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The Chronic Bronchitis Phenotype in COPD: Features and Implications

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Abstract

Purpose of Review—Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem that is projected to rank fifth worldwide in terms of disease burden and third in terms of mortality. Chronic bronchitis (CB) is associated with multiple clinical consequences, including hastening lung function decline, increasing risk of exacerbations, reducing health related quality of life, and possibly raising all-cause mortality. Recent data suggests greater elucidation on the risk factors, radiologic characteristics, and treatment regimens. Our goal was to review the literature on chronic bronchitis that has been published in the last few years.

Recent Findings—A growing body of literature that more carefully describes environmental risk factors, epidemiology, and genetics associated with CB. In addition, as computed tomography technology continues to improve, the radiologic phenotype associated with CB is better understood.

Summary—With these new data, the clinician can recognize the newly described risk factors and the associated phenotype for chronic bronchitis and entertain new treatment options for this high risk population.

Keywords

Chronic Obstructive Pulmonary Disease; Chronic Bronchitis; Genetics; Airway disease; N-Acetylcysteine

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem that is projected to rank fifth worldwide in terms of disease burden and third in terms of mortality.(1) Chronic bronchitis (CB) is a common clinical phenotype in COPD and is classically defined as chronic cough and sputum production for 3 months a year for 2 consecutive years,(2) but many studies have used different definitions to define it. However it is described, it is clear that CB is associated with multiple clinical consequences, including hastening lung function decline, increasing risk of exacerbations, reducing health related quality of life, and possibly raising all-cause mortality.(3-8) Despite its clinical consequences, the literature regarding its pathophysiology, radiologic characteristics, and clinical phenotype has been sparse. Recently, however, there has been a growing body of literature that more carefully describes environmental risk factors, epidemiology, and genetics associated with CB. In addition, as computed tomography technology continues to improve, the radiologic phenotype associated with CB is better understood. Herein, we will describe our current understanding of CB in COPD, with an emphasis on recent literature.

Epidemiology

CB is surprisingly common in the general population, seen in 3.4-22.0% of adults.(9-21). This wide range of prevalence estimates may be due to varying definitions of CB (i.e. chronic phlegm versus chronic cough and phlegm) as well as the possible inclusion of subjects with bronchiectasis. Table 1 provides an overview of the prevalence of cough and sputum production in population based studies.

According to recent statistics, chronic bronchitis (CB) affects approximately 10 million people in the United States, the majority of which are between 44-65 years of age.(24) 24.3% of individuals with CB are older than 65, and surprisingly 31.2% are between the ages of 18 and 44.

The numbers affected by CB dramatically increase with smoking. Pelkonen et al. followed 1,711 Finnish men in rural communities for 30 years and found the incidence of CB was 42% in continuous smokers, 26% in ex-smokers, and 22% in never smokers.(20) A recent cross sectional study of over 5,000 adult current or ex-smokers with over a 10 pack year history, the prevalence of CB, using the classic definition, was a striking 34.6%.(21) The prevalence of CB is higher in COPD patients, affecting 14-74% of all COPD patients.(25-28)

CB seems to affect whites more than blacks, but the majority of studies have been comprised of mostly whites.(11, 14, 19, 20, 29) A recent study of non-Hispanic whites and blacks found that COPD subjects were more likely to be white than black, but the differences in racial distribution between those with and without CB were small.(28) Gender has also been a matter of debate. Many studies have found that CB affects men more than women.(27, 28, 30, 31) However, according to the 2013 American Lung Association report, the prevalence rates of CB in women were nearly twice that of men (59.7 vs. 29.6 per 1000 persons).(24) A 10-year study of Danish 21,130 patients showed that the cumulative prevalence of chronic mucus secretion was 10.7% in females vs. 8.7% in males.(19) The

reasons for the higher prevalence of CB in females compared to males is unclear, but may be due to hormonal influences, gender differences in symptom reporting, and gender diagnostic bias; for example, in the EUROSCOP study, women reported more dyspnea and cough but less phlegm symptoms than men.(32)

Recent evidence has suggested that CB may be underdiagnosed, likely related to the various definitions used for CB. Using a definition of chronic phlegm alone for most days, 3 months a year, for 2 years, the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study estimated a CB prevalence of 14.4 and 6.2% in those with and without COPD, respectively.(27) When using the classic definition, however, the prevalence fell to 7.4 and 2.5%, respectively. In the Genetic Epidemiology of COPD (COPDGene) study,(33) the prevalence of CB was 26.2% in GOLD 1-4 subjects using the classic definition, but was 39% when using a novel definition of cough and phlegm using the Saint George's Respiratory Questionnaire.(unpublished data) A large epidemiologic survey of the French general population showed a CB prevalence of 3.5%, but only 28.6% of these subjects reported a history of respiratory disease.(34) These data highlight the need to ask the appropriate questions when interviewing patients at risk for CB and the need of a more uniform definition across studies.

