

**Rapid Decline in Lung Function and Risk of Cardiovascular Disease: the Atherosclerosis
Risk in Communities Study**

Short title: Lung function decline and incident cardiovascular disease

SUPPLEMENTARY MATERIAL

Supplemental table 1- Adjusted odds ratio of cardiovascular disease for the comparison between quartiles of decline in FEV1 or FVC

Outcomes	FEV₁ criteria		FVC criteria	
	HR (95%CI)	p	HR (95%CI)	p
<i>Heart failure</i>				
Quartile 1 (best)	Ref		Ref	
Quartile 2	1.11(0.94-1.30)	0.23	0.97(0.82-1.15)	0.73
Quartile 3	1.13(0.96-1.33)	0.14	1.11(0.94-1.30)	0.21
Quartile 4 (worst)	1.27(1.08-1.48)	0.003	1.30(1.12-1.52)	0.001
<i>Coronary disease</i>				
Quartile 1 (best)	Ref		Ref	
Quartile 2	1.04(0.86-1.26)	0.68	1.06(0.88-1.28)	0.55
Quartile 3	1.16(0.96-1.40)	0.12	1.05(0.87-1.26)	0.64
Quartile 4 (worst)	1.12(0.93-1.35)	0.22	1.17(0.97-1.40)	0.10
<i>Stroke</i>				
Quartile 1 (best)	Ref		Ref	
Quartile 2	0.78(0.61-1.00)	0.048	0.86(0.67-1.09)	0.21
Quartile 3	0.85(0.67-1.07)	0.17	1.02(0.81-1.29)	0.87
Quartile 4 (worst)	1.10(0.88-1.37)	0.40	1.06(0.84-1.34)	0.61
<i>Death</i>				
Quartile 1 (best)	Ref		Ref	
Quartile 2	1.03(0.91-1.16)	0.66	0.93(0.83-1.05)	0.26
Quartile 3	1.02(0.90-1.14)	0.80	1.03(0.92-1.16)	0.58
Quartile 4 (worst)	1.19(1.07-1.34)	0.002	1.26(1.13-1.41)	<0.001
<i>Composite endpoint without death</i>				
Quartile 1 (best)	Ref		Ref	
Quartile 2	0.98(0.87-1.12)	0.82	0.99(0.87-1.12)	0.89
Quartile 3	1.10(0.97-1.24)	0.13	1.09(0.97-1.24)	0.16
Quartile 4 (worst)	1.18(1.05-1.33)	<0.007	1.23(1.09-1.39)	0.001
<i>Composite endpoint including death</i>				

	Ref		Ref	
Quartile 1 (best)				
Quartile 2	1.03(0.93-1.13)	0.59	0.99(0.90-1.10)	0.92
Quartile 3	1.09(0.99-1.21)	0.072	1.07(0.98-1.18)	0.15
Quartile 4 (worst)	1.19(1.08-1.31)	<0.001	1.24(1.13-1.36)	<0.001

FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; HR (95%CI): hazard ratio and 95% confidence interval

FEV₁ criteria (Δ % predicted FEV₁/yr): quartile 1 < (-0.32); quartile 2= (-0.32) to 0.77; quartile 3= 0.77 to 1.92; quartile 4 >1.92;

FVC criteria (Δ % predicted FVC/yr): quartile 1 < (-0.15); quartile 2= (-0.15) to 0.92; quartile 3= 0.92 to 2.12; quartile 4 >2.12;

Adjusted for baseline FEV₁, age, sex, race, and height, ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking. Composite endpoint includes heart failure, stroke, and coronary disease.

