# Chronic obstructive pulmonary disease in non-smokers

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**Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Tobacco smoking is established as a major risk factor, but emerging evidence suggests that other risk factors are important, especially in developing countries. An estimated 25–45% of patients with COPD have never smoked; the burden of non-smoking COPD is therefore much higher than previously believed. About 3 billion people, half the worldwide population, are exposed to smoke from biomass fuel compared with 1·01 billion people who smoke tobacco, which suggests that exposure to biomass smoke might be the biggest risk factor for COPD globally. We review the evidence for the association of COPD with biomass fuel, occupational exposure to dusts and gases, history of pulmonary tuberculosis, chronic asthma, respiratory-tract infections during childhood, outdoor air pollution, and poor socioeconomic status.**

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See **Editorial** page 663

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## Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow obstruction and destruction of lung parenchyma, and is caused by chronic exposure of genetically susceptible individuals to environmental factors. Tobacco smoking was associated with risk of COPD as early as the 1950s;[1,2] smoking was established as a causative risk factor by the findings of Fletcher and Peto's[3] 8-year prospective study of 792 men, and the larger and longer Framingham cohort offspring study confirmed these results.[4] Consequently, later research has focused on smoking as the most important risk factor for COPD; several prevalence studies have been done solely in smokers,[5,6] and most clinical trials in COPD recruit only smokers with at least 20 pack-years of cigarette smoking exposure.

However, in the past decade and especially the past 5 years, results from a growing number of published studies have suggested that risk factors other than smoking are strongly associated with COPD. These factors include exposure to indoor and outdoor air pollutants, workplace exposure to dust and fumes, history of repeated lower respiratory-tract infections during childhood, history of pulmonary tuberculosis, chronic asthma, intrauterine growth retardation, poor nourishment, and poor socioeconomic status.

## Evidence of COPD in non-smokers

Phillips[7] reported that risk factors other than tobacco smoking were associated with COPD in 1963, and previously Fairbairn[8] had reported that outdoor air pollution was an important risk factor. Overwhelming interest in smoking as the major risk factor has overshadowed the importance of non-smoking causes. However, Husman and colleagues[9] associated occupation with COPD in 1987 in their 6-year study of Finnish farmers and non-farmers, which showed that a higher proportion of farmers (2·7%) than of non-farmers (0·7%) had the disease, an effect that was independent of smoking.

Whittemore and co-workers[10] reported the prevalence of COPD in 12 980 never-smoker participants of the US-based NHANES I, NHANES II, and HHANES studies to be 5·1% (3·7% of men, 5·6% of women) from self-reported physician diagnosis, which was similar to the prevalence of chronic cough, phlegm, or wheezing recorded in never-smokers in Finland.[11] The pooled results of the NHANES I, NHANES II, and HHANES studies rekindled interest in COPD in non-smokers. 10 years later, the NHANES III study[12] reported the prevalence of COPD in never-smokers to be 6·6%. Unlike previous NHANES studies, NHANES III diagnosed COPD from postbronchodilator spirometry (ratio of forced expiratory volume in 1 s [$FEV_1$] to forced vital capacity [FVC] <0·70). Findings from the study also suggested that a quarter of COPD cases in the USA were in never-smokers, which was supported by similar proportions in the UK (22·9%)[13] and Spain (23·4%).[14]

The table summarises data from published studies about the prevalence of COPD and the proportion of COPD patients who have never smoked, and figure 1 shows the proportion of non-smoking COPD patients worldwide. These data suggest that the burden of non-smoking COPD is much higher than previously believed in both developed and developing countries. For example, the Regional COPD Working Group[27] used a validated model to estimate the prevalence of COPD in the Asia-Pacific region (table), but the estimated proportion of patients with COPD who had never smoked was much lower than calculated in epidemiological studies from China,[22] Korea,[29] and Japan.[31] The panel lists additional risk factors for COPD.

