Trajectory and mortality of Preserved Ratio Impaired Spirometry: the Rotterdam Study

S. R. A. Wijnant[1,2,3], E. De Roos[1,2], M. Kabousi[2], B. H. Stricker[2,4], N. Terzikhan[2], L. Lahousse[2,3*], G. G. Brusselle[1,2,5*]

[1]Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium;
[2]Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands;
[3]Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium;
[4]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands;
[5]Department of Respiratory Medicine, Erasmus Medical Center, Rotterdam, the Netherlands
*These authors supervised the work equally.

Corresponding author:

Guy Brusselle
Department of Respiratory medicine, University Hospital Ghent
Corneel Heymanslaan 10
9000 Ghent, Belgium
guy.brusselle@ugent.be

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Table S1. Representativeness of the study subjects with follow-up data.

A. Characteristics of subjects from cohort 1 and 2 with and without follow-up spirometry at phase 2.

	Characteristics at phase 1 of the subgroup with follow-up at phase 2 (n=1603)			Characteristics at phase 1 of the subgroup without follow-up at phase 2 (n=1254)		
	Normal-P1 (n=1276)	PRISm-P1 (n=89)	COPD-P1 (n=238)	Normal-P1 (n=856)	PRISm-P1 (n=121)	COPD-P1 (n=277)
Age (years)	73.7 (4.9)	74.7 (5.7)	74.3 (5.0)	77.8 (6.1)*	78.2 (6.3)*	78.4 (6.1)*
Female sex	729 (57.1)	51 (57.3)	106 (44.5)	523 (61.1)	64 (52.9)	126 (45.5)
BMI (kg/m^2)	27.6 (4.1)	29.1 (3.8)	26.6 (3.9)	27.7 (4.1)	28.7 (5.0)	26.3 (3.8)
Current smoker	85 (6.7)	6 (6.7)	29 (12.2)	55 (6.4)	20 (16.5)	77 (27.8)*
Pack-years (years)	3.2 (0.0, 18.8)	10.8 (0.0, 29.0)	19.8 (1.7, 40.4)	2.3 [0.0, 21.0]	11.3 [0.0, 30.0]	22.8 [5.2, 42.0]
White blood cell count	6.8 (1.7)	7.5 (1.8)	7.2 (1.7)	7.0 (1.8)	7.4 (1.9)	7.9 (3.2)
Diabetes mellitus	97 (7.7)	6 (6.8)	21 (9.1)	79 (9.7)	10 (8.9)	28 (10.3)
Hypertension	1065 (83.5)	80 (89.9)	202 (84.9)	757 (88.5)*	115 (95.0)	240 (86.6)
Heart failure	34 (2.7)	4 (4.5)	11 (4.6)	47 (5.5)*	22 (18.3)*	34 (12.3)*
Coronary heart disease	123 (9.7)	12 (13.5)	33 (13.9)	103 (12.1)	21 (17.5)	47 (17.0)
FEV_1% predicted (%)	104.8 (13.8)	72.6 (6.4)	77.9 (17.8)	104.3 (14.0)	70.4 (8.6)*	72.4 (18.1)*
FVC% predicted (%)	101.9 (13.2)	72.7 (7.6)	92.6 (16.7)	100.7 (13.9)*	69.7 (9.9)*	87.0 (17.6)*
FEV_1/FVC (%)	78.6 (4.7)	76.3 (5.1)	63.5 (6.7)	78.8 (4.9)	76.8 (5.0)	62.4 (7.1)
DLCO (mmol/min/kPA)	7.5 (1.5)	7.2 (1.4)	7.2 (1.7)	7.1 (1.4)*	7.1 (1.6)	6.5 (1.5)*
DLCO/VA (mmol/min/kPA)	1.5 (0.2)	1.6 (0.2)	1.4 (0.3)	1.5 (0.2)*	1.5 (0.3)*	1.3 (0.3)*
Deaths before P2 (%)	NA	NA	NA	223 (26.1)	46 (38.0)	100 (36.1)

PRISm = Preserved Ratio Impaired Spirometry; COPD = Chronic Obstructive Pulmonary Disease; BMI = body mass index; FEV_1 = Forced expiratory volume in one second; FVC = Forced vital capacity; DLCO = diffusion capacity of the lung for carbon monoxide; DLCO/VA = diffusion capacity of the lung for carbon monoxide per alveolar volume. *P<0.05 compared to subjects with follow-up. Results are presented as mean (SD), count (percentage) or median (interquartile range).

B. Characteristics of subjects from cohort 1 and 2 with follow-up and of subjects from cohort 1 and 2 with loss of follow-up at phase 2 (i.e. no follow-up spirometry at phase 2 and no death before end of phase 2 examinations).

