

COUGH IN COPD

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- Pathophysiology of cough in COPD patients
- Clinical implications of cough in COPD patients
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COUGH, COMMONEST REASON IN PRIMARY CARE CLINIC

Principal reason for visit and RVC code ¹	Number of visits in thousands	Percent distribution	Total	Percent distribution				
				Primary care offices	Surgical specialty offices	Medical specialty offices	Outpatient departments	Emergency departments
All visits	1,077,583	100.0	100.0	50.4	15.3	16.4	7.8	10.1
General medical examination X100	71,939	6.7	100.0	81.8	3.0	8.1	7.0	*0.2
Progress visit, not otherwise specified T800	46,340	4.3	100.0	42.9	14.0	30.3	12.7	0.2
Cough S440	33,119	3.1	100.0	73.7	1.2	9.0	7.0	9.2
Postoperative visit T205	24,629	2.3	100.0	17.1	69.4	7.0	5.6	0.9
Prenatal examination, routine X205	22,279	2.1	100.0	88.4	—	*	11.4	*
Stomach pain, cramps, and spasms S545	21,819	2.0	100.0	42.0	5.4	14.8	5.8	32.0
Symptoms referable to throat S455	21,305	2.0	100.0	70.8	5.1	*	9.8	11.4
Fever S010	17,437	1.6	100.0	65.3	*	*	6.1	27.5
Back symptoms S905	17,019	1.6	100.0	49.6	14.5	14.1	6.1	15.8
Medication, other and unspecified kinds T115	16,813	1.6	100.0	64.1	1.8	25.0	7.4	1.8
Chest pain and related symptoms (not referable to body system) S050	16,263	1.5	100.0	40.5	*	19.9	4.5	34.8
Knee symptoms S925	15,741	1.5	100.0	33.0	47.0	7.5	5.0	7.6
Hypertension D510	15,325	1.4	100.0	79.9	*	9.6	7.8	1.9
Well-baby examination X105	14,688	1.4	100.0	89.6	*	*	9.1	*
Skin rash S860	14,420	1.3	100.0	58.3	*	24.5	7.3	9.6
Earache, or ear infection S355	14,282	1.3	100.0	65.0	11.3	*	8.1	12.7
Headache, pain in head S210	13,868	1.3	100.0	48.8	7.6	14.3	7.5	21.7
Vision dysfunctions S305	13,860	1.3	100.0	*	90.6	1.7	3.4	1.1
Diabetes mellitus D205	13,332	1.2	100.0	62.4	11.1	*15.4	10.5	0.6
Nasal congestion S400	12,441	1.2	100.0	60.0	10.5	16.9	6.3	6.4
Gynecological examination X225	11,437	1.1	100.0	92.9	*	*	4.7	*
Depression S110	10,656	1.0	100.0	32.6	*	54.4	9.3	3.6
Blood pressure test X320	10,648	1.0	100.0	91.6	*	*3.1	4.8	*
Low back symptoms S910	10,222	1.0	100.0	40.9	21.3	15.4	8.7	13.8

COUGH AS THE MAJOR SYMPTOM IN COPD

- The Confronting COPD International Survey
- Total of 201,921 households were screened by random-digit dialing in the USA, Canada, France, Italy, Germany, the Netherlands, Spain, and the UK.
- 3,265 subjects with a diagnosis of COPD, chronic bronchitis or emphysema, or with symptoms of chronic bronchitis, were identified.
- Aimed to quantify morbidity and burden in COPD subjects.

Table 2. – Score on Medical Research Council (MRC) dyspnoea scale and cumulative cigarette consumption according to chronic obstructive pulmonary disease (COPD) diagnostic term and sex

	MRC scale			Cumulative cigarette consumption pack-yrs		
	Females	Males	p-value [#]	Females	Males	p-value [#]
All conditions	2 (1–4)	2 (1–3)	0.0035	30 (20–47)	40 (23–60)	<0.0000
COPD	4 (2–4)	3 (2–4)	0.0612	32 (20–50)	40 (20–62)	0.0061
Emphysema	3 (2–4)	2 (1–4)	0.1050	34 (20–50)	40 (26–60)	0.0014
CB	2 (1–3)	2 (1–3)	0.2815	30 (19–43)	38 (21–59)	<0.0000
Undiagnosed/symptomatic CB	2 (1–3)	2 (1–3)	0.0090	30 (19–45)	40 (25–60)	<0.0000



PATHOPHYSIOLOGY OF COUGH IN COPD



WHY DO PATIENTS WITH COPD COUGH?

- Substantial airway inflammation & smoking
- Mechanical sputum clearance by cough
- Neural interaction in cough reflex
- Bronchiectasis as co-morbidity

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HETEROGENEITY IN PATHOPHYSIOLOGY IN COPD

- COPD is a heterogeneous disease in terms of clinical, physiologic, and pathologic presentation.
- Aimed to evaluate whether airflow limitation, airway responsiveness, and airway inflammation are separate entities underlying the pathophysiology of COPD by **using factor analysis**.
- Factor 1 was comprised of FEV1, FEV1/IVC, and residual volume/total lung capacity.
- Factor 2 included reversibility, IgE, provocative concentration of methacholine required to produce a 20% drop in FEV1, and diffusing capacity.
- Factor 3 contained exhaled nitric oxide.
- Factor 4 included sputum % neutrophils and % eosinophils.

AIRFLOW LIMITATION AND AIRWAY INFLAMMATION ARE SEPARATE

- Total of 114 patients
 - 99 males/15 females
 - age 62 +/- 8 years
 - 42 pack-years smoking
 - no inhaled or oral steroids > 6 months
 - irreversible airflow limitation

	Factor 1	Factor 2	Factor 3	Factor 4
Postbronchodilator FEV ₁ , %pred	0.89	-0.16	-0.09	-0.07
Postbronchodilator FEV ₁ /IVC, %	0.82	0.04	-0.23	0.22
RV/TLC, %	-0.59	-0.36	-0.03	0.15
ΔFEV ₁ , %pred	-0.06	-0.72	0.08	0.11
IgE, IU/ml	-0.09	0.61	0.10	-0.07
PC ₂₀ , mg/ml	0.36	0.51	-0.35	0.14
K _{CO₂} , %pred	0.44	0.49	0.25	0.31
eNO, ppb	-0.09	0.10	0.89	-0.11
Sputum eosinophils, %	-0.09	0.02	0.19	-0.84
Sputum neutrophils, %	-0.18	-0.25	0.47	0.54
Eigenvalue	2.67	1.50	1.20	0.99
Total variance explained, %	26.7	15.0	12.0	9.9

SPUTUM EOSINOPHIL AND RESPONSE TO STEROID IN COPD

A randomized, double-blind, cross-over trial.

Hypothesized that response to prednisolone is related to the presence of eosinophilic airway inflammation.

Patients who had COPD treated with bronchodilators only were assigned placebo and 30 mg prednisolone daily for 2 weeks each, in a random order, separated by a 4-week washout period.

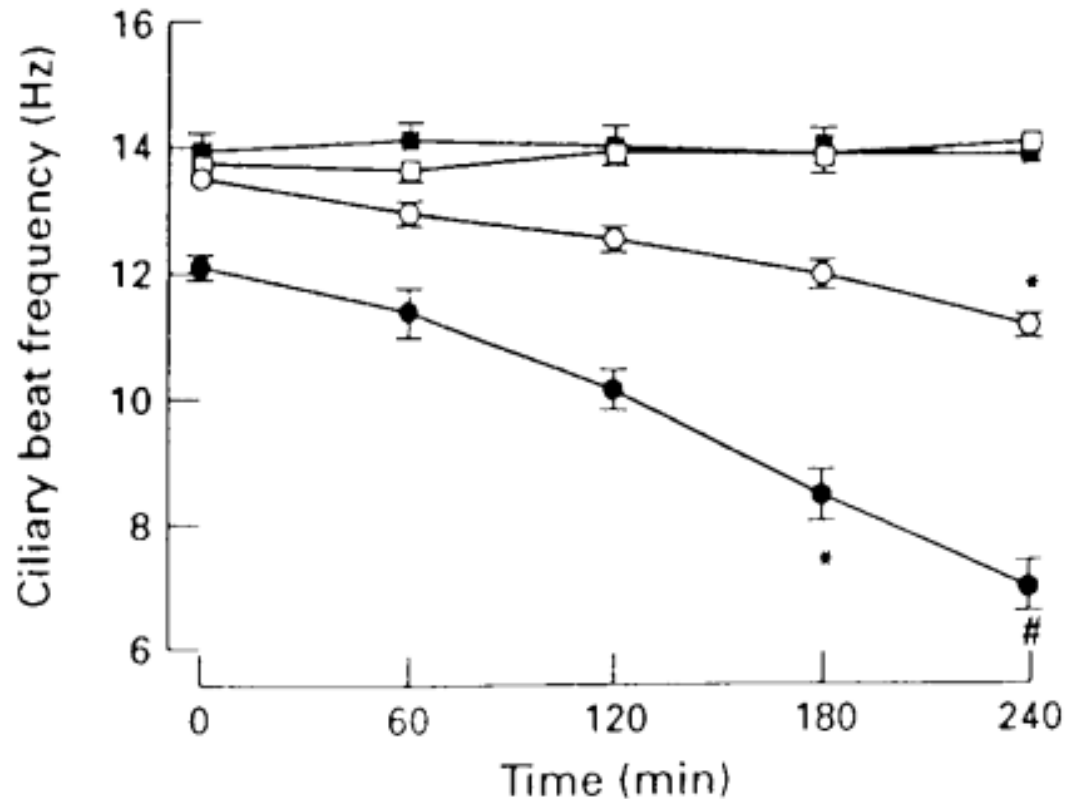
83 patients were recruited, of whom 67 were randomized.

	Before prednisolone	After prednisolone	Before placebo	After placebo
FEV ₁ (L)	1.03 (0.05)	1.09 (0.05)	1.09 (0.05)	1.08 (0.05)
Postbronchodilator FEV ₁ (L)	1.10 (0.05)	1.15 (0.05)	1.15 (0.06)	1.14 (0.06)
CRQ total score	3.98 (0.13)	4.34 (0.14)	4.03 (0.14)	4.08 (0.14)
Shuttle (m)	217 (13)	230 (14)	213 (12)	214 (12)
Total cell count (10 ⁶ cells/g sputum)*	2.79 (0.05)	2.37 (0.04)	2.66 (0.05)	2.63 (0.05)
Eosinophil count (%)*	2.35 (0.09)	0.39 (0.14)†	2.18 (0.09)	2.08 (0.13)
Neutrophils (%)	67.9 (3.2)	70.4 (2.7)	73.7 (2.5)	69.0 (2.7)
Macrophages (%)	21.5 (2.3)	25.4 (2.7)	22.1 (2.5)	22.7 (2.4)
Bronchial epithelial cells (%)	1.17 (0.2)	1.37 (0.23)	0.99 (0.16)	1.47 (0.35)
Lymphocytes (%)	0.40 (0.07)	0.44 (0.15)	0.35 (0.05)	0.71 (0.25)
Squamous cells (%)‡	1.85 (0.51)	3.15 (0.49)	2.6 (0.40)	2.2 (0.51)
Viability (%)‡	76 (28-95)	67 (20-86)	73 (23-91)	71 (18-89)
ECP ng/mL sputum*	1454 (0.08)	801 (0.08)	1149 (0.09)	1236 (0.09)
Elastase µg/mL*	53.2 (0.12)	31 (0.12)	42.5 (0.11)	36.5 (0.11)
Interleukin 8 (ng/mL)*	117 (0.1)	105 (0.1)	112 (0.08)	97 (0.1)