Risk Factors

The primary risk factor of CB is smoking. As mentioned earlier, the cumulative 30-year incidence of CB in current smokers is 42%.(20) A 2011 meta-analysis has found that ever smoking conferred a 2.69, (95% CI 2.50-2.90), and current smoking was associated with a relative risk of 3.41 (95% CI 3.13-3.72).(35) More recent literature has supported the increased risk of CB conferred by smoking.(28, 36) Sumner et al. objectively measured cough in those with and without COPD with 24 hour cough monitoring and found that the greatest cough frequency was in COPD current smokers, followed by COPD ex-smokers and healthy current smokers.(37) In addition, in this study reported sputum production, smoking history, and current smoking predicted cough frequency. However, CB has been described in 4-22% of never smokers,(16, 20) suggesting that other risk factors may exist. Interestingly, two cross sectional studies showed stable rates of CB of 12.5 to 12.6% in young adults, even though the rates of smoking decreased from 33.6% to 26.9%.(38) Recent literature has highlighted that occupational exposures, biomass fuels, dusts, and chemical fumes place individuals at risk for developing CB.

While a significant body of literature exists that ties occupational exposures with worsening asthma control and bronchial hyperresponsiveness, the link between CB and occupational exposures is just beginning to emerge. A study involving 338 hospitalized COPD subjects in 9 Spanish hospitals found that high exposure to gases or fumes was associated with CB symptoms.(39) Dijkstra et al. found that exposures to mineral dusts and gases and fumes was associated with an odds ratio of 1.38 and 2.19, respectively, in 8529 subjects without COPD.(36) There were also significant interactions found between the presence of COPD and exposures to gases, fumes, and aromatic solvents in this cohort, comprised of an additional 1479 subjects with COPD diagnosed by spirometry. Exposure to both dusts and fumes was associated with an increased risk of chronic cough and chronic phlegm (odds

ratios 1.83 and 1.82, respectively) after adjustment for demographic factors and smoking in the COPDGene cohort, a study that involved more than 9600 subjects with and without COPD.(40) These associations show that, regardless of the presence of airflow obstruction, significant gas and fume exposure can result in chronic cough and sputum production. The specific gases or fumes, as well as the amount of exposure necessary, remains unclear and deserves further investigation.

In the last decade it has become apparent that exposure to biomass fuels, such as wood, dung, and crop residues, is a significant risk factor for COPD. Biomass smoke exposure predominantly affects women in rural areas who use these fuels for cooking. With the increasing understanding of the risk of developing COPD conferred by biomass smoke, it is apparent that it also increases risk for developing CB. Compared to COPD due to tobacco smoking, those with COPD related to biomass smoke exposure have more cough, phlegm symptoms and air trapping on CT scan.(41) Two recent studies comparing radiologic phenotypes between tobacco smoke-exposed and biomass smoke-exposed subjects matched for lung function found that the biomass group had more air trapping or peribronchial thickening and less emphysema than the tobacco group, suggesting an airway predominant phenotype.(42, 43) Another study of wood smoke-exposed women with COPD, the most common findings on HRCT scans were bronchial wall thickening, bronchiectasis, mosaic perfusion pattern, parenchymal bands, and tree-in-bud opacities.(44) These radiologic findings suggest a bronchitic clinical phenotype, as CB is associated with greater airway wall thickening and gas trapping on CT scan.(28)

