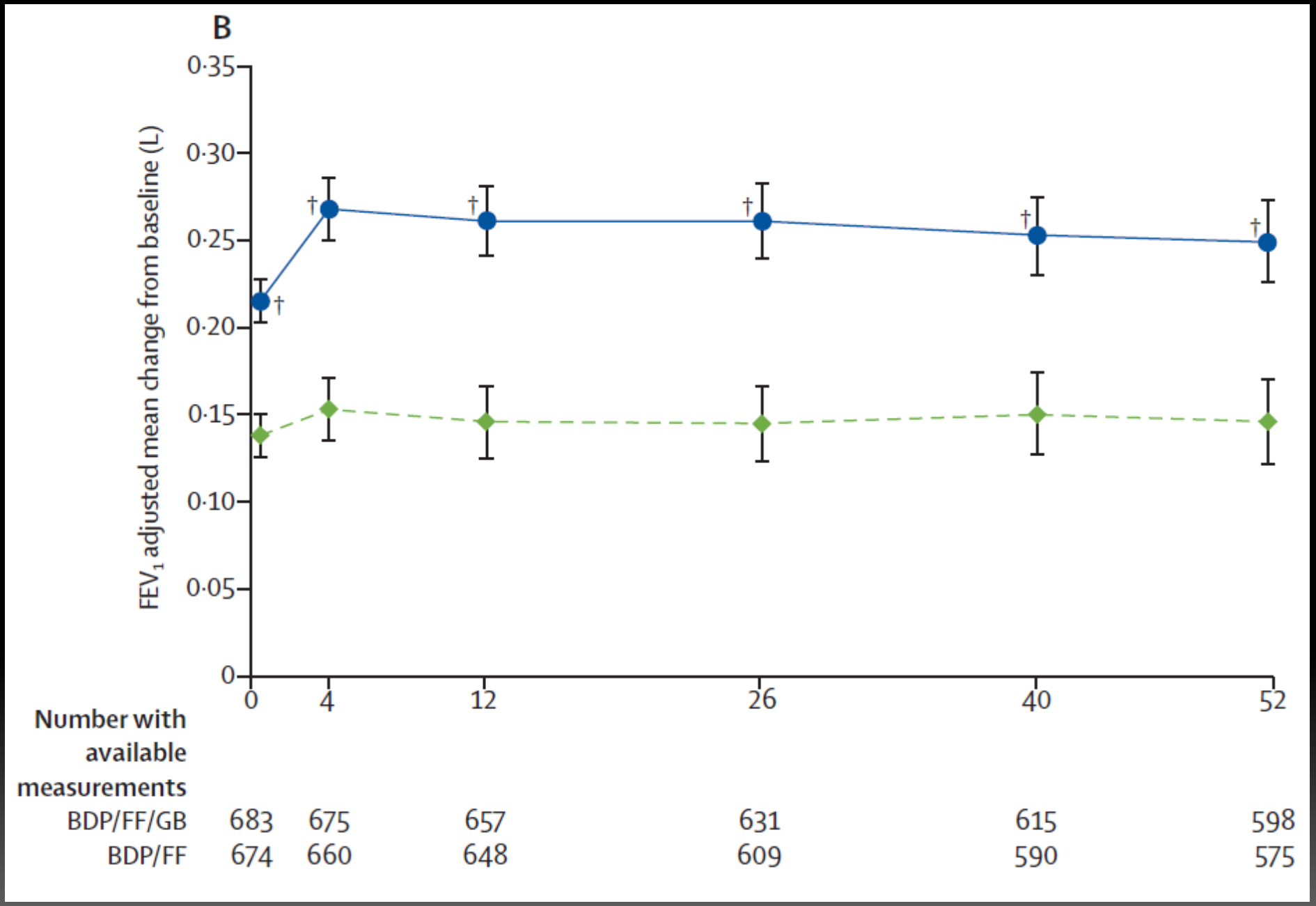
Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial

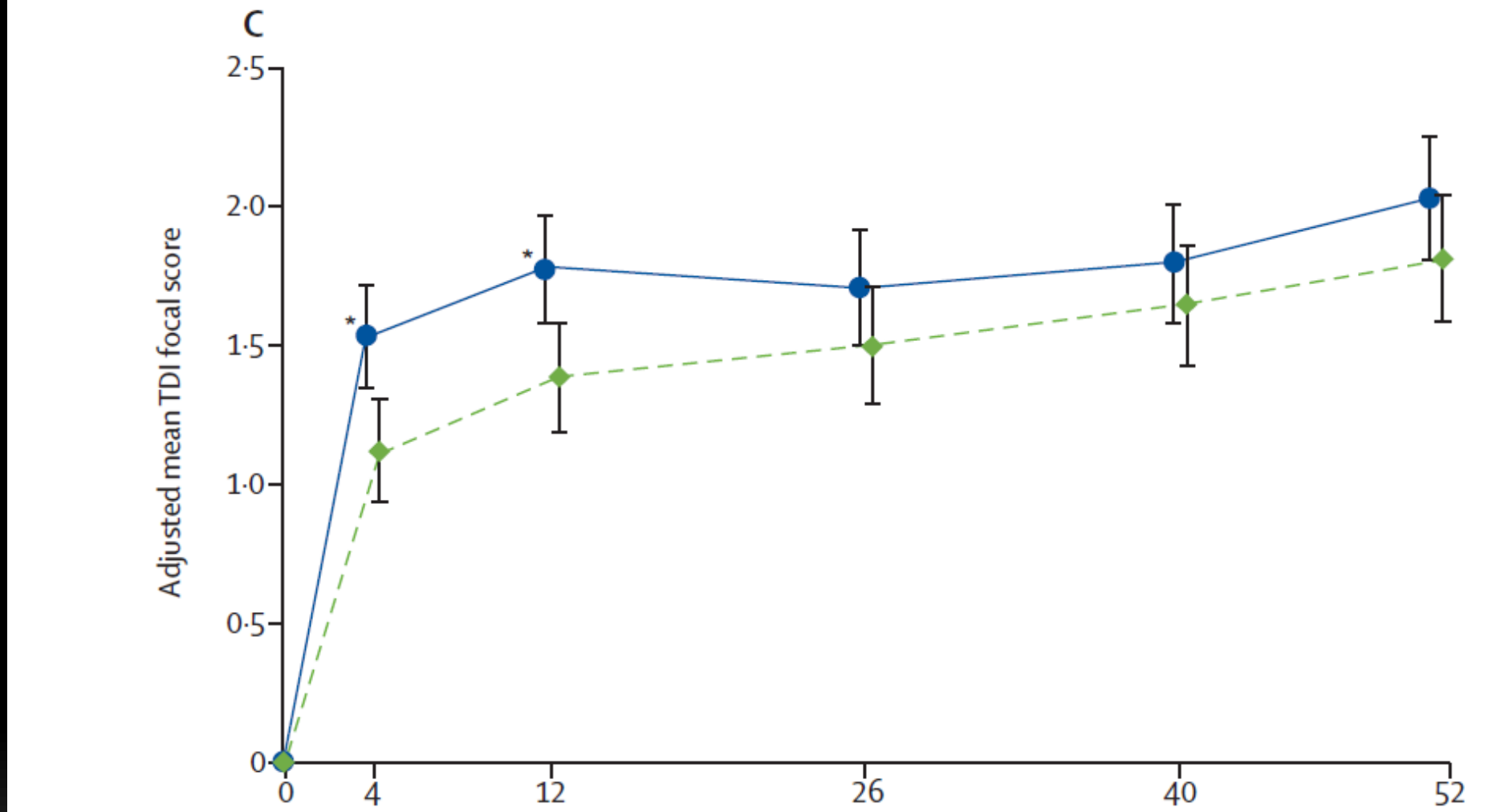
Dave Singh, Alberto Papi, Massimo Corradi, Ilona Pavlišová, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Jørgen Vestbo

- FEV1 < 50%
- One or more COPD AE/yr
- Triple (BDP+FF+GB) vs ICSLABA (BDP+FF)

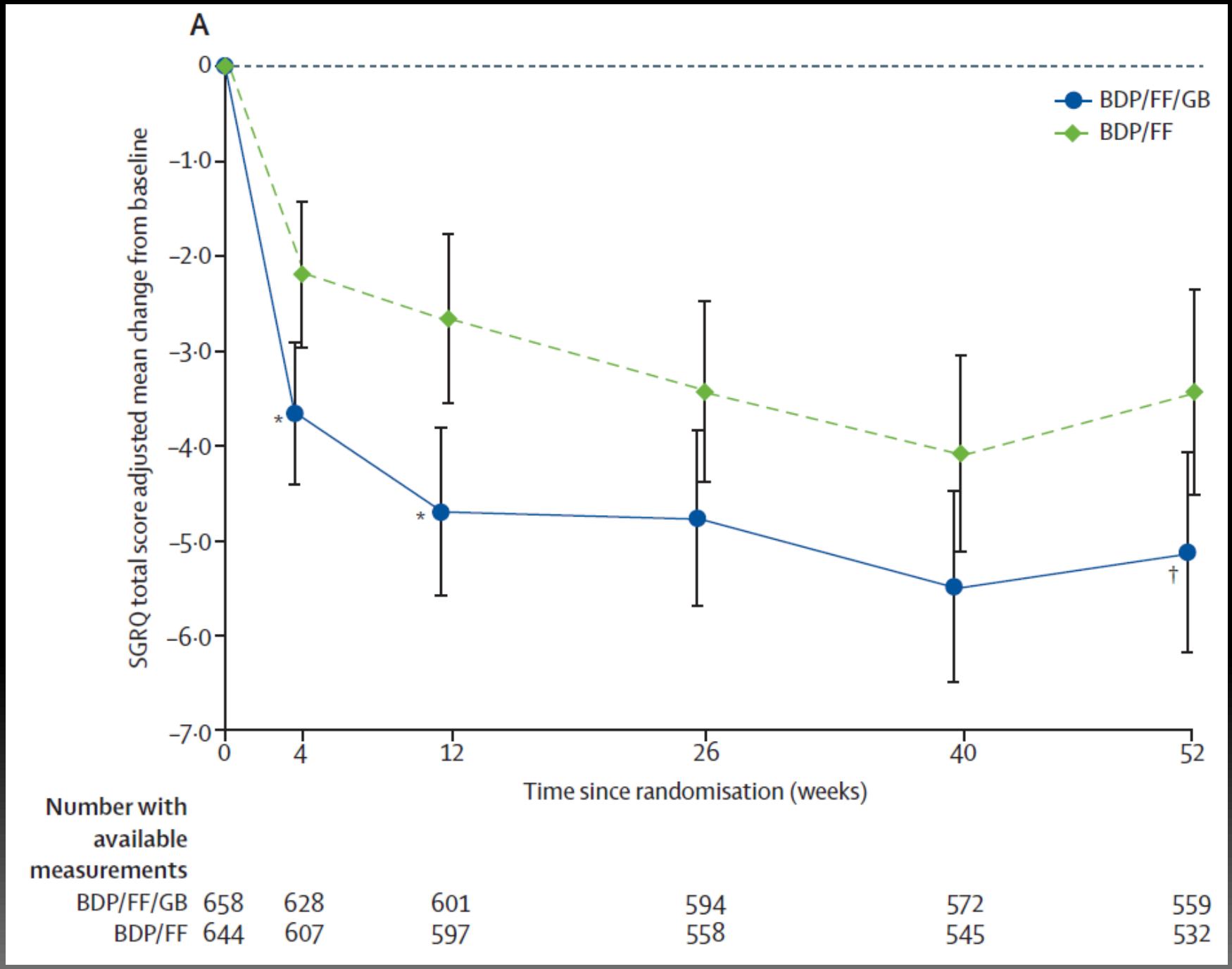
The Lancet. 2016;388(10048):963-973.


