

## Online Supplement

### Impact of Marijuana Smoking on COPD Progression in a Cohort of Middle-Aged and Older Persons

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## **Supplemental Tables**

**e-Table 1. Baseline participant characteristics by Marijuana Use Status: Pairwise P values**

	<b>Never vs. Former</b>	<b>Never vs. Current</b>	<b>Former vs. Current</b>
<b>Age</b>	<.0001	<.0001	0.0004
<b>Gender</b>	0.0187	0.0233	0.3446
<b>Race</b>	0.0260	0.0171	0.1053
<b>Ethnicity [Hispanic]</b>	0.9767	0.7953	0.8099
<b>Height (cm)</b>	0.0105	0.0079	0.2288
<b>BMI (K/m<sup>2</sup>)</b>	0.7981	0.1488	0.1204
<b>Tobacco use status</b>	<.0001	<.0001	0.0019
<b>Tobacco pack-years</b>	<.0001	0.0170	0.7823
<b>Joint years<sup>b</sup></b>	<.0001	<.0001	0.0008
<b>Joint years (categorization)</b>	<.0001	<.0001	<.0001
<b>Gold Stage COPD Severity</b>	0.0087	<.0001	0.0323

	<b>Never vs. Former</b>	<b>Never vs. Current</b>	<b>Former vs. Current</b>
<b>Spirometric values</b>			
<b>Post-bronchodilator FEV1 (L)</b>	<.0001	<.0001	0.0006
<b>Post-bronchodilator FVC (L)</b>	<.0001	<.0001	0.0222
<b>%pred Post-Bronchodilator FEV1</b>	<.0001	<.0001	0.0033
<b>%pred Post-Bronchodilator FVC</b>	0.0001	0.0002	0.1198
<b>QoL/Respiratory symptoms</b>			
<b>CAT Score</b>	0.3486	0.8763	0.7345
<b>SGR Total Score</b>	0.5740	0.8903	0.6659
<b>SGR - Cough</b>	0.0088	0.0046	0.1838
<b>SGR - Sputum</b>	0.2337	0.0006	0.0060
<b>SGR - Wheeze</b>	0.4513	0.5120	0.8220
<b>mMRC Score</b>	0.3852	0.0603	0.1706
<b>HRCT Metrics</b>			
<b>Emphysema (%)</b>	0.0661	<.0001	<.0001
<b>Air trapping (%)</b>	0.0002	<.0001	0.0036
<b>PRM emphysema (%)</b>	0.0487	<.0001	0.0003
<b>PRM fsad (%)</b>	<.0001	<.0001	0.0327
<b>Total tissue volume (cm<sup>3</sup>)</b>	0.0014	<.0001	0.0019
<b>Airway wall thickening (Pi10)</b>	0.9688	0.8577	0.8405
<b>Exacerbation History (12 months prior)</b>			
<b>One or more acute exacerbations</b>	0.8370	0.0146	0.0118
<b>One or more severe exacerbations</b>	0.1636	0.0250	0.0045

For continuous variables we used two-sample t-tests without assuming equal variances and for categorical variables we used a chi-square test or Fisher's exact test when there was a cell with an expected number less than 5

**e-Table 2. Baseline participant characteristics by joint-year history: Pairwise P-values**

	<b>0 JYs vs &gt;0-&lt;10 JYs</b>	<b>0 JYs vs 10-&lt;20 JYs</b>	<b>0 JYs vs ≥20 JYs</b>
<b>Age</b>	<.0001	<.0001	<.0001
<b>Gender</b>	0.0567	0.0034	0.0001
<b>Race</b>	0.0863	0.6242	0.0005
<b>Ethnicity [Hispanic]</b>	0.7027	0.7305	0.4041
<b>Height (cm)</b>	0.0114	0.0014	0.0023
<b>BMI (K/m<sup>2</sup>)</b>	0.9075	0.9595	0.7459
<b>Tobacco use status</b>	0.0018	0.2183	<.0001
<b>Tobacco pack-years</b>	0.0063	0.4781	<.0001
<b>Gold Stage COPD Severity</b>	0.0083	0.0130	0.0220
<b>Spirometric values</b>			
<b>Post-bronchodilator FEV1 (L)</b>	<.0001	<.0001	<.0001
<b>Post-bronchodilator FVC (L)</b>	<.0001	<.0001	<.0001
<b>%pred Post-Bronchodilator FEV1</b>	0.0050	0.0051	0.0033
<b>%pred Post-Bronchodilator FVC</b>	0.0444	0.0005	0.0258
<b>QoL/Respiratory symptoms</b>			
<b>CAT Score</b>	0.8583	0.8917	0.0531
<b>SGR Total Score</b>	0.6579	0.7330	0.2435
<b>SGR - Cough</b>	0.0337	0.0440	0.0001
<b>SGR - Sputum</b>	0.1509	0.1445	0.0025
<b>SGR - Wheeze</b>	0.2762	0.3284	0.0368
<b>mMRC Score</b>	0.9332	0.3338	0.9050
<b>HRCT Metrics</b>			
<b>Emphysema (%)</b>	0.3169	0.1294	0.0252

	<b>0 JYs vs &gt;0-&lt;10 JYs</b>	<b>0 JYs vs 10-&lt;20 JYs</b>	<b>0 JYs vs ≥20 JYs</b>
<b>Air trapping (%)</b>	0.0183	0.0209	0.0002
<b>PRM emphysema (%)</b>	0.3814	0.0463	0.0366
<b>PRM fsad (%)</b>	0.0016	0.0288	<.0001
<b>Total tissue volume (cm<sup>3</sup>)</b>	0.0182	0.0007	<.0001
<b>Airway wall thickening (Pi10)</b>	0.1319	0.4596	0.7594
<b>Exacerbation History (12 months prior)</b>			
<b>One or more acute exacerbations</b>	0.5196	0.1583	0.4928
<b>One or more severe exacerbations</b>	0.9815	0.4203	0.4531