	Characteristics at phase 1 of the subgroup with follow-up at phase 2 (n=1603)			Characteristics at phase 1 of the subgroup with loss of follow-up at phase 2 (i.e. no follow-up spirometry at phase 2 and no death before end of phase 2) (n=884)		
	Normal-P1 (n=1276)	PRISm-P1 (n=89)	COPD-P1 (n=238)	Normal-P1 (n=633)	PRISm-P1 (n=75)	COPD-P1 (n=177)
Age (years)	73.7 (4.9)	74.7 (5.7)	74.3 (5.0)	76.9 (5.8)*	76.4 (5.9)	77.3 (5.8)*
Female sex	729 (57.1)	51 (57.3)	106 (44.5)	412 (65.1)*	46 (61.3)	92 (52.0)
BMI (kg/m^2)	27.6 (4.1)	29.1 (3.8)	26.6 (3.9)	28.0 (4.2)*	29.2 (5.2)	26.5 (3.9)
Current smoker	85 (6.7)	6 (6.7)	29 (12.2)	34 (5.4)	11 (14.7)	45 (25.4)*
Pack-years (years)	3.2 (0.0, 18.8)	10.8 (0.0, 29.0)	19.8 (1.7, 40.4)	1.4 (0.0, 20.0)	8.0 (0.0, 25.0)	19.0 (0.3, 39.0)
White blood cell count	6.8 (1.7)	7.5 (1.8)	7.2 (1.7)	6.9 (1.6)	7.1 (1.8)	7.6 (2.1)*
Diabetes mellitus	97 (7.7)	6 (6.8)	21 (9.1)	59 (9.8)	4 (5.6)	18 (10.3)
Hypertension	1065 (83.5)	80 (89.9)	202 (84.9)	558 (88.2)*	73 (97.3)	148 (83.6)
Heart failure	34 (2.7)	4 (4.5)	11 (4.6)	25 (4.0)	9 (12.2)	11 (6.2)
Coronary heart disease	123 (9.7)	12 (13.5)	33 (13.9)	61 (9.7)	6 (8.1)	23 (13.0)
FEV_1% predicted (%)	104.8 (13.8)	72.6 (6.4)	77.9 (17.8)	104.8 (13.7)	70.9 (7.8)	74.4 (18.1)
FVC% predicted (%)	101.9 (13.2)	72.7 (7.6)	92.6 (16.7)	101.5 (13.6)	70.6 (9.0)	88.5 (17.2)*
FEV_1/FVC (%)	78.6 (4.7)	76.3 (5.1)	63.5 (6.7)	78.7 (4.7)	76.7 (5.0)	63.2 (6.4)
DLCO (mmol/min/kPA)	7.5 (1.5)	7.2 (1.4)	7.2 (1.7)	7.2 (1.4)*	7.5 (1.4)	6.7 (1.5)*
DLCO/VA (mmol/min/kPA)	1.5 (0.2)	1.6 (0.2)	1.4 (0.3)	1.5 (0.2)	1.5 (0.3)	1.3 (0.3)

PRISm = Preserved Ratio Impaired Spirometry; COPD = Chronic Obstructive Pulmonary Disease; BMI = body mass index; FEV_1 = Forced expiratory volume in one second; FVC = Forced vital capacity; DLCO = diffusion capacity of the lung for carbon monoxide; DLCO/VA = diffusion capacity of the lung for carbon monoxide per alveolar volume. *P<0.05 compared to subjects with follow-up. Results are presented as mean (SD), count (percentage) or median (interquartile range).

Table S2. Lung function values at phase 1 and phase 2 stratified by lung function category and smoking status at phase 2.

		Normal spirometry-P1(n=1276)	PRISm-P1 (n=89)	COPD GOLD1-4-P1 (n=238)	COPD GOLD1-P1(n=114)	COPD GOLD 2-4-P1 (n124)
Years between P1 and P2		4.6 (0.5)	4.6 (0.4)	4.6 (0.4)	4.6 (0.4)	4.6 (0.4)
FEV_1% predicted at P1 (%)		104.8 (13.8)	72.6 (6.4)*	77.9 (17.8)*	92.9 (9.8)*	64.1 (11.2)*
FEV_1% predicted at P2 (%)		102.0 (15.9)	72.8 (13.6)*	78.3 (19.9)*	91.5 (13.2)*	66.2 (17.2)*
Δ FEV_1 (ml/year)	All (n=1603)	-45.0 (-75.2, -17.4)	-20.4 (-67.0, 1.9)*	-31.0 (-60.3, 4.4)*	-39.4 (-63.3, -14.1)	-21.6 (-46.9, 19.3)*
	Never smokers (n=534)	-46.0 (-76.4, -20.0)	-25.2 (-44.6, -2.2)	-29.7 (-56.8, 3.7)*	-32.4 (-72.1, -21.3)	-8.2 (-39.5, 15.3)*
	Former smokers (n=949)	-43.5 (-74.5, -15.8)	-16.4 (-71.5, 1.0)*	-29.9 (-58.6, 5.4)*	-37.9 (-61.9, -12.6)	-22.0 (-48.2, 25.9)*
	Current smokers (n=120)	-49.3 (-75.1, -25.3)	-19.7 (-28.6, -1.5)	-40.8 (-65.1, -15.7)	-56.1 (-85.8, -22.0)	-29.2 (-44.8, -6.7)
FVC% predicted at P1 (%)		101.9 (13.2)	72.7 (7.6)*	92.6 (16.8)*	105.4 (11.2)*	81.0 (11.8)*
FVC% predicted at P2 (%)		104.4 (15.3)	78.9 (13.5)*	97.7 (18.1)*	108.7 (15.0)*	87.6 (14.5)*
Δ FVC (ml/year)	All (n=1603)	-20.2 (-55.8, 20.4)	5.5 (-38.4, 59.0)*	-2.0 (-46.4, 50.2)*	-6.7 (-66.1, 34.2)	8.0 (-37.6, 65.5)*
	Never smokers (n=534)	-25.3 (-63.9, 10.6)	-13.4 (-37.0, 48.3)	-9.5 (-59.9, 25.1)	-16.4 (-72.0, 4.5)	-5.6 (-43.8, 29.3)
	Former smokers (n=949)	-17.6 (-53.5, 22.7)	5.7 (-45.2, 60.1)*	2.4 (-43.3, 65.5)*	-4.1 (-48.2, 53.1)	12.0 (-36.8, 81.5)*
	Current smokers (n=120)	-9.0 (-49.0, 23.8]	39.3 (12.6, 105.8)	-23.4 (-57.2, 25.3)	-42.1 (-80.3, 8.1)	7.2 (-33.5, 44.2]