Air pollution is another risk factor for worsening of CB symptoms and exacerbations. Ozone studies have shown diminished lung function, reduced exercise capacity, and lung inflammation at levels at or below the National Ambient Air Quality Standards of air quality.(45) To make matters worse, ambient ozone levels are expected to increase in the upcoming decades.(46) A study of over ten years of ambient ozone levels found that increased ozone levels were associated with greater emergency department visits for CB.(47) In a meta-analysis of 23 studies examining all-cause mortality associated with outdoor fine particulate matter (particles with a median diameter <2.5 μm (PM2.5)) air pollution, a 10 mg/m^3 increment in PM2.5 was associated with an increase in the risk of death, particularly respiratory causes of death (1.51%, 95% CI 1.01-2.01).(48) There is also supportive literature that air pollution increases systemic biomarkers of inflammation in COPD subjects, particularly interleukin 8, C-reactive protein, fibrinogen, and hepatocyte growth factor.(Dadvand) Systemic levels of C-reactive protein and fibrinogen have been shown in univariate analysis to be greater in COPD subjects with CB in the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS).(49) Other studies, however, have not been as supportive of the association between air pollution with CB. A meta-analysis of 5 cross-sectional studies in Europe found no statistically significant associations between any air pollutant and CB except in never smokers (OR 1.31 for PM_{coarse}).(50)

Recently more data have emerged linking the CB phenotype with upper airway symptoms. An analysis of two large epidemiologic cross sectional surveys of young adults conducted at different times (1998/2000 and 2007/2010) found that the likelihood of having CB was significantly higher in subjects with allergic rhinitis.(38) This study also revealed that

although the prevalence of CB remained stable, the rates of current smoking dropped over the timespan between the two surveys and the prevalence of allergic rhinitis increased, strengthening the association between upper airway and lower airway symptoms. In an analysis of the National Health and Nutrition Survey III (NHANES III), the presence of self-reported doctor-diagnosed hay fever or allergic upper respiratory symptoms (21.4% of 1381 subjects) was independently associated with chronic cough and phlegm.(51) Exacerbation rates were greater in those with an allergic phenotype compared to those without it. In the COPDGene cohort, those with COPD and CB (24.5% of 2703 subjects) were more likely to have allergic nasal and ocular symptoms and exacerbation frequency compared to COPD subjects without CB.(28)

Genetics

As CB exists in those without airflow obstruction, and not everyone with COPD develops CB, it is clear that predisposing factors in combination with exposures lead to CB. Recent data have revealed possible genetic predispositions. In a population based study of 13649 twins, from the Danish Twin Registry, CB showed moderate familial aggregation especially in women.(52) Genome wide association analysis in the Netherlands of chronic mucus hypersecretion showed a strong association with a SNP on chromosome 3.(53) An simultaneous analysis of three different cohorts, COPDGene (non-Hispanic whites and blacks), GenKOLS (Bergen, Norway), and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) found a new genome-wide locus of chromosome 11p15.5 in COPD subjects with CB compared to smoking controls.(54) As the understanding of COPD genetics increases, perhaps we will be able to elucidate the gene-environment interactions responsible for the development of CB.

Radiologic features

CB is associated with greater airway disease on CT scan. One of the first studies that compared 20 COPD subjects with CB and 22 COPD subjects without CB found significantly higher bronchial wall percentage areas and thickness-to-diameter ratios in those with CB compared to subjects without CB.(55) More recent studies have corroborated these initial findings in different cohorts and using different quantitative techniques. A recent study showed that sputum purulence in combination with lung function measures strongly predicted airway wall thickness of 10mm airways (Pi10) in 373 COPD subjects.(56) In the COPDGene study, which involved over 2700 COPD subjects with complete radiographic analysis and pertinent clinical histories, airway wall thickness in combination with lung function, smoking history, allergic symptoms, and gastroesphageal reflux was predictive of CB in a multivariate model.(28)

Clinical Features

Table 2 summarizes the current data regarding the outcomes associated with CB. Multiple studies have shown that CB accelerates lung function decline,(3, 57) worsen health related quality of life,(26-28) may increase mortality,(4, 5, 30, 61) and increases the risk of exacerbations.(3, 25, 27) Some literature on exacerbations leaves the link with exacerbations and CB debatable. In the ECLIPSE study, CB defined as chronic cough was a significant

predictor of exacerbations but only on univariate analysis.(66) Another study of smokers without spirometric evidence of COPD found CB to again be a significant risk factor for respiratory exacerbations but only on univariate analysis.(67)

