Supplementary material

Relative and absolute lung function change in a general population aged 60-102 years

Contents:

TABLE S1 Individually calculated absolute FVC change

Characteristics	Crude baseline FVC (mean ± SD)	Crude FVC absolute decline	Adjusted (LSM) FVC absolute change*				Number of trajectories
			BASIC MODEL		FULL MODEL		
	L	mL/yr (95% CI)	mL/yr (95% CI)	p	mL/yr (95% CI)	p	n
Sex							
Male	3.90±0.84	-42.3 (-47.9, -36.7)	-45.9 (-53.4, -38.5)	.	-58.0 (-75.8, -40.2)	.	714
Female	2.70±0.66	-34.0 (-39.2, -28.9)	-38.7 (-45.6, -31.9)	0.041	-54.4 (-72.3, -36.6)	0.40	844
Age years							
60-69	3.58±0.90	-36.8 (-42.0, -31.6)	-38.2 (-43.1, -33.2)	.	-51.6 (-69.4, -33.9)	.	838
70-79	3.16±0.87	-41.7 (-49.9, -33.4)	-44.2 (-52.1, -36.2)	0.2	-58.6 (-77.1, -40.2)	0.18	339
80-89	2.70±0.80	-34.9 (-43.3, -26.5)	-38.3 (-46.7, -29.9)	0.97	-52.8 (-70.8, -34.7)	0.83	325
90-102	2.19±0.70	-46.4 (-66.7, -26.0)	-48.7 (-69.0, -28.4)	0.31	-61.8 (-87.8, -35.8)	0.36	56
Smoking habits							
Current smoker	3.25±0.96	-39.5 (-50.2, -28.8)	-44.9 (-55.7, -34.1)	.	-59.8 (-79.0, -40.6)	.	223
Former smoker	3.39±0.91	-35.7 (-41.9, -29.5)	-38.4 (-45.6, -31.2)	0.23	-51.9 (-69.8, -34.0)	0.19	661
Never smoker	3.12±0.98	-39.3 (-45.5, -33.2)	-43.7 (-50.4, -37.0)	0.83	-56.9 (-75.1, -38.7)	0.64	674
Hypertension							
Yes	3.10±0.93	-36.7 (-43.9, -29.5)			-56.7 (-74.5, -38.9)	.	452
No	3.32±0.96	-38.3 (-42.3, -33.7)			-55.7 (-73.8, -37.7)	0.83	1106
Diabetes type II							
Yes	3.13±0.94	-41.9 (-58.3, -25.5)			-56.3 (-78.2, -34.4)	.	98
No	3.26±0.96	-37.5 (-41.8, -33.2)			-56.1 (-72.1, -40.1)	0.97	1460
CHD							
Yes	3.05±0.94	-33.9 (-45.1, -22.8)			-54.3 (-73.4, -35.3)	.	195
No	3.28±0.96	-38.4 (-42.6, -34.2)			-58.1 (-76.0, -40.2)	0.56	1363

Heart failure							
Yes	2.62±0.76	-26.3 (-46.7, -5.80)			-56.7 (-74.5, -38.9)	.	65
No	3.28±0.96	-38.3 (-42.5, -34.1)			-55.7 (-73.8, -37.7)	0.59	1493
BMI							
<20	3.10±1.01	-46.5 (-75.3, -17.7)			-67.0 (-103, -31.2)	0.47	29
20-24.99	3.30±0.98	-40.4 (-47.4, -33.5)			-54.7 (-72.0, -37.4)	.	490
25-35	3.25±0.95	-36.3 (-41.3, -31.3)			-51.0 (-67.0, -35.1)	0.40	956
>35	3.12±0.88	-36.7 (-53.7, -19.6)			-52.2 (-72.6, -31.7)	0.78	83
Occupation							
Low risk	3.23±0.94	-36.4 (-40.6, -32.2)			-53.4 (-70.0, -36.8)	.	1279
Farming etc.	3.05±1.04	-33.1 (-55.4, -10.8)			-59.8 (-86.2, -33.4)	0.57	46
Unqualified work	2.64±0.80	-37.7 (-55.2, -20.3)			-52.2 (-74.8, -29.7)	0.90	75
Construction etc.	3.75±0.93	-46.1 (-58.1, -34.1)			-59.5 (-79.8, -39.2)	0.36	158
Education							
Low	2.94±0.90	-55.7 (-77.9, -33.4)			-80.3 (-108, -52.9)	.	46
Intermediate	3.17±0.95	-36.4 (-41.0, -32.0)			-41.8 (-57.5, -26.1)	0.0014	1103
High	3.50±0.94	-39.0 (-46.4, -31.5)			-46.5 (-64.4, -28.6)	0.0072	409
ALL	**3.25±0.96**	**-37.8 (-41.6, -34.0)**	**-42.3 (-48,6, -36.1)**		**-56.2 (-73.6, -38.8)**		**1558**

