

# Accelerated FEV<sub>1</sub> decline and risk of cardiovascular disease and mortality in a primary care population of COPD patients

## Supplementary material

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### Table E1: Relationship between accelerated FEV1 decline and risk of composite CVD

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
<b>Accelerated FEV<sub>1</sub> decline</b>	0.99 (0.93 – 1.05)	0.98 (0.90 – 1.06)
<b>AECOPD</b>		
None	Ref	Ref
1 moderate, 0 severe	1.05 (0.98 – 1.13)	1.06 (0.97 – 1.17)
2 moderate, 0 severe	1.14 (1.05 – 1.23)*	1.12 (1.00 – 1.26)*
≥3 moderate, 0 severe	1.26 (1.17 – 1.35)**	1.29 (1.17 – 1.43)**
1 severe, any moderate	1.90 (1.70 – 2.13)**	1.78 (1.52 – 2.08)**
≥2 severe, any moderate	2.59 (2.13 – 3.16)**	2.15 (1.61 – 2.86)**
<b>FEV1 % predicted</b>		
>80%	Ref	Ref
50-80%	1.05 (0.98 – 1.12)	1.06 (0.96 – 1.16)
30-50%	1.15 (1.07 – 1.24)**	1.02 (0.92 – 1.14)
<30%	1.23 (1.10 – 1.38)**	1.10 (0.93 – 1.30)
<b>Age</b>	1.05 (1.04 – 1.05)**	1.04 (1.04 – 1.05)**
<b>Men</b>	1.33 (1.27 – 1.40)**	1.40 (1.29 – 1.51)**
<b>Current smokers</b>	0.83 (0.78 – 0.87)**	1.13 (1.05 – 1.22)*
<b>BMI</b>		
Normal	Ref	Ref
Underweight	1.04 (0.91 – 1.20)	1.08 (0.89 – 1.30)
Overweight	1.10 (1.03 – 1.18)*	1.01 (0.93 – 1.10)
Obese	1.11 (1.04 – 1.19)**	1.09 (0.99 – 1.19)
<b>mMRC</b>		
0	Ref	Ref
1	1.18 (1.07 – 1.30)*	1.05 (0.95 – 1.17)
2	1.50 (1.35 – 1.66)**	1.24 (1.11 – 1.38)**
3	1.94 (1.73 – 2.18)**	1.50 (1.32 – 1.71)**
4	2.27 (1.82 – 2.82)**	1.51 (1.19 – 1.92)*
<b>Asthma</b>	0.91 (0.87 – 0.96)**	1.02 (0.95 – 1.10)
<b>Hypertension</b>	1.66 (1.58 – 1.74)**	1.31 (1.21 – 1.41)**
<b>Diabetes</b>	1.39 (1.30 – 1.50)**	1.09 (0.99 – 1.21)
<b>Statin use</b>	1.40 (1.33 – 1.47)**	1.14 (1.05 – 1.23)*

\*p value <0.05; \*\*p value<0.0001

Table E2: Relationship between accelerated FEV1 decline and risk of heart failure

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
<b>Accelerated FEV<sub>1</sub> decline</b>	1.01 (0.89 – 1.15)	0.99 (0.83 – 1.20)
<b>AECOPD</b>		
None	Ref	Ref
1 moderate, 0 severe	1.09 (0.93 – 1.27)	0.97 (0.78 – 1.22)
2 moderate, 0 severe	1.12 (0.93 – 1.34)	1.22 (0.95 – 1.57)
≥3 moderate, 0 severe	1.47 (1.26 – 1.72)**	1.46 (1.17 – 1.82)*
1 severe, any moderate	2.72 (2.18 – 3.40)**	2.22 (1.62 – 3.02)**
≥2 severe, any moderate	2.54 (1.60 – 4.02)**	1.60 (0.81 – 3.16)
<b>FEV1 % predicted</b>		
>80%	Ref	Ref
50-80%	1.18 (1.00 – 1.39)*	1.21 (0.97 – 1.52)
30-50%	1.74 (1.48 – 2.06)**	1.55 (1.21 – 1.98)*
<30%	2.07 (1.64 – 2.62)**	1.91 (1.34 – 2.70)**
<b>Age</b>	1.06 (1.05 – 1.07)**	1.10 (1.05 – 1.07)**
<b>Men</b>	1.23 (1.10 – 1.38)**	1.61 (1.36 – 1.91)**
<b>Current smokers</b>	0.79 (0.70 – 0.88)**	1.15 (0.97 – 1.36)
<b>BMI</b>		
Normal	Ref	Ref
Underweight	1.27 (0.94 – 1.70)	1.19 (0.80 – 1.78)
Overweight	1.02 (0.87 – 1.18)	0.89 (0.72 – 1.09)
Obese	1.35 (1.16 – 1.56)**	1.31 (1.07 – 1.62)*
<b>mMRC</b>		
0	Ref	Ref
1	1.39 (1.08 – 1.78)*	1.19 (0.91 – 1.55)
2	2.27 (1.73 – 2.87)**	1.60 (1.22 – 2.11)*
3	3.23 (2.47 – 4.23)**	1.94 (1.44 – 2.63)**
4	4.49 (2.91 – 6.93)**	2.10 (1.30 – 3.40)*
<b>Asthma</b>	0.85 (0.76 – 0.95)*	0.88 (0.74 – 1.04)
<b>Hypertension</b>	2.30 (2.05 – 2.58)**	1.70 (1.42 – 2.03)**
<b>Diabetes</b>	1.78 (1.54 – 2.07)**	1.25 (1.00-1.56)*
<b>Statin use</b>	1.43 (1.27 – 1.60)**	0.97 (0.81 – 1.16)