For continuous variables we used two-sample t-tests without assuming equal variances and for categorical variables we used a chi-square test or Fisher's exact test when there was a cell with an expected number less than 5

**e-Table 3. Participant Follow-up Characteristics<sup>a</sup> by Marijuana Use Status**

Marijuana Use Status	Study Population (n=1863)	Never (n=933)	Former (n=775)	Current (n=155)
<b>Follow-up</b>				
Number of clinic visits <sup>c</sup>	3 (2)	3 (1)	3 (2)	3 (2)
Clinic visit follow-up time (years) <sup>b</sup>	4.2 (2.2)	4.2 (2.2)	4.2 (2.2)	4.1 (2.2)
Phone follow-up time (years) <sup>b</sup>	6.6 (2.3)	6.7 (2.4)	6.5 (2.3)	6.5 (2.2)

<sup>a</sup> Reported as N (%) unless otherwise stated. <sup>b</sup> Mean (SD) <sup>c</sup> Median (IQR)

**e-Table 4: Participant Follow-up Characteristics<sup>a</sup> by Joint Year History**

	0 JYs (n=933)	>0-<10 JYs (n=314)	10-<20 JYs (n=66)	≥ 20 JYs (n=137)
<b>Follow-up</b>				
Number of clinic visits <sup>c</sup>	3 (1)	3 (2)	3 (2)	3 (2)
Clinic visit follow-up time (years) <sup>b</sup>	4.2 (2.2)	4.2 (2.1)	4.1 (2.1)	4.3 (2.1)
Phone follow-up time (years) <sup>b</sup>	6.7 (2.4)	6.3 (2.2)	6.5 (2.1)	6.5 (2.2)

<sup>a</sup> Reported as N (%) unless otherwise stated. <sup>b</sup> Mean (SD) <sup>c</sup> Median (IQR)

**e-Table 5. Mean (25<sup>th</sup>, 75<sup>th</sup>) number of non-missing visits for each outcome variable by marijuana smoking status**

<b>Baseline Marijuana Use Status</b>	<b>Never (n=933)</b>	<b>Former (n=775)</b>	<b>Current (n=155)</b>
<b>Outcome</b>	<b>Median (25<sup>th</sup>, 75<sup>th</sup>)</b>	<b>Median (25<sup>th</sup>, 75<sup>th</sup>)</b>	<b>Median (25<sup>th</sup>, 75<sup>th</sup>)</b>
<b>Spirometric values</b>			
Post-bronchodilator FEV1 (L)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Post-bronchodilator FVC (L)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
<b>QoL/Respiratory symptoms</b>			
CAT Score	3.0 (3.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
SGR Total Score	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
<b>HRCT Metrics</b>			
% emphysema	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
% air trapping	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
PRM emphysema (%)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
PRM fsad (%)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
Total tissue volume (cm <sup>3</sup> )	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
Pi10	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)

**e-Table 6. Mean (25<sup>th</sup>, 75<sup>th</sup>) number of non-missing visits for each outcome variable by joint-year category**

<b>Baseline Marijuana Joint-Years</b>	<b>0 JYs (n=933)</b>	<b>&gt;0-&lt;10 JYs (n=314)</b>	<b>10-&lt;20 JYs (n=66)</b>	<b>≥ 20 JYs (n=137)</b>
<b>Outcome</b>	Median (25 <sup>th</sup> , 75 <sup>th</sup> )	Median (25 <sup>th</sup> , 75 <sup>th</sup> )	Median (25 <sup>th</sup> , 75 <sup>th</sup> )	Median (25 <sup>th</sup> , 75 <sup>th</sup> )
<b>Spirometric values</b>				
Post-bronchodilator FEV1 (L)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Post-bronchodilator FVC (L)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
<b>QoL/Respiratory symptoms</b>				
CAT Score	3.0 (3.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 3.0)	3.0 (2.0, 4.0)
SGR Total Score	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
<b>HRCT Metrics</b>				
% emphysema	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
% air trapping	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
PRM emphysema (%)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
PRM fsad (%)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
Total tissue volume (cm <sup>3</sup> )	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
Pi10	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)



**e-Table 7. Differences in Yearly Rates of Change<sup>a</sup> in Continuous Outcomes between Baseline Marijuana Use Status**