LSM: least squares means; CHD: coronary heart disease, CRP: C-reactive protein. Basic model is adjusted for the categorical variables age, sex and smoking status. The Full model is also adjusted for the categorical variables hypertension, CHD, heart failure, diabetes type II, occupation, BMI, education and the continuous variables CRP and alcohol consumption. Values used for for LSM calculations were: alcohol consumption: 8.4 glasses/month and CRP: 5.4 mg/L. Missing values for covariates resulted in 25 trajectories being excluded.

TABLE S2 Individually calculated relative FVC change

Characteristics	**Baseline FVC (mean ± SD)**	**Crude FVC relative change**	**Adjusted (LSM) FVC relative change***				**Number of trajectories**
			BASIC MODEL		**FULL MODEL**		
	L	% per year (95% CI)	% per year (95% CI)	p	% per year (95% CI)	p	n
Sex							
Male	3.90±0.84	-1.18 (-1.39, -0.96)	-1.57 (-1.85, -1.29)	.	-2.29 (-2.92, -1.66)	.	714
Female	2.70±0.66	-1.37 (-1.57, -1.18)	-1.81 (-2.07, -1.56)	0.0618	-2.63 (-3.26, -2.00)	0.0189	844
Age years							
60-69	3.58±0.90	-1.08 (-1.28, -0.89)	-1.15 (-1.34, -0.97)	.	-1.90 (-2.53, -1.27)	.	838
70-79	3.16±0.87	-1.44 (-1.75, -1.13)	-1.54 (-1.83, -1.25)	0.0266	-2.38 (-3.03, -1.72)	0.0095	339
80-89	2.70±0.80	-1.43 (-1.75, -1.12)	-1.58 (-1.89, -1.27	0.0139	-2.35 (-2.99, -1.71)	0.0164	325
90-102	2.19±0.70	-2.45 (-3.20, -1.70)	-2.49 (-3.24, -1.74)	0.0007	-3.21 (-4.13, -2.29)	0.0009	56
Smoking habits							
Current smoker	3.25±0.96	-1.35 (-1.75, -0.94)	-1.87 (-2.27, -1.47)	.	-2.70 (-3.38, -2.02)	.	223
Former smoker	3.39±0.91	-1.15 (-1.38, -0.92)	-1.53 (-1.80, -1.26)	0.0907	-2.27 (-2.90, -1.63)	0.0411	661
Never smoker	3.12±0.98	-1.39 (-1.62, -1.16)	-1.68 (-1.93, -1.46)	0.3484	-2.41 (-3.06, -1.77)	0.1786	674