\*p value &lt;0.05; \*\*p value&lt;0.0001

Table E3: Relationship between accelerated FEV1 decline and risk of myocardial infarction

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
<b>Accelerated FEV<sub>1</sub> decline</b>	1.02 (0.87 – 1.19)	0.89 (0.70 – 1.12)
<b>AECOPD</b>		
None	Ref	Ref
1 moderate, 0 severe	1.07 (0.89 – 1.29)	1.21 (0.94 – 1.56)
2 moderate, 0 severe	1.10 (0.88 – 1.37)	1.13 (0.83 – 1.55)
≥3 moderate, 0 severe	1.44 (1.20– 1.74)**	1.38 (1.04 – 1.81)*
1 severe, any moderate	2.19 (1.63 – 2.94)**	1.57 (1.01 – 2.45)*
≥2 severe, any moderate	3.49 (2.16 – 5.62)**	2.58 (1.29 – 5.16)*
<b>FEV1 % predicted</b>		
>80%	Ref	Ref
50-80%	1.01 (0.84 – 1.21)	1.08 (0.83 – 1.40)
30-50%	1.30 (1.08 – 1.58)*	1.18 (0.88 – 1.59)
<30%	1.31 (0.97 – 1.78)	1.08 (0.68 – 1.72)
<b>Age</b>	1.04(1.03 – 1.04)**	0.14 (2.03 -1.05)**
<b>Men</b>	1.50 (1.31 -1.72)**	1.44(1.17 – 1.77)*
<b>Current smokers</b>	1.09(0.95 – 1.26)	1.45 (1.17 – 1.81)*
<b>BMI</b>		
Normal	Ref	Ref
Underweight	1.36 (0.98 – 1.88)	1.43 (0.94 – 2.17)
Overweight	0.97 (0.82 – 1.16)	0.87 (0.69 – 1.10)
Obese	0.76 (0.63 – 0.93)*	0.69 (0.53- 0.91)*
<b>mMRC</b>		
0	Ref	Ref
1	1.23 (0.92- 1.63)	1.14 (0.85 – 1.54)
2	1.65 (1.23-2.21)*	1.45 (1.06 – 1.99)*
3	2.50 (1.82 – 3.44)**	2.11(1.48 – 2.99)**
4	2.85 (1.60 -5.06)**	2.07 (1.11 – 3.7)*
<b>Asthma</b>	0.90 (0.79 – 1.03)	1.07 (0.88 – 1.31)
<b>Hypertension</b>	1.21 (1.06 – 1.39)*	1.08 (0.88 – 1.34)
<b>Diabetes</b>	1.30 (1.06 – 1.60)*	1.03(1.11 – 3.87)*
<b>Statin use</b>	1.01 (0.87 – 1.17)	1.16 (0.93 -1.44)

\*p value &lt;0.05; \*\*p value&lt;0.0001

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
<b>Accelerated FEV<sub>1</sub> decline</b>	0.99 (0.86- 1.14)	1.01(0.82- 1.23)
<b>AECOPD</b>		
None	Ref	Ref
1 moderate, 0 severe	0.97 (0.82 – 1.14)	1.01 (0.81- 1.27)
2 moderate, 0 severe	1.23 (1.03 – 1.47)*	1.06 (0.81- 1.39)
≥3 moderate, 0 severe	1.00 (0.84 – 1.20)	1.14 (0.88 – 1.46)
1 severe, any moderate	1.58 (1.19 -2.11)*	1.54 (1.04 – 2.29)*
≥2 severe, any moderate	2.50 (1.56 – 4.01)**	1.22 (0.50 – 3.01)
<b>FEV1 % predicted</b>		
>80%	Ref	Ref
50-80%	1.16 (0.99 – 1.36)	1.20 (0.95 – 1.50)
30-50%	1.07 (0.90 – 1.28)	1.03 (0.79 – 1.36)
<30%	1.28 (0.97 – 1.68)	1.26 (0.83-1.91)
<b>Age</b>	1.06 (1.05 – 1.06)**	1.05 (1.04 – 1.06)**
<b>Men</b>	1.24 (1.10 – 1.40)*	1.29 (1.07 – 1.55)*
<b>Current smokers</b>	0.87 (0.77 – 0.98)*	1.24 (1.03 – 1.50)*
<b>BMI</b>		
Normal	Ref	Ref
Underweight	0.83 (0.59 – 1.17)	0.85 (0.54 – 1.35)
Overweight	0.97 (0.83-1.12)	0.97 (0.80 – 1.18)
Obese	0.63 (0.53 – 0.76)**	0.65 (0.51-0.84)*
<b>mMRC</b>		
0	Ref	Ref
1	1.09 (0.87 – 1.36)	0.96 (0.76 – 1.22)
2	1.17 (0.91 – 1.49)	0.94 (0.72 – 1.24)
3	1.62 (1.23 -2.14)*	1.31 (0.96 – 1.78)
4	2.27 (1.38 – 3.74)*	1.56 (0.89 – 2.75)
<b>Asthma</b>	0.77 (0.68 – 0.87)**	0.82(0.68 – 0.99)*
<b>Hypertension</b>	1.37 (1.22 – 1.55)**	1.00 (0.83 – 1.21)