	Eosinophil-count tertile		
	<1.3 (n=22)	1.3-4.5 (23)	>4.5 (22)
CRQ domain*			
Dyspnoea CRQ	0.15 (-0.04 to 0.35)	0.27 (-0.11 to 0.65)	0.93 (0.50 to 1.35)†
Fatigue CRQ	0.09 (-0.28 to 0.46)	0.42 (0.06 to 0.79)‡	0.56 (0.20 to 0.91)†
Emotion CRQ	0.08 (-0.18 to 0.35)	0.12 (-0.15 to 0.39)	0.19 (-0.11 to 0.49)
Mastery CRQ	0.03 (-0.23 to 0.30)	0.20 (-0.202 to 0.59)	0.82 (0.37 to 1.26)†
Symptom scores§			
Cough VAS†	2 (-27 to 31)	41 (9 to 74)‡	53 (-1 to 106)
Sputum VAS†	6 (-15 to 26)	34 (2 to 66)‡	45 (18 to 72)†
Dyspnoea VAS†	5 (-3 to 14)	14 (3 to 27)‡	32 (9 to 55)†
Wheeze VAS†	-1 (-15 to 13)	21 (-1 to 14)	42 (-0 to 85)
Sputum indices 			
Total cell count	1.03 (0.62 to 1.72)	1.38 (0.93 to 2.03)	1.11 (0.74 to 1.65)
Eosinophil count	3.1 (0.9 to 10.6)	5.4 (1.2 to 24.2)†	6.9 (1.3 to 36.4)†
Neutrophil count	-3.0 (-12.5 to 6.5)	-4.5 (-15.2 to 6.2)	-19.3 (-31.8 to -6.8)‡
Oesinophilic cationic protein	1.2 (0.6 to 2.7)	1.5 (0.7 to 3.1)	3.4 (1.4 to 8.1)†
Elastase	1.9 (0.5 to 7.5)	1.2 (0.2 to 6.5)	2.8 (0.5 to 13.8)
Interleukin 8	1.3 (0.3 to 5.6)	0.7 (0.1 to 2.9)	2.1 (0.7 to 6.2)

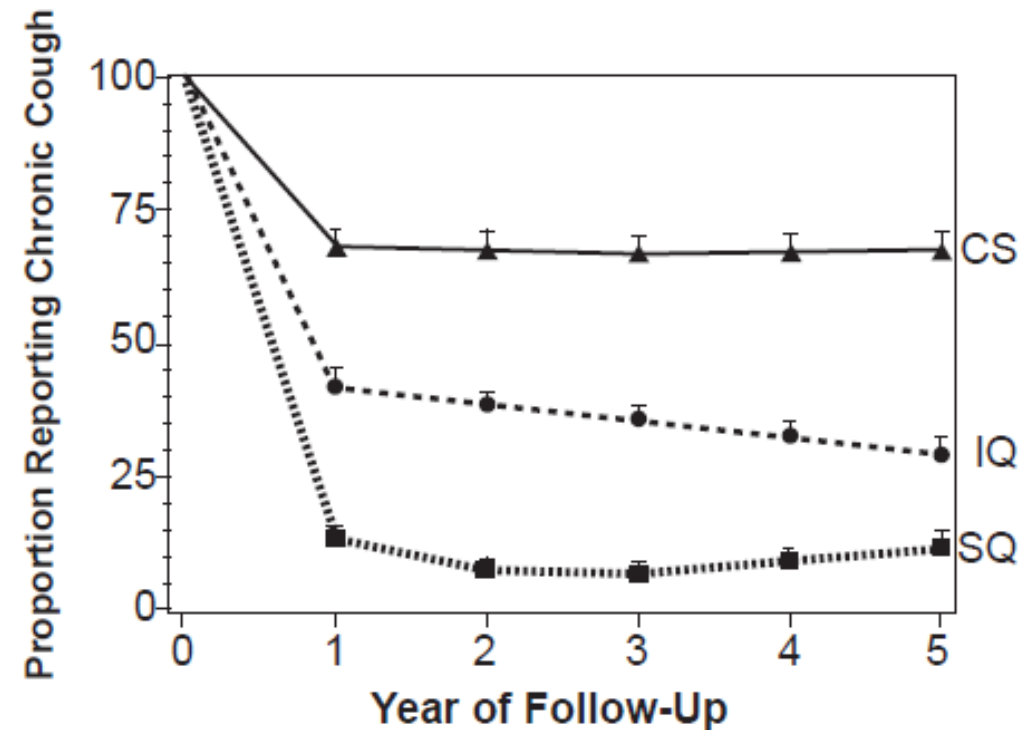
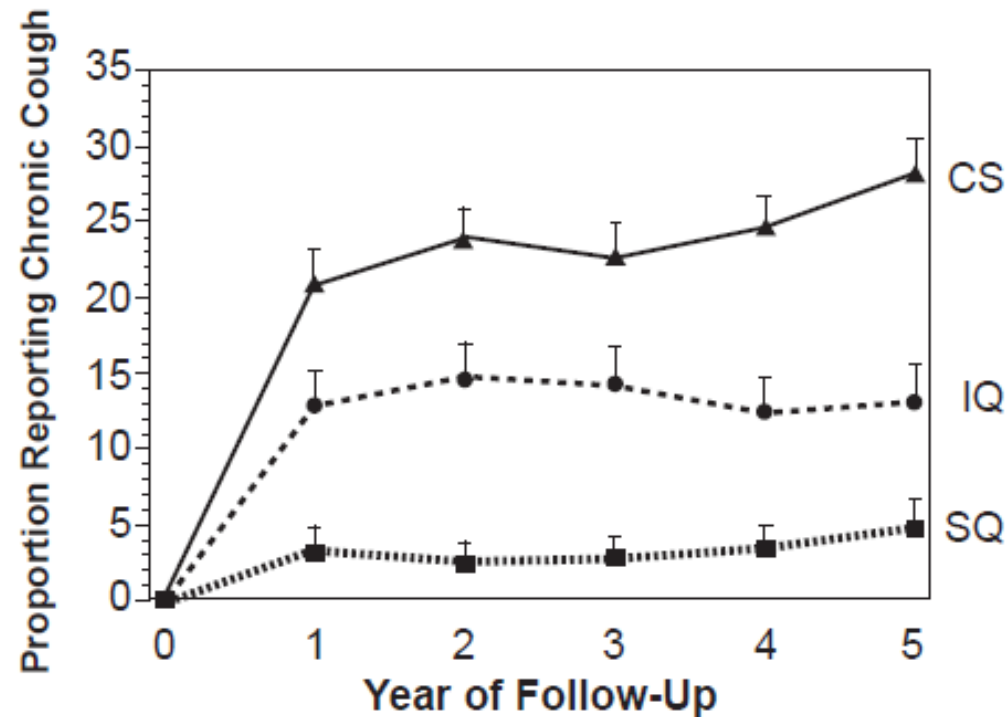
EFFECT OF SALMETEROL ON PYOCYANIN-INDUCED CILIARY BEAT

- Effective mucociliary movement
 - prevent bacterial adherence
 - protect against the development of infection
- Stimulation of epithelial β_2 -adrenergic receptors by LABAs may increase ciliary beat frequency (CBF) and mucociliary transport.



COUGH AND SMOKING IN COPD

- Total of 5,887 smokers 35 to 60 years of age with early COPD ($55\% < FEV_1/FVC < 90\%$) were enrolled in a 5-year clinical trial.
- To evaluate the effects of randomly assigning smokers who have early COPD to a smoking-cessation intervention on the symptoms of chronic cough, chronic phlegm production, wheezing and shortness of breath, and to determine the effects of quitting smoking on these symptoms



AIRWAY INFLAMMATION IS SIMILAR IN SMOKER AND EX-SMOKER

- Smoking cessation affects the rate of forced expiratory volume in one second (FEV1) decline in COPD, but the effect on inflammation is uncertain. Bronchial biopsy inflammatory cell counts were compared in current and ex-smokers with COPD.
- A **pooled analysis** of subepithelial inflammatory cell count **data from three bronchial biopsy studies** that included COPD patients who were either current or ex-smokers was performed.

TABLE 1 Demographic characteristics		
	Smokers	Ex-smokers
Males/females n	55/10	30/6
Age yrs	61 (40–77)	65 (49–78)
Smoking pack-yrs	46±25	59±36
Chronic bronchitis n	55	32
FEV ₁ L	1.55±0.45	1.58±0.49
FEV ₁ % pred	51±12	54±13
FVC L	3.09±0.77	3.01±0.81
FEV ₁ /FVC %	51±11	53±10
Reversibility [#] %	6.7±5.9	8.1±5.6

TABLE 3 Details of outcomes measured in the three studies presented in the pooled analysis of smokers <i>versus</i> ex-smokers			
	Subjects n	Mean difference (95% CI)	p-value [#]
FEV ₁ pred % [†]	101	1.94 (-4.35–8.32) ⁺	0.43
FVC [†] L	101	-0.18 (-0.50–0.14)	0.26
FEV ₁ /FVC [†] %	101	0.02 (-0.20–0.06)	0.31
CD8 count [§]	101	-0.18 (-0.50–0.14)	0.26
CD68 count [§]	101	0.02 (-0.02–0.06)	0.31
Neutrophil count [§]	101	0.13 (-0.28–0.54)	0.54
CD4 count [§]	100	-0.25 (-0.67–0.16)	0.23
TNF- α count [§]	101	0.03 (-0.38–0.45)	0.88
EG2 count [§]	45	0.38 (-0.04–0.80)	0.07
Mast cell count [§]	50	0.38 (-0.05–0.81)	0.09

Pooled analysis to investigate whether there is any difference in airway inflammation between smokers and ex-smokers with COPD.

→ The results show no differences between current and ex-smokers in inflammatory markers

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ACCUMULATION OF INFLAMMATORY MUCOUS EXUDATES IN THE SMALL AIRWAYS

- The small airways were assessed in surgically resected lung tissue from 159 patients
 - 39 with stage 0 (at risk)
 - 39 with stage 1
 - 22 with stage 2
 - 16 with stage 3
 - 43 with stage 4 (very severe) COPD
- To examine the evolution of the pathological effects of airway obstruction in patients with COPD.