Hypertension						
Yes	3.10±0.93	-1.26 (-1.71, -0.80)		-2.44 (-3.07, -1.81)	.	452
No	3.32±0.96	-1.29 (-1.47, -1.12)		-2.48 (-3.12, -1.84)	0.7808	1106
Diabetes type II						
Yes	3.13±0.94	-1.37 (-1.99, -0.75)		-2.55 (-3.32, -1.77)	.	98
No	3.26±0.96	-1.28 (-1.44, -1.11)		-2.38 (-2.94, -1.81)	0.5560	1460
CHD						
Yes	3.05±0.94	-1.24 (-1.66, -0.82)		-2.42 (-3.09, -1.74)	.	195
No	3.28±0.96	-1.29 (-1.45, -1.13)		-2.51 (-3.14, -1.87)	0.6977	1363
Heart failure						
Yes	2.62±0.76	-1.11 (-1.88, -0.33)		-2.44 (-3.25, -1.63)	.	65
No	3.28±0.96	-1.29 (-1.45, -1.13)		-2.48 (-3.05, -1.91)	0.91	1493
BMI						
<20	3.10±1.01	-1.67 (-2.74, -0.58)		-2.83 (-4.08, -1.56)	0.43	29
20-24.99	3.30±0.98	-1.37 (-1.63, -1.11)		-2.35 (-2.96, -1.73)	.	490
25-35	3.25±0.95	-1.23 (-1.42, -1.05)		-2.34 (-2.91, -1.78)	0.97	956
>35	3.12±0.88	-1.21 (-1.88, -0.56)		-2.33 (-3.05, -1.60)	0.94	83
Occupation						
Low risk	3.23±0.94	-1.25 (-1.41, -1.09)		-2.42 (-3.01, -1.83)	.	1279
Farming etc.	3.05±1.04	-0.68 (-1.52, 0.17)		-2.42 (3.34, -1.49)	0.9949	46
Unqualified work	2.64±0.80	-1.76 (-2.41, -1.10)		-2.52 (-3.31, -1.72)	0.7494	75
Construction etc.	3.75±0.93	-1.26 (-1.71, -0.80)		-2.48 (-3.20, -1.77)	0.7834	158
Education						
Low	2.94±0.90	-2.08 (-2.91, -1.25)		-3.69 (4.64, -2.73)	.	46
Intermediate	3.17±0.95	-1.25 (-1.42, -1.08)		-1.75 (-2.31, -1.19)	<.0001	1103
High	3.50±0.94	-1.25 (-1.53, -0.97)		-1.94 (-2.57, -1.30)	<.0001	409
ALL	**3.25±0.96**	**-1.28 (-1.42, -1.14)**	**-1.69 (-1.93, -1.46)**	**-2.46 (-3.07, -1.85)**		**1558**

LSM: least squares means; CHD: coronary heart disease, CRP: C-reactive protein. Basic model is adjusted for the categorical variables age, sex and smoking status. The Full model is also adjusted for the categorical variables hypertension, CHD, heart failure, diabetes type II, occupation, BMI, education and the continuous variables CRP and alcohol consumption. Values used for LSM calculations were: alcohol consumption: 8.4 glasses/month and CRP: 5.4 mg/L. Missing values for covariates resulted in 25 trajectories being excluded.