Table E4:  
Relationship  
between accelerated  
FEV1 decline and  
risk of stroke

<b>Diabetes</b>	1.23 (1.03 – 1.48)*	1.23 (0.94-1.61)
<b>Statin use</b>	2.30 (1.14 – 1.47)**	0.97 (0.80 – 1.19)

\*p value <0.05; \*\*p value<0.0001

Table E5: Relationship between accelerated FEV1 decline and risk of atrial fibrillation

<b>Exposure and covariates</b>	<b>Unadjusted HR 95% CI</b>	<b>Adjusted HR* (95% CI)</b>
<b>Accelerated FEV<sub>1</sub> decline</b>	0.92(0.82-1.04)	0.97 (0.81 -1.15)
<b>AECOPD</b>		
None	Ref	Ref
1 moderate, 0 severe	1.14 (0.99 – 1.30)	1.06 (0.87 – 1.28)
2 moderate, 0 severe	1.12 (0.95 – 1.32)	1.06 (0.83- 1.34)
≥3 moderate, 0 severe	1.27 (1.10-1.47)*	1.31 (1.07 – 1.61)*
	1.57 (1.22 – 2.03)*	1.53 (1.07 – 2.17)*

1 severe, any moderate ≥2 severe, any moderate	2.56 (1.68- 3.88)**	2.64 (1.49 – 4.66)*
<b>FEV1 % predicted</b>		
>80%	Ref	Ref
50-80%	1.11 (0.97 – 1.28)	1.06 (0.88 – 1.28)
30-50%	1.26 (1.09-1.46)*	1.09(0.87 – 1.36)
<30%	1.20(0.94 – 1.53)	1.09 (0.75 -1.60)
<b>Age</b>	1.07 (1.06 – 1.07)**	1.07 (1.06 – 1.-8)**
<b>Men</b>	1.39 (1.25 – 1.54)**	1.44 (1.23- 1.68)**
<b>Current smokers</b>	0.61 (0.55 – 0.68)**	0.91 (0.78 – 1.06)
<b>BMI</b>		
Normal	Ref	Ref
Underweight	0.95 (0.69 -1.32)	1.28 (0.84 – 1.93)
Overweight	1.29 (1.12-1.48)**	1.26 (1.05- 1.52)*
Obese	1.37 (1.18 – 1.58)**	1.50 (1.23 – 1.83)**
<b>mMRC</b>		
0	Ref	Ref
1	1.11 (0.91 -1.34)	0.98 (0.79 – 1.20)
2	1.36 (1.11 – 1.66)*	1.06(0.85 – 1.33)
3	1.43 (1.12 – 1.82)*	1.03 (0.78 – 1.37)
4	1.75 (1.09 – 2.82)*	1.16 (0.69 – 1.93)
<b>Asthma</b>	0.01 (0.82-1.01)	1.09 (0.94-1.27)
<b>Hypertension</b>	1.82 (1.64 – 2.12)**	1.42 (1.21- 1.67)**
<b>Diabetes</b>	1.25 (1.07 -1.46)*	1.09 (0.88 – 1.35)
<b>Statin use</b>	1.25 (1.12- 1.40)**	0.99 (0.84-1.16)

\*p value <0.05; \*\*p value<0.0001

Table E6: Relationship between accelerated FEV1 decline and risk of coronary artery disease excluding myocardial infarction

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
<b>Accelerated FEV<sub>1</sub> decline</b>	1.03(0.93-1.15)	1.02(0.87 – 1.19)
<b>AECOPD</b>		
None	Ref	Ref
1 moderate, 0 severe	0.98 (0.87 – 1.12)	1.11 (0.93 – 1.32)
2 moderate, 0 severe	1.09 (0.94- 1.26)	1.18 (0.96 – 1.44)
≥3 moderate, 0 severe	1.14 (1.00 – 1.31)*	1.20 (0.99 – 1.45)
1 severe, any moderate	1.64 (1.32 -2.04)**	1.86 (1.39 – 2.50)**
≥2 severe, any moderate	2.17 (1.46 - 3.21)**	2.69 (1.61 – 4.49)**
<b>FEV1 % predicted</b>		
>80%	Ref	Ref
50-80%	0.90 (0.80 – 1.01)	0.91 (0.77 – 1.07)
30-50%	0.77 (0.68 – 0.89)**	0.68 (0.56 – 0.84)**
<30%	0.82 (0.66 – 1.03)	0.70 (0.50- 0.99)*
<b>Age</b>	1.02 (1.02 -1.02)**	1.02 (0.87 – 1.19)
<b>Men</b>	1.28 (1.25 -1.52)**	1.33 (1.15 – 1.53)*
<b>Current smokers</b>	0.97 (0.88- 1.07)	1.31 (1.04 -1.39)*
<b>BMI</b>		
Normal	Ref	Ref
Underweight	0.94 (0.71 -1.25)	0.74 (0.47 – 1.16)
Overweight	1.17 (1.03-1.33)*	1.02 (0.87 – 1.20)
Obese	1.27 (1.12- 1.45)**	1.13 (0.95 – 1.35)
<b>mMRC</b>		
0	Ref	1.05 (0.87 – 1.27)
1	1.14 (0.95 – 1.37)	1.30 (1.06 -1.60)*
2	1.43 (1.18 – 1.73)**	1.59 (1.26 – 2.01)**
3	1.77 (1.43 – 2.20)**	1.04 (0.60 – 1.79)
4	1.26 (0.75 – 2.10)	
<b>Asthma</b>	1.07 (0.97 – 1.18)	1.17(1.03 -1.34)*
<b>Hypertension</b>	1.61 (1.46 – 1.77)**	1.32 (1.14 – 1.53)**
<b>Diabetes</b>	1.42 (1.24 – 1.63)**	0.94 (0.78 – 1.15)
<b>Statin use</b>	1.80 (1.64 – 1.99)**	1.60 (1.39 – 1.85)**