Clinical findings in COPD according to FEV1 severity

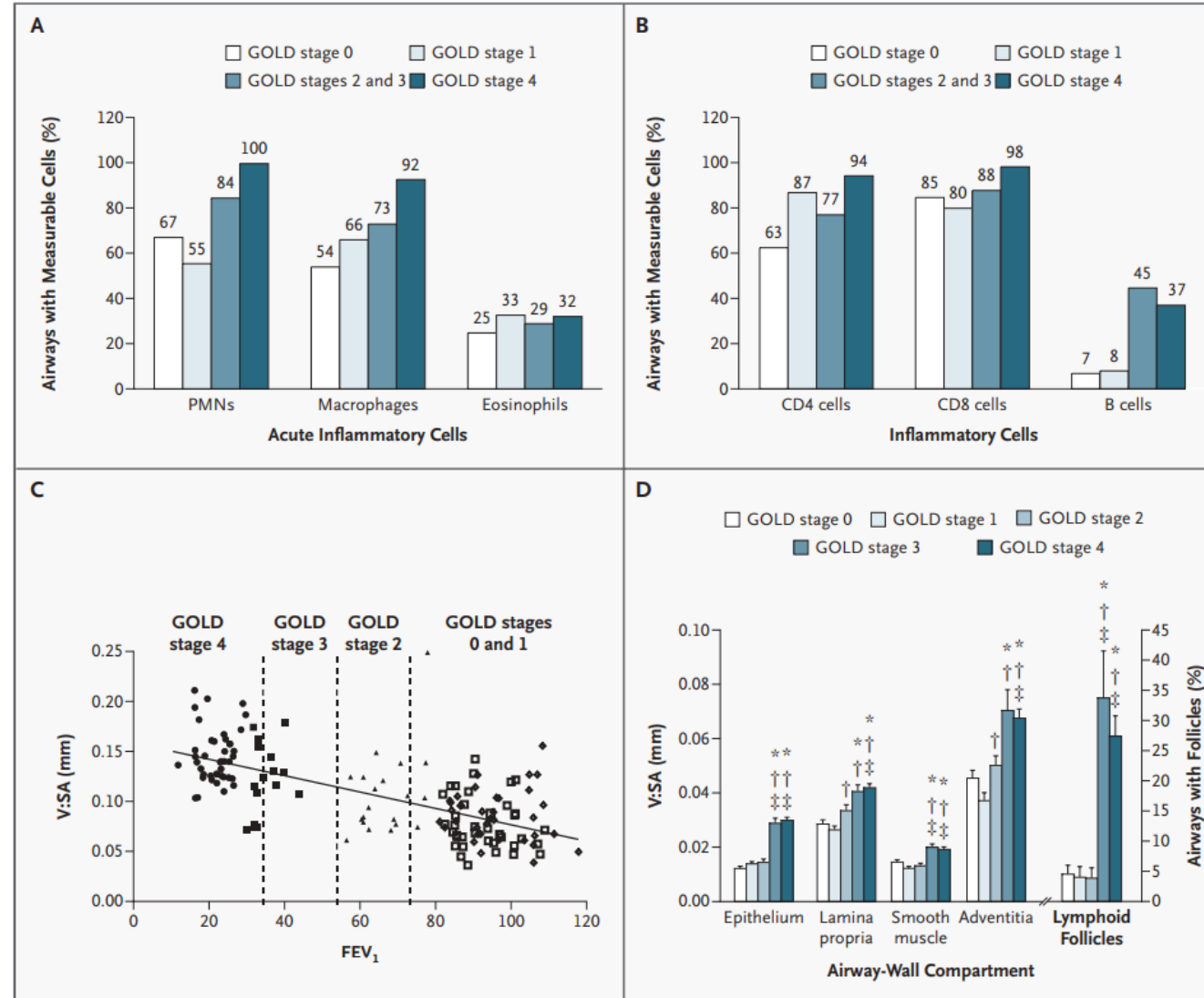


Table 2. Relationship of FEV₁ to Small-Airway Abnormalities.*

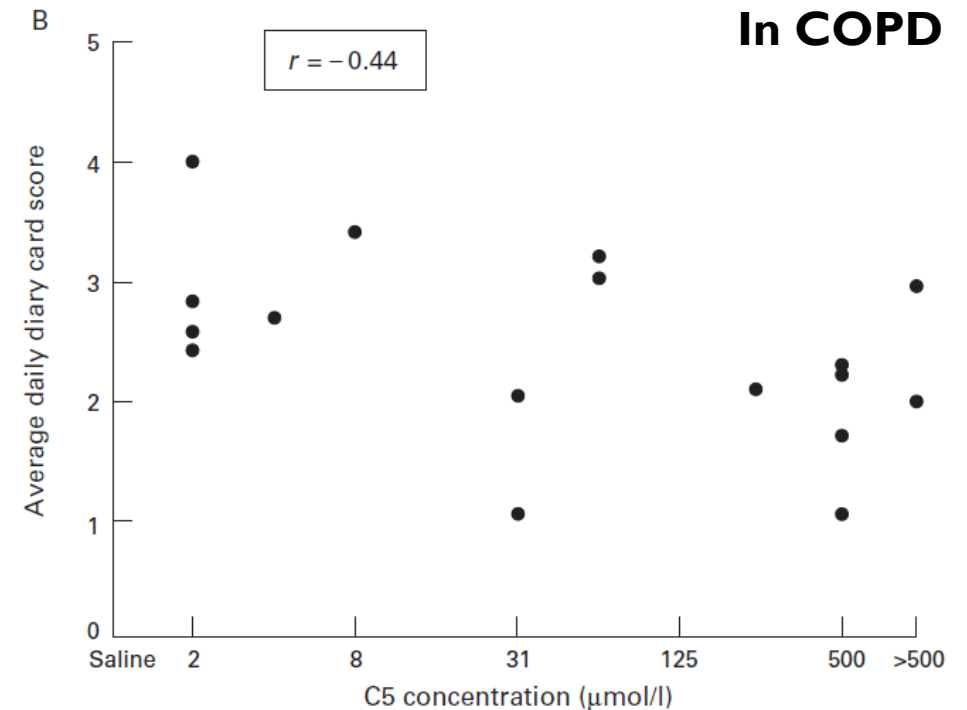
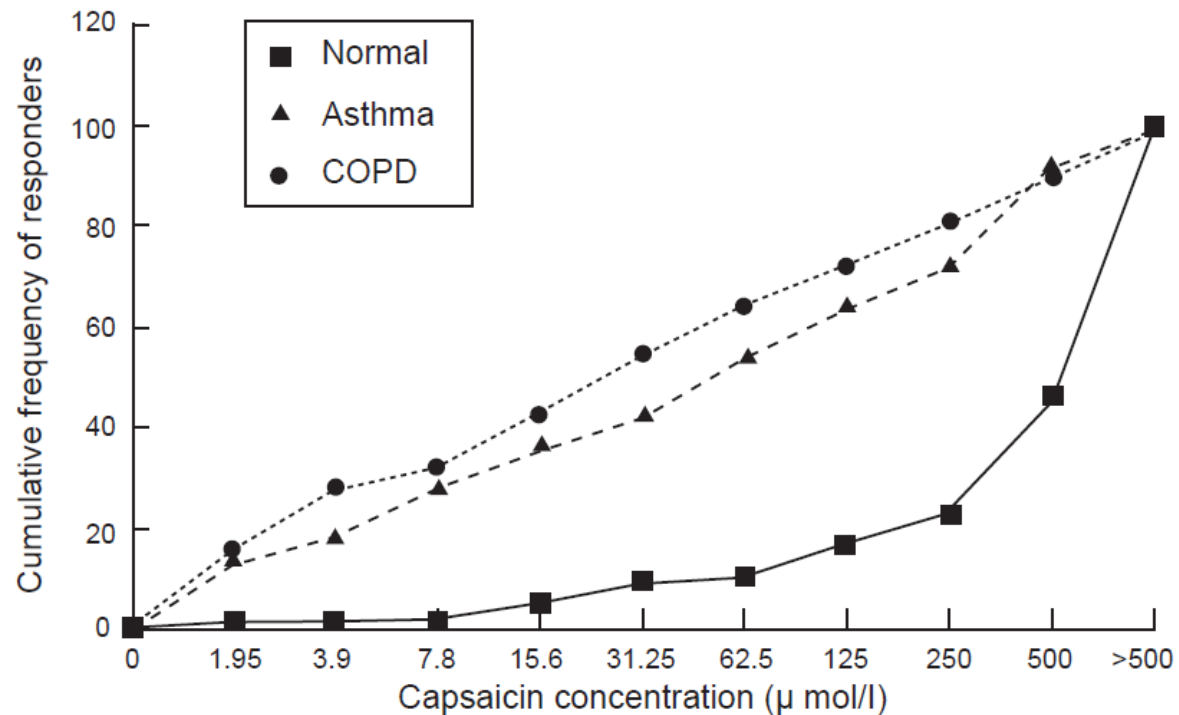
Variable	All 159 Patients		Subgroup of 40 Patients	
	R Value	P Value	Coefficient of Variation	P Value
Univariate analysis				
Extent of inflammation†				
% of airways with PMN			-0.0065	<0.001
% of airways with macrophages			-0.0068	<0.001
% of airways with eosinophils			-0.0060	0.19
% of airways with CD4 cells			-0.0035	0.02
% of airways with CD8 cells			-0.0029	0.038
% of airways with B cells			-0.0245	<0.001
% of airways with lymphoid follicles	-0.575	<0.001	-0.467	0.003
	R Value	P Value	R Value	P Value
Degree of infiltrate‡				
Accumulated volume of PMN	—	—	-0.0118	0.91
Accumulated volume of macrophages	—	—	-0.26	0.11
Accumulated volume of eosinophils	—	—	-0.049	0.76
Accumulated volume of CD4 cells	—	—	-0.25	0.12
Accumulated volume of CD8 cells	—	—	-0.36	0.02
Accumulated volume of B cells	—	—	-0.35	0.03
Expanded lumen	-0.505	<0.001	-0.359	0.02
Wall thickness				
Epithelium	-0.723	<0.001	-0.689	<0.001
Lamina propria	-0.583	<0.001	-0.542	<0.001
Adventitia	-0.544	<0.001	-0.428	0.006
Total	-0.687	<0.001	-0.607	<0.001
	R ² Value	P Value	R ² Value	P Value
Multivariate analysis				
Luminal content	—	<0.001	—	0.76
Wall thickness	—	<0.001	—	0.004

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- **Neural interaction in cough reflex**
- Bronchiectasis as co-morbidity

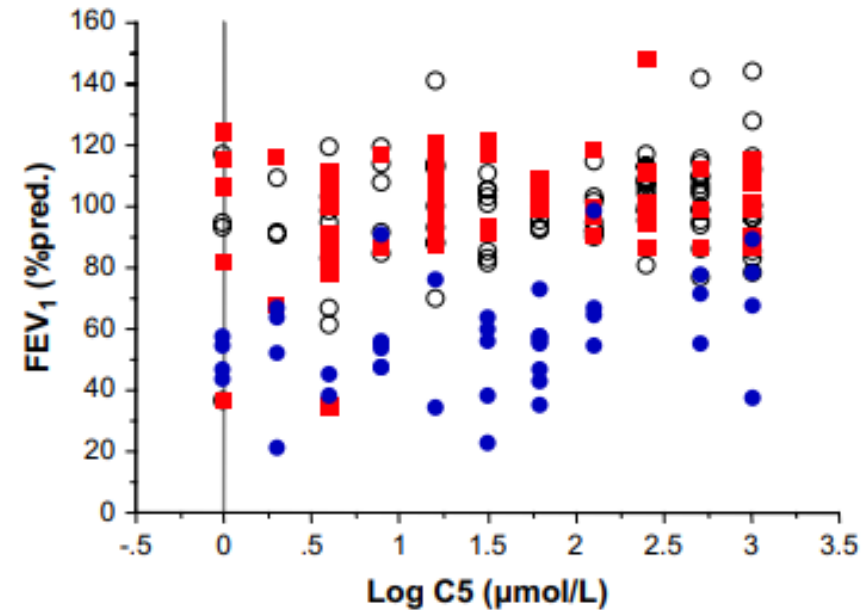
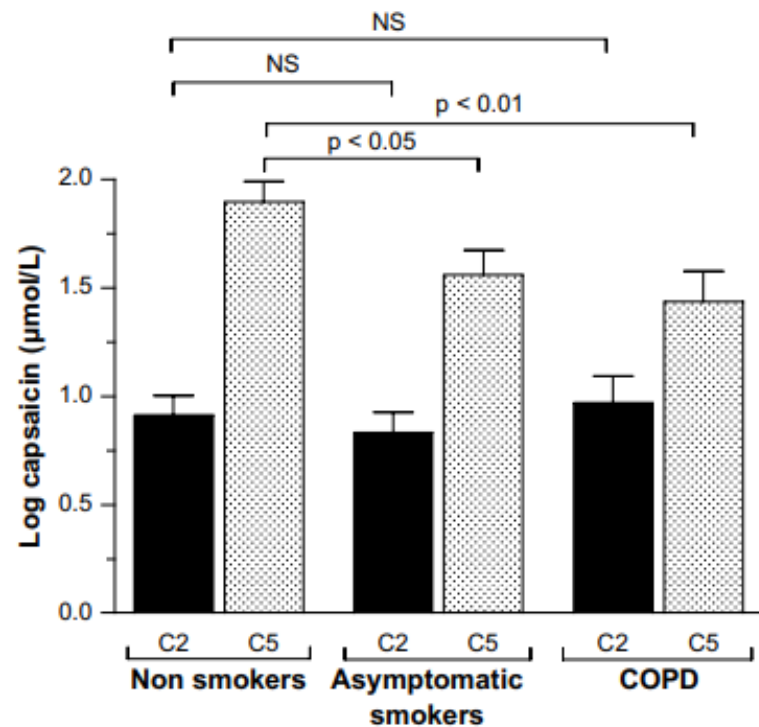
COUGH REFLEX SENSITIVITY TO CAPSAICIN IN COPD

- The cough response to capsaicin in 53 subjects with asthma, 56 subjects with COPD, and 96 healthy individuals was recorded.
- Compared with a number of subjective measures of self-reported cough, measures of airway obstruction, and prescribed medication.



COUGH REFLEX SENSITIVITY TO CAPSAICIN ACCORDING TO SMOKING

- Determined whether chronic cigarette smoking is associated with an increase in capsaicin cough response in the absence of cough.
- Asymptomatic smokers with normal lung function vs. in patients with established COPD without cough symptoms vs. healthy non-smoking volunteers as control
- Using an incremental capsaicin concentration challenge protocol



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COUGH IN BRONCHIECTASIS

- Large cohort of adult patients presenting to Monash Medical Centre (MMC) to survey the course of their disease up to the time of diagnosis.

Table 1 Demographic data on patients with newly diagnosed bronchiectasis.

Number of patients	103
Age, years (mean \pm SD)	56 \pm 14
Sex ratio	
Male, <i>n</i> (%)	38 (37)
Female, <i>n</i> (%)	65 (63)
Smoking History	
Lifetime non-smokers, <i>n</i> (%)	79 (77)
Smokers/ex-smokers, <i>n</i> (%)	24 (23)
Pack years (mean \pm SD)	24 \pm 14 years
Patients with idiopathic bronchiectasis, <i>n</i> (%)	76 (74)

Table 4 Spirometry/radiology findings.