TABLE S3 Lung volumes, FEV_1Q and GLI 2012 Z-scores for ages 60-102*

	FEV_1 (L) [n]				
Never smokers					
Male	3.41 (3.33, 3.48) [366]	2.92 (2.84, 2.99) [295]	2.32 (2.24, 2.40) [284]	2.02 (1.88, 2.17) [59]	1029
Female	2.39 (2.34, 2.43) [431]	1.98 (1.94, 2.02) [501]	1.59 (1.56, 1.63) [804]	1.32 (1.26, 1.37) [264]	2046
Current/former smokers					
Male	3.17 (3.11, 3.23) [760]	2.68 (2.61, 2.74) [557]	2.26 (2.19, 2.33) [525]	1.97 (1.81, 2.12) [82]	1968
Female	2.23 (2.19, 2.27) [781]	1.86 (1.82, 1.91) [465]	1.49 (1.43, 1.54) [369]	1.26 (1.13, 1.39) [59]	1725
	FVC (L) [n]				
Never smokers					
Male	4.19 (4.09, 4.29) [366]	3.69 (3.59, 3.79) [297]	2.96 (2.86, 3.06) [289]	2.56 (2.35, 2.77) [60]	1037
Female	2.96 (2.91, 3.02) [432]	2.52 (2.46, 2.57) [505]	2.04 (2.00, 2.09) [814]	1.72 (1.65, 1.79) [267]	2064
Current/former smokers					
Male	4.10 (4.03, 4.16) [759]	3.55 (3.48, 3.62) [557]	2.96 (2.88, 3.03) [531]	2.66 (2.45, 2.87) [82]	1973
Female	2.92 (2.88, 2.97) [781]	2.51 (2.46, 2.57) [465]	1.95 (1.89, 2.01) [372]	1.67 (1.52, 1.82) [60]	1730
	FEV_1/FVC [n]				
Never smokers					
Male	0.82 (0.81, 0.83) [366]	0.79 (0.78, 0.80) [295]	0.78 (0.77, 0.80) [284]	0.79 (0.76, 0.82) [59]	1029
Female	0.81 (0.80, 0.82) [431]	0.79 (0.78, 0.80) [501]	0.78 (0.78, 0.79) [804]	0.77 (0.76, 0.79) [264]	2046
Current/former smokers					
Male	0.78 (0.77, 0.78) [759]	0.75 (0.75, 0.76) [556]	0.76 (0.75, 0.78) [525]	0.75 (0.72, 0.78) [82]	1966
Female	0.77 (0.76, 0.77) [781]	0.74 (0.73, 0.75) [465]	0.77 (0.75, 0.78) [369]	0.75 (0.72, 0.78) [59]	1725
	FEV_1 GLI-2012 Z-score [n]				
Never smokers					
Male	0.01 (-0.12, 0.14) [365]	-0.07 (-0.25, 0.06) [294]	-0.51 (-0.66, -0.36) [282]	-0.53 (-0.81, -0.25) [59]	1025
Female	-0.00 (-1.0, 0.097) [431]	-0.17 (-0.27, -0.07) [501]	-0.36 (-0.46, -0.26) [801]	-0.64 (-0.81, -0.47) [262]	2040
Current/former smokers					
Male	-0.41 (-0.50, -0.31) [758]	-0.56 (-0.67, -0.45) [557]	-0.65 (-0.78, -0.53) [523]	-0.72 (-1.01, -0.43) [82]	1963
Female	-0.52 (-0.62, -0.41) [781]	-0.62 (-0.74, -0.51) [464]	-0.80 (-0.95, -0.65) [367]	-0.91 (-1.30, -0.52) [58]	1720
	FVC GLI-2012 Z-score [n]				
Never smokers					
Male	-0.39 (-0.52, -0.25) [365]	-0.40 (-0.55, -0.26) [296]	-0.89 (-1.04, -0.75) [287]	-1.00 (-1.35, -0.66) [60]	1033
Female	-0.21 (-0.31, -0.12) [432]	-0.32 (-0.42, -0.22) [505]	-0.52 (-0.61, -0.43) [811]	-0.79 (-0.96, -0.63) [265]	2058
Current/former smokers					
Male	-0.50 (-0.58, -0.41) [757]	-0.66 (-0.76, -0.56) [557]	-0.92 (-1.04, -0.81) [529]	-0.92 (-1.25, -0.60) [82]	1968
Female	-0.41 (-0.49, -0.32) [781]	-0.45 (-0.56, -0.35) [464]	-0.85 (-0.98, -0.71) [370]	-1.00 ('-1.34, -0.66) [59]	1725
	FEV_1/FVC GLI-2012 Z-score [n]				

Never smokers					
Male	0.74 (0.62, 0.87) [365]	0.51 (0.39, 0.64) [294]	0.46 (0.32, 0.61) [282]	0.56 (0.24, 0.87) [59]	1025
Female	0.35 (0.25, 0.44) [431]	0.21 (0.12, 0.31) [501]	0.25 (0.15, 0.35) [801]	0.20 (0.046, 0.36) [262]	2040
Current/former smokers					
Male	0.17 (0.06, 0.27) [757]	0.052 (-0.06, 0.17) [556]	0.25 (0.12, 0.39) [523]	0.16 (-0.13, 0.44) [82]	1961
Female	-0.20 (-0.31, -0.089) [781]	-0.38 (-0.50, -0.26) [464]	0.066 (-0.091, 0.22) [367]	-0.022 (-0.34, 0.30) [58]	1720

FEV_1Q [n]