\*p value <0.05; \*\*p  
value<0.0001

Table E7: Relationship between accelerated FEV1 decline and risk of CVD death

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
<b>Accelerated FEV<sub>1</sub> decline</b>	0.96 (0.79-1.17)	0.94 (0.71-1.25)



<b>AECOPD</b>		
None	Ref	Ref
1 moderate, 0 severe	1.12 (0.90-1.39)	1.19 (0.89-1.61)
2 moderate, 0 severe	1.06 (0.90-1.38)	1.13 (0.78-1.63)
≥3 moderate, 0 severe	1.03 (0.81-1.31)	0.73 (0.50-1.09)
1 severe, any moderate	2.61 (0.80-1.61)**	1.94 (1.24-3.05)*
≥2 severe, any moderate	2.13 (1.90-4.34)*	0.91 (0.29-2.92)
<b>FEV1 % predicted</b>		
>80%	Ref	Ref
50-80%	1.23 (0.97-1.57)	1.12 (0.81-1.54)
30-50%	1.87 (1.46-2.40)**	1.23 (0.86-1.77)
<30%	2.18 (1.53-3.09)**	1.40 (0.83-2.38)
<b>Age</b>	1.06 (1.05-1.08)**	1.06 (1.04-1.07)**
<b>Men</b>	1.50 (1.26-1.78)**	1.80 (1.40-2.32)**
<b>Current smokers</b>	1.08 (0.91-1.29)	1.62 (1.24-2.10)**
<b>BMI</b>		
Normal	Ref	Ref
Underweight	1.28 (0.87-1.89)	1.03 (0.59-1.81)
Overweight	0.73 (0.59-0.92)*	0.63 (0.47-0.86)*
Obese	0.84 (0.67-1.06)	0.94 (0.70-1.27)
<b>mMRC</b>		
0	Ref	Ref
1	1.08 (0.75-1.55)	0.94 (0.64-1.39)
2	2.02 (1.41-2.89)	1.57 (1.06-2.32)*
3	3.16 (2.16-4.63)	2.52 (1.66-3.83)**
4	5.15 (2.90-9.16)	2.94 (1.52-5.69)*
<b>Asthma</b>	0.78 (0.66-0.93)*	0.80 (0.62-1.03)
<b>Hypertension</b>	1.83 (1.55-2.16)**	1.49 (1.15-1.93)*
<b>Diabetes</b>	1.62 (1.29-2.04)**	0.90 (0.63-1.29)
<b>Statin use</b>	1.27 (1.-7-1.51)*	1.17 (0.90-1.52)

\*p value <0.05; \*\*p value<0.0001

Table E8: Relationship between risk of CVD outcomes and accelerated FEV<sub>1</sub> decline (by quartiles, measured relative to baseline, measured as percent predicted, and linearly)

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Quartile 1 (slowest decline)	Ref	Ref
Quartile 2	1.05 (0.98 – 1.13)	0.96 (0.87 – 1.06)
Quartile 3	1.06 (0.98 – 1.14)	0.96 (0.87 – 1.06)
Quartile 4 (accelerated decline)	1.02 (0.95– 1.10)	0.95 (0.85 – 1.05)
Decline in relative FEV <sub>1</sub>	1.06 (1.00 – 1.13)	1.00 (0.91 – 1.09)
Decline in FEV <sub>1</sub> % predicted	1.05 (0.98 – 1.13)	1.00 (0.90 – 1.11)
Linear FEV <sub>1</sub> decline	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)

\*p value

\*\*p

<0.05;