<i>Spirometry</i>	
FEV ₁	
Litres (mean and SD)	1.92 \pm 0.74
% predicted (mean and SD)	76 \pm 26
FVC	
Litres (mean and SD)	2.82 \pm 2.82
% predicted (mean and SD)	89 \pm 25
FEV ₁ /FVC	67.7
> 15% reversibility after BD	21 (patients)
<i>Radiology (CT/bronchogram)</i>	
Patients with multilobar disease	82
<i>Lobes involved</i>	
RUL	13
RML	30
RLL	71
LUL	25
LLL	66

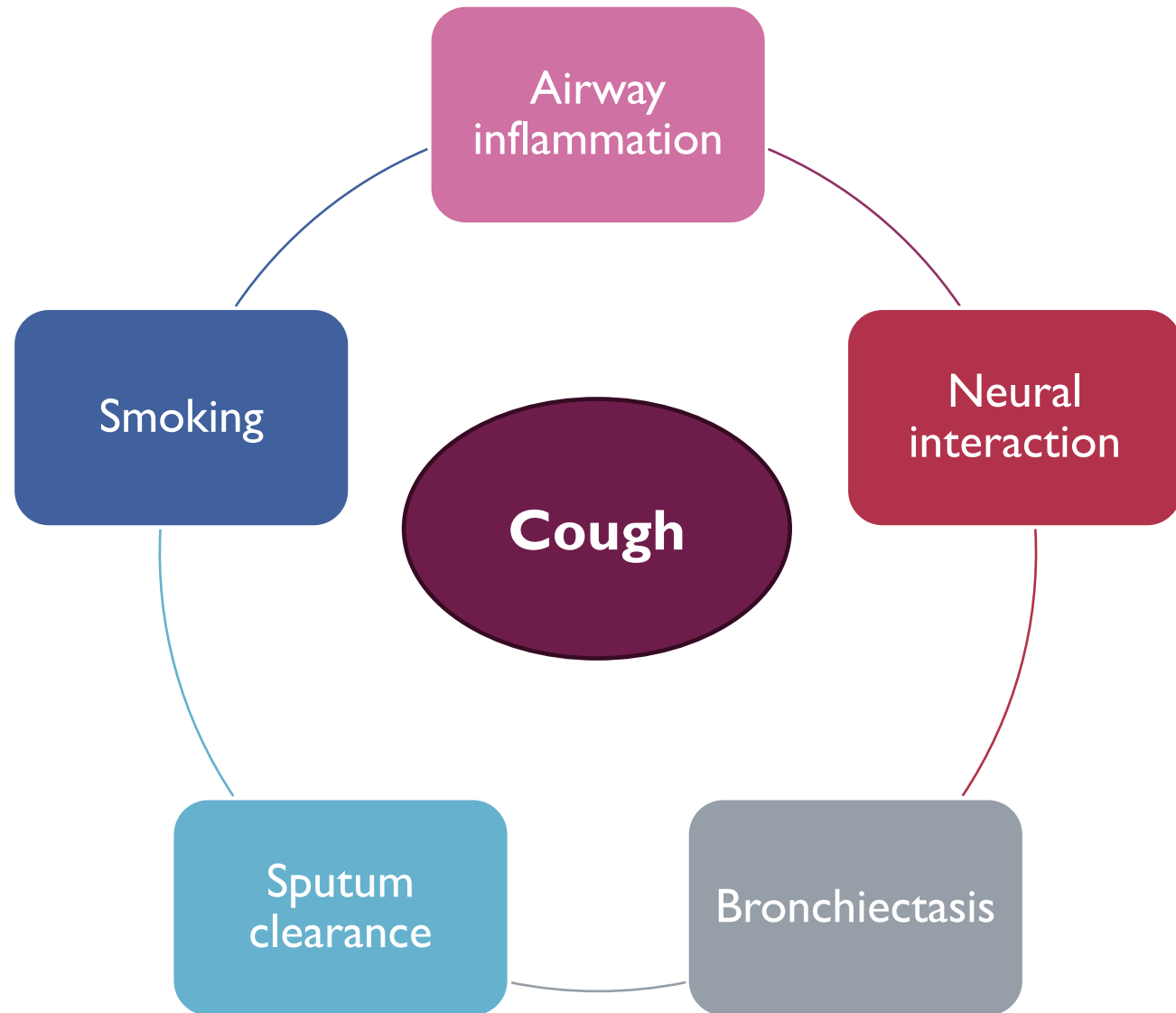
Table 2 Clinical Findings in 103 patients with bronchiectasis at time of diagnosis.

Symptoms, n (%) or mean \pm sd as appropriate

Productive cough	99 (96)
Sputum most days of week	90 (87); daily in 78 (76)
Daily sputum volume, ml	38 \pm 34
Dyspnoea	62 (60)
MRC dyspnoea score	2.1 \pm 1.2
Rhinosinusitis	73 (71)
Chest pain	20 (19)
Exacerbations	2.4 \pm 1.6
Haemoptysis	27 (26)
Fatigue	75 (73)
<i>Signs, n (%)</i>	
Crackles	75 (73)
Wheeze	22 (21)
Clubbing	2 (2)

Table 3 Reason for initial referral to MMC in the group of 103 patients, n (%).

Productive cough	55 (53)
Follow up after pneumonia/chest infection	18 (18)
Combination of chronic respiratory symptoms	9 (9)
Haemoptysis	5 (5)
Assessment of poorly controlled asthma	3 (3)
Dry cough	2 (2)
Chest pain	2 (2)
Other	9 (9)
Hospitalisation in past year	7 (7)





CLINICAL IMPLICATION OF COUGH IN COPD



FREQUENCY AND INTENSITY OF COUGH

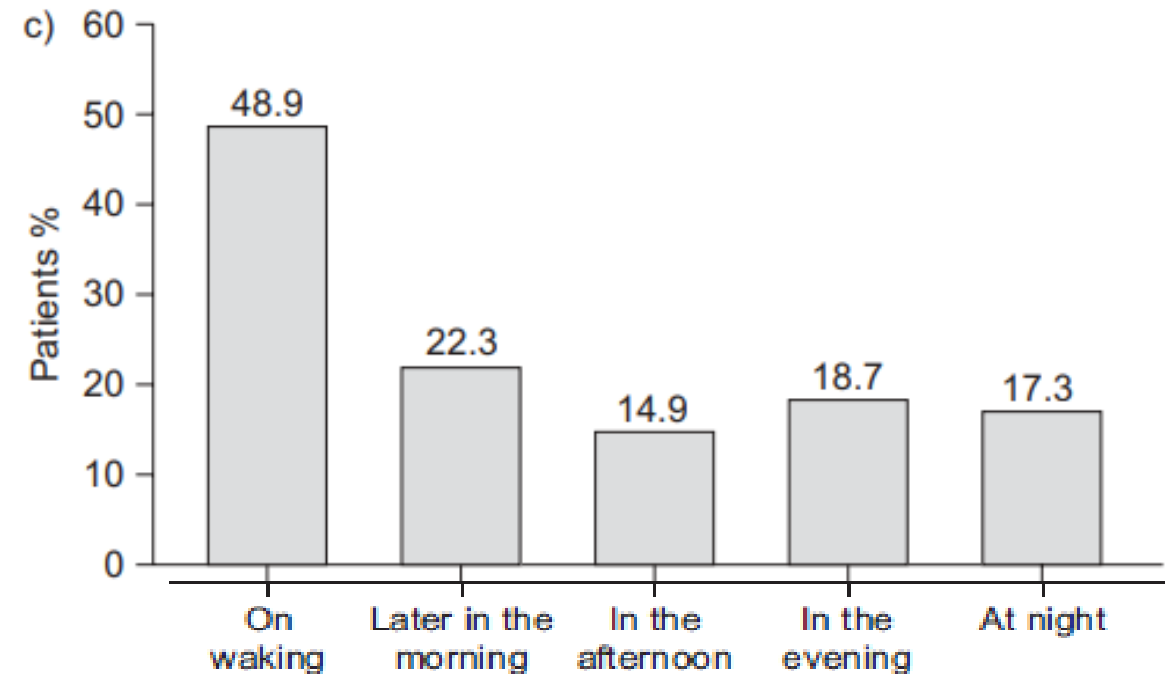
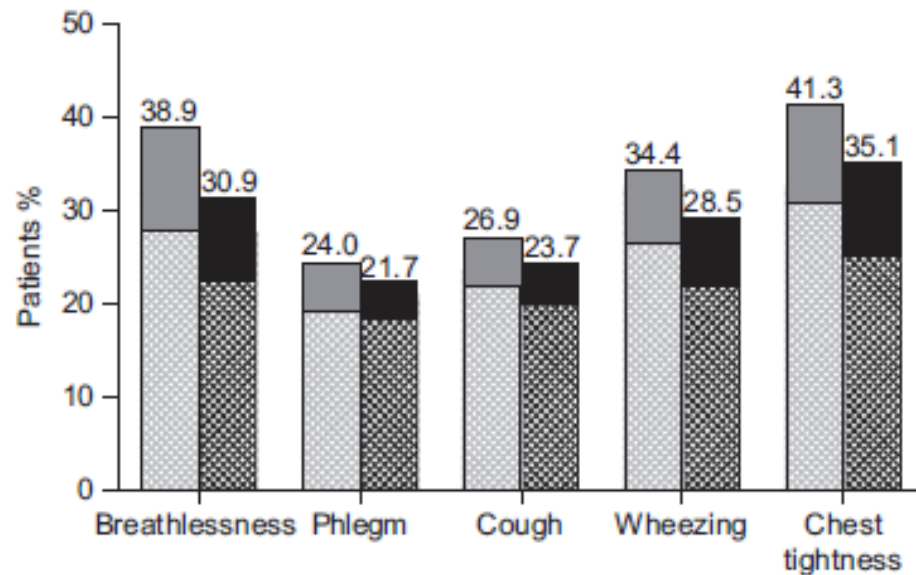
- How often should the subject cough and with what intensity before it is classified as significant?
- This Gordian knot was cut by the Medical Research Council in the 1960's when they developed an epidemiological definition of chronic bronchitis.

SELF-REPORTED COUGH IN COPD PATIENTS

	Persistently normal n = 4181	Incident stage I n = 683	Incident stage II n = 85	Persistent stage I n = 294	Stage I progressing n = 56	Persistent stage II n = 61	Non-persistent n = 113
Female sex (%)	54.7	54.2	44.7	39.1	33.9	32.8	40.7
Age in years (mean/SD)	39.2/11.2	45.3/10.3	44.5/11.9	48.8/9.6	48.5/9.2	49.5/9.1	47.0/9.1
No professional education (%)	12.1	16.4	23.5	15.6	21.4	19.7	8.8
FEV ₁ % of predicted value (mean/SD)	109.9/13.6	107.4/12.5	91.3/12.5	101.3/10.9	89.1/7.0	67.4/10.4	99.6/13.5
FVC % of predicted value (mean/SD)	114.0/0.2	119.2/0.1	100.6/0.1	125.9/0.1	116.0/0.1	96.0/0.1	122.4/0.2
FEV ₁ /FVC % of predicted value (mean/SD)	100.9/0.1	94.6/0.1	94.9/0.1	84.1/0.0	80.2/0.1	73.3/0.1	84.8/0.0
Never smoker (%)	49.9	44.7	35.3	36.7	19.6	31.1	38.9
Light smoker at baseline (<15 pack-years)† (%)	28.7	19.3	13.6	20.9	9.3	11.8	24.5
Heavy smoker at baseline (≥15 pack-years)† (%)	18.2	31.8	42.4	38.4	62.5	52.5	29.2
Shortness of breath at baseline (%)	21.7	25.0	42.4	25.5	44.6	47.5	14.2
Chronic bronchitis at baseline (%)	7.3	11.6	20.0	13.3	19.6	27.9	9.7
Wheezing in last 12 months at baseline	4.8	7.8	22.4	9.9	28.6	20.0	8.0
Non-current asthma at baseline (%)	5.6	10.5	17.6	12.2	21.4	27.9	9.7
Current asthma at baseline (%)	1.8	3.4	11.8	4.4	16.1	16.4	4.4
Health service use for respiratory problems at baseline (%)	18.0	22.0	27.1	26.9	33.9	42.6	23.0

SYMPTOM VARIABILITY IN PTS WITH SEVERE COPD

- Cross-sectional study assessed patients' perception of symptom variability.
- Participants were outpatients >45 yrs old with COPD, current or ex-smokers, FEV1 < 50% predicted, and no exacerbation leading to therapeutic intervention in the previous 3 months.
- **COPD symptoms were experienced by 2,258 (92.5%)** out of 2,441 patients during the 7 days before interview



FREQUENCY AND INTENSITY OF COUGH

- How often should the subject cough and with what intensity before it is classified as significant?
- This Gordian knot was cut by the Medical Research Council in the 1960's when they developed an epidemiological definition of chronic bronchitis.