Supplemental Table 2- Comparison between non-included and included individuals for the analysis

Characteristics	Non-included (n=2224)	Included (n=10351)	p-value
Age –years	54.6 ± 5.9	53.1 ± 5.7	<0.001
Male gender (%)	907 (41)	4543 (44)	0.007
Race – White (%)	1131 (51)	8331 (81)	<0.001
Center			<0.001
Forsyth (%)	521 (23)	2717 (26)	
Jackson (%)	971 (44)	1755 (17)	
Minneapolis (%)	312 (14)	3167 (31)	
Washington (%)	420 (19)	2712 (26)	
Height - cm	167.9 ± 9.3	168.5 ± 9.3	0.006
BMI(kg/m ²)	28.4 ± 5.9	27.3 ± 4.9	<0.001
Heart rate - bpm	67.5 ± 11.1	66.2 ± 9.8	<0.001
Systolic BP (mmHg)	123.9 ± 20.7	119.4 ± 17.3	<0.001
Diastolic BP (mmHg)	75.4 ± 12.1	73.0 ± 10.6	<0.001
Hypertension (%)	884 (40)	2920 (28)	<0.001
Diabetes (%)	341 (16)	845 (8)	<0.001
LDL cholesterol	136.2 ± 40.1	136.9 ± 38.5	0.43
Current smoking (%)	597 (27)	2418 (23)	<0.001
Lipid lowering medications (%)	49 (2)	255 (3)	0.48
Anti-hypertensive medications (%)	684 (31)	2411 (23)	<0.001
NT-proBNP (pg/mL)	50 [27 - 94]	49 [26 - 88]	0.029
hs-CRP (mg/L)	2.7 [1.2 - 5.8]	2.1 [1.0 - 4.3]	<0.001

*Non-included were individuals with poor-quality or missing spirometry at Visit 2 who were not included in the study sample.

Supplemental Table 3. Risk of cardiovascular disease according to decline in FEV₁/FVC ratio

Outcomes	n	Events	Incidence rate/1000p-y	Model 1		Model 2		Model 3	
				HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
<i>Heart failure</i>									
Non-rapid decliners	7764	1061	7.4 (7.0-7.8)	Ref		Ref		Ref	
Rapid decliners	2587	412	8.9 (8.1-9.8)	1.21(1.08-1.35)	0.001	1.27(1.14-1.43)	<0.001	1.23(1.09-1.40)	0.001
<i>Coronary disease</i>									
Non-rapid decliners	7764	786	5.5 (5.1-5.9)	Ref		Ref		Ref	
Rapid decliners	2587	307	6.6 (5.9-7.4)	1.20(1.05-1.37)	0.006	1.18(1.04-1.35)	0.015	1.14(0.99-1.32)	0.073
<i>Stroke</i>									
Non-rapid decliners	7764	489	3.4 (3.1-3.7)	Ref		Ref		Ref	
Rapid decliners	2587	175	3.8 (3.3-4.4)	1.11(0.93-1.32)	0.24	1.13(0.95-1.34)	0.17	1.05(0.87-1.27)	0.59
<i>Death</i>									
Non-rapid decliners	7764	2027	13.5 (12.9-14.1)	Ref		Ref		Ref	
Rapid decliners	2587	825	16.7 (15.6-17.9)	1.25(1.15-1.35)	<0.001	1.28(1.18-1.39)	<0.001	1.12(1.02-1.22)	0.013
<i>Composite endpoint without death</i>									
Non-rapid decliners	7764	1789	13.0 (12.4-13.6)	Ref		Ref		Ref	
Rapid decliners	2587	676	15.3 (14.2-16.5)	1.19(1.09-1.30)	<0.001	1.21(1.10-1.32)	<0.001	1.15(1.05-1.27)	0.004
<i>Composite endpoint including death</i>									
Non-rapid decliners	7764	2899	21.1 (20.3-21.9)	Ref		Ref		Ref	
Rapid decliners	2587	1110	25.2 (23.8 -26.7)	1.20(1.12-1.29)	<0.001	1.22(1.14-1.31)	<0.001	1.11(1.03-1.20)	0.005

Model 1: unadjusted; Model 2: adjusted for baseline FEV₁, age, sex, race, and height; Model 3: additionally adjusted for ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking. Composite endpoint includes heart failure, stroke, and coronary disease.

FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; HR (95%CI): hazard ratio and 95% confidence interval

Supplemental Table 4. Risk of heart failure according to decline in percentage of predicted FEV₁ by baseline FEV₁ (normal versus abnormal)

Outcome	Baseline FEV ₁ <80%				Baseline FEV ₁ ≥80%			
	n	Events	HR (95% CI)	p	n	Events	HR (95% CI)	p
<i>Heart failure</i>								
Non-rapid decliners	1043	255	Ref		6724	788	Ref	
Rapid decliners	380	119	1.53(1.20-1.95)	0.001	2204	311	1.06(0.92-1.23)	0.38

p for interaction=0.004; FEV₁: forced expiratory volume in 1 s; HR (95% CI): hazard ratio and 95% confidence interval. HRs are from a fully adjusted Model 3: baseline FEV₁, age, sex, race, height, ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking.

Supplemental Table 5. Risk of cardiovascular disease according to change in the percentage of predicted FEV₁ and FVC modeled as a continuous variable

Outcomes	Model 1		Model 2		Model 3	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
<i>Heart failure</i>						
Delta in FEV ₁ (%/year)	1.05 (1.03-1.08)	<0.001	1.06 (1.04-1.08)	<0.001	1.04 (1.02-1.06)	0.001
Delta in FVC (%/year)	1.06 (1.04-1.08)	<0.001	1.08 (1.06-1.09)	<0.001	1.04 (1.02-1.07)	<0.001
<i>Coronary disease</i>						
Delta in FEV ₁ (%/year)	1.04 (1.02-1.07)	0.002	1.04 (1.01-1.07)	0.002	1.03 (1.00-1.05)	0.076
Delta in FVC (%/year)	1.04 (1.02-1.07)	<0.001	1.05 (1.02-1.07)	<0.001	1.03 (1.00-1.05)	0.041
<i>Stroke</i>						
Delta in FEV ₁ (%/year)	1.02 (0.98-1.05)	0.37	1.03 (0.99-1.06)	0.13	0.99 (0.96-1.03)	0.89
Delta in FVC (%/year)	1.04 (1.01-1.08)	0.01	1.05 (1.02-1.08)	0.003	1.02 (0.99-1.05)	0.20
<i>Death</i>						
Delta in FEV ₁ (%/year)	1.05 (1.04-1.07)	<0.001	1.05 (1.04-1.07)	<0.001	1.03 (1.02-1.05)	<0.001
Delta in FVC (%/year)	1.06 (1.04-1.07)	<0.001	1.05 (1.04-1.07)	<0.001	1.04 (1.02-1.05)	<0.001
<i>Composite endpoint without death</i>						
Delta in FEV ₁ (%/year)	1.04 (1.02-1.06)	<0.001	1.04 (1.03-1.06)	<0.001	1.02 (1.00-1.04)	0.013
Delta in FVC (%/year)	1.05 (1.03-1.07)	<0.001	1.06 (1.04-1.07)	<0.001	1.03 (1.01-1.05)	<0.001
<i>Composite endpoint including death</i>						
Delta in FEV ₁ (%/year)	1.04 (1.02-1.06)	<0.001	1.04 (1.03-1.06)	<0.001	1.03 (1.01-1.04)	<0.001
Delta in FVC (%/year)	1.05 (1.03-1.06)	<0.001	1.06 (1.04-1.07)	<0.001	1.03 (1.02-1.04)	<0.001

Model 1: unadjusted; Model 2: adjusted for baseline FEV₁, age, sex, race, and height; Model 3: additionally adjusted for ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking. Composite endpoint includes heart failure, stroke, and coronary disease.

FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; HR (95%CI): hazard ratio and 95% confidence interval

Supplemental Table 6. Risk of cardiovascular disease according to decline in percentage of predicted FEV₁ stratified for smokers (current and former) versus never smokers

Outcomes	Smokers (current and former)				Never smokers				p for interaction*
	Model 1		Model 3		Model 1		Model 3		
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	
<i>Heart failure</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.31(1.14-1.49)	<0.001	1.18(1.02-1.37)	0.027	1.31(1.06-1.61)	0.011	1.17(0.93-1.46)	0.18	0.85
<i>Coronary disease</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.10(0.93-1.29)	0.26	0.96(0.80-1.14)	0.64	1.46(1.16-1.85)	0.001	1.28(0.99-1.66)	0.062	0.047
<i>Stroke</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.26(1.03-1.56)	0.028	1.19(0.95-1.49)	0.13	1.49(1.13-1.97)	0.005	1.33(0.99-1.81)	0.062	0.72
<i>Death</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.37(1.25-1.50)	<0.001	1.17(1.06-1.30)	0.003	1.32(1.14-1.54)	<0.001	1.16(0.98-1.36)	0.083	0.85
<i>Composite endpoint without death</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.22(1.10-1.36)	<0.001	1.10(0.98-1.23)	0.09	1.39(1.19-1.63)	<0.001	1.25(1.05-1.42)	0.010	0.10
<i>Composite endpoint including death</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.27(1.18-1.38)	<0.001	1.12(1.02-1.22)	0.012	1.33(1.17-1.51)	<0.001	1.18(1.03-1.35)	0.014	0.25