Never smokers					
Male	6.84 (6.71, 6.97) [376]	5.83 (5.70, 5.96) [300]	4.68 (4.55, 4.81) [293]	4.05 (3.77, 4.33) [60]	1029
Female	5.98 (5.89, 6.08) [445]	4.97 (4.87, 5.06) [507]	3.99 (3.92, 4.06) [822]	3.35 (3.23, 3.47) [272]	2046
Current/former smokers					
Male	6.38 (6.29, 6.48)[783]	5.38 (5.27, 5.49) [566]	4.55 (4.44, 4.66) [537]	3.94 (3.67, 4.21) [82]	1968
Female	5.63 (5.54, 5.71) [811]	4.65 (4.54, 4.75) [473]	3.75 (4.65, 3.86) [381]	3.14 (2.86, 3.41) [60]	1725

***Presented results are from repeated measurements models containing intercepts only. All Z-Scores are calculated from the GLI-2012 reference equations**

TABLE S4

NHANES III Z-scores for ages 60-102 (SUPPLEMENTARY MATERIAL) *

FEV_1 NHANES Z-score [n]

All	**60-69**	**70-79**	**80-89**	**90-102**	**Exams (n)**
Male	-0.11 (-0.14, -0.086) [1123]	-0.15 (-0.18, -0.12) [851]	-0.15 (-0.20, -0.10) [805]	0.087 (0.057, 0.23) [141]	2988
Female	-0.18 (-0.20, -0.15) [1212]	-0.20 (-0.23, -0.17) [965]	0.089 (-0.14, -0.043) [1168]	0.14 (0.013, 0.26) [320]	3760
Never smokers					
Male	-0.018 (-0.06, 0.025) [365]	-0.021 (-0.073, 0.031) [294]	-0.092 (-0.17, -0.017) [282]	0.21 (-0.0017, 0.43) [59]	1025
Female	0.065 (0.034, 0.097) [431]	0.10 (0.061, 0.14) [501]	-0.010 (-0.065, 0.045) [801]	-0.24 (-0.39, -0.11) [262]	2040
Current/former smokers					
Male	-0.15 (-0.18, -0.12) [758]	-0.22 (-0.26, -0.18) [557]	-0.17 (-0.23, -0.11) [523]	0.033 (-0.17, 0.24) [82]	1963
Female	-0.24 (-0.27, -0.21) [781]	-0.29 (-0.34 -0.25) [464]	-0.27 (-0.34, -0.19) [367]	-0.069 (-0.35, 0.21) [58]	1720

FVC NHANES Z-score [n]

All	**60-69**	**70-79**	**80-89**	**90-102**	**Exams (n)**
Male	-0.20 (-0.22, -0.18) [1122]	-0.26 (-0.29, -0.23) [853]	-0.35 (-0.38, -0.31) [816]	-0.26 (-0.36, -0.15) [142]	3001
Female	-0.20 (-0.22, -0.18) [1256]	-0.22 (-0.25, -0.19) [984]	-0.18 (-0.22, -0.15) [1210]	-0.031 (-0.13, 0.069) [333]	3783
Never smokers					
Male	-0.18 (-0.22, -0.14) [365]	-0.20 (-0.25, -0.15) [296]	-0.33 (-0.39, -0.27) [287]	-0.26 (-0.42, -0.091) [60]	1033
Female	-0.16 (-0.19, -0.13) [432]	-0.19 (-0.23, -0.15) [505]	-0.12 (-0.16, -0.074) [811]	0.049 (-0.06, -0.16) [265]	2058
Current/former smokers					
Male	-0.21 (-0.24, -0.18) [757]	-0.29 (-0.32, -0.25) [557]	-0.34 (-0.39, -0.30) [529]	-0.25 (-0.40, -0.10) [82]	1968
Female	-0.22 (-0.25, -0.19) [781]	-0.25 (-0.29, -0.21) [464]	-0.30 (-0.37, -0.24) [370]	-0.16 (-0.38, 0.052) [59]	1725