A
BDP/FF/GB
BDP/FF
FEV1 adjusted mean change from baseline (L)
0·14
0·12
0·10
0·08
0·06
0·04
0·02
0
−0·02
−0·04
0
4
12
26
40
52
Number with available measurements
BDP/FF/GB 686 679 660 642 622 606
BDP/FF 679 669 654 616 597 578


B
0·35
0·30
0·25
0·20
0·15
0·10
0·05
0
FEV1 adjusted mean change from baseline (L)
†
0
4
12
26
40
52
Number with available measurements
BDP/FF/GB 683 675 657 631 615 598
BDP/FF 674 660 648 609 590 575



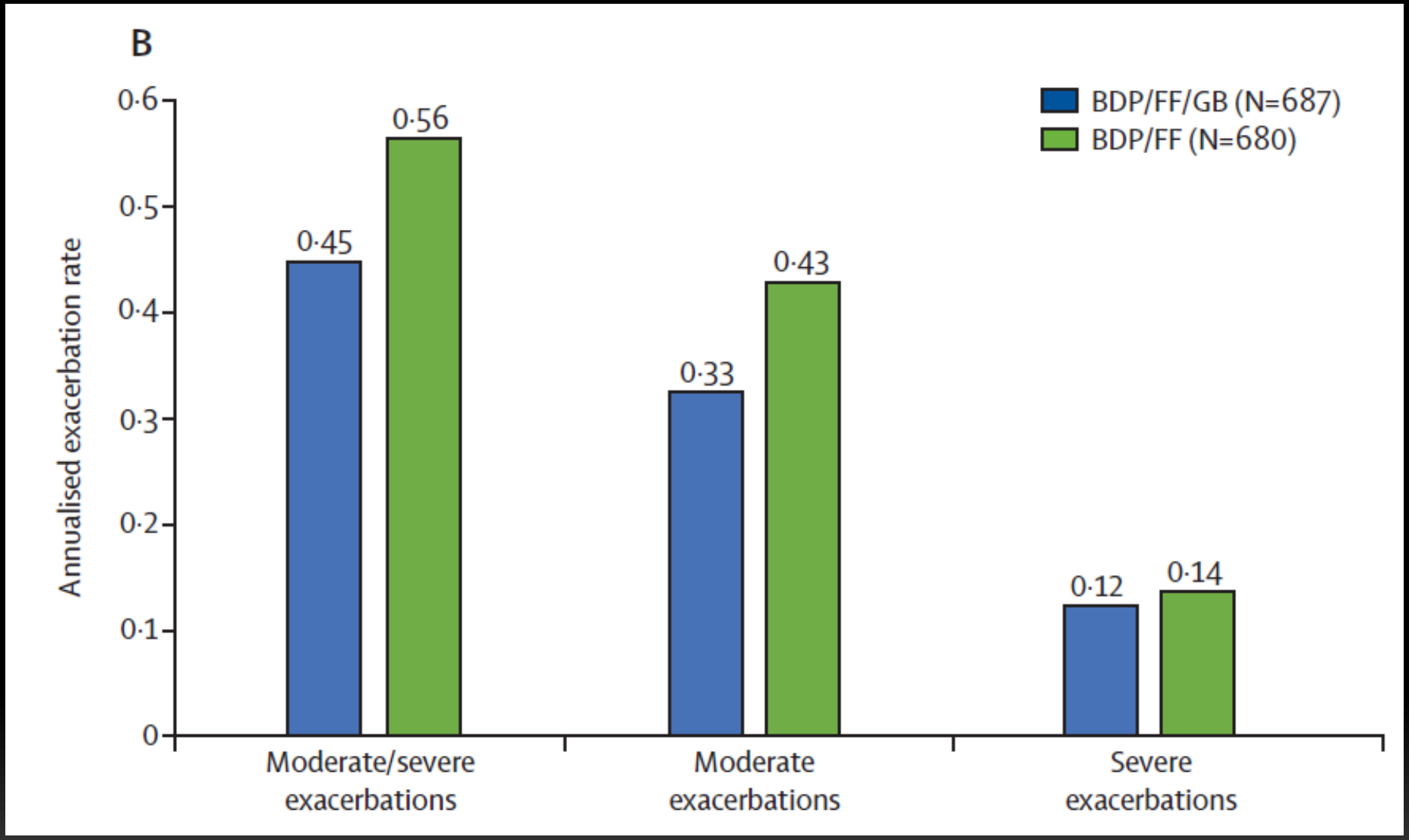
Number with available measurements						
BDP/FF/GB	687	680	661	642	622	608
BDP/FF	680	672	651	619	596	579

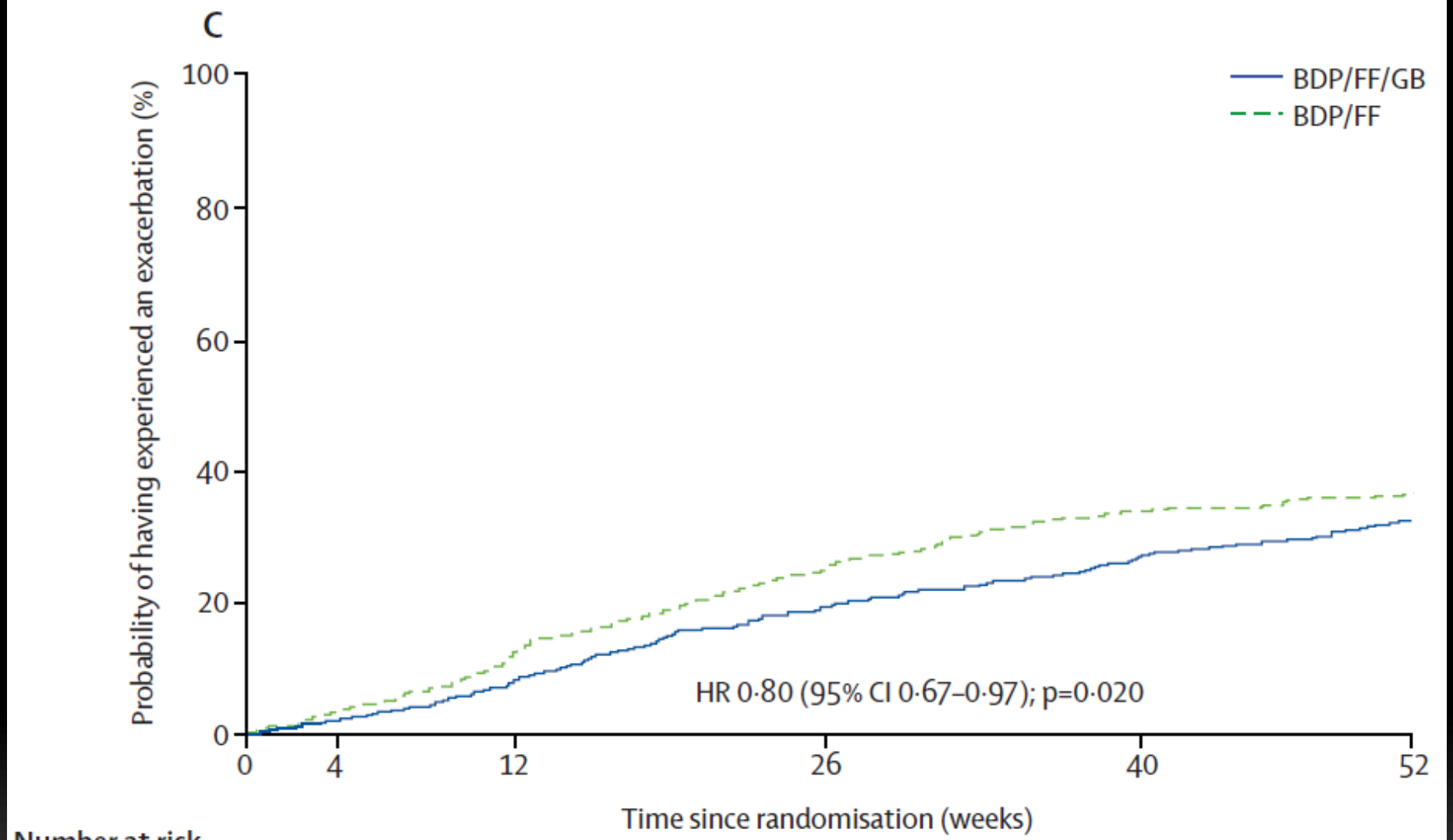

A
0
−1·0
−2·0
−3·0
−4·0
−5·0
−6·0
−7·0
SGRQ total score adjusted mean change from baseline
BDP/FF/GB
BDP/FF
*
*
†
0
4
12
26
40
52
Time since randomisation (weeks)
Number with available measurements
BDP/FF/GB 658 628 601 594 572 559
BDP/FF 644 607 597 558 545 532