Marijuana Use Status Outcome	Current vs. Never		Former vs. Never		Current vs. Former	
	Diff. (95% CI)	p-value	Diff. (95% CI)	p-value	Diff. (95% CI)	p-value
<b>Spirometric values</b>						
Post-bronchodilator FEV1 (L)	-0.009 (-0.020,0.003)	0.136	0.003 (-0.004,0.009)	0.424	-0.011 (-0.023,0.000)	0.058
Post-bronchodilator FVC (L)	-0.007 (-0.025,0.010)	0.415	0.001 (-0.008,0.011)	0.816	-0.008 (-0.026,0.009)	0.355
<b>QoL/Respiratory symptoms</b>						
CAT Score	0.201 (-0.033,0.435)	0.091	0.001 (-0.128,0.130)	0.987	0.200 (-0.037,0.438)	0.099
SGRQ Total Score	0.029 (-0.444,0.502)	0.903	-0.116 (-0.380,0.148)	0.388	0.146 (-0.335,0.626)	0.552
<b>HRCT Metrics</b>						
% emphysema	-0.021 (-0.168,0.127)	0.781	-0.042 (-0.120,0.036)	0.289	0.021 (-0.128,0.171)	0.780
% air trapping	-0.164 (-0.622,0.294)	0.483	0.014 (-0.227,0.255)	0.912	-0.178 (-0.643,0.288)	0.454
PRM emphysema (%)	-0.061 (-0.220,0.098)	0.452	-0.077 (-0.162,0.007)	0.073	0.016 (-0.144,0.177)	0.841
PRM fsad (%)	-0.114 (-0.508,0.281)	0.572	0.050 (-0.157,0.256)	0.637	-0.163 (-0.563,0.237)	0.424
Total tissue volume (cm <sup>3</sup> )	-1.238 (-3.841,1.364)	0.351	-1.721 (-3.090,-0.351)	0.014	0.482 (-2.160,3.125)	0.720
Pi10	0.002 (-0.001,0.005)	0.311	0.001 (-0.001,0.002)	0.258	0.001 (-0.002,0.004)	0.680

<sup>a</sup> at average age at visit 1, average tobacco smoking pack-years at visit 1, average %predFEV1 at visit 1, and reference groups male gender, white race, and not current tobacco smoker at visit 1. Models were fit using available case analysis

**e-Table 8. Differences in Yearly Rates of Change<sup>a</sup> in Continuous Outcomes between Baseline Marijuana Joint Years**

Marijuana Joint Years	>0-<10 JYs vs. 0 JYs	10-<20 JYs vs. 0 JYs	≥ 20 JYs vs. 0 JYs
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Outcome	Diff. (95% CI)	p- value	Diff. (95% CI)	p- value	Diff. (95% CI)	p- value
<b>Spirometric values</b>						
Post-bronchodilator FEV1 (L)	0.002 (-0.007,0.010)	0.709	-0.004 (-0.020,0.011)	0.586	-0.003 (-0.014,0.009)	0.652
Post-bronchodilator FVC (L)	0.006 (-0.007,0.019)	0.368	-0.009 (-0.034,0.016)	0.498	-0.006 (-0.024,0.012)	0.487
<b>QoL/Respiratory symptoms</b>						
CAT Score	0.093 (-0.086,0.272)	0.310	-0.066 (-0.414,0.281)	0.709	-0.153 (-0.399,0.093)	0.223
SGR Total Score	-0.104 (-0.464,0.256)	0.572	0.074 (-0.629,0.776)	0.837	-0.351 (-0.846,0.143)	0.164
<b>HRCT Metrics</b>						
% emphysema	-0.033 (-0.133,0.068)	0.527	-0.029 (-0.239,0.181)	0.789	-0.010 (-0.147,0.127)	0.886
% air trapping	0.031 (-0.284,0.346)	0.848	-0.402 (-1.062,0.257)	0.231	0.277 (-0.151,0.704)	0.204
PRM emphysema (%)	-0.095 (-0.210,0.020)	0.106	-0.053 (-0.284,0.178)	0.653	-0.061 (-0.217,0.095)	0.445
PRM fsad (%)	0.043 (-0.230,0.315)	0.760	-0.463 (-1.016,0.091)	0.101	0.393 (0.023,0.762)	0.037
Total tissue volume (cm <sup>3</sup> )	-1.242 (-3.082,0.598)	0.185	-3.210 (-7.059,0.640)	0.102	-0.191 (-2.690,2.308)	0.881
Pi10	0.000 (-0.002,0.003)	0.791	0.001 (-0.003,0.006)	0.583	0.002 (-0.001,0.005)	0.304

**e-Table 9. Estimated Subject-Specific Yearly Change<sup>a</sup> in Odds of More Symptoms by Baseline Marijuana Use Status (A) and by Baseline Marijuana Joint Years (B)**

**A**

Baseline Marijuana Use Status	Never (n=933)	Former (n=775)	Current (n=155)
Outcome	OR (95% CI)	OR (95% CI)	OR (95% CI)
<b>QoL/Respiratory symptoms</b>			
SGRQ - Cough	0.95 (0.92,0.99)	0.91 (0.88,0.95)	1.02 (0.93,1.11)
SGRQ - Sputum	0.98 (0.94,1.01)	0.95 (0.91,0.99)	1.03 (0.94,1.12)
SGRQ - Wheeze	1.01 (0.98,1.05)	0.98 (0.94,1.02)	1.00 (0.92,1.09)
mMRC Score	1.14 (1.10,1.18)	1.07 (1.03,1.11)	1.19 (1.08,1.30)

<sup>a</sup>at average age at visit 1, average tobacco smoking pack-years at visit 1, average %predFEV<sub>1</sub> at visit 1, and reference groups male gender, white race, and not current tobacco smoker at visit 1. Models were fit using available case analysis.