	FEV$_1$/FVC NHANES Z-score [n]				
All	**60-69**	**70-79**	**80-89**	**90-102**	**Exams (n)**
Male	0.10 (0.088, 0.11) [1122]	0.11 (0.088, 0.13) [850]	0.17 (0.14, 0.19) [805]	0.21 (0.16, 0.27) [141]	2986
Female	0.024 (0.0095, 0.039) [1212]	0.040 (0.023, 0.056) [965]	0.13 (0.11, 0.15) [1168]	0.16 (0.12, 0.19) [141]	3760
Never smokers					
Male	0.17 (0.15, 0.20) [365]	0.17 (0.15, 020) [294]	0.20 (0.17, 0.24) [282]	0.28 (0.19, 0.36) [59]	1025
Female	0.092 (0.074, 0.11) [431]	0.10 (0.083, 0.12) [501]	0.14 (0.12, 0.17) [801]	0.17 (0.13, 0.21) [262]	2040
Current/former smokers					
Male	0.070 (0.051, 0.089) [757]	0.071 (0.045, 0.096) [556]	0.15 (0.12, 0.19) [523]	0.17 (0.09, 0.24) [82]	1961
Female	-0.014 (-0.035, 0.0060) [781]	-0.025 (-0.051, -0.0001) [464]	0.095 (0.059, 0.13) [367]	0.10 (0.018, 0.18) [58]	1720

Statistical appendix

Absolute and relative change

Absolute change is straightforward, relatable and useful for many purposes. However, if change in lung volume is proportional to the starting volume an absolute model of change will be inappropriate. In theory, when analysing risk factors for increased lung function decline risk factors leading to increased decline will result in smaller lung volumes and eventually resulting in smaller absolute changes if change is proportional to the starting volume (Thomsen et al., 2014; Vestbo & Lange, 2017). Thus, applying an absolute model of change may lead to completely incorrect conclusions regarding effects of risk factors. It has recently been proposed that measuring change in lung function relatively is preferable to absolute change, especially in an old or diseased population where the starting volumes are on average lower with higher age or increased morbidity(Raimondi, 2017; Thomsen et al., 2014). We have measured change both absolutely and relatively to allow for comparison and this manuscript highlights the effects that the choice of analysis method will have on risk factor analysis. For example, in the absolute analysis, lung function decline was unaffected by age but the relative analysis showed that age had a marked effect on rate of decline. Males, who have on average greater lung capacity compared to females, had a greater absolute decline in lung function. However, females had the greater relative decline. This is consistent with previous findings (Celli et al., 2008). Thus, risk factors for increased lung function decline will depend on how we model change.

Absolute and relative change models

In what follows, $V(t)$ denotes the volume at time $t \geq 0$, $dV(s)$ the change in volume during an infinitesimally short time period after time $s \geq 0$ and α is the model parameter (may differ between patients).

In the absolute change model it is assumed that

$$dV(s) = \alpha ds, s < t$$

This leads to the following relationship between α (unit: ml/yr) and the absolute change in V.

$$\big(V(t) - V(0)\big)/t = \alpha \quad (1)$$

According to what we refer to as the relative change model (in which α has unit 1/yr)

$$dV(s) = \alpha V(s) ds, s < t,$$

which means that $dV(s)$ is proportional to $V(s)$. By dividing both sides of the equation by $V(s)$ and integrating from 0 to t, we obtain

$$(\log V(t) - \log V(0))/t = \log \sqrt[t]{V(t)/V(0)} = \alpha \quad (2)$$

Now, we let $\alpha = \mu + \varepsilon$ where μ is a parameter that may depend on the patient's characteristics and ε is a perturbation (random error with mathematical expectation equal to zero). It is clear that (1) (under the absolute model) and (2) (under the relative model) together with appropriate regularity assumptions regarding the perturbations provide a way to conduct inference about μ and factors that possibly affect μ given observations of t, $V(0)$, $V(t)$ and other relevant variables coming from a group of patients.