	BDP/FF/GB (N=687)	BDP/FF (N=680)	Odds ratio	p value
Pre-dose FEV_1 (≥100 mL increase from baseline)				
Week 26	287 (42%)	165 (24%)	2·30 (1·82–2·91)	p<0·001
Week 52	259 (38%)	158 (23%)	2·06 (1·62–2·62)	p<0·001
TDI (focal score ≥1)				
Week 26	394 (57%)	352 (52%)	1·28 (1·03–1·59)	p=0·027
Week 52	370 (54%)	354 (52%)	1·09 (0·88–1·36)	p=0·430
SGRQ (≥4 unit decrease from baseline in total score)				
Week 26	321 (47%)	246 (36%)	1·52 (1·21–1·91)	p<0·001
Week 52	297 (43%)	244 (36%)	1·33 (1·06–1·66)	p=0·014

Data are n (%) or odds ratio (95% CI), unless otherwise stated.
BDP=beclometasone dipropionate. FF=formoterol fumarate. GB=glycopyrronium bromide. FEV_1=forced expiratory volume in 1 s. TDI=Transition Dyspnea Index. SGRQ=St George's Respiratory Questionnaire.

Table 3: Patients with a clinically relevant change from baseline for FEV_1, TDI, and SGRQ responder analyses at weeks 26 and 52 in the intention-to-treat population


B
BDP/FF/GB (N=687)
BDP/FF (N=680)
Annualised exacerbation rate
0·6
0·5
0·4
0·3
0·2
0·1
0
0·45
0·56
0·33
0·43
0·12
0·14
Moderate/severe exacerbations
Moderate exacerbations
Severe exacerbations


C
Probability of having experienced an exacerbation (%)
100
80
60
40
20
0
BDP/FF/GB
BDP/FF
HR 0·80 (95% CI 0·67–0·97); p=0·020
0
4
12
26
40
52
Time since randomisation (weeks)
Number at risk
BDP/FF/GB 687 669 620 528 465 292
BDP/FF 680 649 588 483 414 265

- **Conclusion**
- Triple is better than ICSLABA

	BDP/FF/GB	BDP/FF
Hypertension	21 (3%)	16 (2%)
Headache	12 (2%)	16 (2%)
Ischaemic heart disease	10 (1%)	16 (2%)
Angina pectoris	5 (1%)	3 (<1%)
Myocardial infarction	1 (<1%)	6 (1%)
Myocardial ischaemia	1 (<1%)	6 (1%)
Coronary artery disease	3 (<1%)	1 (<1%)
Respiratory tract infection viral	16 (2%)	10 (1%)
Oral candidosis	15 (2%)	4 (1%)

ORIGINAL ARTICLE

Understanding the impact of second-hand smoke exposure on clinical outcomes in participants with COPD in the SPIROMICS cohort

Nirupama Putcha,[1] R Graham Barr,[2] Meilan K Han,[3] Prescott G Woodruff,[4] Eugene R Bleecker,[5] Richard E Kanner,[6] Fernando J Martinez,[7] Benjamin M Smith,[2] Donald P Tashkin,[8] Russell P Bowler,[9] Mark D Eisner,[4,10] Stephen I Rennard,[11] Robert A Wise,[1] Nadia N Hansel,[1] for the SPIROMICS Investigators

- SPIROMICS cohort
- Recent SHS exposure was quantified
  - (1) hours of reported exposure in the past week
  - (2) reported living with a smoker

Thorax 2016;71:411–420.

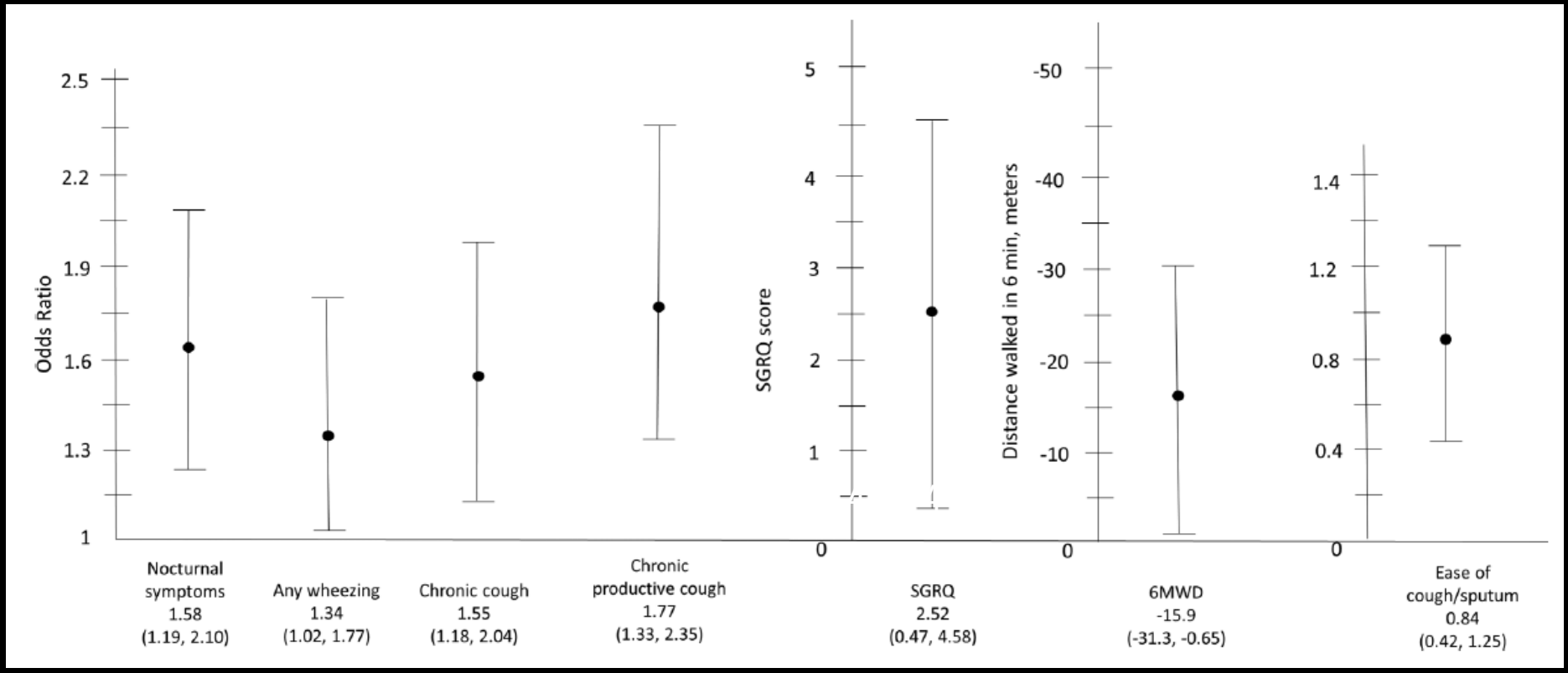
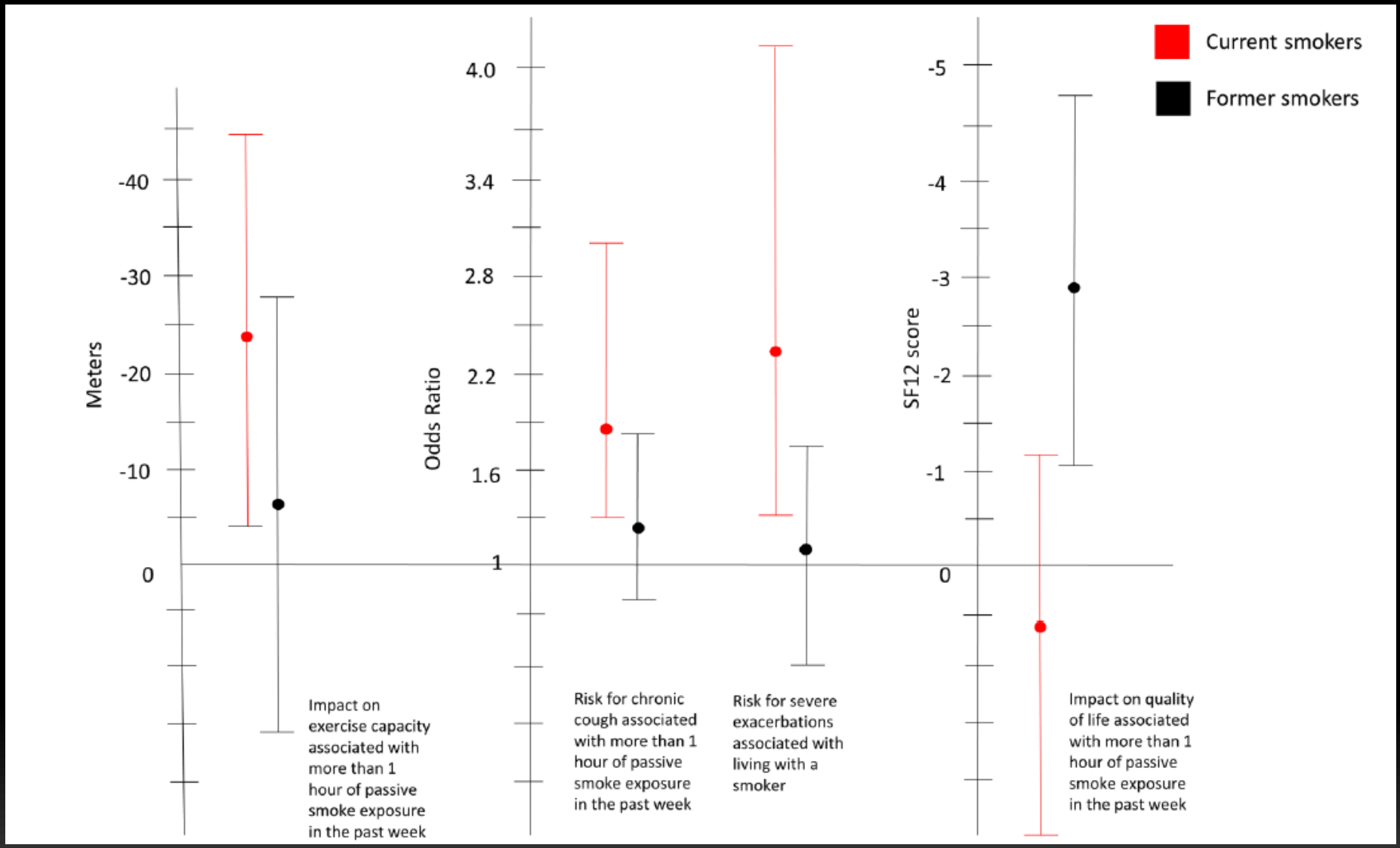