**B**

<b>Baseline Marijuana Joint-Years</b>	<b>0 JYs (n=933)</b>	<b>&gt;0-&lt;10 JYs (n=314)</b>	<b>10-&lt;20 JYs (n=66)</b>	<b>≥ 20 JYs (n=137)</b>
<b>Outcome</b>	<b>OR (95% CI)</b>	<b>OR (95% CI)</b>	<b>OR (95% CI)</b>	<b>OR (95% CI)</b>
<b>QoL/Respiratory symptoms</b>				
SGRQ - Cough	0.95 (0.92,0.99)	0.91 (0.85,0.96)	0.92 (0.80,1.05)	0.87 (0.80,0.96)
SGRQ - Sputum	0.98 (0.94,1.01)	0.90 (0.84,0.96)	0.99 (0.86,1.13)	0.99 (0.90,1.09)
SGRQ - Wheeze	1.01 (0.98,1.05)	0.95 (0.89,1.01)	0.93 (0.81,1.07)	0.94 (0.86,1.03)
mMRC Score	1.14 (1.10,1.18)	1.06 (1.00,1.13)	1.13 (0.99,1.29)	1.08 (0.98,1.18)

<sup>a</sup>at average age at visit 1, average tobacco smoking pack-years at visit 1, average %predFEV<sub>1</sub> at visit 1, and reference groups male gender, white race, and not current tobacco smoker at visit 1. Models were fit using available case analysis.

**Supplemental Figure Legends**

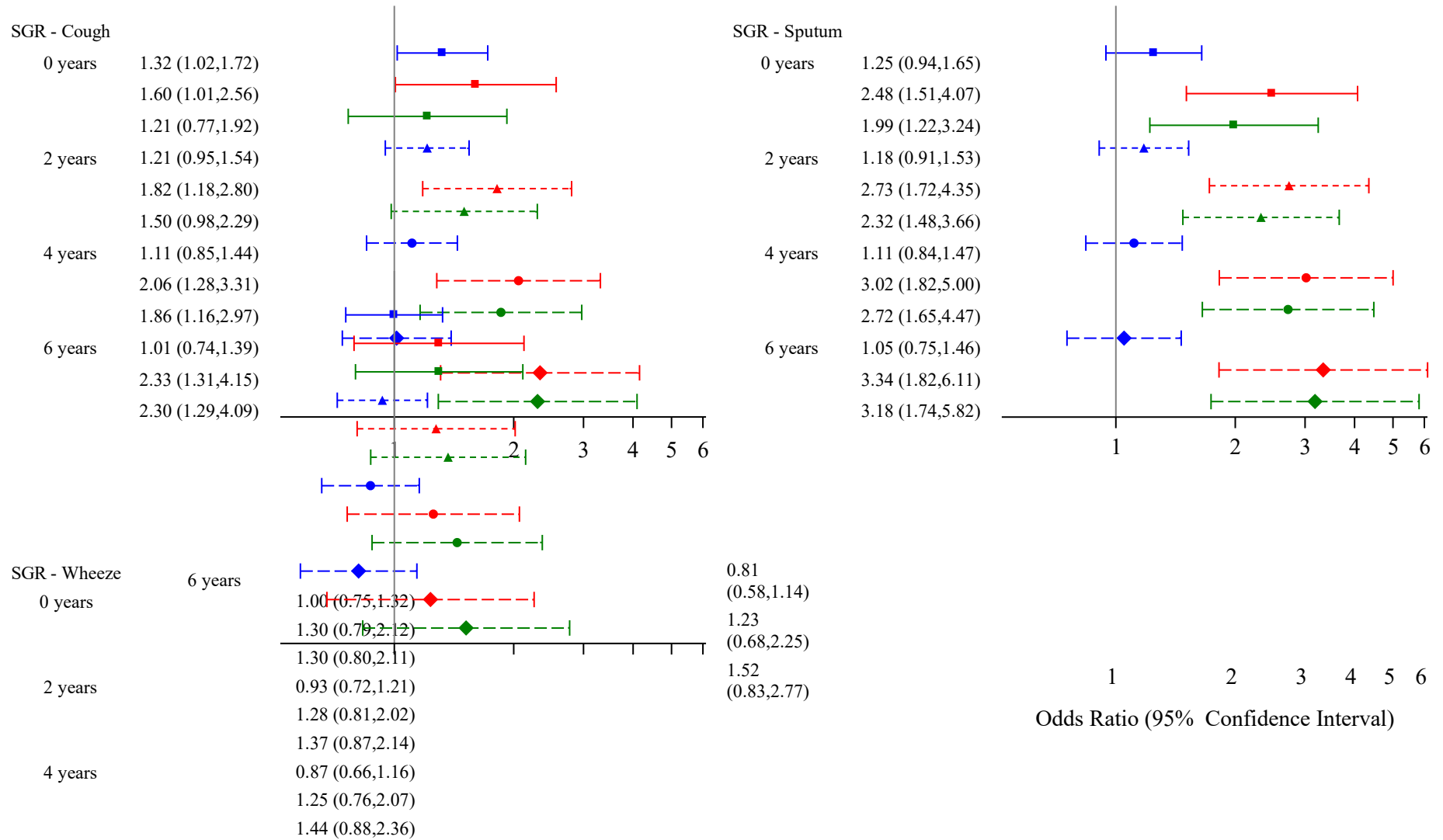
- e- Figure 1. Estimated yearly changes in odds of more respiratory symptoms during follow-up by baseline marijuana use status.**
- e- Figure 2. Estimated yearly changes in odds of more respiratory symptoms during follow-up by baseline marijuana joint-years categories.**
- e- Figure 3. Estimated yearly rates of all exacerbations (moderate or severe) and severe exacerbations during the first 365 days of follow-up and the total follow-up period by baseline marijuana exposure status.**
- e- Figure 4. Estimated yearly rates of all exacerbations (moderate or severe) and severe exacerbations during the first 365 days of follow-up and the total follow-up period by baseline marijuana joint-years categories.**
- e- Figure 5. Estimated hazard ratios for development of spirometry-defined COPD during follow-up by baseline marijuana exposure status.**

**e- Figure 6. Estimated hazard ratios for development of spirometry-defined COPD during follow-up by baseline marijuana joint-year categories.**