PRISm = Preserved Ratio Impaired Spirometry; COPD = Chronic Obstructive Pulmonary Disease; GOLD = Global initiative for Chronic Obstructive Lung Disease; P1 = phase 1; P2 = phase 2; FEV_1 = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity; Δ = delta. *P<0.05 compared to subjects with normal spirometry. Results are presented as mean (SD) or median (interquartile range).

Table S3. Characteristics at phase 1 by lung function category at phase 1 and phase 2.

	Normal (n=1276)			PRISm (n=89)			COPD (n=238)		
	Normal (n=931)	PRISm (n=47)	COPD (n=298)	Normal (n=14)	PRISm (n=31)	COPD (n=44)	Normal (n=25)	PRISm (n=5)	COPD (n=208)
Years between P2 and P2	4.7 (0.5)	4.9 (0.5)	4.8 (0.5)	4.6 (0.4)	4.8 (0.4)	4.8 (0.4)	4.7 (0.3)	5.3 (0.4)	4.7 (0.4)
Age (years)	73.3 (4.6)	75.5 (5.9)	74.6 (5.2)	72.9 (3.3)	74.9 (6.4)	75.1 (5.7)	73.7 (4.4)	80.3 (3.8)	74.3 (5.1)
Female sex	561 (60.3)	27 (57.4)	141 (47.3)	12 (85.7)	15 (48.4)	24 (54.5)	15 (60.0)	2 (40.0)	89 (42.8)
BMI (kg/m^2) P1	27.7 (4.2)	29.0 (4.7)	27.2 (3.7)	28.3 (3.9)	30.2 (4.1)	28.7 (3.6)	26.0 (4.3)	29.5 (4.8)	26.6 (3.8)
BMI (kg/m^2) P2	27.5 (4.2)	29.3 (5.0)	27.0 (3.8)	28.2 (4.0)	29.7 (4.4)	28.5 (3.9)	25.9 (4.3)	27.4 (5.4)	26.3 (3.9)
Δ BMI (kg/m^2)	-0.2 (1.6)	0.3 (1.9)	-0.1 (1.5)	-0.1 (1.1)	-0.5 (2.2)	-0.2 (1.2)	-0.02 (0.2)	-0.4 (0.9)	-0.1 (0.3)
Δ BMI > 1.5 kg/m^2 (%)	109 (11.7)	12 (25.5)	32 (10.7)	1 (7.1)	5 (16.1)	3 (6.8)	2 (8.0)	1 (20.0)	25 (12.0)
Waist circumference (cm) P1	92.9 (11.7)	97.2 (14.5)	92.9 (11.7)	92.8 (12.4)	101.1 (9.4)	99.1 (12.1)	88.1 (14.0)	101.6 (16.9)	94.1 (12.3)
Waist circumference (cm) P2	94.5 (12.3)	101.4 (15.2)	95.2 (12.0)	93.4 (11.5)	101.1 (11.0)	101.1 (12.2)	90.7 (12.5)	99.1 (17.4)	95.4 (12.4)
Δ waist circumference (cm)	1.6 (6.9)	4.2 (6.8)	2.3 (5.6)	0.6 (3.7)	-0.1 (6.8)	2.0 (6.6)	2.6 (4.8)	-2.5 (8.8)	1.3 (5.5)
Height (cm)	166.9 (9.0)	167.1 (7.3)	169.1 (9.0)	162.5 (7.7)	167.0 (9.7)	167.9 (9.5)	166.7 (9.7)	173.6 (9.9)	170.5 (9.6)
Current smokers	44 (4.7)	4 (8.5)	37 (12.4)	1 (7.1)	1 (3.2)	4 (9.1)	3 (12.0)	0 (0.0)	26 (12.5)
Pack-years (years)	1.9 (0.0, 16.0)	3.0 (0.0, 20.5)	8.8 (0.0, 25.4)	0.5 (0.0, 7.1)	16.2 (0.1, 32.5)	11.2 (0.0, 30.8)	6.5 (0.5, 15.8)	16.0 (8.5, 25.0)	21.6 (2.9, 44.3)
Total cholesterol (mmol/l)	5.5 (1.1)	5.4 (1.2)	5.3 (1.1)	5.4 (0.9)	5.0 (1.0)	5.2 (1.2)	5.2 (1.1)	5.0 (1.1)	5.4 (1.0)
HDL-cholesterol (mmol/l)	1.5 (0.4)	1.4 (0.3)	1.5 (0.4)	1.5 (0.4)	1.4 (0.4)	1.4 (0.4)	1.6 (0.5)	1.3 (0.6)	1.5 (0.4)
Tryglicerides (mmol/l)	1.3 (1.0, 1.7)	1.3 (1.1, 1.6)	1.2 (1.0, 1.7)	1.5 (1.1, 1.7)	1.4 (1.1, 1.9)	1.4 (1.0, 1.9)	1.1 (0.9, 1.4)	1.4 (1.1, 1.6)	1.2 (0.9, 1.6)
Glucosis (mmol/l)	5.5 (5.1, 6.1)	5.7 (5.2, 6.5)	5.5 (5.2, 6.1)	5.5 (4.9, 5.9)	5.9 (5.5, 6.5)	5.5 (5.1, 6.3)	5.3 (4.9, 5.7)	5.7 (5.4, 6.5)	5.5 (5.1, 6.0)
White blood cell count	6.8 (1.7)	7.0 (1.9)	6.9 (1.5)	7.1 (1.1)	7.6 (2.2)	7.5 (1.8)	7.1 (1.7)	7.1 (3.0)	7.2 (1.7)
Diabetes mellitus	73 (8.0)	6 (12.8)	18 (6.1)	1 (7.7)	2 (6.5)	3 (6.8)	1 (4.0)	0 (0.0)	20 (9.9)
Hypertension	775 (83.2)	40 (85.1)	250 (83.9)	13 (92.9)	29 (93.5)	38 (86.4)	23 (92.0)	5 (100.0)	174 (83.7)
Prevalent Heart failure	25 (2.7)	1 (2.1)	8 (2.7)	0 (0.0)	2 (6.5)	2 (4.5)	0 (0.0)	0 (0.0)	11 (5.3)
Incident Heart failure	8 (0.9)	5 (10.9)	2 (0.7)	0 (0.0)	4 (13.8)	3 (7.1)	1 (4.0)	0 (0.0)	6 (339)
Prevalent coronary heart disease	91 (9.8)	5 (10.6)	27 (9.1)	1 (7.1)	4 (12.9)	7 (15.9)	5 (20.0)	0 (0.0)	28 (13.5)
Incident coronary heart diease	14 (1.7)	1 (2.4)	11 (4.1)	0 (0.0)	0 (0.0)	1 (2.7)	2 (10.0)	0 (0.0)	6 (3.3)
Deaths after P2	42 (4.5)	7 (14.6)	20 (6.7)	1 (7.1)	4 (12.9)	2 (4.5)	1 (4.0)	2 (40.0)	17 (8.2)
Follow-up after P2 (person-years)	3135.4	157.6	1009.0	45.7	96.0	147.2	88.4	17.3	701.7
Mortality rate per 1000 PY after P2	13.4	44.4	19.8	21.9	41.7	13.6	11.3	115.5	24.2
Mortality rate ratio after P2	Ref	3.3	1.5	1.6	3.1	1.0	0.8	8.6	1.8