Odds Ratio
2.5
2.2
1.9
1.6
1.3
1
SGRQ score
5
4
3
2
1
0
Distance walked in 6 min, meters
-50
-40
-30
-20
-10
0
1.4
1.2
0.8
0.4
0
Nocturnal symptoms 1.58 (1.19, 2.10)
Any wheezing 1.34 (1.02, 1.77)
Chronic cough 1.55 (1.18, 2.04)
Chronic productive cough 1.77 (1.33, 2.35)
SGRQ 2.52 (0.47, 4.58)
6MWD -15.9 (-31.3, -0.65)
Ease of cough/sputum 0.84 (0.42, 1.25)

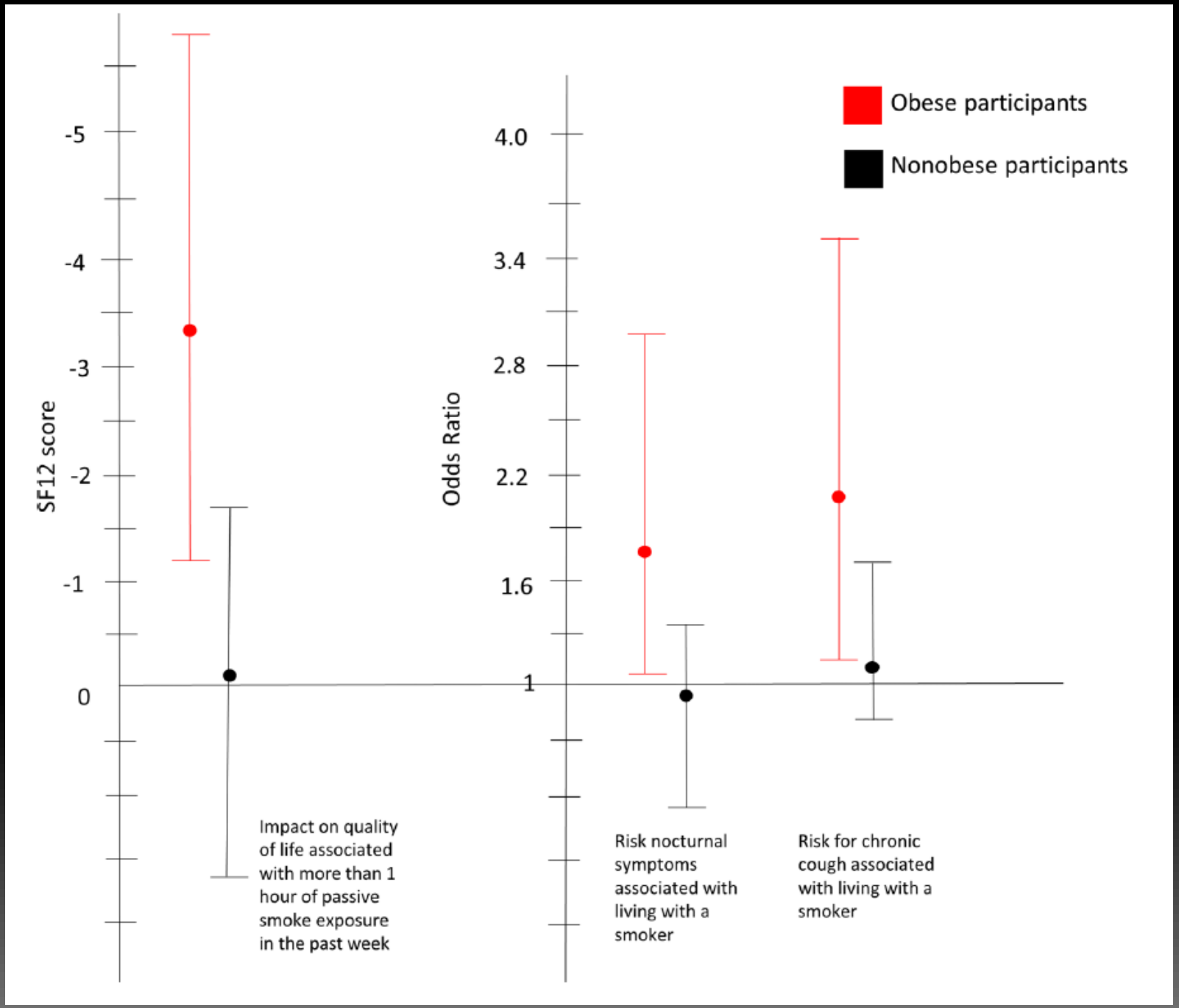
Table 2 Associations of living with a smoker and COPD outcomes in SPIROMICS

Linear regression models	Absolute difference	95% CI	p Value
6 MWD, m	−7.68	(−23.50 to 8.15)	0.341
FEV_1% predicted	−2.13	(−4.87 to 0.62)	0.129
SGRQ score	**3.10**	**(0.99 to 5.21)**	**0.004**
SF12 GH score	**−1.53**	**(−2.90 to −0.16)**	**0.029**
CAT score	**1.43**	**(0.52 to 2.35)**	**0.002**
mMRC score	0.07	(−0.05 to 0.20)	0.223
Ease of Cough and Sputum score in past day	**0.76**	**(0.34 to 1.19)**	**<0.0001**
% emphysema	0.35	(−0.92 to 1.55)	0.573
% gas-trapping	0.06	(−1.65 to 1.88)	0.946
Pi 10 (all airways)	**0.16**	**(0.03 to 0.29)**	**0.020**
Airway dimensions (fifth generation airways)			
Wall area percentage	**0.431**	**(0.023 to 0.840)**	**0.039**
Wall area	−0.79767	(−1.64367 to 0.04832)	0.065
Lumen area	**−1.08644**	**(−2.00936 to −0.16352)**	**0.021**
Lumen diameter	−0.0799	(−0.1697 to 0.0098)	0.081
Logistic regression models	**OR**	**95% CI**	**p Value**
Nocturnal symptoms	1.17	(0.87 to 1.57)	0.295
Any wheezing	1.16	(0.86 to 1.54)	0.325
Chronic cough	**1.41**	**(1.06 to 1.87)**	**0.019**
Chronic productive cough	**1.71**	**(1.28 to 2.30)**	**<0.0001**
Exacerbation risk in past year	1.11	(0.81 to 1.51)	0.511
Severe exacerbation risk in past year	**1.51**	**(1.04 to 2.17)**	**0.029**
Poisson models	**RR**	**95% CI**	**p Value**
Exacerbations experienced over follow-up	1.04	(0.84 to 1.30)	0.696
Severe exacerbations experienced over follow-up	1.11	(0.82 to 1.52)	0.497

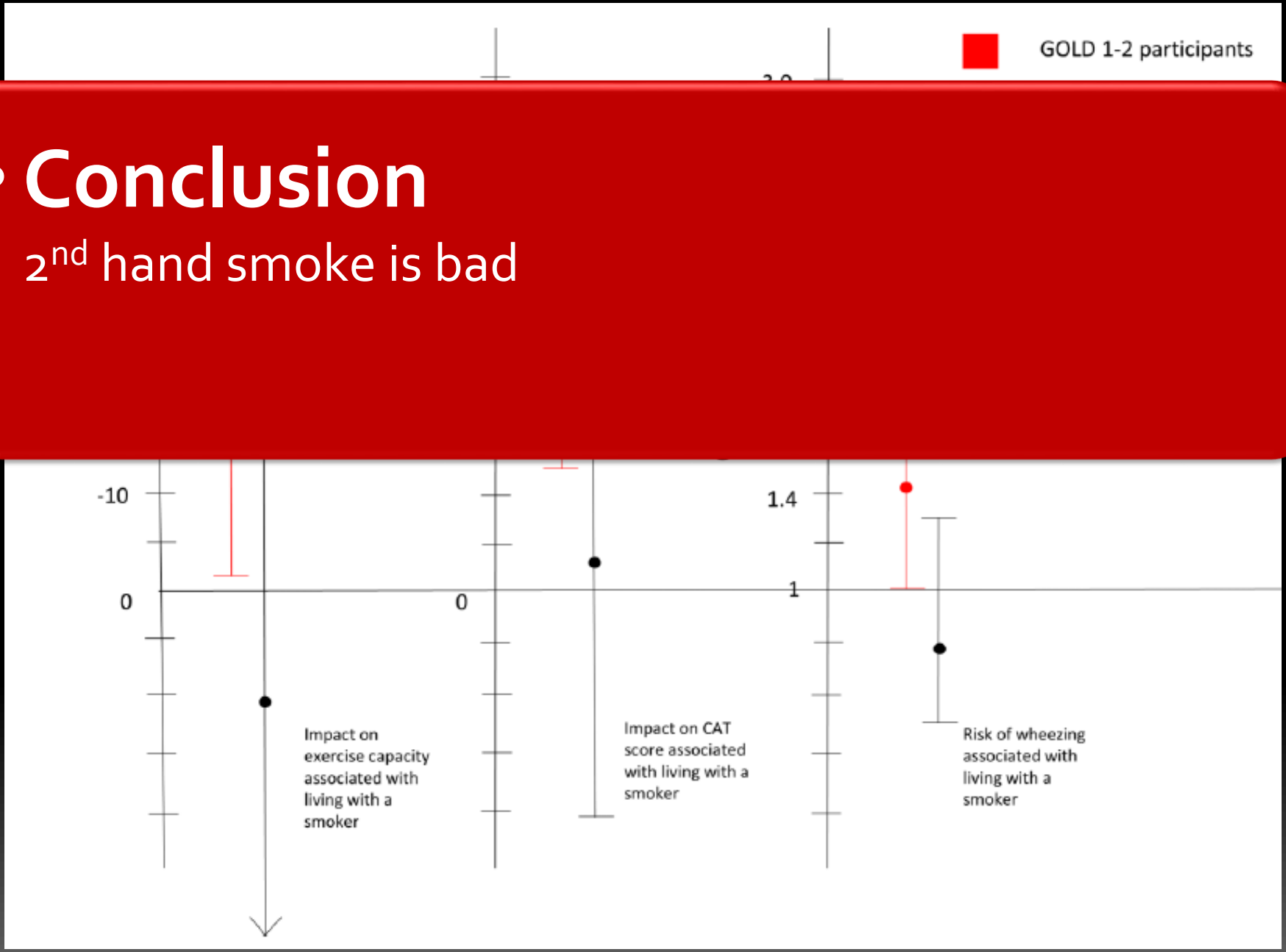
Table 3 Associations of ≥2 h of SHS exposure in past week with COPD outcomes in SPIROMICS