**Supplemental Figures**

**See following pages**

**e-Figure 1. Estimated Subject-Specific Odds Ratios of More Symptoms Over Time Between Baseline Marijuana Use Status (adjusted for age at visit 1, gender, tobacco smoking status at visit 1, tobacco smoking pack-years at visit 1, and %predFEV1 at visit 1)**



mMRC Score 0

years

1.07  
(0.83,1.36)

2 years

0.85  
(0.55,1.34)

4 years

0.94  
(0.75,1.18)

6 years

0.93  
(0.62,1.40)

0.99  
(0.67,1.48)

0.83  
(0.64,1.06)

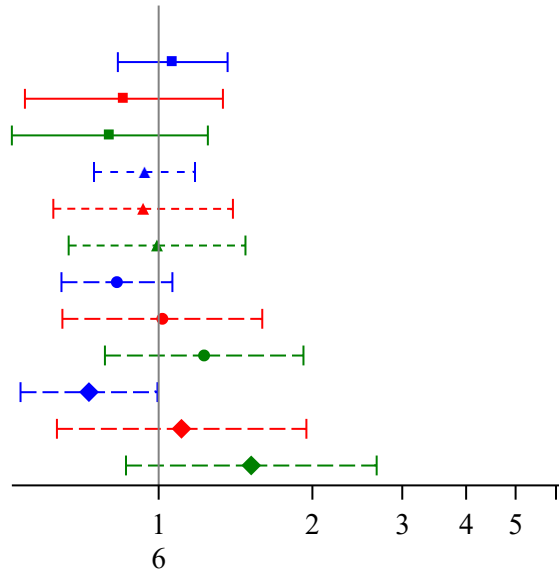
1.02  
(0.65,1.60)

1.23  
(0.78,1.92)

0.73  
(0.54,0.99)

1.11  
(0.63,1.95)

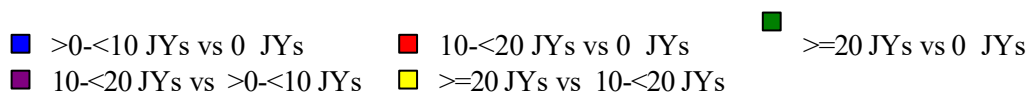
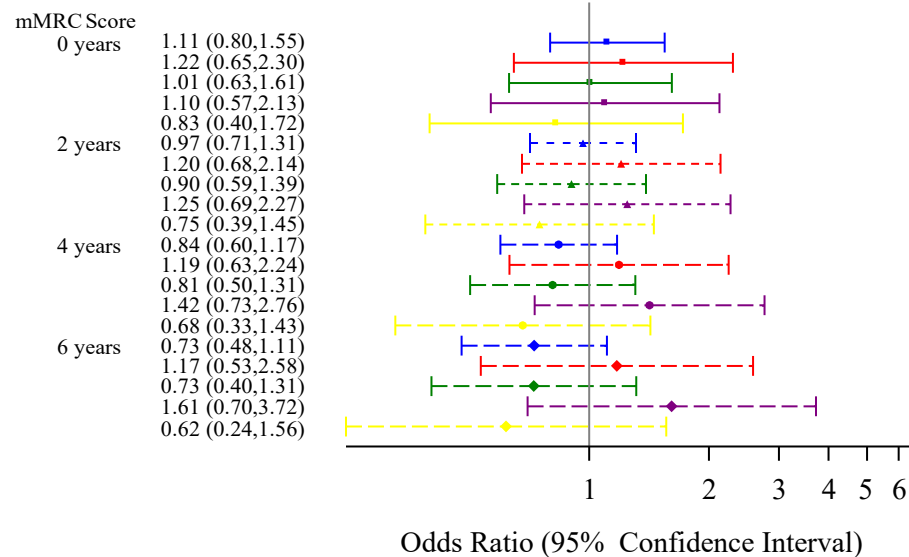
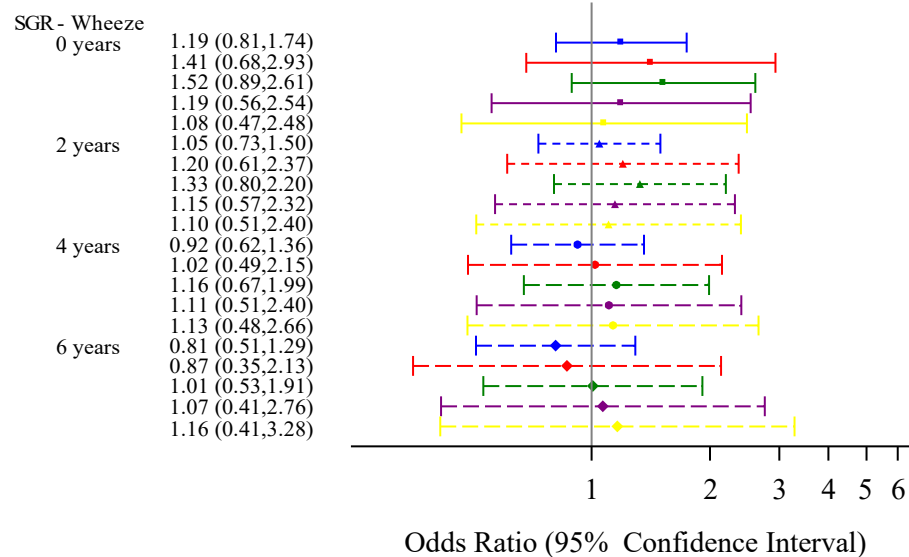
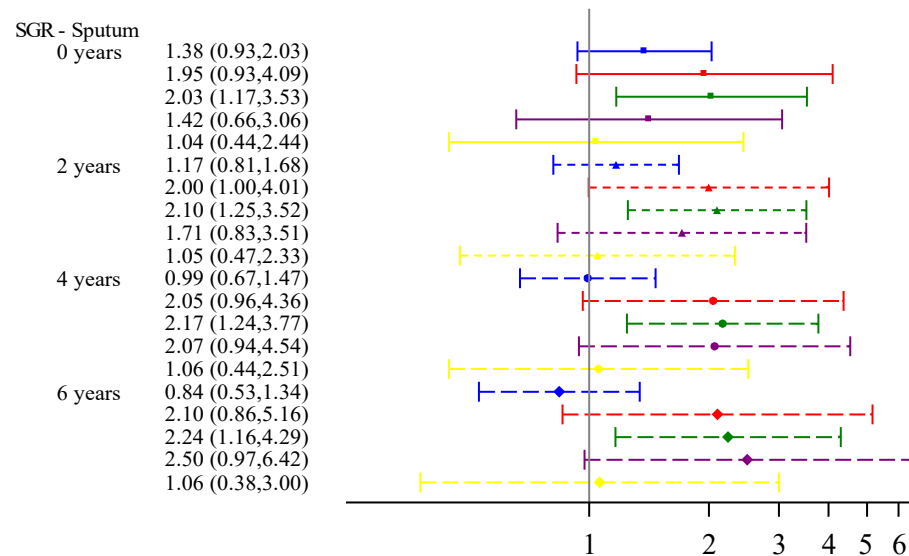
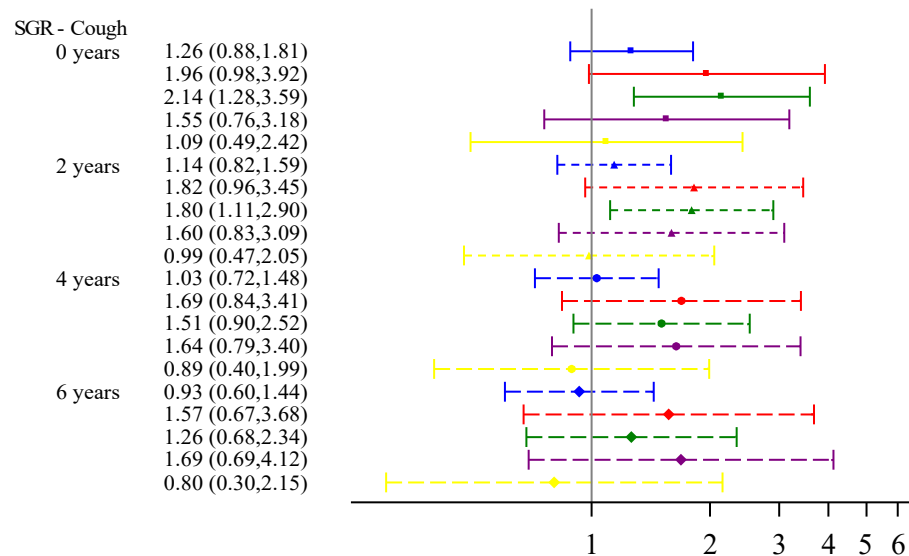
1.52  
(0.86,2.67)