However, recent data has more firmly established the link between CB and exacerbations. A multicenter cross sectional study of 975 GOLD 2-4 COPD subjects, where the prevalence of CB was 64%, found that the CB group had more exacerbations (2.08±2.78 vs. 1.05±1.71 exacerbations/patient/year, $p<0.0001$), a higher percentage of subjects with frequent exacerbations (37.3 vs. 14.2%, $p<0.0001$), more hospital admissions due to COPD (0.28±0.75 vs. 0.15±0.43 hospitalizations/patient/year, $p=0.0027$), and more all cause hospitalizations (0.52±0.91 vs. 0.38±0.83 hospitalizations/patient/year, $p=0.0185$).(60) An analysis of the COPDGene study (cross sectional, multicenter) of GOLD 1-4 subjects found similar trends in total exacerbation frequency (0.96±1.46 vs 0.52±1.04 exacerbations in the past year, $p<0.0001$) and history of severe exacerbations (24.2 vs. 15.2%, $p<0.0001$).(28) An analysis of the GOLD 0 subjects from the COPDGene study also found that those with CB (12.2% of 4880 subjects) had an increased rate of respiratory exacerbations.(68) In long term follow-up of 8246 subjects in the COPDGene study, CB was independently associated with exacerbation risk in all subjects (HR 1.15, 95% CI 1.03-1.28), including GOLD 0 and GOLD U (undefined, indicating smokers at risk for COPD with restrictive lung disease on spirometry).(69) Similar trends were seen in the COPD Clinical Research Network Azithromycin trial (MACRO) and the SPIROMICS cohorts.(49, 70) Using a novel definition of severe CB, defined as chronic cough, phlegm, and chest trouble, we found that severe CB was associated with increased mortality and all-cause hospitalizations in the National Emphysema Treatment Trial cohort.(71)

Implications for treatment

Treatment for COPD and CB is multifold and includes both pharmacologic and nonpharmacologic strategies. Please refer to a recent review for more extensive discussion on this topic.(72) Exacerbation rates remain high in those with CB, despite treatment with COPD maintenance medications.(73) Therefore, the primary focus in recent research has been on reducing exacerbations in this high risk population.

Macrolide antibiotics have been shown to have anti-inflammatory properties and have been used to decrease COPD exacerbations. Independent of their antibiotic properties, macrolides have been shown to reduce neutrophil-elastase induced mucus stasis, suggesting benefit in CB.(74) The effect of chronic macrolide therapy on COPD exacerbations was assessed in 109 patients randomly assigned to receive erythromycin 250 mg or placebo twice daily for 1 year.(75) The erythromycin group had significantly fewer exacerbations than the placebo group. A recent large, prospective, placebo-controlled, randomized trial on the use of azithromycin (250 mg daily for 1 year) to prevent acute exacerbations of COPD showed that azithromycin was associated with a significant decrease in exacerbation frequency and an improvement in HRQoL.(76) There was, however, no additional benefit conferred to those with CB.(77) What future studies with macrolides will show in those with CB remains to be determined.

Phosphodiesterase-4 inhibitors, particularly roflumilast, may be beneficial in the treatment of CB. Acquired dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) in airway epithelial cells can delay mucociliary transport, and has been associated with CB.(78) Moreover, roflumilast activates CFTR-mediated anion transport,(79) which may be at least one mechanism of its benefit in CB. In two 24-week trials, 933 patients with moderate to severe COPD were randomly assigned to roflumilast plus salmeterol or salmeterol alone, and 743 patients were randomly assigned to roflumilast plus tiotropium or tiotropium alone.(80) The overwhelming majority of patients (78–100%) endorsed chronic cough and sputum production. In both trials, roflumilast significantly reduced exacerbation rate. Thus, as CB increases risk for exacerbation, roflumilast may play a preferential role in preventing exacerbations in patients with CB and COPD. The Global Initiative on Obstructive Lung Disease (GOLD) currently recommends roflumilast for those with CB and in those with frequent exacerbations as second line therapy.(1)

As oxidative stress is crucial to the pathogenesis of COPD, antioxidant therapy may be of benefit in COPD treatment. The two most extensively studied antioxidant medications for COPD are N-acetylcysteine (NAC) and carbocysteine. Unfortunately, the two largest trials showed either no or weak reductions in exacerbations in long term follow-up.(81, 82) A more recent study, High-Dose N-Acetylcysteine in Stable COPD (HIACE) study, enrolled 120 subjects with stable COPD from one center and randomized them to receive NAC 600mg twice daily or placebo for one year.(83) The NAC group had a statistically significant increase in small airways function as measured by FEF_{25-75} compared to placebo but there was no difference in exacerbation frequency. A larger multicenter randomized controlled trial randomized 1006 subjects to the same NAC regimen or placebo and found significant reductions in exacerbation frequency (risk ratio 0.78, 95% CI 0.67-0.90).(84)

Conclusions

The recent data on chronic bronchitis has shed more light on the epidemiology, risk factors, radiologic features, genetic influences, and therapeutic strategies. This should influence the clinician to maintain a higher index of suspicion for chronic bronchitis given the recent growing body of literature on risk factors and phenotype. However, more study is needed to determine why some smokers develop CB and others do not and on how smoking cessation affects its natural history. In addition, more research on the pathophysiology of this disease process will help development of better therapies that directly target CB in order to improve quality of life, decrease exacerbations, and reduce mortality.