⇒ **Cough** as productive or unproductive, presenting for at least 3 months of 2 consecutive years

- 1) Do you experience a cough most days, for at least 3 months per year?
- 2) Have you had cough for more than two consecutive years?
- 3) Do you produce sputum most days, for at least 3 months per year?
- 4) Have you had sputum for more than two consecutive years?

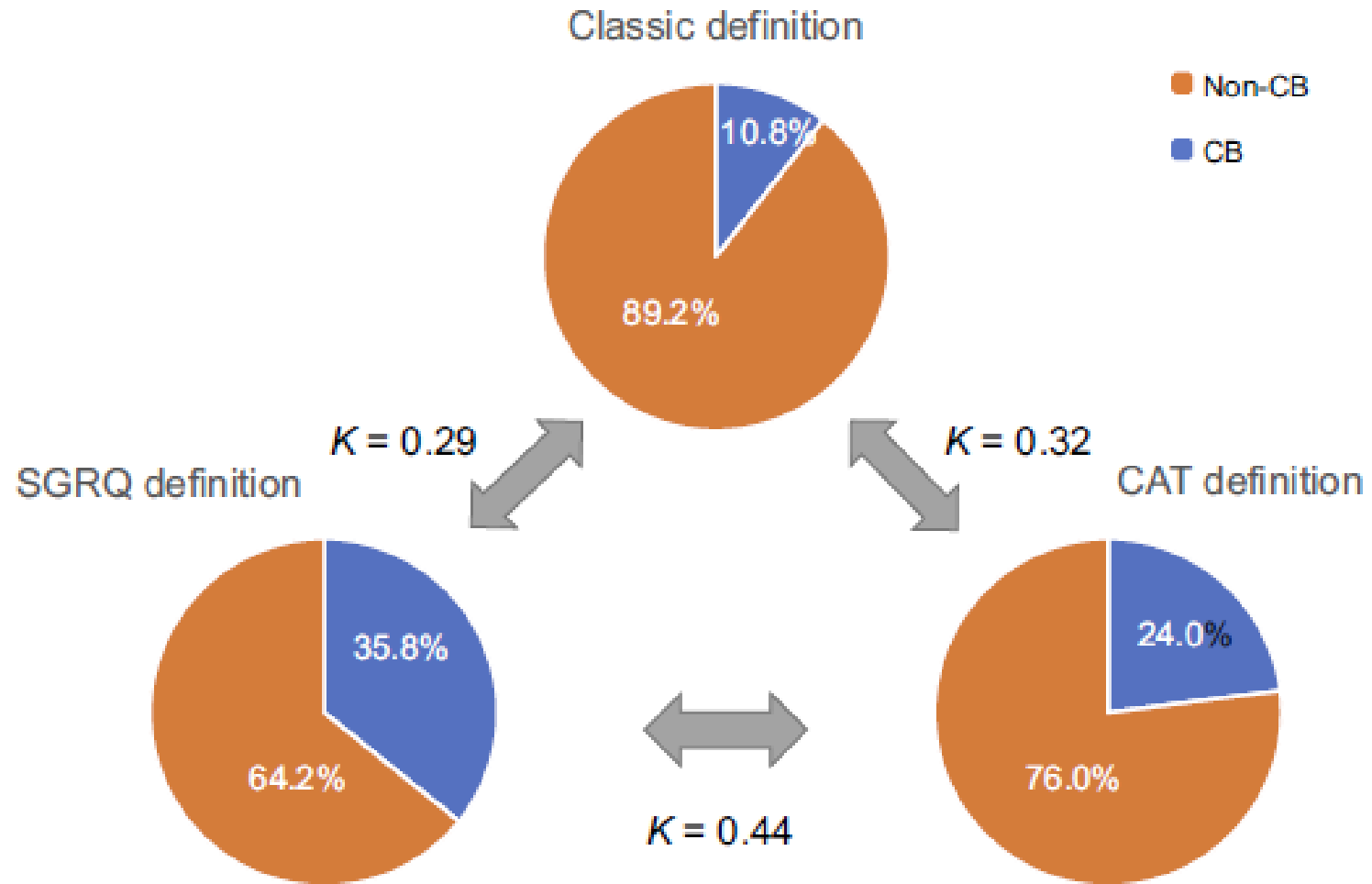
CAT ASSESSMENT IN CHRONIC BRONCHITIS

- **Classic definition** of chronic bronchitis
 - 1) Do you experience a cough most days, for at least 3 months per year?
 - 2) Have you had cough for more than two consecutive years?
 - 3) Do you produce sputum most days, for at least 3 months per year?
 - 4) Have you had sputum for more than two consecutive years?
- Extracted data from the multicenter Korea COPD Subgroup Study (KOCOSS) cohort.
- Performed to compare clinical characteristics between CB and non-CB according to three different definitions of CB.
 - **Classic definition**
 - **The SGRQ definition of CB**
 - : 1) How often do you complain of cough during the week?
 - 2) How often do you complain of sputum production during the week?
 - **The CAT definition** of CB with both CAT 1(cough) and 2 (sputum) scores ≥ 3

COMPARISON ABOUT THREE DEFINITIONS IN CHRONIC BRONCHITIS

Table 3 Multiple Logistic Regression of CB Phenotype of Each Definition with High-Risk Group

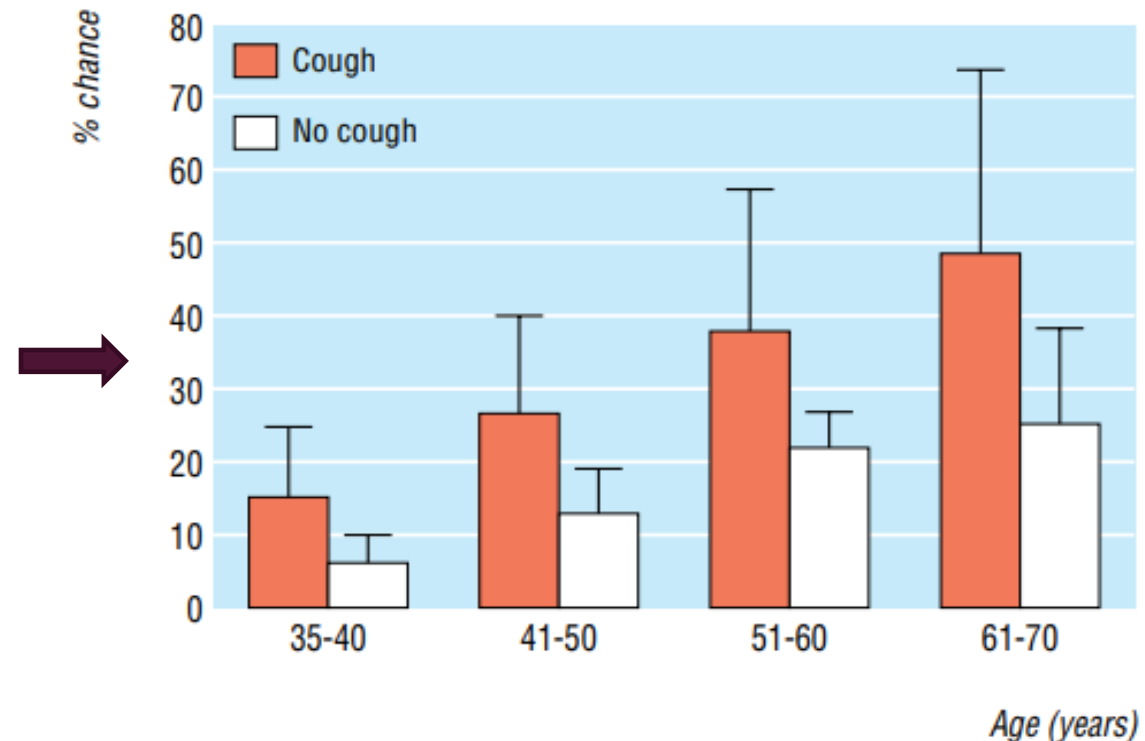
Variable	OR (95% CI)	P-value	Variable	OR (95% CI)	P-value	Variable	OR (95% CI)	p-value
CB (Classic)	2.39 (1.53–3.73)	<0.01	CB (SGRQ)	1.83 (1.30–2.57)	<0.01	CB (CAT)	1.69 (1.17–2.44)	<0.01
Sex (male)	1.39 (0.76–2.57)	0.29	Sex (male)	1.54 (0.85–2.78)	0.16	Sex (male)	1.58 (0.87–2.86)	0.14
Age	1.04 (1.02–1.07)	<0.01	Age	1.04 (1.02–1.07)	<0.01	Age	1.05 (1.02–1.07)	<0.01
Current smoker	0.81 (0.52–1.26)	0.35	Current smoker	0.75 (0.48–1.07)	0.21	Current smoker	0.84 (0.54–1.31)	0.43
FEV1	0.97 (0.96–0.98)	<0.01	FEV1	0.97 (0.96–0.98)	<0.01	FEV1	0.97 (0.96–0.98)	<0.01



COUGH AS THE BEST PREDICTOR OF AIRFLOW OBSTRUCTION

- Two semirural general practices in the Netherlands as cross-sectional study
- 651 smokers aged 35 to 70 years
- To investigate the effectiveness of case finding of patients at risk of developing COPD

Symptom	No of patients reporting symptom	No (% , 95% CI) of patients with FEV ₁ <80%	Odds ratio* (95% CI)	Negative predictive value (%)
Family history:				
Asthma	33	6 (18, 7 to 35)	1.03 (0.38 to 2.77)	82
Allergy	28	6 (21, 8 to 41)	1.35 (0.49 to 3.70)	83
Symptom:				
Tiredness	90	19 (21, 13 to 31)	1.77 (0.77 to 4.06)	87
Chronic wheeze	44	12 (27, 15 to 43)	2.15 (0.94 to 4.88)	85
Chronic dyspnoea	79	19 (24, 15 to 35)	2.19 (0.98 to 4.90)	87
Chronic cough	64	17 (27, 16 to 39)	2.50 (1.14 to 5.52)	87
No of symptoms:				
1	105	23 (22, 14 to 31)	2.28 (0.93 to 5.60)	89
2	59	17 (29, 18 to 42)	3.02 (1.37 to 6.64)	88
3	23	8 (35, 16 to 57)	3.01 (1.17 to 7.70)	85



*Estimates of common odds ratio by Mantel-Haenszel test.

- In the SAPALDIA (Swiss Study on Air Pollution and Lung Disease in Adults) cohort
- Determinants were assessed in 5490 adults with spirometry and respiratory symptom data in 1991 and 2002.