value<0.0001

Table E9: Relationship between rate of FEV1 decline and risk of composite CVD

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
<b>Decline</b>		
>-20ml/year	Ref	Ref
-20 to -40 ml/year	1.05 (0.99 – 1.12)	1.00 (0.91 - 1.09)
-40 to -60ml/year	0.98(0.91 – 1.07)	0.91 (0.81-1.02)
<-60ml	1.01 (0.93 – 1.09)	1.02 (0.91 – 1.14)
<b>AECOPD</b>		
None	Ref	Ref
1 moderate, 0 severe	1.05 (0.98 – 1.13)	1.06 (0.97 – 1.17)
2 moderate, 0 severe	1.14 (1.05 – 1.23)*	1.12 (1.00 – 1.26)*
≥3 moderate, 0 severe	1.26 (1.17 – 1.35)**	1.29 (1.17 – 1.43)**
1 severe, any moderate	1.90 (1.70 – 2.13)**	1.78 (1.52 – 2.08)**
≥2 severe, any moderate	2.59 (2.13 – 3.16)**	2.15 (1.61 – 2.86)**
<b>FEV1 % predicted</b>		
>80%	Ref	Ref
50-80%	1.05 (0.98 – 1.12)	1.06 (0.96 – 1.16)
30-50%	1.15 (1.07 – 1.24)**	1.02 (0.92 – 1.14)
<30%	1.23 (1.10 – 1.38)**	1.10 (0.92 – 1.30)
<b>Age</b>	1.05 (1.04 – 1.05)**	1.04 (1.04 – 1.05)**
<b>Men</b>	1.33 (1.27 – 1.40)**	1.39 (1.29 – 1.50)**
<b>Current smokers</b>	0.83 (0.78 – 0.87)**	1.13 (1.05 – 1.22)*
<b>BMI</b>		
Normal	Ref	Ref
Underweight	1.04 (0.91 – 1.20)	1.08 (0.89 – 1.30)
Overweight	1.10 (1.03 – 1.18)*	1.01 (0.93 – 1.10)
Obese	1.11 (1.04 – 1.19)**	1.08 (0.99 – 1.19)
<b>mMRC</b>		
0	Ref	Ref
1	1.18 (1.07 – 1.30)*	1.05 (0.95 – 1.17)
2	1.50 (1.35 – 1.66)**	1.24 (1.10 – 1.38)**
3	1.94 (1.73 – 2.18)**	1.50 (1.32 – 1.71)**
4	2.27 (1.82 – 2.82)**	1.52 (1.19 – 1.92)*
<b>Asthma</b>	0.91 (0.87 – 0.96)**	1.02 (0.95 – 1.10)
<b>Hypertension</b>	1.66 (1.58 – 1.74)**	1.31 (1.21 – 1.41)**
<b>Diabetes</b>	1.39 (1.30 – 1.50)**	1.09 (0.99 – 1.21)
<b>Statin use</b>	1.40 (1.33 – 1.47)**	1.14 (1.05 – 1.23)*

\*p value &lt;0.05; \*\*p value&lt;0.0001

Table E10: Relationship between accelerated FEV<sub>1</sub> decline and risk of composite CVD in patients without a history of asthma

Model	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Accelerated FEV1 decline	0.98 (0.90 – 1.07)	0.96 (0.85 – 1.08)

\*p value <0.05; \*\*p value<0.0001

Model	Crude HR (95% CI)	Adjusted HR (95% CI)
GP diagnosed CVD	0.96 (0.89 – 1.04)	0.93 (0.83 – 1.05)
Hospitalised CVD	1.02 (0.90 – 1.16)	0.96 (0.79 – 1.16)
Death from CVD	0.96 (0.70 – 1.17)	0.94 (0.71 – 1.25)

Table E11: Relationship between accelerated FEV1 decline and risk of GP diagnosed CVD, hospitalised CVD, and death from CVD

\*p value <0.05; \*\*p value<0.0001

Model	Crude HR (95% CI)	Adjusted HR (95% CI)
Males	0.93 (0.85 – 1.03)	0.98 (0.85 – 1.12)
Females	0.97 (0.90 – 1.04)	0.98 (0.88 – 1.09)
<b>Stratified by age</b>		
35-50	0.92 (0.62 – 1.38)	0.58 (0.30 – 1.12)
50-65	1.07 (0.95 – 1.20)	1.02 (0.86 – 1.21)
65-80	1.04 (0.96 – 1.13)	0.91 (0.81 – 1.02)
80≤	1.15 (1.00 – 1.32)	1.11 (0.92 – 1.35)
<b>Stratified by smoking status</b>		
Ex-smoker	0.94 (0.86 – 1.03)	0.93 (0.81 – 1.07)
Current smoker	1.03 (0.96 – 1.11)	1.00 (0.89 – 1.11)
<b>Stratified by AECOPD</b>		
0, 1, or 2 mod & no severe	0.98 (0.92 – 1.05)	0.98 (0.89 – 1.09)
3 mod & no severe <u>or</u> any severe	0.98 (0.88 – 1.09)	0.99 (0.84 – 1.16)
<b>Stratified by mMRC</b>		
0	1.05 (0.86 – 1.27)	1.02 (0.82 – 1.26)
1	1.00 (0.88 – 1.14)	0.98 (0.85 – 1.12)
2	0.94 (0.81 – 1.09)	0.99 (0.84 – 1.16)
3	0.89 (0.73 – 1.08)	0.95 (0.77 – 1.17)
4	0.73 (0.46 – 1.16)	0.73 (0.44 – 1.21)
<b>Stratified by airflow obstruction</b>		
≥80% FEV <sub>1</sub> predicted	1.01 (0.88 – 1.16)	0.97 (0.83 – 1.12)
50-80% FEV <sub>1</sub> predicted	0.99 (0.90 – 1.08)	1.02 (0.93 – 1.13)
30-50% FEV <sub>1</sub> predicted	0.92 (0.83 – 1.02)	0.99 (0.88 – 1.11)
≤30% FEV <sub>1</sub> predicted	1.02 (0.83 – 1.26)	1.08 (0.86 – 1.36)

Table E12: Relationship between accelerated FEV<sub>1</sub> decline and risk of composite CVD stratified by gender, age, smoking status, AECOPD, mMRC, and airflow obstruction

\*p value <0.05; \*\*p value <0.0001

Table E13: Relationship between accelerated FEV1 decline and risk of composite CVD in patients with at least 4 FEV1 measurements during baseline period