### Search strategy and selection criteria

We searched PubMed (January, 1995–July, 2009) using the search terms "COPD and prevalence", "COPD and risk factors", "COPD and occupation", "COPD and air pollution", "COPD and tuberculosis", and "COPD and respiratory-tract infection". We focused on reports published in the past 5 years, but did not exclude frequently referenced and highly regarded reports published more than 5 years ago. We also searched reference lists of reports identified by this search strategy and selected those we judged relevant, and we have been actively involved in original research in this discipline. No language restrictions were placed on the searches.

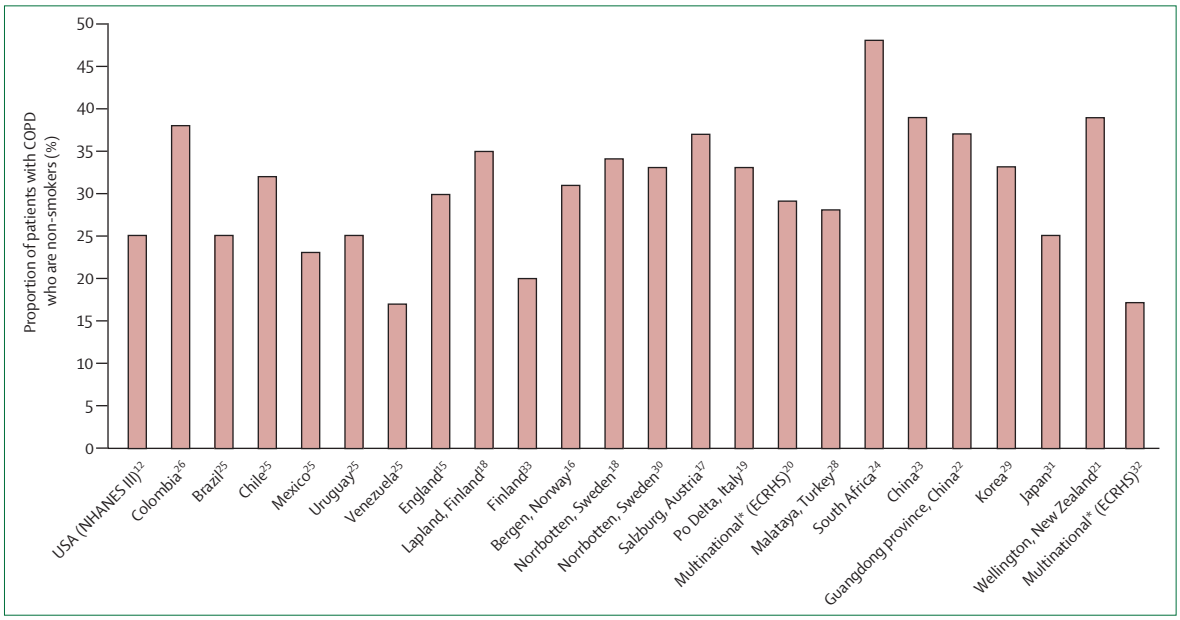


***Figure 1:*** **Proportion of patients with chronic obstructive pulmonary disease (COPD) who are non-smokers worldwide**
*Australia, Belgium, Denmark, France, Germany, Iceland, Ireland, Italy, Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, UK, and USA.

## Indoor air pollution

### Use of biomass fuel

Worldwide, about 50% of all households and 90% of rural households use biomass fuel (wood, charcoal, other vegetable matter, and animal dung) and coal as their main source of domestic energy. About 3 billion people worldwide are exposed to smoke from biomass fuel compared with 1·01 billion people who smoke tobacco, suggesting that exposure to biomass smoke might be the most important global risk factor for COPD.[34] About 50% of deaths from COPD in developing countries are attributable to biomass smoke, of which about 75% are of women.[34] More than 80% of homes in China, India, and sub-Saharan Africa use biomass fuel for cooking, and in rural areas of Latin America, the proportion ranges from 30% to 75% (figure 2). Nearly 2 billion kg biomass are burnt everyday in developing countries alone,[36,37] and in some developed and developing countries the decline in biomass use has slowed or even reversed, especially in poorer households.[38]