Table 2 Incidence rate of obstruction (FEV₁/FVC <0.7) using prebronchodilator spirometry during 11 years of follow-up according to a set of baseline characteristics

Predictor at baseline	Person-years at risk (in 1000)	No. of cases	Incidence rate (cases per 1000 person years) (95% CI)	Crude incidence rate ratio (95% CI)	Adjusted [‡] incidence rate ratio (95% CI)
All (n = 4945)*	54.00	765	14.17 (13.20 to 15.21)		
Gender:					
Men	24.55	357	14.54 (13.11 to 16.13)	1.00 (Ref)	1.00 (Ref)
Women	29.45	408	13.85 (12.57 to 15.27)	0.95 (0.84 to 1.09)	1.03 (0.90 to 1.18)
Age (years) at baseline					
18–30	11.62	70	6.02 (4.77 to 7.61)	1.00 (Ref)	1.00 (Ref)
>30–40	14.70	165	11.22 (9.64 to 13.07)	1.86 (1.43 to 2.43)	1.72 (1.33 to 2.24)
>40–50	15.81	253	16.00 (14.15 to 18.10)	2.66 (2.08 to 3.40)	2.38 (1.85 to 3.06)
>50	11.86	277	23.35 (20.75 to 26.27)	3.88 (3.05 to 4.93)	3.77 (2.94 to 4.83)
Smoking status at baseline [†] :					
Never smoker	28.02	362	12.92 (11.65 to 14.32)	1.00 (Ref)	1.00 (Ref)
Ever smoker:					
<15 pack-years	14.94	153	10.24 (8.74 to 12.00)	0.79 (0.66 to 0.95)	0.87 (0.73 to 1.04)
≥15 pack-years	11.03	250	22.66 (20.02 to 25.65)	1.75 (1.52 to 2.03)	1.51 (1.29 to 1.77)
Chronic bronchitis at baseline:					
Absent	49.62	671	13.52 (12.54 to 14.59)	1.00 (Ref)	1.00 (Ref)
Present	4.38	94	21.45 (17.53 to 26.26)	1.59 (1.30 to 1.93)	1.23 (1.00 to 1.51)
Asthma at baseline					
Absent	50.47	678	13.43 (12.46 to 14.48)	1.00 (Ref)	1.00 (Ref)
Present, but non-current	2.34	54	23.12 (17.70 to 30.18)	1.72 (1.33 to 2.22)	1.39 (1.01 to 1.92)
Present, current	1.18	33	28.02 (19.92 to 39.41)	2.09 (1.51 to 2.88)	0.79 (0.51 to 1.23)
Asthma at follow-up					
Absent	49.75	662	13.31 (12.33 to 14.36)	1.00 (Ref)	1.00 (Ref)
Present, but non-current	2.64	49	18.54 (14.01 to 24.53)	1.39 (1.07 to 1.82)	1.19 (0.85 to 1.65)
Present, current	1.60	54	33.77 (25.86 to 44.09)	2.54 (1.97 to 3.28)	1.68 (1.13 to 2.50)
Wheezing without a cold at baseline					
Absent	50.81	689	13.56 (12.59 to 14.61)	1.00 (Ref)	1.00 (Ref)
Present	2.96	71	23.99 (19.01 to 30.27)	1.77 (1.41 to 2.21)	1.04 (0.81 to 1.35)
Wheezing without a cold at follow-up					
Absent	50.34	655	13.01 (12.05 to 14.05)	1.00 (Ref)	1.00 (Ref)
Present	3.65	110	30.10 (24.97 to 36.29)	2.31 (1.92 to 2.79)	1.95 (1.57 to 2.42)

CHANGE IN SEVERITY OF AIRWAY OBSTRUCTION AT FOLLOW-UP

Table 3 Association* of categories of change in severity of obstruction† with shortness of breath while walking at follow-up

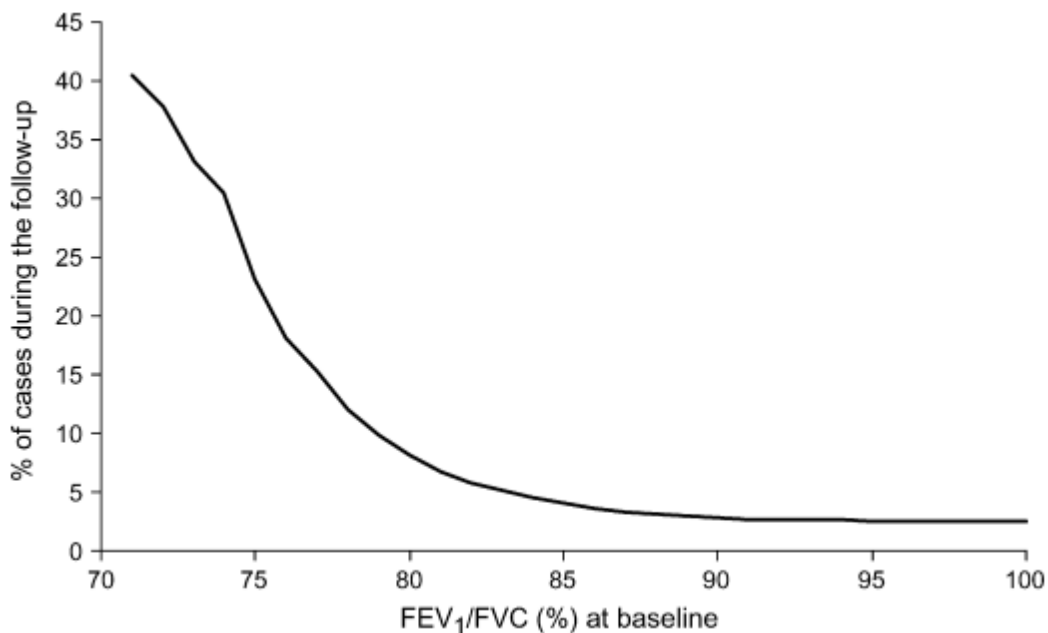
Variable	Crude model		Adjusting for all but asthma covariates‡		Adjusting for asthma and wheezing at baseline or follow-up	
	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value
Incident stage I (n = 683)	1.59 (1.32 to 1.91)	0.000	1.24 (0.99 to 1.56)	0.056	1.12 (0.89 to 1.41)	0.344
Incident stage II (n = 85)	2.74 (1.74 to 4.30)	0.000	1.43 (0.84 to 2.45)	0.192	1.10 (0.63 to 1.90)	0.743
Persistent stage I (n = 294)	1.48 (1.13 to 1.94)	0.004	1.14 (0.82 to 1.60)	0.428	1.02 (0.73 to 1.44)	0.903
Stage I progressing (n = 56)	3.76 (2.18 to 6.48)	0.000	2.21 (1.10 to 4.45)	0.026	1.71 (0.83 to 3.54)	0.148
Persistent stage II (n = 61)	5.43 (3.15 to 9.37)	0.000	4.38 (2.19 to 8.75)	0.000	3.11 (1.50 to 6.42)	0.002
Non-persistent (n = 113)	1.02 (0.64 to 1.62)	0.947	1.40 (0.80 to 2.44)	0.237	1.39 (0.80 to 2.43)	0.246
Asthma at baseline non-current§					1.08 (0.70 to 1.65)	0.739
Asthma at baseline current§					0.50 (0.27 to 0.91)	0.024
Asthma at follow-up non-current§					1.09 (0.73 to 1.63)	0.667
Asthma at follow-up current§					2.18 (1.28 to 3.72)	0.004
Wheezing without a cold at baseline					1.41 (1.03 to 1.94)	0.034
Wheezing without a cold at follow-up					2.07 (1.55 to 2.75)	0.000

INCIDENCE OF COPD ACCORDING TO COUGH AND PHLEGM

- **5,002 subjects** without asthma (ages 20–44 yr) with normal lung function (FEV1/FVC ratio 70%) from 12 countries was followed from 1991–2002 in the frame of the European Community Respiratory Health Survey II.
- Incident cases of COPD were those who had an FEV1/FVC ratio less than 70% at the end of the follow-up, but did not report having had a doctor diagnose asthma during the follow-up.
- To assess **the incidence of COPD** in a cohort of young adults and to test whether chronic cough/phlegm and dyspnea are independent predictors of COPD.

Variables at Baseline (ECRHS I)	No. of Subjects [‡]	Person-Years [§]	No. of Cases [‡]	Incidence Rate, Cases/1,000/Yr (95% CI)	Crude IRR [§] (95% CI)	Adjusted IRR [¶] (95% CI)
Sex						
Men	2,369	21,148	68	3.2 (2.5–4.1)	1	1
Women	2,611	23,286	55	2.4 (1.8–3.1)	0.73 (0.52–1.04)	0.86 (0.63–1.19)
Age, yr						
20–30	1,600	14,364	22	1.5 (1.0–2.3)	1	1
30–40	2,097	18,734	48	2.6 (1.9–3.4)	1.67 (1.01–2.76)	1.26 (0.88–1.82)
40–45	1,283	11,336	53	4.7 (3.6–6.1)	3.05 (1.87–4.99)	2.15 (1.25–3.70)
Chronic cough/phlegm						
Absent	4,479	40,019	99	2.5 (2.0–3.0)	1	1
Present	454	4,000	23	5.7 (3.8–8.7)	2.32 (1.49–3.62)	1.85 (1.17–2.93)
Dyspnea						
Absent	4,089	36,478	98	2.7 (2.2–3.3)	1	1
Present	767	6,865	24	3.5 (2.3–5.2)	1.30 (0.84–2.02)	0.98 (0.64–1.50)
Smoking habits						
Nonsmokers	2,175	19,417	28	1.4 (1.0–2.1)	1	1
Light smokers*	1,845	16,518	38	2.3 (1.7–3.2)	1.60 (0.98–2.59)	1.42 (1.02–1.98)
Heavy smokers [†]	884	7,831	55	7.0 (5.4–9.1)	4.87 (3.11–7.62)	3.76 (2.76–5.12)
Educational level						
High	4,016	36,010	92	2.6 (2.1–3.1)	1	1
Low	934	8,135	28	3.4 (2.4–5.0)	1.35 (0.89–2.04)	1.06 (0.67–1.67)
Total cohort	4,980	44,434	123	2.8 (2.3–3.3)		

Chronic cough/sputum



- The median length of the follow-up was 8.9 yr, ranging from a minimum of 5.8 yr to a maximum of 11.4 yr
- Overall, the incidence rate of COPD was 2.8 cases/1,000/yr (95%CI, 2.3–3.3)

ECRHS I
(1991-1993)

ECRHS II
(1999-2002)

no chronic
cough / phlegm
(n = 4,407)

4,083 (92.6%)

absence

324 (7.4%)

new occurrence

chronic
cough / phlegm
(n = 447)

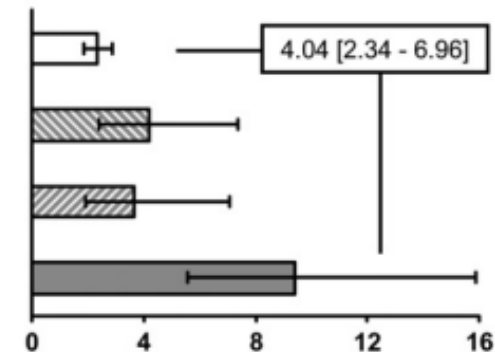
277 (62.0%)

remission

170 (38.0%)

persistence

incidence rate (cases/1,000/year)



Dyspnea

ECRHS I
(1991-1993)

ECRHS II
(1999-2002)

no dyspnea
(n = 3,641)

3,245 (89.1%)

absence

396 (10.9%)

new occurrence

dyspnea
(n = 700)

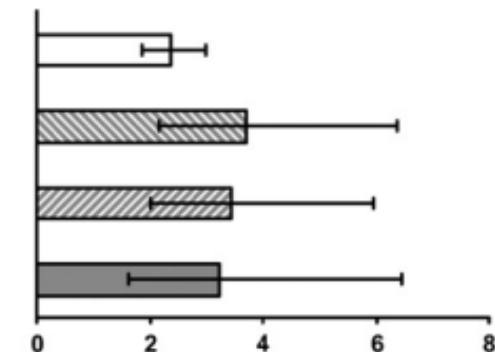
422 (60.3%)

remission

278 (39.7%)