PRISm = Preserved Ratio Impaired Spirometry; COPD = Chronic Obstructive Pulmonary Disease; BMI = body mass index; HDL = high-density cholesterol; P1 = phase 1; P2 = phase 2. Results are presented as mean (SD), count (percentage) or median (interquartile range)

Table S4. Lung function values at phase 1 and phase 2 stratified by lung function category at phase 1 and phase 2.

	Normal (1276)			PRISm (89)			COPD (238)		
	Normal (931)	PRISm (47)	COPD (298)	Normal (14)	PRISm (31)	COPD (44)	Normal (25)	PRISm (5)	COPD (208)
FEV1% predicted P1	107.2 (13.9)	91.5 (8.9)	99.5 (11.5)	75.5 (4.0)	72.0 (6.9)	72.1 (6.6)	86.7 (15.8)	68.9 (7.6)	77.0 (17.9)
FEV1% predicted P2	106.3 (14.1)	73.8 (5.6)	92.9 (13.8)	92.5 (12.3)	69.0 (8.9)	69.2 (11.3)	101.5 (13.5)	65.9 (8.9)	75.8 (18.9)
Δ FEV1 (ml/year)	-40.6 (-65.9, -13.0)	-104.9 (-146.6, -73.1)	-62.2 (-92.8, -32.1)	43.7 (7.7, 75.7)	-31.0 (-69.6, -7.7)	-36.7 (-74.3, -10.6)	27.1 (-22.1, 106.7)	-24.9 (-86.9, 0.0)	-36.2 (-64.0, -4.1)
FVC% predicted P1	102.9 (13.4)	87.8 (8.1)	101.3 (11.9)	72.8 (5.9)	69.1 (7.4)	75.3 (7.3)	101.7 (15.8)	76.5 (6.1)	91.9 (16.6)
FVC% predicted P2	105.6 (14.3)	74.2 (7.6)	105.3 (14.6)	91.8 (11.2)	70.1 (9.9)	81.0 (12.3)	99.2 (12.9)	64.9 (8.3)	98.4 (18.1)
Δ FVC (ml/year)	-20.6 (-56.8, 19.3)	-91.3 (-171.6, -52.7)	-11.9 (-40.1, 51.9)	76.2 (49.5, 119.5)	-20.6 (-48.9, 22.2)	-11.9 (-40.1, 51.9)	-51.3 (-82.6, -8.7)	-103.3 (-157.7, -47.7)	7.1 (-39.8, 56.3)
FEV1/FVC P1	79.8 (4.4)	79.4 (3.9)	74.7 (3.6)	80.3 (5.5)	79.7 (4.5)	72.7 (2.1)	65.0 (5.1)	67.1 (4.7)	63.2 (6.9)
FEV1/FVC P2	76.4 (4.4)	75.3 (4.8)	66.4 (2.9)	77.0 (3.5)	74.6 (3.5)	64.3 (4.0)	77.5 (5.9)	75.1 (2.2)	57.7 (8.7)
Δ FEV1/FVC (%)	-3.4 (4.5)	-4.1 (5.4)	-8.3 (4.1)	-3.3 (5.9)	-5.1 (4.7)	-8.4 (4.4)	12.5 (8.9)	8.0 (3.1)	-5.5 (5.6)
DLCO (mmol/min/kPA)	7.5 (1.5)	7.2 (1.2)	7.5 (1.5)	6.4 (1.0)	7.2 (1.2)	7.6 (1.6)	7.2 (1.1)	8.4 (1.1)	7.1 (1.8)
DLCO % predicted (%)	97.7 (13.7)	95.3 (17.1)	96.0 (14.9)	89.1 (12.5)	95.7 (22.0)	94.6 (20.0)	96.6 (9.9)	109.9 (15.9)	88.5 (19.4)
DLCO/VA (mmol/min/kPA)	1.5 (0.2)	1.6 (0.2)	1.4 (0.2)	1.6 (0.2)	1.7 (0.3)	1.6 (0.2)	1.5 (0.2)	1.6 (0.2)	1.3 (0.3)
DLCO/VA % predicted (%)	112.3 (16.0)	120.7 (17.2)	109.1 (17.4)	116.6 (11.0)	125.8 (21.1)	109.1 (17.4)	110.8 (14.9)	129.6 (16.3)	102.2 (20.2)