Even in some developed countries, such as Canada, Australia, and western states of the USA, the persistent rise in the cost of energy has prompted an increasing number of households to use wood or other biomass products for heating.[39] For example, a study in New Mexico, USA, reported that 26% of participants had been exposed to smoke from biomass fuel.[40]

### Epidemiology of COPD

Many studies have identified biomass smoke as a primary risk factor for COPD in rural areas.[41–45] Results from studies in India,[46,47] Saudi Arabia,[41] Turkey,[48–51] Mexico,[52] Nepal,[53] and Pakistan[54] have shown that women using biomass fuel for cooking have increased prevalence of respiratory symptoms attributable to COPD and substantially greater decline in lung function than women who do not use these fuels. In a meta-analysis of 36 studies, Po and co-workers[55] showed that exposure to biomass smoke was significantly associated with COPD (odds ratio 2·3, 95% CI 1·5–3·5), acute respiratory-tract infection (3·64, 2·1–6·4), and wheeze (2·1, 1·5–2·9).

Ekici and colleagues'[56] case-control study of 596 never-smoking women in Turkey reported the prevalence of COPD due to biomass smoke to be 23% (95% CI 13–33) after adjustment for possible confounding factors. For these women, probability of COPD was twice as high if they cooked with biomass fuel than with liquefied petroleum gas (28·5% *vs* 13·6%), which is similar to results from China.[57] Findings from another Turkish study reported that the odds of COPD were increased by 6·6 times (95% CI 2·2–20·2) for women exposed to biomass smoke for at least 30 years, and 4·5 times (1·7–14·9) for women exposed to environmental tobacco smoke.[58]

Sood and colleagues,[40] studied the association between exposure to wood smoke and the prevalence of COPD (defined as postbronchodilator $FEV_1/FVC$ <0·70) in 2012 adults living in New Mexico, USA. They reported that exposure to wood smoke was associated with a 70% (95% CI 30–220) increased risk of having COPD in both men and women, and that this association remained even after adjustment for age, tobacco smoking, and educational attainment. Therefore, even developed countries such as the USA could have a substantial burden of COPD due to exposure to biomass smoke.