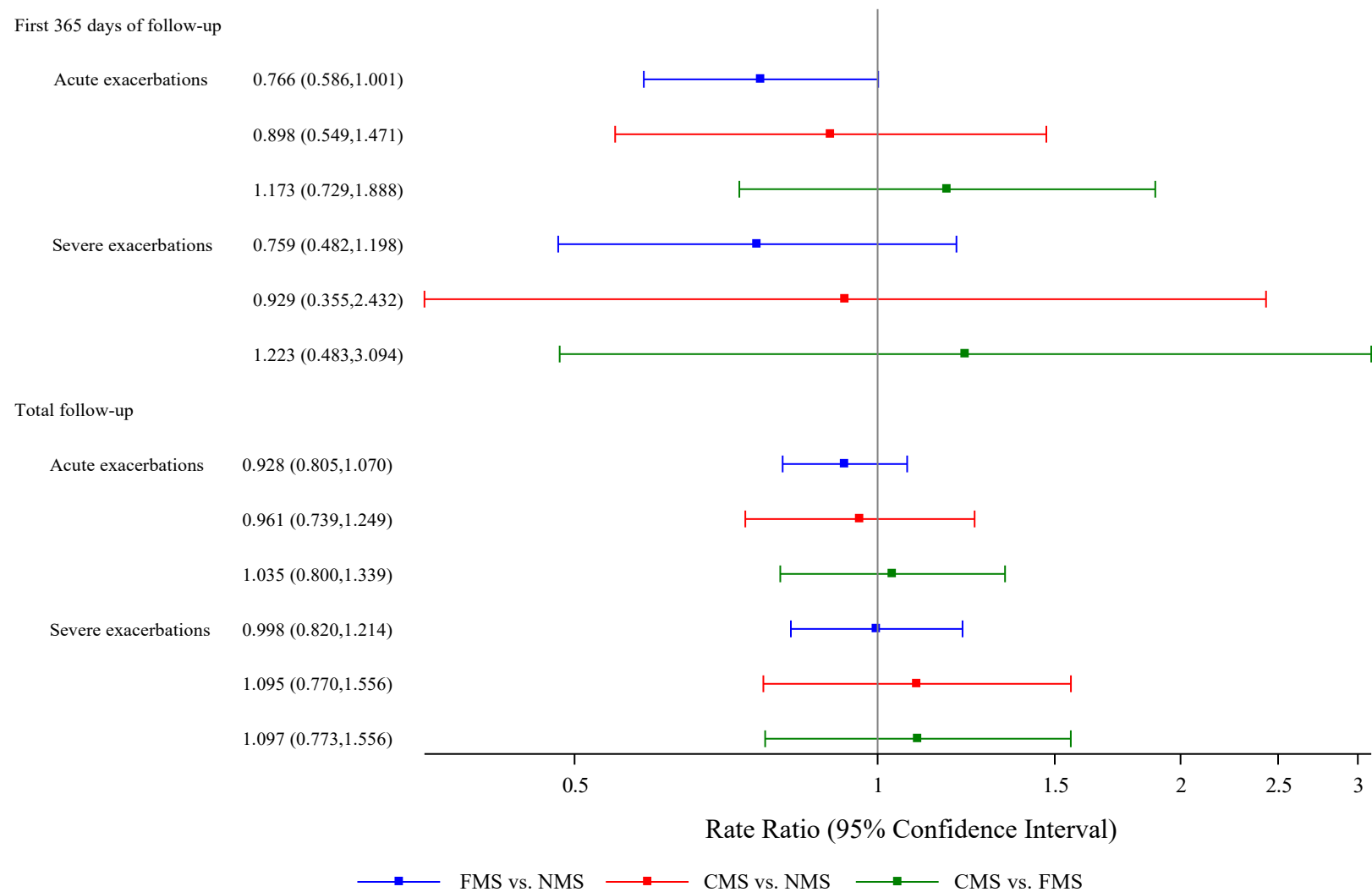
Odds Ratio (95% Confidence Interval)