PRISm = Preserved Ratio Impaired Spirometry; COPD = Chronic Obstructive Pulmonary Disease; FEV_1 = Forced expiratory volume in one second; FVC = Forced vital capacity; P1 = phase 1; P2 = P2; Δ = delta; DLCO = diffusion capacity of the lung for carbon monoxide; DLCO/VA = diffusion capacity of the lung for carbon monoxide per alveolar volume. Results are presented as mean (SD) and median (interquartile range)

Table S5. Estimates of mortality stratified by lung function categories.

	Number at risk	All deaths	Follow-up (years)	Mortality rate (per 1000 PY)	Mortality rate ratio	HR [95%CI][1]	HR [95%CI][2]	HR [95%CI][3]	HR [95%CI][4]	CV deaths	Follow-up (years)	Mortality rate (per 1000 PY)	Mortality rate ratio	HR [95%CI][1]	HR [95%CI][4]
Total population	5446	686	35766	19.2	NA	NA	NA	NA	NA	82	15771	5.2	NA	NA	NA
Global initiative for Obstructive Lung Disease (GOLD) definition															
Normal	4150	425	27517	15.4	Reference	Reference	Reference	Reference	Reference	43	11973	3.6	Reference	Reference	Reference
PRISm	384	71	2441	29.1	1.9	1.6 [1.2-2.0]	1.6 [1.3, 2.1]	1.6 [1.2, 2.0]	1.6 [1.2, 2.0]	15	111	13.5	3.8	2.7 [1.5, 5.0]	2.6 [1.4, 4.7]
FEV_1≥74%	*194*	*30*	*1261*	*23.8*	*1.5*	*1.3 [0.9, 1.8]*	*NP*	*NP*	*1.4 [1.0, 1.9]*	*7*	*566*	*12.4*	*3.4*	*2.6 [1.1, 5.7]*	*2.5 [1.1, 5.5]*
FEV_1<74%	*190*	*41*	*1180*	*34.7*	*2.3*	*1.9 [1.4, 2.6]*	*NP*	*NP*	*1.7 [1.3, 2.3]*	*8*	*545*	*14.7*	*4.1*	*2.8 [1.3, 6.0]*	*2.6 [1.2, 5.7]*
FVC≥73%	*191*	*28*	*1226*	*22.8*	*1.5*	*1.4 [1.0, 2.1]*	*NP*	*NP*	*1.4 [0.9, 2.0]*	*4*	*536*	*7.5*	*2.1*	*1.8 [0.7, 5.1]*	*1.7 [0.6, 4.8]*
FVC<73%	*193*	*43*	*1215*	*35.4*	*2.3*	*1.7 [1.2, 2.3]*	*NP*	*NP*	*1.7 [1.3, 2.3]*	*11*	*575*	*19.1*	*5.3*	*3.2 [1.6, 6.4]*	*3.1 [1.6, 6.1]*
COPD GOLD1	419	52	2735	19.0	1.2	1.0 [0.7, 1.3]	1.0 [0.7, 1.3]	1.0 [0.7, 1.3]	0.7 [0.5, 0.9]	3	1187	2.5	0.7	0.5 [0.2, 1.6]	0.5 [0.1, 1.5]
COPD GOLD2-4	493	138	3073	44.9	2.9	1.7 [1.4, 2.1]	1.8 [1.4, 2.2]	1.7 [1.4, 2.1]	1.5 [1.2, 1.8]	21	1499	14.0	3.9	1.9 [1.1, 3.4]	1.8 [1.0, 3.1]
Global Lung Initiative definition (GLI): Lower Limit of Normal (LLN)															
NL	4791	541	31712	17.1	Reference	Reference	NP	NP	Reference	62	13944	4.4	Reference	Reference	Reference
PRISm	279	63	1751	36.0	2.1	1.9 [1.5, 2.5]	NP	NP	1.8 [1.4, 2.3]	9	816	11.0	2.5	2.2 [1.1, 4.5]	2.1 [1.0, 4.2]
FEV_1≥66%	*139*	26	847	30.7	1.8	*1.2 [1.4, 2.3]*	NP	NP	NP	2	364	5.5	*1.3*	*1.8 [0.8,4.0]*	NP
FEV_1<66%	*140*	37	904	40.9	2.4	*1.8 [1.4, 2.4]*	NP	NP	NP	7	452	15.5	*3.5*	*2.6 [1.5, 4.5]*	NP
FVC≥69%	*141*	27	891	30.3	1.8	*1.4 [1.0, 1.8]*	NP	NP	NP	1	402	2.5	*0.6*	*1.7 [0.8, 3.6]*	NP
FVC<69%	*138*	36	860	41.9	4.5	*1.7 [1.3, 2.2]*	NP	NP	NP	8	414	19.3	*4.4*	*3.3 [1.8, 5.9]*	NP
COPD GOLD1	131	17	822	20.7	1.2	1.4 [0.8, 2.2]	NP	NP	1.1 [0.7, 1.7]	1	335	3.0	0.7	0.7 {0.1, 5.4}	NA
COPD GOLD2-4	245	65	1480	43.9	2.6	1.9 [1.5, 2.5]	NP	NP	1.6 [1.3, 2.1]	10	676	14.8	3.4	2.1 [1.0, 4.3]	2.0 [1.0, 4.2]
Subgroup with spirometry measurements at both phase 1 and phase 2*															
Persistent NL	924	42	3135	13.4	Reference	Reference	NP	NP	NA	1	NA	NA	NA	NA	NA
Persistent PRISm	31	4	96	42.7	3.2	2.2 [0.8, 6.1]	NP	NP	NA	0	NA	NA	NA	NA	NA
Incident PRISm	52	9	174	51.5	3.8	2.4 [1.1, 4.9]	NP	NP	NA	0	NA	NA	NA	NA	NA
Persistent COPD	208	17	702	24.2	1.8	1.0 [0.6, 1.9]	NP	NP	NA	0	NA	NA	NA	NA	NA
Incident COPD	342	22	1156	19.0	1.4	0.9 [0.5, 1.5]	NP	NP	NA	0	NA	NA	NA	NA	NA