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Key Points

1. The main risk factor for chronic bronchitis remains current smoking but exposure to air pollution, dusts and fumes and biomass fuels are newly described risk factors.
2. Chronic bronchitis significantly increases the rate of COPD exacerbations.
3. Chronic bronchitis is seen variably in smokers but also is seen to a surprising degree in nonsmokers, suggesting other risk factors are significant.
4. New treatments like N-Acetyl Cysteine may be beneficial in those with chronic bronchitis.

Table 1

Prevalence of Chronic Bronchitis in Multiple Studies.

Study	Subjects	Findings
Lange 1989[9]	General population, Copenhagen; 12,698 adults	Bronchial hypersecretion: 10.1%
Sobradillo 1999[22]	General population, Spain; 4035 adults aged 40-69 years	Cough: 13.5% Expectoration: 10.7% Chronic Bronchitis: 4.8%
Pallasaho 1999[10]	Random sample, Finland; 8000 subjects aged 20-69 years	Productive cough: 27%
von Hertzen 2000[11]	Random subjects, Finland; 7217 subjects age >30 years	Chronic bronchitis and/or emphysema: 22% in men, 7% in women
Cerveri 2001[12]	General population, Europe; 17,966 subjects aged 20-44 years	Chronic Bronchitis: 2.6% (range 0.7-9.7% across countries)
Janson 2001[13]	Multinational; 18,277 subjects aged 20-48 years	Productive cough: 10.2%
Huchon 2002[14]	General population, France; 14,076 subjects	Chronic bronchitis: 4.1% Chronic cough and/or expectoration: 11.7%
Lundback 2003[15]	5892 subjects from OLIN Study cohort	Chronic productive cough: 60% in COPD subjects
Miravitlles 2006[16]	General population, Spain; 6758 adults aged >40 years	Cough: 5% in never smokers, 11% in smokers or ex-smokers Expectoration: 4% in never smokers, 11% in smokers and ex-smokers
Pelkonen 2006[20]	Finnish cohort of 1711 adult men aged 40-59	Incidence of chronic productive cough: 42% current smokers, 26% past smokers, 22% never smokers
De Marco 2007[17]	International cohort of 5002 subjects aged 20-44 years with normal lung function	Chronic cough/phlegm production: 9.2%
Miravitlles 2009[18]	Population based sample, Spain; 4274 adults aged 40-80 years	Chronic cough: 3.4% Chronic sputum production: 11.7%
Harmsen 2010[19]	Danish cohort of 29180 (in 1994) and 21130 (in 2004) twins aged 12-41 years	Cumulative prevalence of chronic mucus secretion over 10 years of study, 10.7% in females and 8.7% in males
Martinez 2014[21].	United States cohort of 5858 adult past or previous smokers without airflow obstruction	Chronic bronchitis: 34.6%

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Table 2

Summary of the Effects of Chronic Bronchitis on Outcomes.