■ FMS vs. NMS ■ CMS vs. NMS ■ CMS vs. FMS

**e-Figure 2. Estimated Subject-Specific Odds Ratios of More Symptoms Over Time Between Baseline Marijuana Joint Years (adjusted for age at visit 1, gender, tobacco smoking status at visit 1, tobacco smoking pack-years at visit 1, and %predFEV1 at visit 1)**

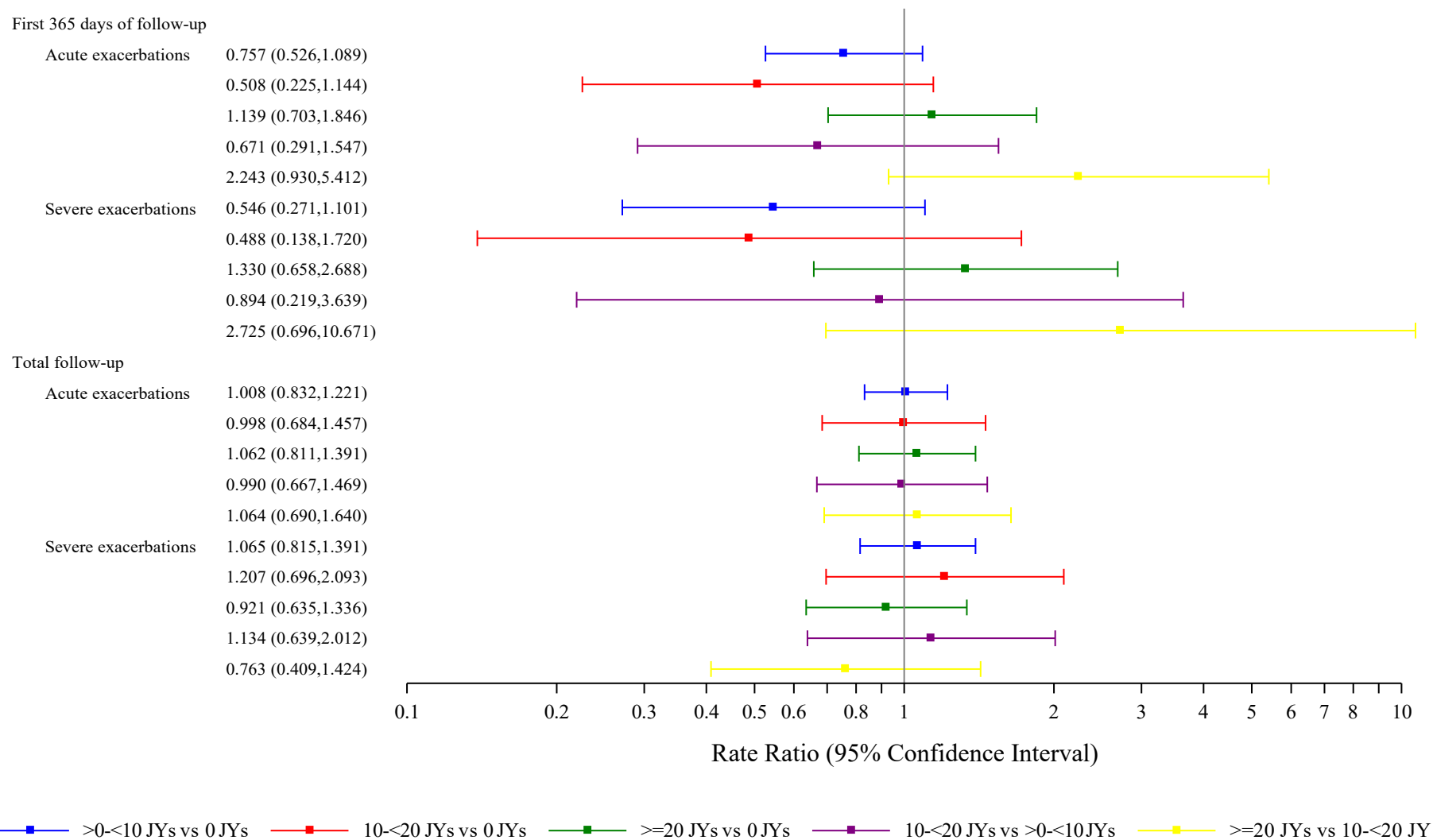


**e-Figure 3. Estimated Rate Ratios of Exacerbations among the Susceptible Population Between Baseline Marijuana Use Status Groups (adjusted for age at visit 1, gender, race, tobacco smoking status at visit 1, tobacco smoking pack-years at visit 1, and %predFEV1 at visit 1)**