HR = Hazard Ratio; CV = cardiovascular; GOLD = Global initiative for Chronic Obstructive Lung Disease; PRISm = Preserved Ratio Impaired Spirometry; COPD = Chronic Obstructive Pulmonary Disease; FEV_1 = Forced Expiratory volume in one second; FVC = Forced Vital Capacity; PY = person-years; NA = not applicable; NP = Not Performed; [1] = HR adjusted for age, sex, BMI, current smoking and pack-years; [2] = HR adjusted for age, sex, BMI, current smoking and pack-years and subjects with physician-diagnosed asthma excluded; 3 = HR adjusted for age, sex, BMI, current smoking, pack-years and cardiovascular comorbidity (heart failure and/or coronary heart disease); [4] = time-dependent HR adjusted for age, sex, BMI, current smoking and pack-years with lung function category at phase 2 as time varying covariate; * follow-up time start after spirometry at phase 2. Subjects with missing information for one of the covariates were excluded (n=13, of whom 6 died).

Table S6. ICD10 classification of cause-specific mortality.

ICD10 code		Normal	PRISm	COPD
C00-D48	Neoplasms	81 (47.6%)	11 (29.7%)	38 (48.7%)
I00–I99	Diseases of the circulatory system	43 (25.3%)	15 (40.6%)	24 (30.8%)
F00–F99	Mental and behavioural disorders	12 (7.1%)	3 (8.1%)	6 (7.7%)
R00–R99	Symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified	15 (8.8%)	3 (8.1%)	2 (2.6%)
J00–J99	Diseases of the respiratory system	4 (2.3%)	4 (10.8%)	6 (7.7%)
G00–G99	Diseases of the nervous system	4 (2.3%)	1 (2.7%)	0 (0.0%)
K00–K93	Diseases of the digestive system	4 (2.3%)	0 (0.0%)	0 (0.0%)
V01–Y98	External causes of morbidity and mortality	3 (1.8%)	0 (0.0%)	1 (1.3%)
S00–T98	Injury, poisoning and certain other consequences of external causes	2 (1.2%)	0 (0.0%)	1 (1.3%)
A00-B99	Certain infectious and parasitic diseases	1 (0.6%)	0 (0.0%)	0 (0.0%)
M00–M99	Diseases of the musculoskeletal system and connective tissue	1 (0.6%)	0 (0.0%)	0 (0.0%)
	Total deaths with ICD10 code registration (until 01/01/2015)	170 (39.5%)	37 (51.4%)	78 (41.1%)
	Total deaths (until 30/06/2018)	430	72	190

ICD = International Classification Of Diseases; PRISm = Preserved Ratio Impaired Spirometry; COPD = Chronic Obstructive Pulmonary Disease.