Exposure and covariates	Unadjusted HR 95% CI	Adjusted HR* (95% CI)
<b>Accelerated FEV1 decline</b>	1.02 (0.92 – 1.14)	1.04 (0.90 – 1.21)
<b>AECOPD</b>		
None	Ref	Ref
1 moderate, 0 severe	1.11 (0.97 – 1.27)	1.17 (0.98 – 1.40)
2 moderate, 0 severe	1.20 (1.03 – 1.40)*	1.22 (0.99 – 1.50)
≥3 moderate, 0 severe	1.33 (1.17 – 1.51)**	1.46 (1.22 – 1.76)**
1 severe, any moderate	2.12 (1.75 – 2.58)**	2.07 (1.59 – 2.69)**
≥2 severe, any moderate	2.41 (1.72 – 3.39)**	2.17 (1.33 – 3.53)*
<b>FEV1 % predicted</b>		
>80%	Ref	Ref
50-80%	1.00 (0.88 – 1.14)	1.09 (0.92 – 1.30)
30-50%	1.09 (0.95 – 1.25)	1.39 (0.85 – 1.28)
<30%	1.00 (0.81 – 1.24)	1.02 (0.74 – 1.41)
<b>Age</b>	1.05 (1.04 – 1.05)**	1.05 (1.04 – 1.05)**
<b>Men</b>	1.51 (1.37 – 1.67)**	1.65 (1.43 – 1.90)**
<b>Current smokers</b>	0.85 (0.77 – 0.93)*	1.23 (1.07 -1.42)*
<b>BMI</b>		
Normal	Ref	Ref
Underweight	0.80 (0.60 – 1.07)	0.91 (0.62 – 1.32)
Overweight	1.01 (0.90 – 1.14)	0.88 (0.75 – 1.03)
Obese	1.01 (0.88 – 1.15)	0.97 (0.81 – 1.15)
<b>mMRC</b>		
0	Ref	Ref
1	1.14 (0.94 – 1.38)	1.03 (0.84 – 1.26)
2	1.55 (1.27 – 1.88)**	1.28 (1.03 – 1.58)*
3	1.84 (1.48 – 2.29)**	1.49 (1.18 – 1.89)*
4	2.35 (1.58 – 3.50)**	1.50 (0.97 – 2.31)
<b>Asthma</b>	0.90 (0.81 – 0.99)*	1.01 (0.89 – 1.16)

<b>Hypertension</b>	1.64 (1.49 – 1.81)**	1.41 (1.22 – 1.62)**
<b>Diabetes</b>	1.40 (1.21 – 1.61)**	1.19 (0.99 – 1.44)
<b>Statin use</b>	1.39 (1.26 – 1.53)**	1.02 (0.88 – 1.18)

\*p value <0.05; \*\*p value<0.0001

Table E14: Relationship between accelerated FEV1 decline and risk of composite CVD in patients with at least 2 FEV1 measurements at least 2 years apart.

<b>Exposure and covariates</b>	<b>Unadjusted HR 95% CI</b>	<b>Adjusted HR* (95% CI)</b>
<b>Accelerated FEV1 decline</b>	1.07 (0.95 – 1.20)	0.95 (0.79 – 1.14)
<b>AECOPD</b>		
None	Ref	Ref
1 moderate, 0 severe	1.05 (0.98 – 1.13)	0.95 (0.78 – 1.15)
2 moderate, 0 severe	1.14 (1.05 – 1.23)*	0.96 (0.75 – 1.22)
≥3 moderate, 0 severe	1.26 (1.17 – 1.35)**	1.13 (0.91 – 1.39)
1 severe, any moderate	1.90 (1.70 – 2.13)**	1.54 (1.11 -2.14)*
≥2 severe, any moderate	2.59 (2.13 – 3.16)**	1.63 (0.83 – 3.20)
<b>FEV1 % predicted</b>		
>80%	Ref	Ref
50-80%	0.94 (0.77 – 1.15)	0.94 (0.77 – 1.15)
30-50%	1.14 (0.91 – 1.43)	1.14 (0.91 – 1.43)
<30%	1.15 (1.07 – 1.24)**	1.33 (0.95 – 1.86)
<b>Age</b>	1.23 (1.10 – 1.38)**	
<b>Men</b>	1.05 (1.-4 – 1.05)**	1.04(1.02 – 1.05)**
<b>Current smokers</b>	1.33 (1.27 – 140)**	1.32 (1.12 – 1.55)*
<b>BMI</b>	0.82 (0.78 – 0.87)**	1.07 (0.91 – 1.26)
Normal	Ref	Ref
Underweight	1.04 (0.91 – 1.20)	1.19 (0.79 – 1.77)
Overweight	1.10 (1.03 – 1.18)*	1.23 (1.02 – 1.48)*
Obese	1.11 (1.04 – 1.19)*	1.11 (0.90 – 1.37)
<b>mMRC</b>		
0	Ref	Ref
1	1.18 (1.07 – 1.30)*	1.13 (0.90 – 1.41)
2	1.50 (1.35 – 1.66)**	1.39 (1.10 – 1.76)*
3	1.94 (1.72 – 2.18)**	1.52 (1.15 – 2.01)*
4	2.27 (1.82 – 2.82)**	1.76 (1.08 – 2.85)*
<b>Asthma</b>	0.92 (0.87 – 0.96)**	1.01 (0.86 – 1.18)



<b>Hypertension</b>	1.66 (1.58 – 1.74)**	1.34 (1.14 – 1.59)**
<b>Diabetes</b>	1.39 (1.30 – 1.50)**	1.06 (0.85 – 1.34)
<b>Statin use</b>	1.40 (1.33 – 1.47)**	1.29 (1.09 – 1.53)*

\*p value <0.05; \*\*p value<0.0001

Figure E1: Number of FEV<sub>1</sub> measurements over the three-year baseline period (N=36,382)