Linear regression models Hours of SHS smoke in the past 7 day 0–1 h (REF) 2+ h	Absolute difference	95% CI	p Value
6 MWD, m	−15.9	(−31.33 to −0.65)	0.041
SGRQ score	2.52	(0.47 to 4.58)	0.016
SF12 GH score	−1.17	(−2.50 to 0.16)	0.084
CAT score	0.82	(−0.06 to 1.71)	0.068
mMRC score	0.097	(−0.018 to 0.21)	0.098
Ease of Cough and Sputum total score	0.84	(0.42 to 1.25)	<0.0001
Pi10 (all airways)	0.18	(0.05 to 0.31)	0.006
Airway dimensions (fifth generation airways)			
Wall area percentage	0.432	(0.048 to 0.816)	0.027
Wall area	−0.67611	(−1.47355 to 0.12133)	0.097
Lumen area	−0.89061	(−1.76076 to −0.02046)	0.045
Lumen diameter	−0.07514	(−0.1597 to 0.00939)	0.081
Logistic regression models	**OR**	**95% CI**	**p Value**
Nocturnal symptoms	1.58	(1.19 to 2.10)	0.001
Any wheezing	1.34	(1.02 to 1.77)	0.039


Current smokers
Former smokers
Meters
-40
-30
-20
-10
0
Impact on exercise capacity associated with more than 1 hour of passive smoke exposure in the past week
Odds Ratio
4.0
3.4
2.8
2.2
1.6
1
Risk for chronic cough associated with more than 1 hour of passive smoke exposure in the past week
Risk for severe exacerbations associated with living with a smoker
SF12 score
-5
-4
-3
-2
-1
0
Impact on quality of life associated with more than 1 hour of passive smoke exposure in the past week


Obese participants
Nonobese participants
SF12 score
-5
-4
-3
-2
-1
0
Odds Ratio
4.0
3.4
2.8
2.2
1.6
1
Impact on quality of life associated with more than 1 hour of passive smoke exposure in the past week
Risk nocturnal symptoms associated with living with a smoker
Risk for chronic cough associated with living with a smoker

- **Conclusion**
- 2nd hand smoke is bad



Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma

M.J. McGeachie, K.P. Yates, X. Zhou, F. Guo, A.L. Sternberg, M.L. Van Natta, R.A. Wise, S.J. Szefler, S. Sharma, A.T. Kho, M.H. Cho, D.C. Croteau-Chonka, P.J. Castaldi, G. Jain, A. Sanyal, Y. Zhan, B.R. Lajoie, J. Dekker, J. Stamatoyannopoulos, R.A. Covar, R.S. Zeiger, N.F. Adkinson, P.V. Williams, H.W. Kelly, H. Grasemann, J.M. Vonk, G.H. Koppelman, D.S. Postma, B.A. Raby, I. Houston, Q. Lu, A.L. Fuhlbrigge, K.G. Tantisira, E.K. Silverman, J. Tonascia, S.T. Weiss, and R.C. Strunk, for the CAMP Research Group*

- Childhood Asthma Management Program (CAMP) Research Group
- Classified children with asthma according to four characteristic patterns
- From childhood into adulthood

N Engl J Med. 2016;374(19):1842-1852.

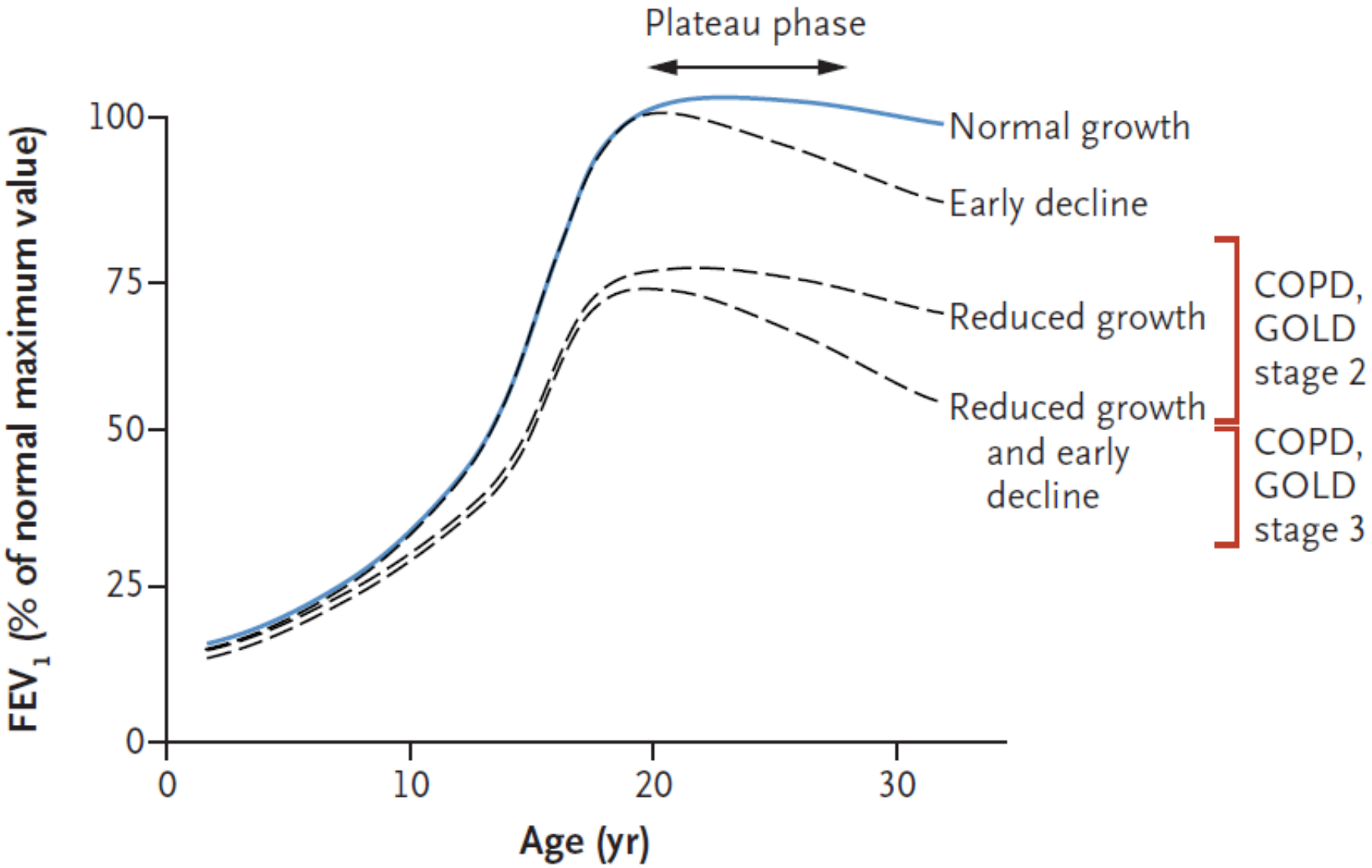
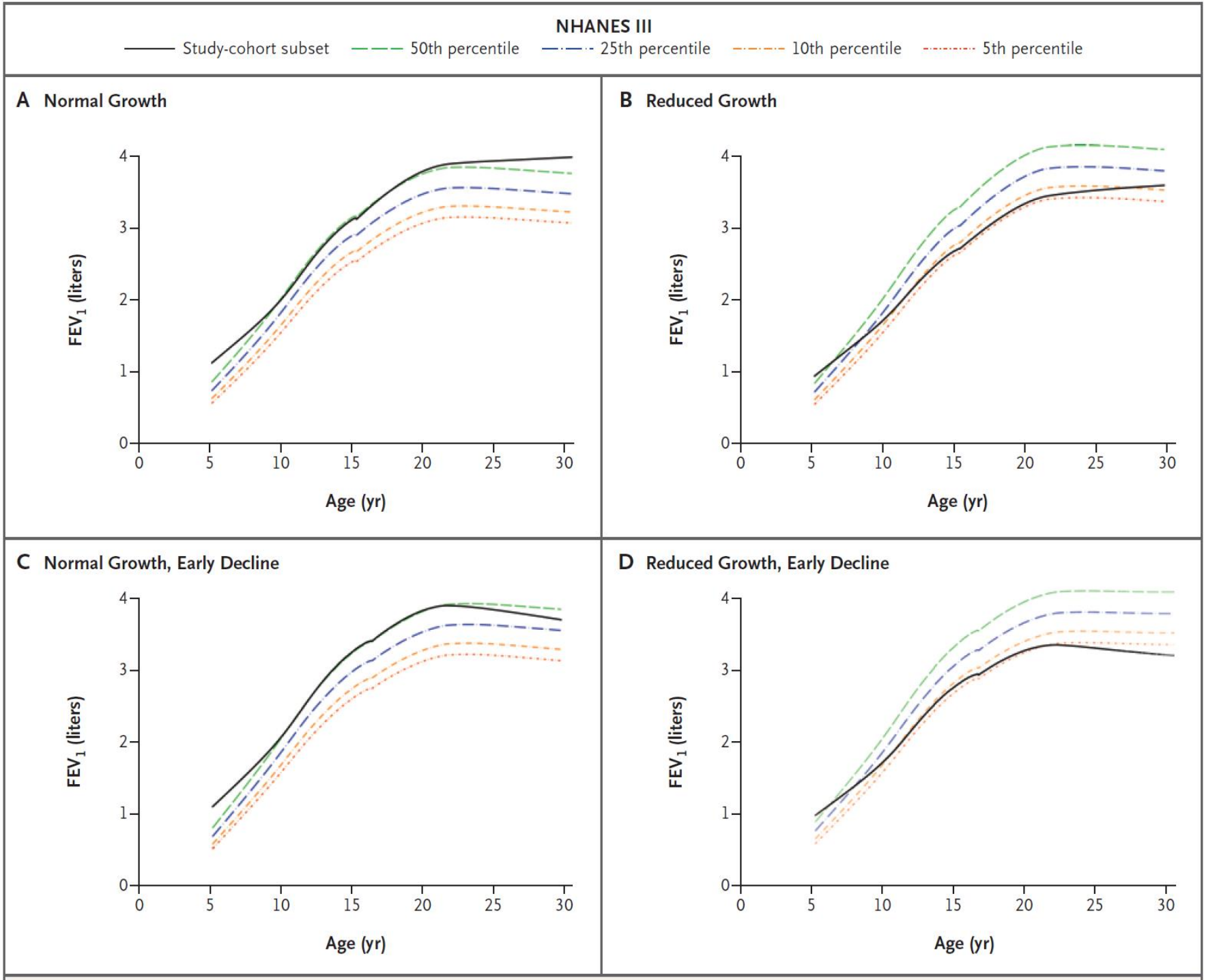