If the relative model is true $|V(t) - V(0)|$, unlike $V(t)/V(0)$, increases with increasing initial volume (for fixed α). To see this, just note that $V(t)/V(0) = e^{\alpha t}$ and

$$|V(t) - V(0)| = V(0)|V(t)/V(0) - 1| = V(0)|e^{\alpha t} - 1|$$

In other words, $V(0)$ sets the scale of the change. Conversely, if nature is properly described by the absolute model there is an impact by $V(0)$ on $V(t)/V(0)$ but not on $|V(t) - V(0)|$.

To assess if an application of the relative change model to our data made sense we did the following. We selected the group of never-smoking men aged 60 years with at least two measurements of volume and focused on FEV_1. We visually inspected the data and removed patients corresponding to obvious outliers in absolute change in volume (it seemed likely that some of these over/under

performed at baseline or were exceptional in some other sense). We were left with 192 observations. Next, we recorded (through variables taking values in (1, 2, 3)) which tertile of change (absolute and relative), initial volume and height the patients belonged to. These variables seemed crude but less sensitive to e.g. measurement error than the original ones. We cross-tabulated the variables corresponding to initial volume and absolute change. There was a strong effect of initial volume on change with 'highest initial volume' group having a much larger proportion of 'steep change' than the other groups (p=0.0003). Two plausible explanations of this result were: 1. It was an artefact due to random under/over performance at baseline ('regression to the mean') and 2. Initial volume represented potential volume that could be lost subsequently. As a second step we cross-tabulated the variables corresponding to body height and absolute change (the variable corresponding to body height served as a rough proxy for the variable corresponding to initial lung volume). It seemed as if the tallest patients lost the largest volumes (p=0.0096). If explanation 1 above was true this was unexpected and we were more willing to accept explanation 2. Finally, we cross-tabulated the variables corresponding to initial volume and relative change and there was no association (p=0.18) between initial volume and relative change. Given the above, the relative model seemed feasible.

Note that there are many change models other than the relative and absolute that may be of interest. This issue will not be pursued here.

The ideal population

Let E denote mathematical expectation. By combining (2) and $\alpha = \mu + \varepsilon$ we obtain the following interpretation of μ in the relative model:

$$E \log \sqrt[t]{V(t)/V(0)} = \mu$$

In the presentation of the results we wish to return to the 'original scale' as we believe that this makes the interpretation easier. We note that $V(t)/V(0) = e^{\mu t} e^{\varepsilon t}$which implies that $E\,(V(t)/V(0)) = e^{\mu t} E e^{\varepsilon t}$ from which we infer that in general $E(V(t)/V(0)) \neq e^{\mu t}$. An 'ideal population' corresponding to the study population is a hypothetical construct with the same mechanism governing μ and perturbations degenerate at zero, i.e. every member of the ideal population has an α which coincides with the expected α for a member of the study population sharing his/her characteristics. Given a point estimate μ_p and a confidence interval $[\mu_l, \mu_u]$ for μ (based on data coming from the real population) we obtain a point estimate and a confidence interval for the expected relative change (expressed as % in

one year) in the ideal population according to $100(e^{\mu_p} - 1)$ and $[100(e^{\mu_l} - 1), 100(e^{\mu_u} - 1)]$, respectively. Note that one can compute point estimates and confidence limits for the model parameter μ by applying the transformation $x \to \log(x/100 + 1)$ to the corresponding numbers for relative change presented in the text and tables.

Sampling strategy

Data were collected on two distinct cohorts recruited in 2001 and 2006, respectively. Participants younger than 80 years were re-invited to examinations every six years and patients older than 80 years every three years. Note that the design was flexible in the sense that it took into account that participants aged during the course of the study. For example, a participant aged 78 years when entering the study would receive a re-invitation after six years and subsequently every three years. For each participant we identified pairs of examinations with non-missing information regarding lung volumes and examination dates 5.5 to 6.5 years apart. Pairs could be of three types: initial measurement at baseline, 3 years after baseline and 6 years after baseline. For the analysis of change we picked existing pairs of the first or third kind. If there were no pairs of the first or third kind we chose the pair of the second kind (if it existed). Note that the time periods between visits were disjoint for chosen pairs coming from the same patient. For the analysis of absolute levels of lung function we used all available measurements of lung volumes.