persistence

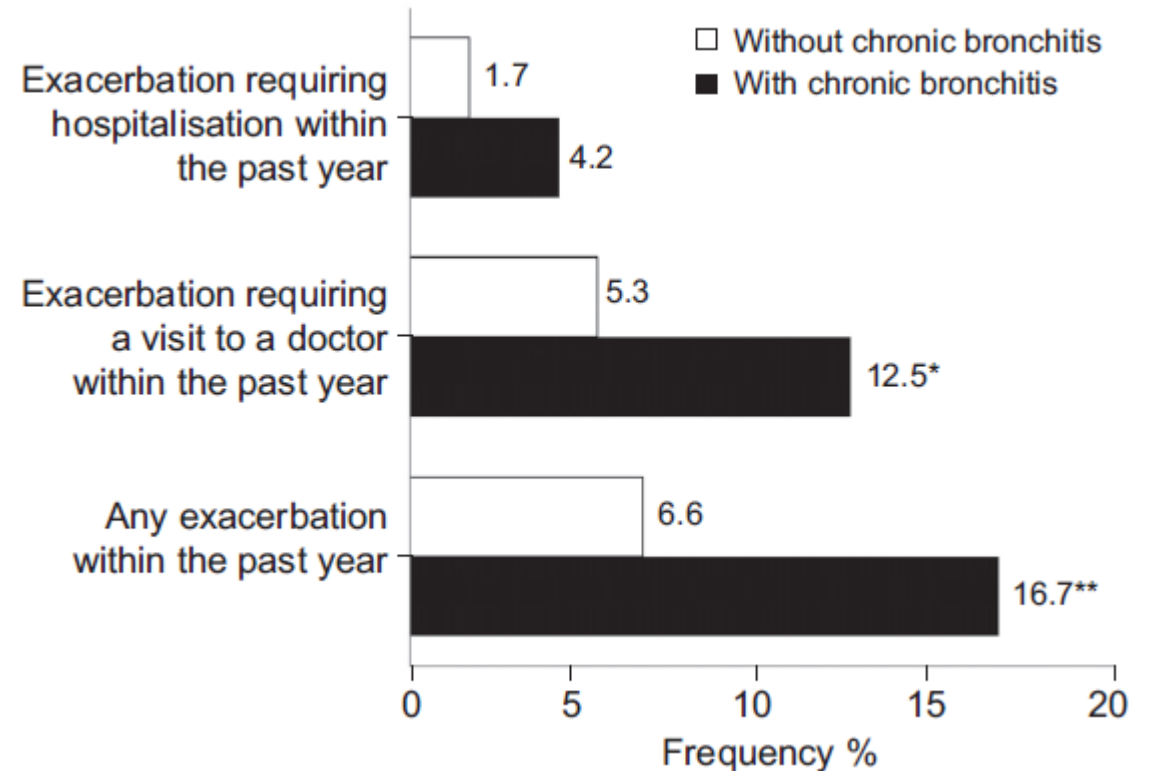
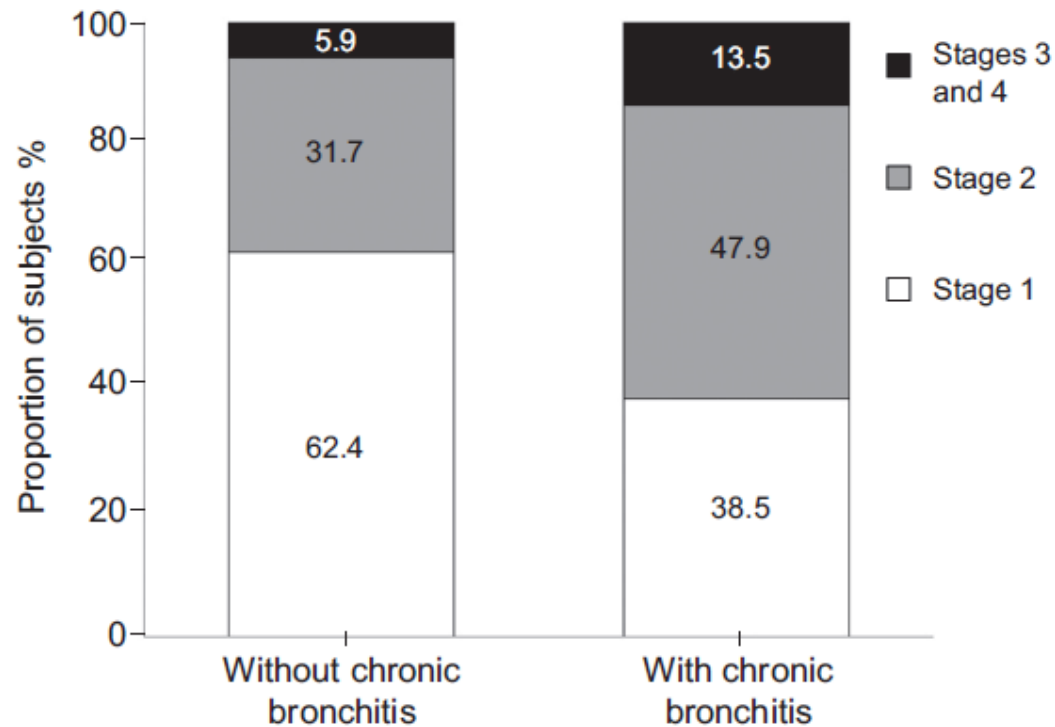
incidence rate (cases/1,000/year)



CHRONIC BRONCHITIS PHENOTYPE FROM PLATINO STUDY

- **Chronic bronchitis** has been defined as the presence of productive cough for 3 months in two successive years in a patient in whom other causes of chronic cough, such as tuberculosis, lung cancer and heart failure, have been excluded.
- Although chronic productive cough is considered a major manifestation in about 30-40% of COPD patients, there is limited information about the prevalence of chronic bronchitis in COPD patients.
- **The PLATINO study** was to assess different aspects of the chronic bronchitis phenotype in a large international population-based sample from five Latin American cities with high (80%) participation and robust, well-established methods.

CLINICAL OUTCOMES ACCORDING TO CHRONIC BRONCHITIS



CHRONIC COUGH AS A NOVEL PHENOTYPE OF COPD

- Recruited patients enrolled in the KOrea COpd Subgroup Study (KOCOSS),
- KOCOSS includes following questionnaires to define C₁
 - 1) Do you experience a cough most days, for at least 3 months per year?
 - 2) Have you had cough for more than two consecutive years?
 - 3) Do you produce sputum most days, for at least 3 months per year?
 - 4) Have you had sputum for more than two consecutive years?

	Total	Chronic cough		P-value
		(+)	(-)	
Patients	1,613	377 (23.4%)	1,236 (76.6%)	
Age, years	72.6 ± 7.9	71.8 ± 7.8	72.9 ± 7.9	0.02
Male sex	1,380 (91.6%)	317 (89.8%)	1,063 (92.2%)	0.16
BMI, kg/m ²	23.1 ± 8.9	22.5 ± 3.2	23.2 ± 10.0	0.14
Smoking status				
Current	434 (27.1%)	126 (33.5%)	308 (25.1%)	0.001
Amount, PY	43.8 ± 25.0	44.8 ± 24.8	43.5 ± 25.1	0.41
Previous AE	405 (25.2%)	122 (32.5%)	283 (23.0%)	<0.001
Laboratory				
WBC, /μL	7,750 ± 2,675	7,950 ± 2,942	7,690 ± 2,579	0.13
Eosinophil, %	3.4 ± 3.6	3.4 ± 3.3	3.5 ± 3.7	0.61
Hb, g/dL	14.2 ± 1.5	14.2 ± 1.5	14.2 ± 1.6	0.86
Pulmonary function				
FEV ₁ , % predicted	59.2 ± 18.3	55.8 ± 17.4	60.2 ± 18.4	<0.001
FVC, % predicted	84.6 ± 18.3	83.9 ± 18.5	84.8 ± 18.2	0.39
DL _{CO} , % predicted	74.6 ± 23.8	69.3 ± 20.9	76.3 ± 24.5	<0.001
Quality of life				
mMRC score	1.45 ± 0.93	1.71 ± 0.98	1.38 ± 0.90	<0.001
0	189 (11.8%)	31 (8.3%)	158 (12.8%)	<0.001
1	770 (47.9%)	147 (39.2%)	623 (50.5%)	
2	408 (25.4%)	108 (28.8%)	300 (24.3%)	
3	211 (13.1%)	79 (21.1%)	132 (10.7%)	
4	30 (1.9%)	10 (2.7%)	20 (1.6%)	
CAT score	15.4 ± 7.9	19.3 ± 8.5	14.2 ± 7.3	<0.001
SGRQ-C				
Symptom	44.6 ± 20.5	57.2 ± 21.1	40.6 ± 18.6	<0.001
Activity	46.0 ± 23.1	52.6 ± 24.8	43.9 ± 22.1	<0.001
Impact	24.1 ± 19.7	33.4 ± 23.1	21.2 ± 17.5	<0.001
Total	34.1 ± 18.9	43.1 ± 21.3	31.2 ± 17.1	<0.001
6MWD, m	373.8 ± 116.1	379.7 ± 101.7	371.9 ± 120.2	0.27

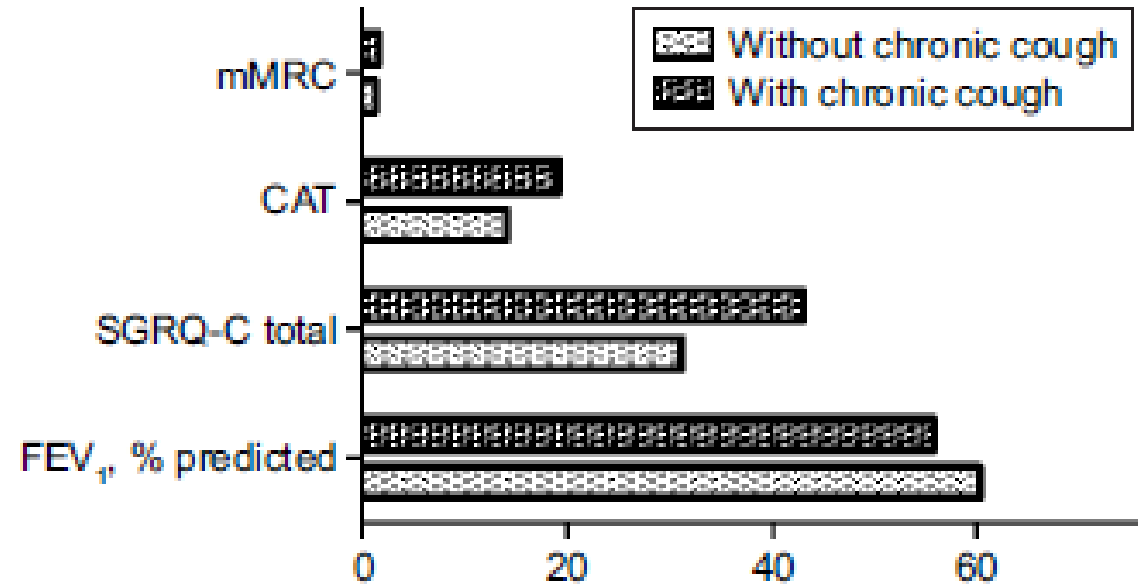
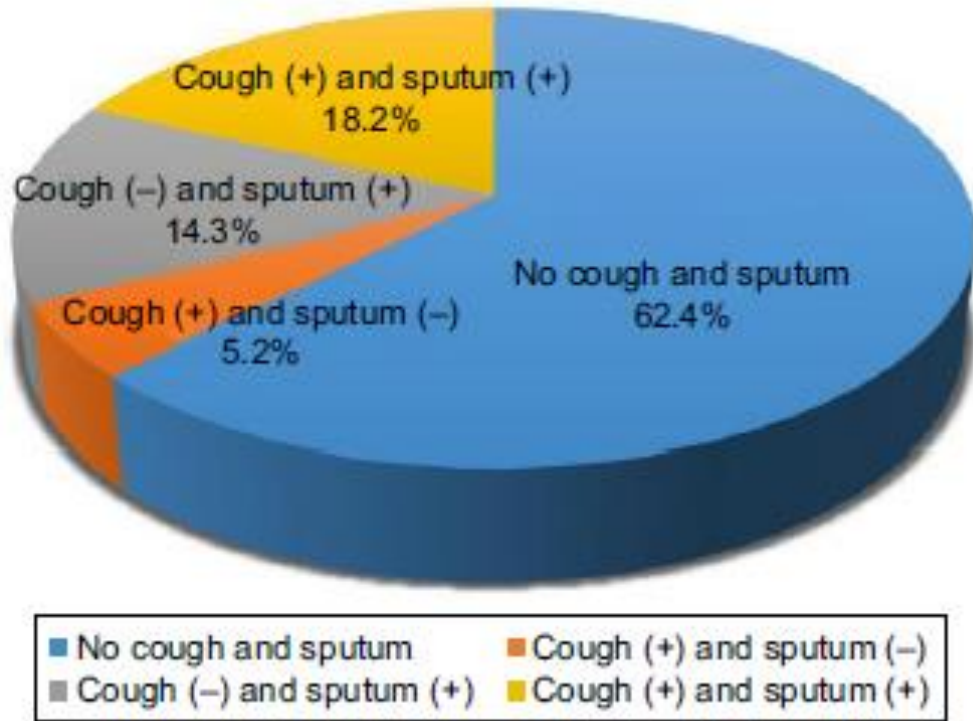


Table 3 Multivariate analysis for the effects of chronic cough and chronic phlegm on the lung function, dyspnea, and quality of life in patients with chronic obstructive pulmonary disease