Plateau phase
100
75
50
25
0
0
10
20
30
FEV1 (% of normal maximum value)
Age (yr)
Normal growth
Early decline
Reduced growth
Reduced growth and early decline
COPD, GOLD stage 2
COPD, GOLD stage 3

Table 1. Characteristics of the Study Participants According to the Pattern of Lung-Function Growth and Decline.*

Characteristic	Normal Growth (N=170)	Normal Growth and Early Decline (N=178)	Reduced Growth (N=160)	Reduced Growth and Early Decline (N=176)	P Value†
Maximum lung function attained — no. (%)	45 (26)	178 (100)	30 (19)	176 (100)	<0.001
Age at maximum lung function — yr	22.3±2.2	20.6±2.2	21.9±1.7	20.6±1.8	<0.001
Plateau phase					<0.001
Plateau not attained, maximum lung function not reached — no. (%)	125 (74)	0	130 (81)	0	
No plateau, immediate decline — no. (%)	0	112 (63)	0	106 (60)	
Maximum lung function reached, plateau attained — no. (%)	45 (26)	66 (37)	30 (19)	70 (40)	
Age when plateau attained — yr	22.3±2.2	20.6±2.1	21.9±1.7	20.5±1.6	<0.001
Plateau phase completed — no. (%)	1 (1)‡	66 (37)	—	70 (40)	0.60
Duration of plateau — yr	2.0‡	1.5±0.6	—	1.8±0.9	0.03
Decline phase begun — no. (%)	1 (1)‡	178 (100)	0	176 (100)	
Had an early decline — no. (%)	0	178 (100)	0	176 (100)	
Age at start of any decline — yr	24.0‡	21.1±2.3	—	21.3±2.0	0.46
Demographic and physical characteristics					
Male sex — no. (%)	82 (48)	100 (56)	114 (71)	109 (62)	<0.001
Age at randomization — yr	9.3±1.7	9.7±1.7	9.3±1.8	9.9±1.7	0.006
Prepubertal at randomization — no. (%)§	119 (70)	106 (60)	112 (70)	106 (60)	0.04
Body-mass index at randomization — z score	0.50±0.97	0.78±0.94	0.18±1.04	0.44±1.05	<0.001
Interval between diagnosis of asthma and enrollment — no. (%)					0.003
<3 yr	50 (29)	45 (25)	31 (19)	28 (16)	
3–6 yr	85 (50)	84 (47)	81 (51)	79 (45)	
≥7 yr	35 (21)	49 (28)	48 (30)	69 (39)	
Maternal cigarette smoking during gestation — no. (%)	17 (10)	27 (15)	20 (12)	27 (15)	0.40
Lung function at randomization					
Prebronchodilator FEV_1 — % of predicted value	100.5±13.4	99.7±12.9	87.5±12.6	83.8±12.9	<0.001
Prebronchodilator FEV_1:FVC — % of predicted value	81.9±6.9	81.6±7.5	76.5±7.9	76.5±8.4	<0.001
Bronchodilator response — %¶	8.9±7.8	8.2±7.8	12.7±9.9	12.4±11.3	<0.001
Airway responsiveness — log mg/ml‖	0.3±1.2	0.4±1.1	−0.2±1.1	−0.2±1.1	<0.001
Lifetime smoking — pack-yr**	0.5±1.5	0.4±1.4	0.4±1.1	0.5±1.5	0.97
Age and spirometry at last visit					
Age — yr	25.7±1.7	26.0±1.8	25.8±1.9	26.3±1.7	0.01
Prebronchodilator FEV_1 — % of predicted value	104.3±7.6	97.7±9.5	87.1±7.9	79.7±10.0	<0.001
Prebronchodilator FEV_1:FVC — % of predicted value	80.4±6.4	78.1±7.2	73.0±8.0	71.2±9.6	<0.001


NHANES III
Study-cohort subset
50th percentile
25th percentile
10th percentile
5th percentile
A Normal Growth
B Reduced Growth
C Normal Growth, Early Decline
D Reduced Growth, Early Decline
FEV1 (liters)
Age (yr)
0
1
2
3
4
0
5
10
15
20
25
30

- **Conclusion**
- Childhood severe asthma is risk factor for COPD

Table 2. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Classification According to the Pattern of Lung-Function Growth and Decline.*

	Normal	Normal Growth	Reduced	Reduced Growth	
Stage 1, FEV_1 ≥80% of predicted value	10 (6)	18 (10)	47 (29)	38 (22)	113 (17)
Stage 2, FEV_1 ≥50% and <80% of predicted value	0	1 (1)	10 (6)	24 (14)	35 (5)
Stage 3, FEV_1 ≥30% and <50% of predicted value	0	0	0	1 (1)	1 (<1)
P value†	—	0.10	<0.001	<0.001	<0.001

ORIGINAL ARTICLE

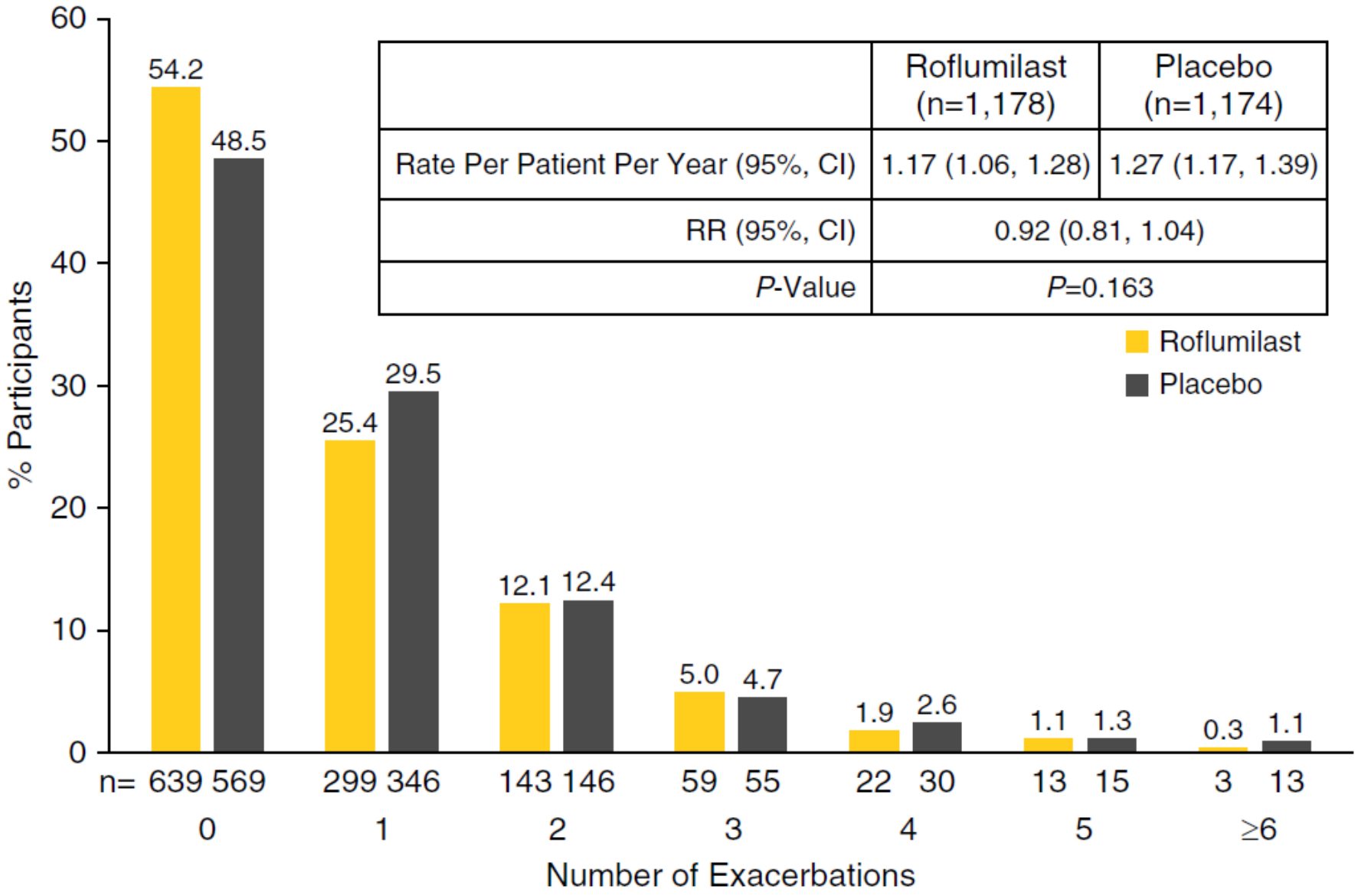
Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting β_2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE^2SPOND)