Model 1: unadjusted; Model 3: adjusted for baseline FEV₁, age, sex, race, height, ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking. Composite endpoint includes heart failure, stroke, and coronary disease. *P for interaction was assessed in Model 3.

FEV₁: forced expiratory volume in 1 s; HR (95%CI): hazard ratio and 95% confidence interval.

Supplemental Table 7. Risk of cardiovascular disease according to decline in percentage of predicted FVC stratified for smokers (current and former) versus never smokers

Outcomes	Smokers (current and former)				Never smokers				p for interaction*
	Model 1		Model 3		Model 1		Model 3		
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	
<i>Heart failure</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.38(1.21-1.58)	<0.001	1.23(1.05-1.43)	0.009	1.57(1.27-1.92)	<0.001	1.35(1.09-1.67)	0.007	0.26
<i>Coronary disease</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.28(1.09-1.49)	0.002	1.12(0.94-1.34)	0.21	1.29(1.02-1.65)	0.034	1.11(0.85-1.45)	0.43	0.77
<i>Stroke</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.16(0.94-1.44)	0.17	1.04(0.82-1.32)	0.76	1.33(1.00-1.76)	0.051	1.21(0.89-1.65)	0.22	0.4
<i>Death</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.47(1.34-1.61)	<0.001	1.17(1.06-1.30)	0.003	1.33(1.15-1.55)	<0.001	1.22(1.03-1.43)	0.018	0.72
<i>Composite endpoint without death</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.27(1.15-1.42)	<0.001	1.15(1.02-1.29)	0.024	1.44(1.23-1.67)	<0.001	1.28(1.08-1.51)	0.004	0.13
<i>Composite endpoint including death</i>									
Non-rapid decliners	Ref		Ref		Ref		Ref		
Rapid decliners	1.32(1.22-1.44)	<0.001	1.18(1.08-1.30)	<0.001	1.38(1.22-1.56)	<0.001	1.25(1.10-1.43)	0.001	0.25

Model 1: unadjusted; Model 3: adjusted for baseline FVC, age, sex, race, height, ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking. Composite endpoint includes heart failure, stroke, and coronary disease. *P for interaction was assessed in Model 3.