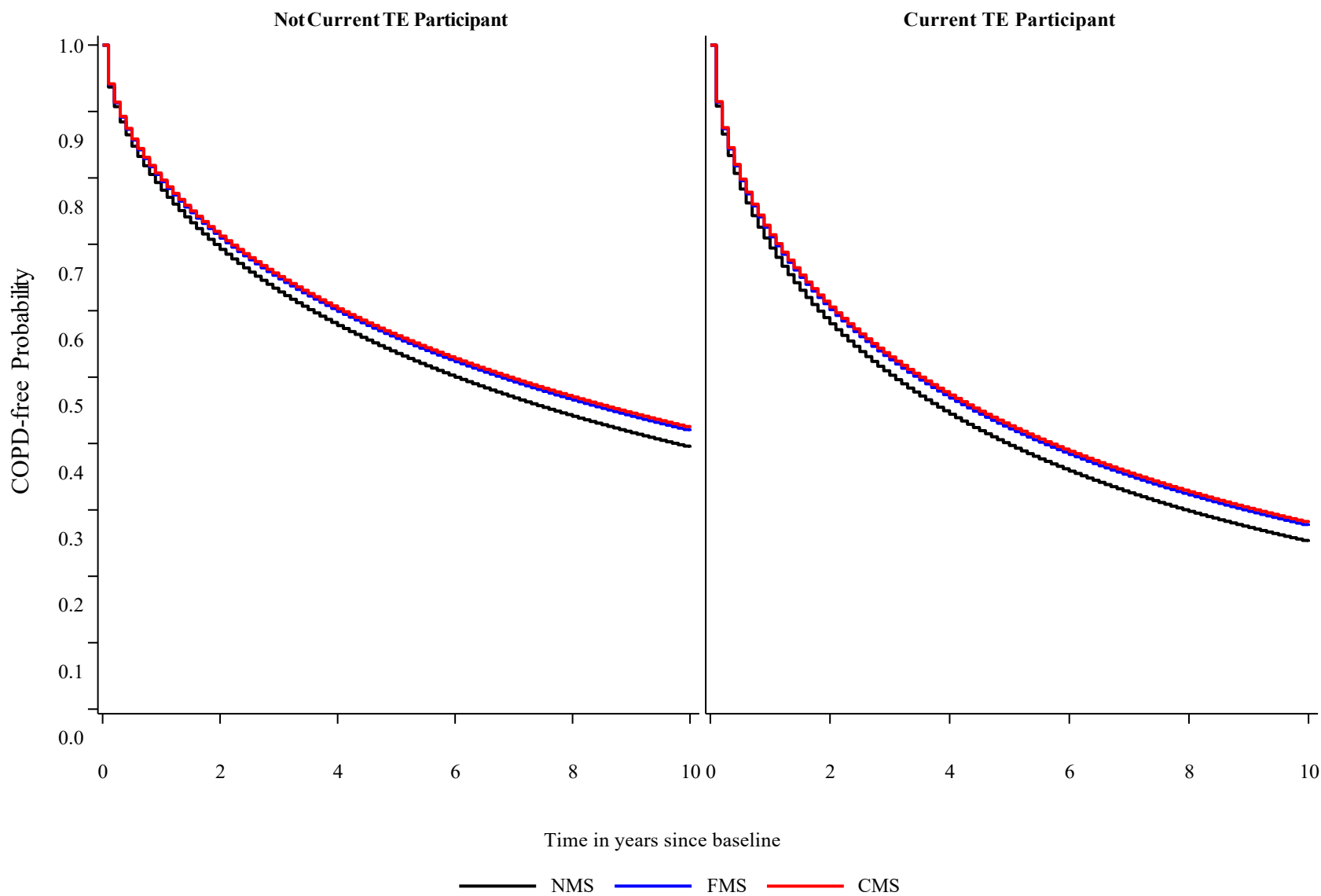




**e-Figure 4. Estimated Rate Ratios of Exacerbations among the Susceptible Population Between Baseline Marijuana Joint Years (adjusted for age at visit 1, gender, race, tobacco smoking status at visit 1, tobacco smoking pack-years at visit 1, and %predFEV1 at visit 1)**



**e-Figure 5. Estimated COPD-free Probability for Time to Obstruction (FEV1/FVC<0.70) by Baseline Marijuana Status (at average age at visit 1, average tobacco smoking pack-years at visit 1, and average %predFEV1 at visit 1, male gender, white race; by current tobacco smoking status at visit 1)**



**e-Figure 6. Estimated COPD-free Probability for Time to Obstruction (FEV1/FVC<0.70) by Baseline Marijuana Joint Years (at average age at visit 1, average tobacco smoking pack-years at visit 1, and average %predFEV1 at visit 1, male gender, white race; by current tobacco smoking status at visit 1)**