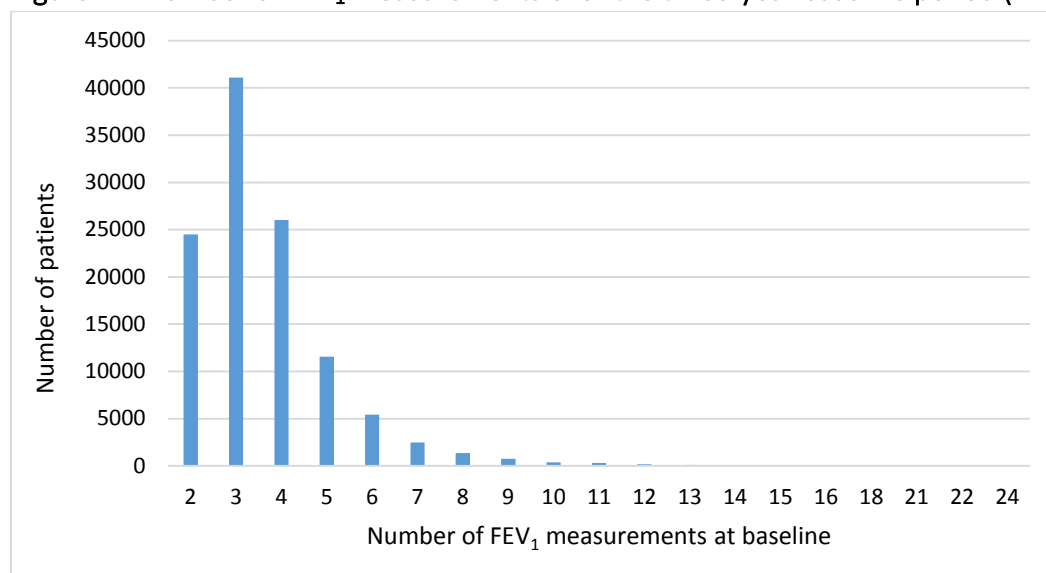


Figure E2: Time intervals between FEV<sub>1</sub> measurements over the three-year baseline period

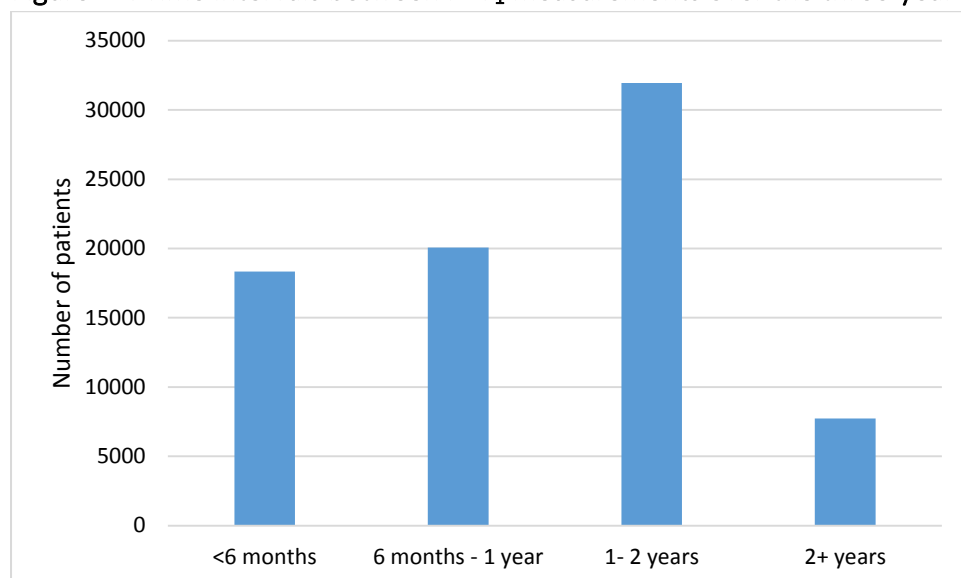


Figure E3: Spline regression with knots at the 10<sup>th</sup>, 50<sup>th</sup>, and 90<sup>th</sup> percentile