Figure S1. Flowchart of the Rotterdam Study

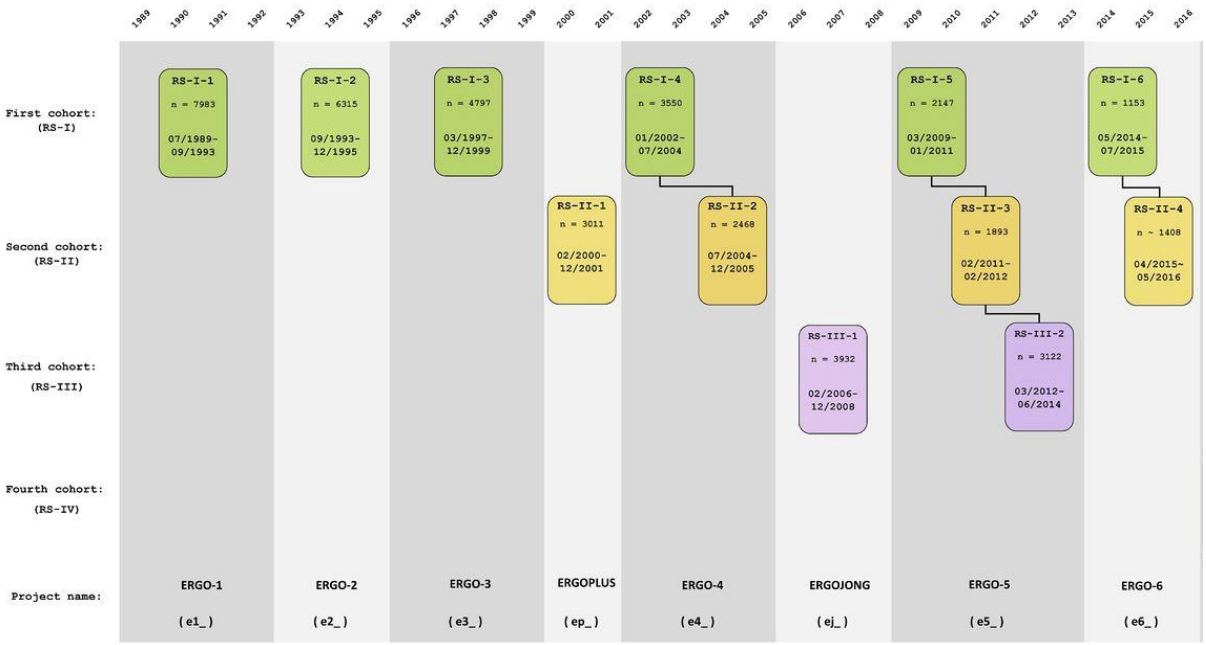
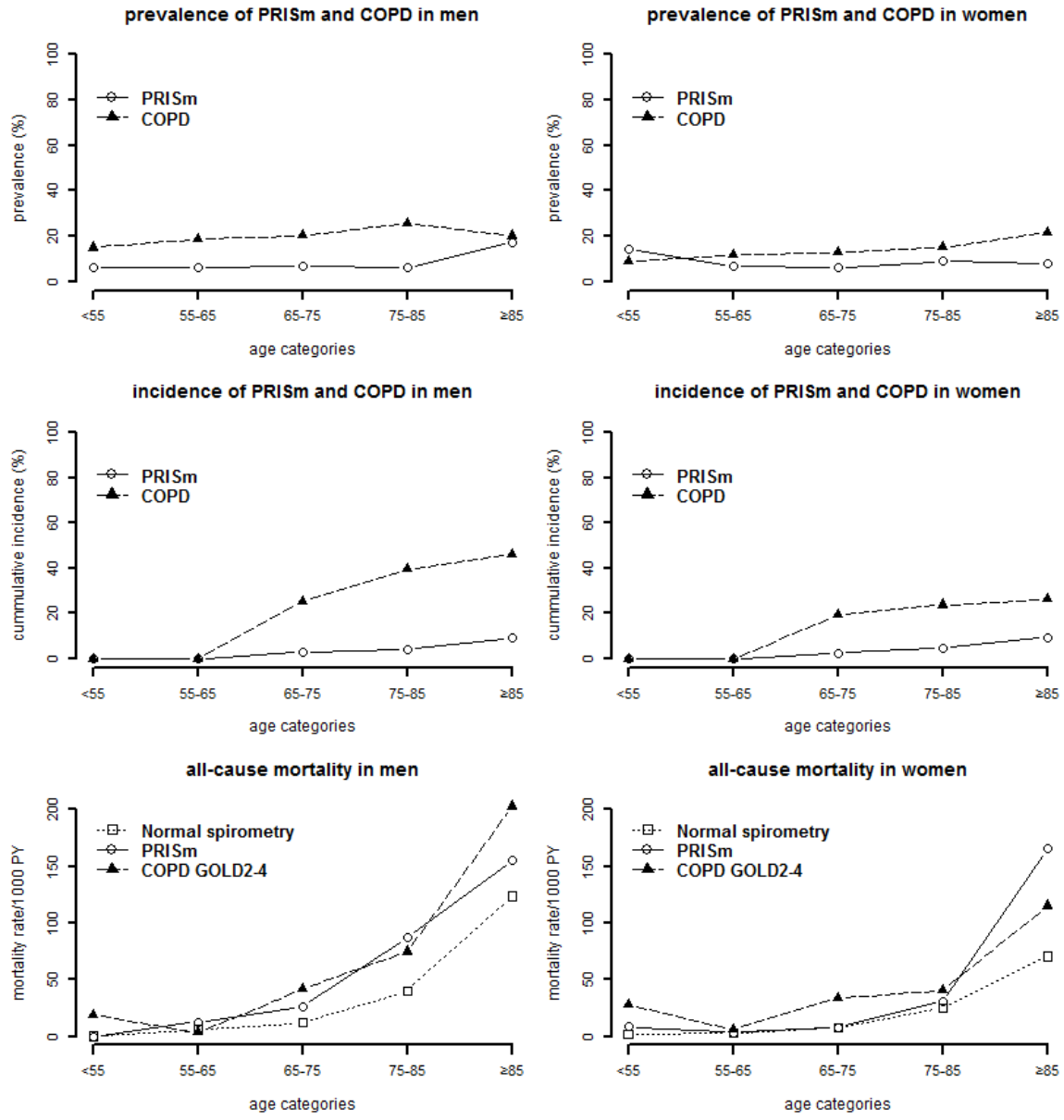