Adjusted values	Cough			Sputum		
	(+)	(-)	P-values	(+)	(-)	P-values
FEV ₁ , %	57.3 ± 1.3	60.9 ± 0.8	0.02	58.5 ± 0.9	59.8 ± 1.2	0.37
DL _{CO} , %	70.8 ± 1.8	76.9 ± 1.1	0.02	72.2 ± 1.3	74.6 ± 1.7	0.28
mMRC	1.87 ± 0.11	1.49 ± 0.07	0.003	1.78 ± 0.10	1.60 ± 0.09	0.18
CAT	20.0 ± 0.94	15.6 ± 0.6	<0.001	19.6 ± 0.8	16.3 ± 0.7	0.003
SGRQ-C						
Symptom	57.5 ± 2.3	45.8 ± 1.5	<0.001	57.1 ± 2.0	47.0 ± 1.9	<0.001
Activity	58.7 ± 2.7	46.2 ± 1.7	<0.001	54.3 ± 2.4	51.1 ± 2.2	0.32
Impact	38.5 ± 2.3	24.5 ± 1.5	<0.001	34.8 ± 2.1	28.9 ± 1.9	0.04
Total	47.8 ± 2.2	34.5 ± 1.4	<0.001	44.4 ± 1.9	38.6 ± 1.8	0.03

	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age, years	1.04	1.02–1.05	<0.001	1.04	1.02–1.06	<0.001
Male sex	1.02	0.64–1.62	0.94	–	–	–
BMI, kg/m ²	0.99	0.96–1.02	0.58	–	–	–
Current smoker	0.81	0.60–1.09	0.17	0.90	0.65–1.25	0.54
Previous AE	1.95	1.49–2.56	<0.001	1.72	1.28–2.30	<0.001
FEV ₁ , % predicted	0.98	0.97–0.99	<0.001	0.98	0.97–0.99	<0.001
Chronic cough	1.52	1.15–2.02	0.004	1.56	1.08–2.24	0.02
Chronic sputum	1.16	0.88–1.51	0.29	0.92	0.65–1.30	0.63

COUGH AT RISKS OF EXACERBATION AND MORTALITY

- All subjects with COPD (n = 993) were identified together with sex- and age matched reference subjects without obstructive lung function impairment from four population-based cohorts in 2002-04.
 - 993 with COPD
 - 993 age- and sex matched subjects without obstructive lung function impairment.
- To evaluate the relationship between productive cough, exacerbations and mortality among subjects with and without COPD.

COMPARING SUBJECTS WITH AND WITHOUT COUGH

	COPD		<i>P</i> ^a	Non-COPD		<i>P</i> ^a
	Productive cough <i>n</i> = 394	No productive cough <i>n</i> = 599		Productive cough <i>n</i> = 209	No productive cough <i>n</i> = 784	
Sex						
Women	165(38.8)	286(50.4)		94(40.3)	357(47.0)	
Men	260(61.2)	282(49.6)	< 0.001	139(59.7)	403(53.0)	0.075
Age, mean (SD)	65.8	64.3	0.034	67.4	63.7	< 0.001
Smoking habits						
Non smoker	71(16.8)	161(28.6)		97(42.5)	369(49.1)	
Ex smoker	162(38.4)	259(46.1)		90(39.5)	298(39.6)	
Smoker	189(44.8)	142(25.3)	< 0.001	41(18.0)	85(11.3)	0.022
Exacerbations						
Any	126(29.6)	80(14.1)	< 0.001	45(19.3)	44(5.8)	< 0.001
Frequent ^b	60(14.1)	25(4.4)	< 0.001	18(7.7)	12(1.6)	< 0.001
Heart disease	85(20.0)	100(17.6)	0.338	47 (20.2)	113(14.9)	0.054
GOLD grade						
1	190(44.7)	309(54.4)				
2	186(43.8)	229(40.3)				
3–4	49(11.5)	30(5.3)	< 0.001			
Mortality	124(29.2)	107(18.8)	< 0.001	54 (23.2)	121(15.9)	0.011

Any exacerbation during last 12 months

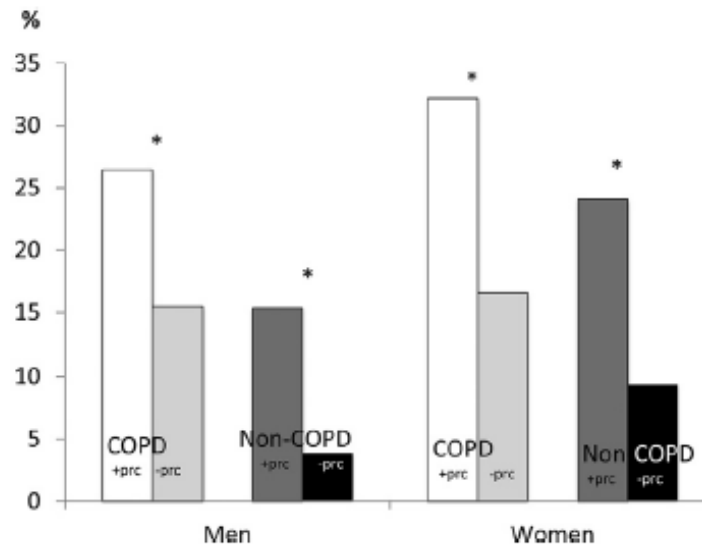


Table 3 Productive cough (prc) and COPD evaluated as risk factors for 'any exacerbation during the last 12 months', analyses also performed stratified by sex, in a multiple logistic regression model^a (OR, 95% CI).

	'Any exacerbation during the last 12 months'					
	All subjects N = 1986		Men N = 1084		Women N = 902	
	Or	95% CI	Or	95% CI	Or	95% CI
Women	1					
Men	0.61	0.46–0.80				
Non-COPD –prc	1		1		1	
Non-COPD +prc	4.13	2.61–6.54	4.83	2.34–9.98	4.09	2.21–7.55
COPD –prc	2.85	1.92–4.23	4.38	2.30–8.32	2.20	1.32–3.67
COPD +prc	9.25	6.23–13.75	12.34	6.62–22.99	7.88	4.57–13.59

Mortality

Table 4 Productive cough (prc) and COPD evaluated as risk factors for mortality among all subjects and stratified by sex in a multivariate Cox regression analysis^a, expressed as hazard ratios (HR) with 95% confidence intervals (95% CI).

	Mortality					
	All subjects N = 1964 ^b		Men N = 1070		Women N = 894	
	HR	95% CI	HR	95% CI	HR	95% CI
Women	1					
Men	1.56	1.25–1.94				
Non-COPD –prc	1		1		1	
Non-COPD +prc	1.01	0.73–1.41	1.10	0.74–1.65	0.84	0.47–1.51
COPD –prc	1.08	0.83–1.42	1.04	0.73–1.49	1.15	0.76–1.74
COPD +prc	1.48	1.13–1.94	1.63	1.17–2.26	1.23	0.76–1.99

COUGH AS RISK FACTOR OF EXACERBATION IN COPD

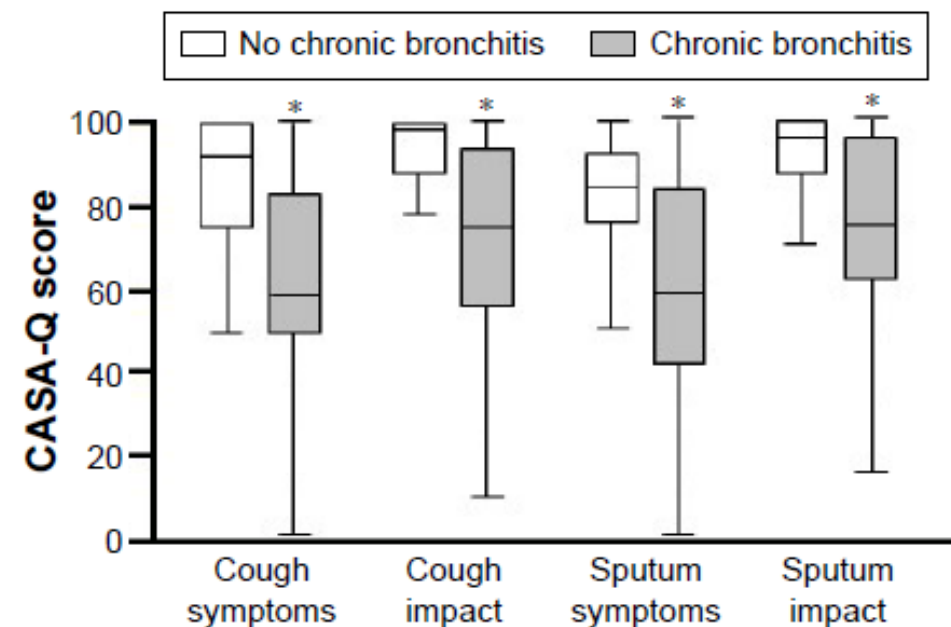
Variables	Relative Hazard of Failure	95% Confidence Interval	p Value
Age > 40 yr, 5 yr*	1.09	1.04–1.15	< 0.001
Duration COPD diagnosis < 8 yr, 1 yr*	1.04	1.00–1.09	0.047
Presence of productive cough	1.32	1.10–1.60	0.003
Percentage of predicted FEV ₁ , 5 %*	0.96	0.93–0.99	0.019
No antibiotics for COPD prior year	0.57	0.47–0.70	< 0.001
Systemic steroids for COPD prior year			
No courses	0.54	0.42–0.69	< 0.001
One course	0.75	0.58–0.98	0.033
Two or more courses	1		
No hospitalizations for COPD prior year	0.80	0.65–1.00	0.047
Theophylline at entry	1.26	1.02–1.57	0.035

*Interval change in the variable associated with the relative hazard.

IMPACT OF CURRENT COUGH ON HEALTH-RELATED QOL

- Cross-sectional multicenter study was conducted in the French Initiatives COPD cohort
- Assessed **cough and sputum production within the past 7 days** using the cough and sputum assessment questionnaire (CASA-Q), health-related quality of life, spirometry, smoking status, dyspnea, exacerbations, anxiety and depression, and comorbidities.

Variables	Missing data, n	Median (Q1–Q3) or n (%)
Age, years	0	62 (56–69)
Male	0	128 (72)
Smoking, pack-year	2	36 (24–53)
Current smokers	2	63 (36)
Body mass index	0	25 (22–29)
Chronic bronchitis	8	123 (69)
Exacerbations in previous year	1	
0		61 (34)
1		51 (29)
>2		65 (37)
Congestive heart failure and coronary artery disease	0	41 (23)
mMRC dyspnea scale	4	
0		19 (11)
1		69 (40)
2		44 (25)
3		37 (21)
4		5 (3)
FEV ₁	0	57 (37–72)
Anxiety HADS ≥10	6	49 (28)
Depression HADS ≥10	5	29 (16)
SGRQ total score	0	44 (29–57)
CASA-Q score		
Cough symptoms	0	70.8 (50.0–91.7)
Cough impact	1	84.4 (59.4–100.0)
Sputum symptoms	5	66.7 (41.7–88.1)
Sputum impact	6	87.5 (66.7–100.0)



RELATIONSHIP BETWEEN SGRQ AND CASA-Q DOMAIN

Table 3 Relationships between the SGRQ total score, and CASA-Q domain scores and clinical variables in multivariate analyses

Candidate variables	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
CASA-Q cough impact	<0.0001	<0.0001	<0.0001				
CASA-Q cough symptoms	0.0435	NS		0.00012			
CASA-Q sputum impact	0.0581	NS			<0.0001		
CASA-Q sputum symptoms	NS	NS				0.0020	
FEV ₁ , %		0.0058	0.0024	0.00019	0.0072	0.0068	0.0042
mMRC dyspnea scale		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Exacerbations		0.0334	0.0266	0.0028	0.0320	0.0046	0.0037
Depression		0.0558	0.0229	0.0037	0.0338	0.0080	0.0017
Anxiety		0.0889	0.0995	0.0331	0.0542	0.0169	0.0090
Cardiovascular comorbidities		0.0072	0.00043	0.0019	0.0167	0.0101	0.0068
Chronic bronchitis							0.0498
R ²	0.38	0.60	0.62	0.56	0.58	0.54	0.54

SUMMARY

- Cough is a common symptom in both General population and COPD, one of the chronic respiratory disease.
- Reasons of cough in COPD patients
 - Substantial airway inflammation & smoking
 - Mechanical sputum clearance by cough
 - Neural interaction in cough reflex
 - Bronchiectasis as co-morbidity
- Chronic cough assessment using classic definition, SGRQ-c score, and CAT score
- Clinical implications of cough in COPD patients
 - incidence of COPD development, exacerbation, mortality and health-related quality of life