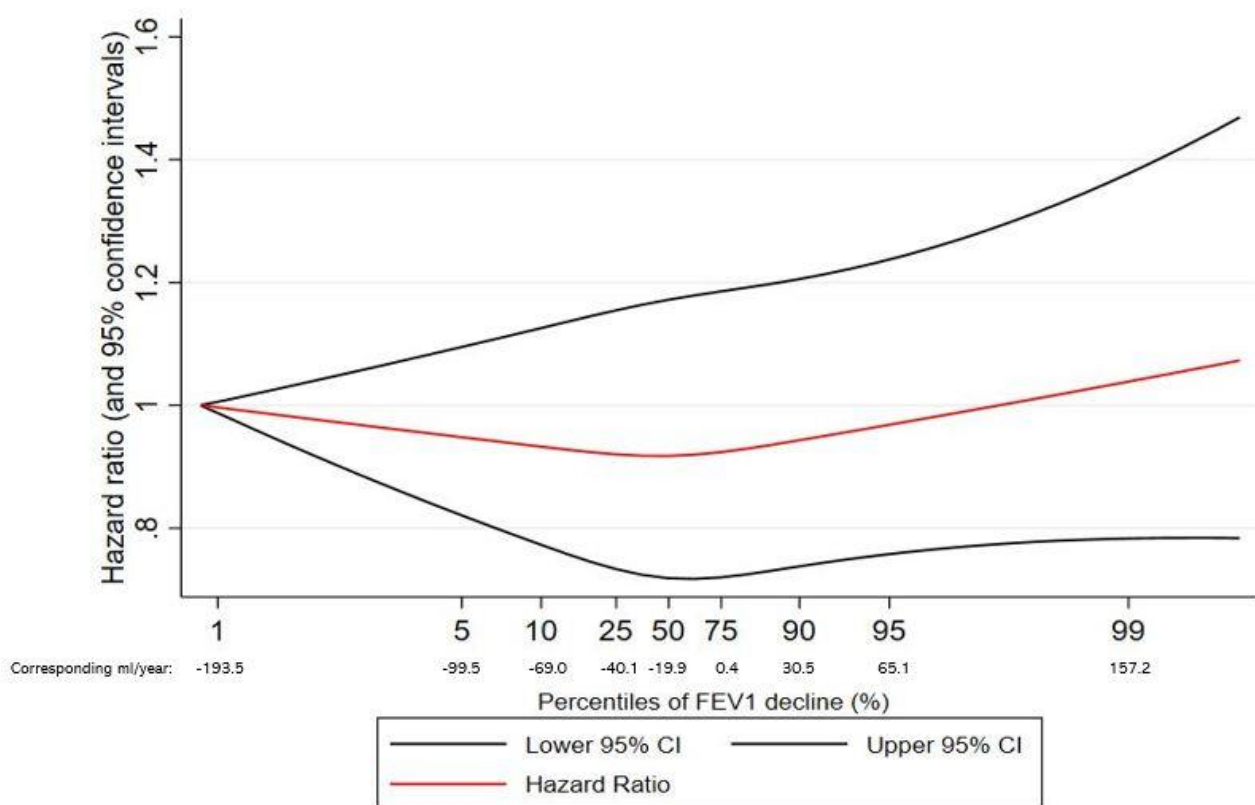


Figure E4: Association between composite CVD, heart failure, myocardial infarction, stroke, atrial fibrillation, and coronary artery disease and angina and accelerated FEV<sub>1</sub> decline compared to non-accelerated FEV<sub>1</sub> decline in the first year of follow-up.

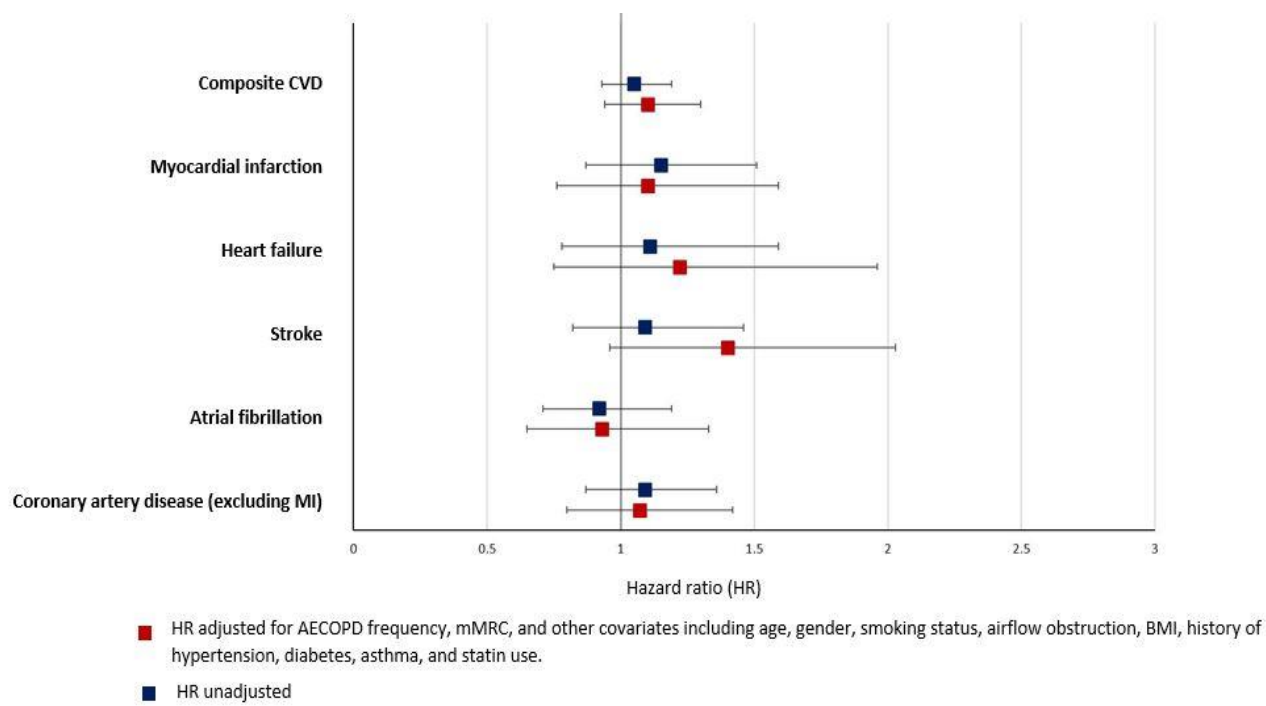


Figure E5: Rate of CVD in patients with accelerated FEV1 decline compared to non-accelerated FEV1 decline using multiple CVD events (IRR 95% CI)