A few additional details regarding the statistical analysis.

The covariates included in the statistical analyses were all chosen a-priori to analysing, i.e., no form of data driven covariate selection process was applied. Each covariate was assigned a 'block' to which it belonged. The blocks were: Basic block (sex, smoking and age), co-morbidity block (heart failure, hypertension, diabetes and coronary-heart disease), socio-economic block (education, profession and alcohol consumption), bio-marker and BMI block (level of CRP and BMI) and functional-status block (GUG, grip strength and walking speed).

We modelled annual absolute change and the logarithm of annual relative change in lung function through identical Gaussian repeated measurements models with a general within patient covariance structure. Since we had at most two measurements per patient this structure involved three covariance parameters.

We modelled absolute levels of lung function through Gaussian repeated measurements models with a within patient spatial power covariance structure, i.e., the covariance between within patient measurements was assumed to decay exponentially with time distance. This structure involved two covariance parameters.

For all regression models involving lung volumes we conducted a standard multicollinearity check (very closely related to principal component analysis) implemented in e.g. PROC REG in SAS and briefly described in the procedure's online documentation. It appeared that multicollinearity was not a serious issue as long as we did not adjust for more than one covariate belonging to the functional-status block (details not shown).

All repeated measurements regression models were implemented using PROC MIXED in SAS. Note that the regression models described above contained no random effects.

In the 'crude' analyses presented in the tables, the data were stratified by one covariate at a time and repeated measurements models containing only intercepts were run. In adjusted models, all covariates belonging to the same block were entered simultaneously (if entered) into the regression analyses, except for covariates belonging to the functional-status block. These were added one at a time to the model containing all other blocks. The results for the models containing either only the basic block or all blocks except the functional-status block were presented in the tables. The effect of age on change in lung volumes was modelled with age acting both as a categorical and continuous covariate. The latter analyses were conducted in order to produce figures. In these cases, the effect of age was modelled via restricted cubic splines. In an attempt to capture some additional dynamics of the data, age (when viewed as a categorical covariate) was re-classified into the next higher age category if a majority of the between-visits time period was spent in that category. For example, for a trajectory for which a patient was 69 years old at the initial examination and 75 years old at the follow up, we classified the patient as belonging to the '70-79' age category rather than the '60-69' category.

Sensitivity analyses

A bronchodilator was administrated at all examinations except for the baseline examination of cohort I. As a way to assess the impact of this design flaw on the results regarding change we conducted a straightforward sensitivity analysis. All change measurements with initial measurement stemming from the baseline examination of cohort I were separated from the rest. This resulted in two data sets. For

all outcomes regarding change we ran the analysis including all blocks but the functional-status block separately for both data sets. Subsequently, we tested whether the adjusted average decline was larger in the analysis corresponding to 'bronchodilator inhaled at initial measurement' and if the effects of risk factors differed between the analyses. All tests were statistically non-significant suggesting that the effect of this inconsistency in the design was limited and that no adjustment or stratification to compensate for it was necessary. It should be added that this sensitivity analysis ignored that measurements corresponding to the same patient are (likely to be) dependent. The reason for this was that the algorithm applied to estimate regression parameters when taking the repeated measurements design into account failed to converge after inclusion of the interaction terms necessary to assess the effects of interest.

In order to assess whether (or rather: to what extent) the results of the regression analyses were due to influential outliers (observations with an extreme value of the dependent variable given covariate values) we used PROC ROBUSTREG in SAS to run additional robust regression analyses (results not shown). More precisely, for each outcome under consideration we ran regression analyses with M-estimation of effects using a bi-square weight function and an unspecified scale parameter. These were adjusted for covariates that were statistically significant in the original analyses. We could confirm that significant effects from the original analyses remained and that parameter estimates were similar except for the significant effects of education on changes in lung volumes. It appeared that the significant effects of low level of education in the original analyses were largely due to a combination of the small number of participants in this group and a few extreme measurements of lung volumes. Note that this did not rule out the possibility that the low education group actually represented a truly different pattern of change in lung volumes (e.g. through large heterogeneity).

References for Supplementary material

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