A Randomized Clinical Trial

Fernando J. Martinez[1], Klaus F. Rabe[2,3,4], Sanjay Sethi[5], Emilio Pizzichini[6], Andrew McIvor[7], Antonio Anzueto[8,9], Vijay K. T. Alagappan[10], Shahid Siddiqui[10], Ludmyla Rekeda[11], Christopher J. Miller[10], Sofia Zetterstrand[12], Colin Reisner[13], and Stephen I. Rennard[14,15]

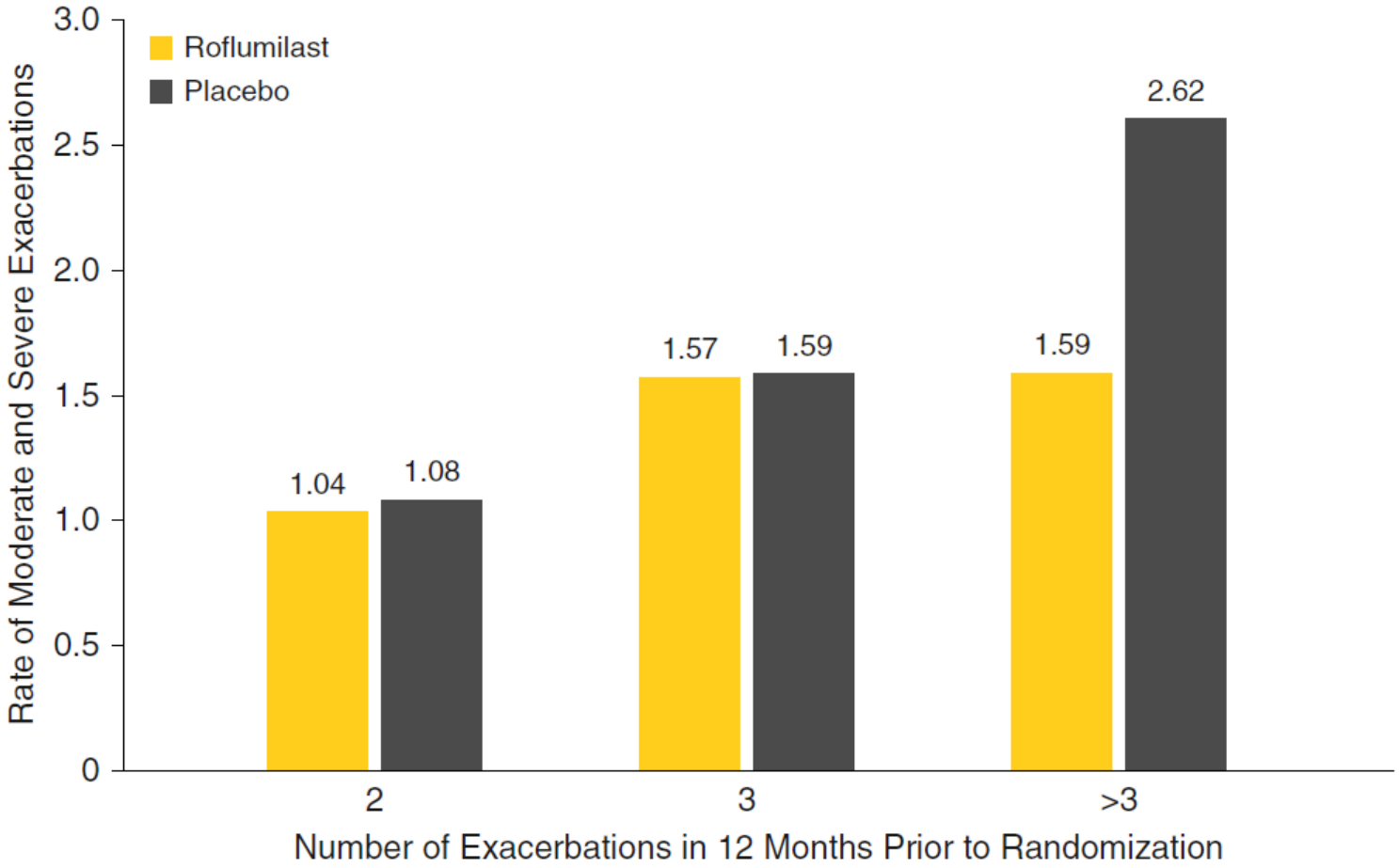
- 52-week
- ICSLABA vs ICSLABA + roflumilast
- GOLD 3/4 & CB & freq exc

Am J Respir Crit Care Med. 2016;194(5):559-567.



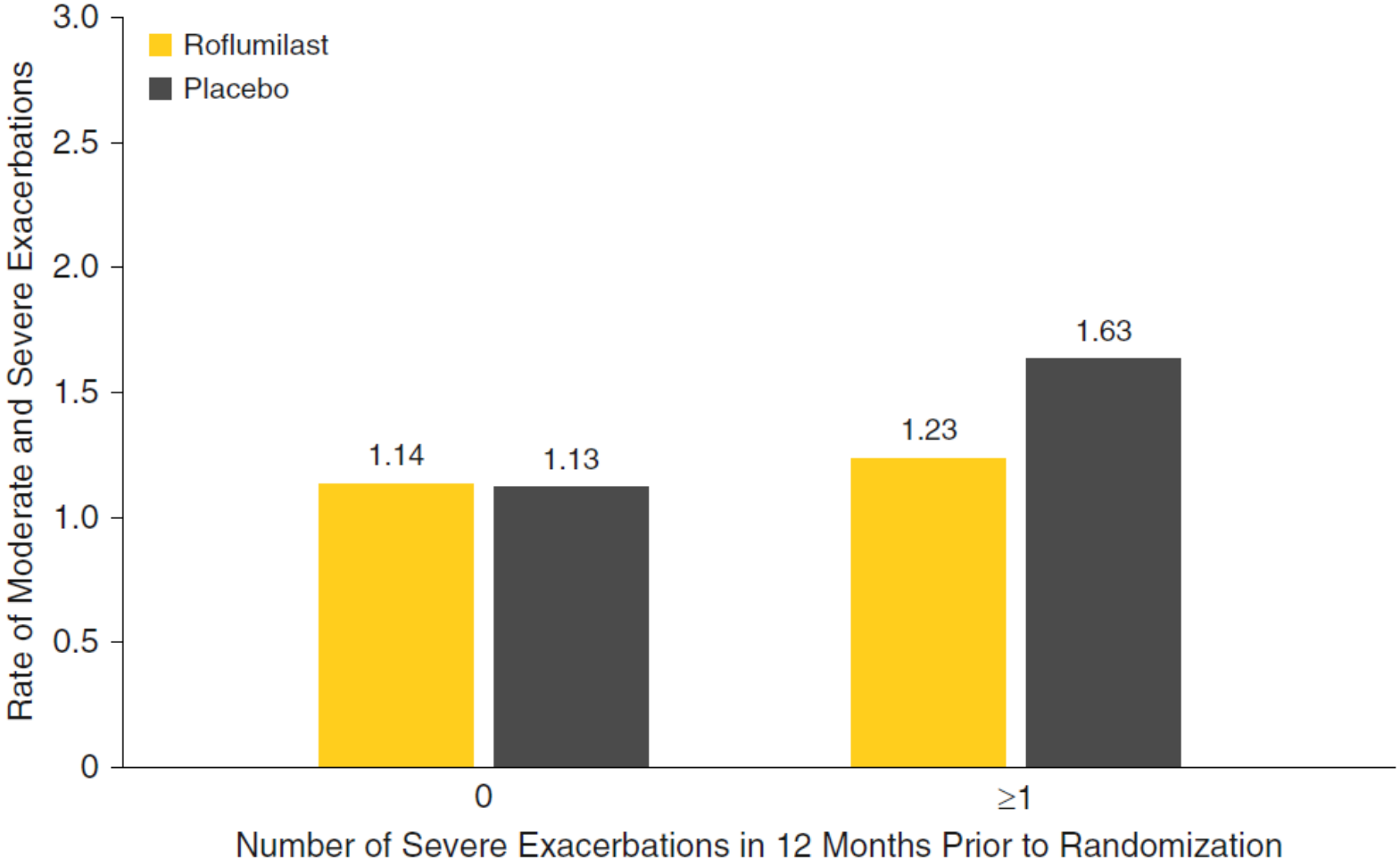
	Roflumilast (n=1,178)	Placebo (n=1,174)
Rate Per Patient Per Year (95%, CI)	1.17 (1.06, 1.28)	1.27 (1.17, 1.39)
RR (95%, CI)	0.92 (0.81, 1.04)	
P-Value	*P*=0.163	

A



Number of Exacerbations in 12 Months Prior to Randomization	Number of Participants at Risk		Rate Ratio (95% CI)	*P*-Value
	Roflumilast (n=1,178)	Placebo (n=1,174)		
2	874	876	0.96 (0.83, 1.11)	0.586
3	179	180	0.99 (0.77, 1.27)	0.921
>3	112	108	0.61 (0.39, 0.95)	0.030