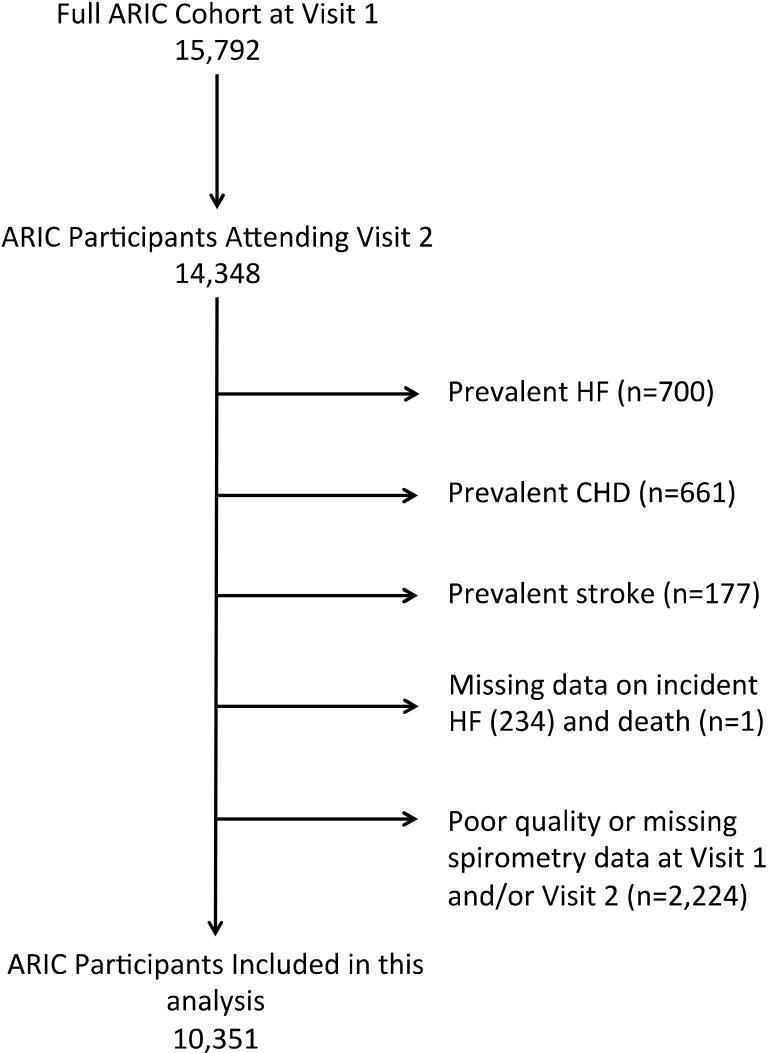
FVC: forced vital capacity; HR (95% CI): hazard ratio and 95% confidence interval.

Supplemental Table 8. Risk of cardiovascular disease according to decline in percentage of predicted FEV1 or FVC after excluding those with probable COPD at Visit 1 (sample for this analysis 10,091 subjects)*

Outcomes	FEV ₁ criteria		FVC criteria	
	HR (95%CI)	p	HR (95%CI)	p
<i>Heart failure</i>				
Non-rapid decliners	Ref		Ref	
Rapid decliners	1.15 (1.01-1.30)	0.035	1.24 (1.09-1.41)	0.001
<i>Coronary disease</i>				
Non-rapid decliners	Ref		Ref	
Rapid decliners	1.02 (0.88-1.18)	0.82	1.07 (0.91-1.24)	0.42
<i>Stroke</i>				
Non-rapid decliners	Ref		Ref	
Rapid decliners	1.22 (1.01-1.47)	0.035	1.09 (0.89-1.32)	0.40
<i>Death</i>				
Non-rapid decliners	Ref		Ref	
Rapid decliners	1.15 (1.05-1.26)	0.002	1.22 (1.12-1.34)	<0.001
<i>Composite endpoint without death</i>				
Non-rapid decliners	Ref		Ref	
Rapid decliners	1.12 (1.02-1.24)	0.019	1.16 (1.05-1.28)	0.003
<i>Composite endpoint including death</i>				
Non-rapid decliners	Ref		Ref	
Rapid decliners	1.12 (1.04-1.21)	0.003	1.18 (1.09-1.28)	<0.001

*Adjusted for: baseline parameter, age, sex, race, and height; ARIC center, body mass index, heart rate, low-density-lipoprotein cholesterol, lipid-lowering medication, NT-proBNP, diabetes, hypertension, and smoking. Composite endpoint includes heart failure, stroke, and coronary disease. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; HR (95%CI): hazard ratio and 95% confidence interval.

Supplemental Figure 1. TITLE: Flow chart showing derivation of the study sample from the overall ARIC cohort.



Supplemental Figure 2. TITLE: Association of rapid decline in FEV₁ with incident heart failure at ≤ or > 1 year follow-up. CAPTION: Rapid decline is defined as greatest quartile of decline in FEV₁ over a mean of 2.9 years. Kaplan-Meier curves demonstrate the rates of incident heart failure among the rapid decliner and non-rapid decliner groups either (A) during the first year of follow-up, or (B) after the first year of follow-up. P for interaction for decline in percentage of predicted FEV₁ and time with respect to incident HF was significant at p=0.003. Hazard ratios (HR) and associated 95% confidence intervals are calculated from Cox regression models adjusted for age, sex, race, ARIC center, height, heart rate, body mass index, LDL-cholesterol, NT-proBNP, diabetes, hypertension, and smoking.