Outcome	Study	Subjects	Important Findings
Lung Function	Sherman et al. 1992.[57]	3,948	Adjusted FEV1 decline: 4.5 mL per year ± 2 (SE) in males *; 1.7 mL per year ± 1.5 (SE) in females
	Vestbo et al. 1996.[3]	9,435	Adjusted FEV1 decline: 22.8 ml/year (95% CI 8.2 to 37.4) in males*; 12.6 ml/year (95% CI 0.7 to 24.6) in females
	Lindberg et al. 2006.[58]	963	FEV1/FVC<0.7 and FEV1<80% predicted, OR: 2.56 (95% CI 1.32 to 4.95)*
	de Marco et al. 2007.[59]	5,002	FEV1/FVC<0.7, IRR: 1.85 (95% CI 1.17 to 2.93)*
	Guerra et al. 2008.[5]	1,412	FEV1/FVC<0.7, HR: 2.2 (95% CI 1.3 to 3.8) in <50 years*; 0.9 (95% CI 0.6 to 1.4) in ≥50 years
Health Related Quality of Life	Agusti et al. 2010.[26]	2,164	CB+ vs CB-: GOLD II: SGRQ total 50.3±18 vs 38.9±20.5*; mMRC 1.5±1 vs 1.3±1* GOLD III: SGRQ total 58.8±17.6 vs 51.2±18.2*; mMRC 1.8±1 vs 1.8±1.1 GOLD IV: SGRQ total 65±16.5 vs 59.4±15.2*; mMRC 2.4±1 vs 2.3±1
	de Oca et al. 2012.[27]	759	CB+ vs CB-: Short Form-12 physical score 44.6±1.01 vs 49.5±0.36* Limitation due to physical health 39(40.6) vs 148(22.4)*
	Kim et al. 2014.[28]	2,703	CB+ vs CB-: SGRQ total 48.0±21.3 vs 30.6±21.8* mMRC 2.3±1.4 vs 1.6±1.5*
COPD Exacerbations and Hospitalizations	Vestbo et al. 1996.[3]	9,435	COPD-related hospitalization, RR: 2.4 (95% CI 1.3 to 4.5) in males*; 2.6 (95% CI 1.2 to 5.3) in females*
	Burgel et al. 2009.[25]	433	All exacerbations: OR 4.15 (95% CI 2.43 to 7.08)* Moderate exacerbations: OR 4.65 (95% CI 2.54 to 8.48)* Severe exacerbations: OR 4.08 (95% CI 1.18 to 14.09)*
	Agusti et al. 2010.[26]	2,164	CB+ vs CB-, exacerbations in past year: GOLD II: 0.7±1.1 vs 0.6±1 GOLD III: 1±1.2 vs 1±1.4 GOLD IV: 1.2±1.6 vs 1.2±1.3

Outcome	Study	Subjects	Important Findings
	de Oca et al. 2012.[27]	759	CB+ vs CB-, exacerbations in past year: 5.3±3.83 vs 2.1±0.95
	Corhay et al. 2013.[60]	974	CB+ vs CB-, exacerbations per patient per year: 2.08±2.78 vs. 1.05±1.71*
	Kim et al. 2014.[28]	2,703	CB+ vs CB-, exacerbations in past year: Total, number/patient: 0.96±1.46 vs 0.52±1.04* Severe, %: 24.2 vs 15.2*
Mortality	Annesi et al. 1986.[61]	1,061	All-cause, RR: 1.35±0.111*
	Speizer et al. 1989.[30]	8,427	COPD-related, OR: 3.75 (95% CI 1.28 to 11) in males*; 11.04 (95% CI 2.52 to 48.5) in females* All-cause, OR: 1.37 (95% CI 1.09 to 1.72) in males*; 0.98 (95% CI 0.68 to 1.41) in females
	Tockman et al. 1989.[62]	884	All cause, RR: 1.65 (95% CI 0.95 to 2.89)
	Lange el al. 1990.[29]	13,756	All-causes, RR: 1.3 (95% CI 1.1 to 1.4) in males* and 1.1 (95% CI 0.9 to 1.3) in females
	Prescott et al. 1995.[63]	14,223	COPD-related with pulmonary infection, RR: 3.5 (95% CI 1.8 to 7.1)* COPD-related without pulmonary infection, RR: 0.9 (95% CI 0.5 to 1.8)
	Mannino et al. 2003.[64]	5,542	All-cause, RR: 1.2 (95% CI 0.97 to 1.4)
	Pelkonen et al. 2006.[4]	1,711	Respiratory-related, HR: 2.54 (95% CI 1 to 6.46)* All-cause, HR: 1.64 (95% CI 1.23 to 2.19)*
	Guerra et al. 2009.[5]	1,412	All-cause mortality, HR: 2.2 (95% CI 1.3 to 3.8) in <50 years*; 1 (95% CI 0.7 to 1.3) in ≥50 years

*Statistically significant. Data are presented as mean±SD or number (percentage) except as indicated. Incident rate ratio, odds ratio, relative risk, and hazard ratio are all from multivariate analysis with adjustments for covariates.

FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, SE = standard error, CI = confidence interval, HR = hazard ratio, RR = relative risk, OR = odds ratio, CB+ = group with chronic bronchitis, CB - = group without chronic bronchitis, SGRQ = St. George's Respiratory Questionnaire, and mMRC = modified Medical Research Council. Updated and modified from Ramos F, Krahnke J, Kim V. Clinical Issues of Mucus Accumulation in COPD. *IJCOPD* 2014:9 139–150.(65) With permission.