B



Number of Severe Exacerbations in 12 Months Prior to Randomization	Number of Participants at Risk		Rate Ratio (95% CI)	*P*-Value
	Roflumilast (n=1,178)	Placebo (n=1,174)		
0	789	805	1.01 (0.87, 1.18)	0.879
≥1	381	364	0.75 (0.60, 0.93)	0.010

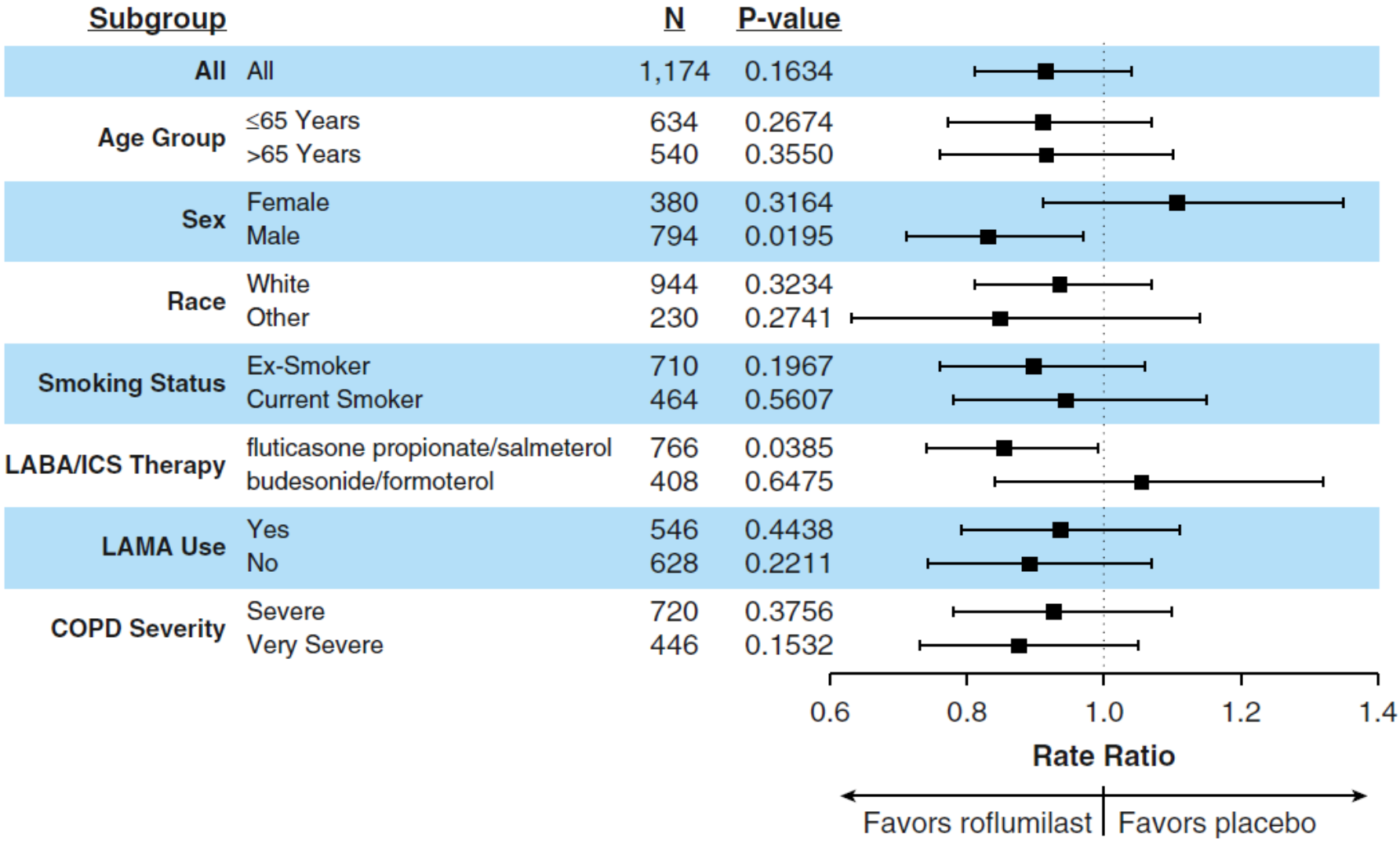


Figure 4. Rates of moderate or severe exacerbations per patient per year by subgroup (intention-to-treat population). COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist.

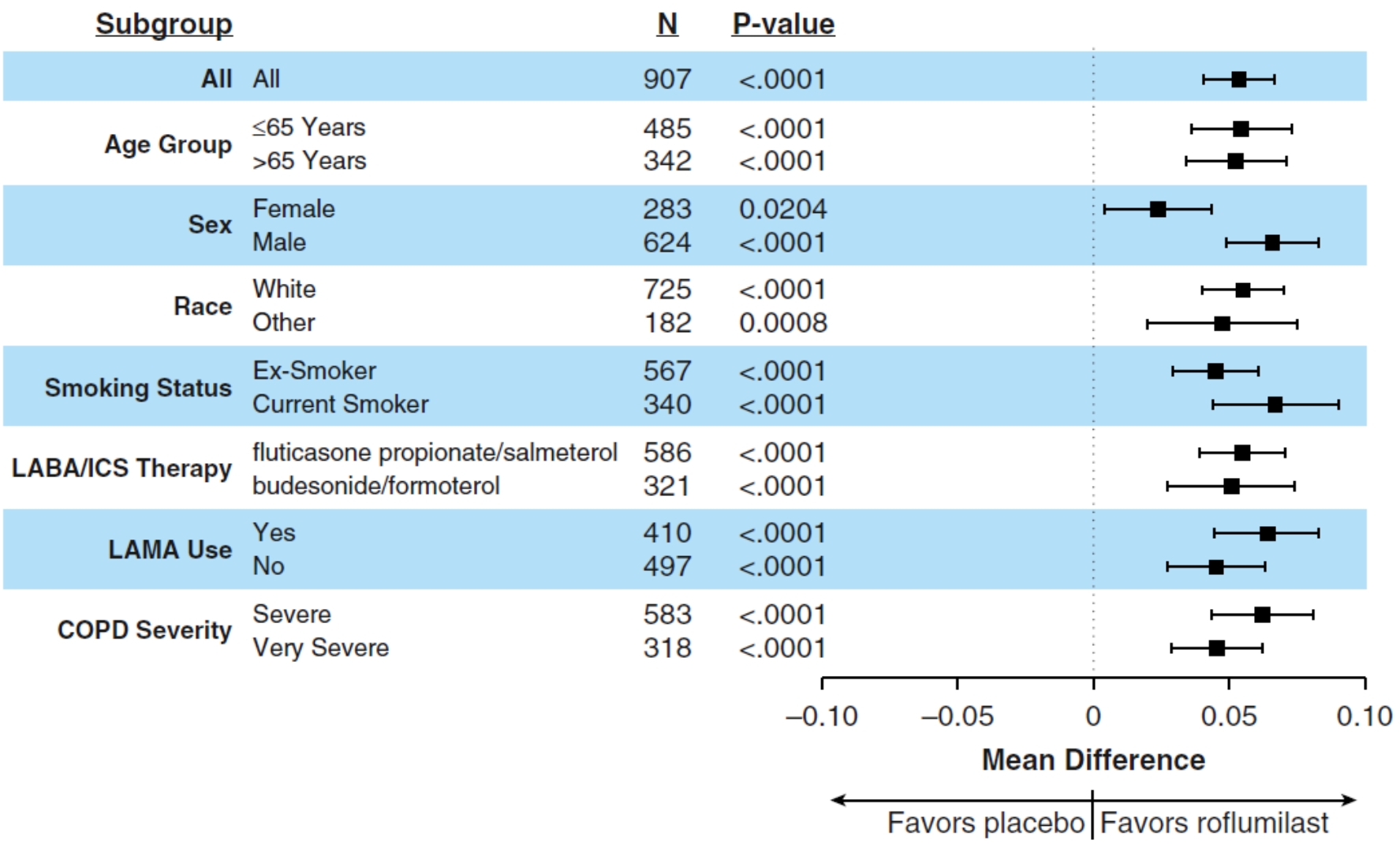


Figure 5. Mean change from baseline to Week 52 in predose FEV_1 by subgroup (intention-to-treat population). COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist.

Table 2. Key Safety Outcomes (Safety Population)

- **Conclusion**
- Roflumilast decrease AE in frequent AE patients

Upper respiratory tract infection	60 (5)	66 (6)
Nausea	64 (5)	30 (3)
Urinary tract infection	48 (4)	44 (4)
Nasopharyngitis	47 (4)	58 (5)
Insomnia	55 (5)	21 (2)
Influenza	31 (3)	30 (3)
Hypertension	33 (3)	43 (4)
Back pain	33 (3)	27 (2)
Appetite decreased	38 (3)	10 (<1)
Participants with SAEs, n (%)	180 (15)	162 (14)
Suicidal ideation, n (%)*	99 (8)	90 (8)
Suicidal behavior, n (%)*	29 (3)	20 (2)
Suicidal attempt, n (%)*	13 (1)	12 (1)
Deaths, n (%)†	30 (3)	25 (2)

Table 3. Annual Exacerbation Rates (ITT and EXT Populations)

Annual Rate of COPD Exacerbations	Up to 24 Weeks		Up to 52 Weeks	
	FF/UMEC/VI 100/62.5/25 µg (n = 911)	BUD/FOR 400/12 µg (n = 899)	FF/UMEC/VI 100/62.5/25 µg (n = 210)	BUD/FOR 400/12 µg (n = 220)
Population, n	907	892	210	219
Moderate and severe exacerbations				
Mean rate	0.22	0.34	0.20	0.36
Ratio (95% CI); *P*-value	0.65 (0.49,0.86); 0.002		0.56 (0.37,0.85); 0.006	
Reduction in rate, % (95% CI)	35 (14,51)		44 (15,63)	

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