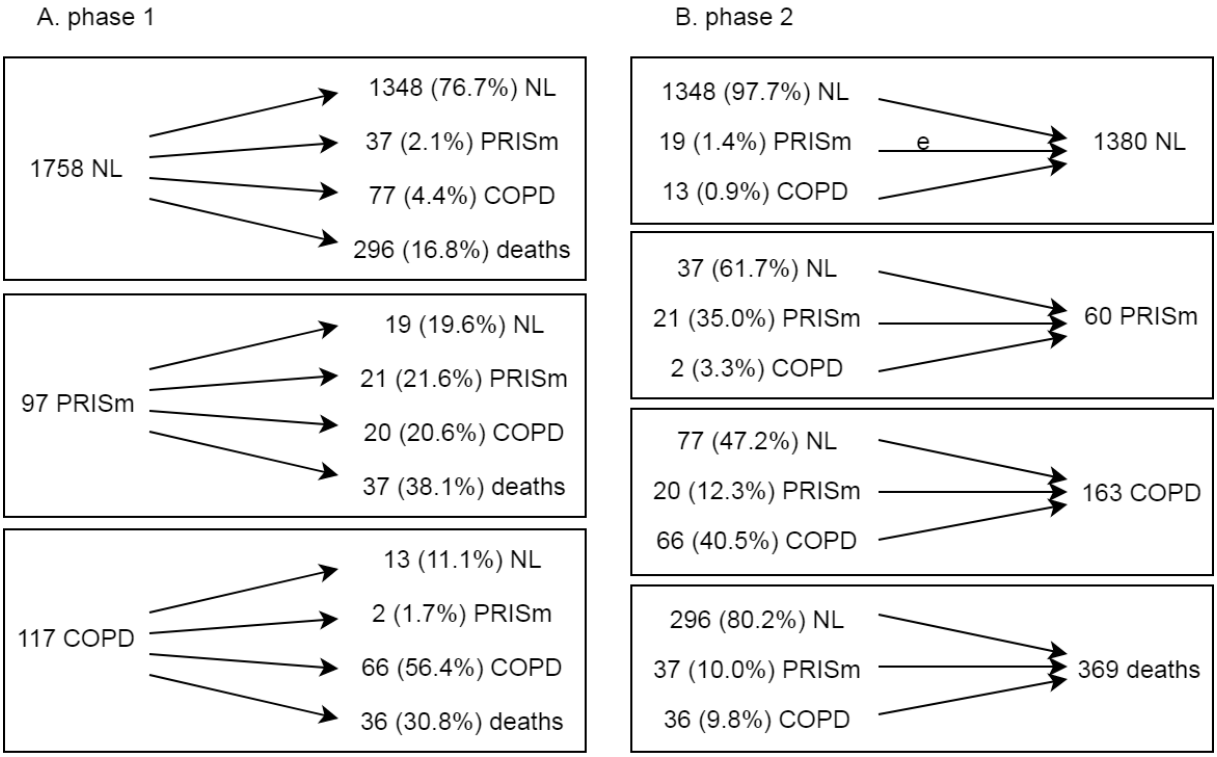
Diagram of examination cycles of the Rotterdam Study (RS). RS-I-1 refers to the baseline examination of the original cohort (pilot phase 07/1989–12/1989; cohort recruitment 01/1990–09/1993). RS-I-2, RS-I-3, RS-I-4, RS-I-5, and RS-I-6 refer to re-examinations of the original cohort members. RS-II-1 refers to the extension of the cohort with persons in the study district that became 55 years since the start of the study or those of 55 years or over that migrated into the study district. RS-II-2, RS-II-3, and RS-II-4 refer to re-examinations of the extension cohort. RS-III-1 refers to the baseline examination of all persons aged 45 years and over living in the study district that had not been examined already (i.e., mainly comprising those aged 45–60 years). RS-III-2 refers to the first re-examination of this third cohort. Examination RS-I-4 and RS-II-2 were conducted as one project and feature an identical research program. Similarly, examinations RS-I-5, RS-II-3, and RS-III-2 share the same program items. Also, examinations RS-I-6 and RS-II-4 are conducted as one project. RS-IV-1 refers to the baseline visit of a new cohort, to be established in February 2016.

Figure S2. Age- and sex-specific prevalence, incidence and mortality of PRISm and COPD.



PRISm = Preserved Ratio Impaired Spirometry; COPD = Chronic Obstructive Pulmonary Disease; PY = person-years. Cumulative incidence of PRISm and COPD was calculated in a subset of individuals with spirometry at both phase 1 and phase 2, after exlusion for prevalent PRISm and COPD in the case of incident PRISm (n=1278), and after exclusion of prevalent COPD in the case of incident COPD (n=1365).

Figure S3. Transitions between lung function categories according to GLI definition for FEV_1 and the FEV_1/FVC ratio.



NL = normal spirometry; PRISm = Preserved Ratio Impaired Spirometry; COPD = Chronic Obstructive Pulmonary Disease.