| | Study centre | Participants | Age (years) | Method of diagnosis | Prevalence of COPD | | Proportion of patients with COPD who never smoked | | | Risk factors identified |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Overall | Never-smokers | Overall | Men | Women | |
| Behrendt (2005)[12] | USA (nationwide; NHANES III) | 13 995 | 18–80 | Prebronchodilator spirometry ($FEV_1$/FVC <0·70) | 6·6% | .. | 24·9% | .. | .. | Age, asthma |
| Shahab et al (2006)[15] | England (nationwide) | 8215 | ≥35 | Prebronchodilator spirometry ($FEV_1$/FVC <0·70) | 13·3% | 8·2% | 29·5% | .. | .. | Not studied |
| Hardie et al (2005)[16] | Bergen, Norway | 1649 | ≥70 | Respiratory symptoms questionnaire | 4·0% | .. | 30·8% | 26·0% | 39·3% | Not studied |
| Lamprecht et al (2008)[17] | Salzburg, Austria | 1258 | ≥40 | Postbronchodilator spirometry ($FEV_1$/FVC <0·70) | 26·1% | .. | 36·9% | 30·2% | 44·6% | Age, male sex, occupational exposure to organic dust |
| Lindström et al (2001)[18] | Norrbotten, Sweden; Lapland, Finland | 13 737 | 45–69 | Symptoms; respiratory symptoms questionnaire; self-reported physician | 3·8% (Sweden); 3·2% (Finland) | .. | 34·0% (Sweden); 35·4% (Finland) | 30·8% (Sweden); 26·6% (Finland) | 36·6% (Sweden); 45·0% (Finland) | Age, family history, indoor air pollution from biomass fuel, manual work |
| Viegi et al (2000)[19] | Po Delta, Italy | 1727 | >25 | Spirometry: ERS (prebronchodilator $FEV_1$/FVC <0·88 for men and <0·89 for women), BOLD (postbronchodilator $FEV_1$/FVC <0·70), ATS (prebronchodilator $FEV_1$/FVC <0·75); clinical examination | 11·0% (ERS); 18·3% (BOLD); 40·4% (ATS) | .. | 33·0% (ATS); 29·5% (ERS); 25·5% (clinical) | 13·8% (ATS); 13·2% (ERS); 10·6% (clinical) | 56·0% (ATS); 46·2% (ERS); 55·9% (clinical) | Family history (men only), childhood respiratory infections, low socioeconomic status (men only) |
| de Marco et al (2004)[20] | Multinational (16 countries*; ECRHS) | 20 245 | 20–44 | Prebronchodilator spirometry ($FEV_1$/FVC <0·70) | 2·5% (GOLD stage I); 1·1% (GOLD stage II/III) | .. | 29·1% | .. | .. | Respiratory infection in childhood, low socioeconomic class |
| Shirtcliffe et al (2007)[21] | Wellington, New Zealand | 749 | ≥40 | Respiratory symptoms questionnaire; postbronchodilator spirometry ($FEV_1$/FVC <0·70) | .. | .. | 38·8% | .. | .. | Not studied |
| Liu et al (2007)[22] | Guangdong province, China | 3286 | ≥40 | Postbronchodilator spirometry ($FEV_1$/FVC <0·70); physician; respiratory symptoms questionnaire | 9·4%; 12% (rural), 7·4% (urban) | 7· 2% (rural women), 2·5% (urban women) | 36·7% | .. | .. | Age, rural residence, cough during childhood, low body-mass index, use of biomass fuel for cooking |
| Zhou et al (2009)[23] | China (nationwide; CESCOPD) | 20 245 | ≥40 | Postbronchodilator spirometry ($FEV_1$/FVC <0·70) | 5·2% | .. | 38·6% | 18·2% | 76·0% | Male sex, age, low educational attainment, low body-mass index, family history of respiratory disease, exposure to biomass for cooking, exposure to coal for heating, poor ventilation in kitchen, chronic cough in childhood |
| Ehrlich et al (2004)[24] | South Africa (nationwide) | 13 826 | >18 | Respiratory symptoms questionnaire | 2·6%; 2·3% (men), 2·8% (women) | .. | 47·6% | 24·8% | 61·0% | Domestic fuel, occupational exposure, history of pulmonary tuberculosis, female sex |
| Brashier B, Chest Research Foundation, Pune, personal communi-cation | Pune, India (slum in city) | 12 055 | >45 | Respiratory symptoms questionnaire | 6·7% | .. | 68·6% | .. | .. | Old age, exposure to smoke from biomass fuel |

(Continues on next page)

| | Study centre | Participants | Age (years) | Method of diagnosis | Prevalence of COPD | | Proportion of patients with COPD who never smoked | | | Risk factors identified |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Overall | Never-smokers | Overall | Men | Women | |
| (Continued from previous page) | | | | | | | | | | |
| Menezes et al (2005)[25] | Brazil, Chile, Mexico, Uruguay, Venezuela (PLATINO) | 5571 | ≥40 | Postbronchodilator spirometry ($FEV_1$/FVC <0·70) | 15·8% (Brazil), 16·9% (Chile), 7·8% (Mexico), 19·7% (Uruguay), 12·1% (Venezuela) | .. | 25·0% (Brazil), 31·8% (Chile), 23·2% (Mexico), 25·0% (Uruguay), 17·0% (Venezuela) | .. | .. | Male sex, age, low educational attainment |
| Caballero et al (2008)[26] | Colombia (five cities;† PREPOCOL) | 5536 | 40 | Postbronchodilator spirometry ($FEV_1$/FVC <0·70); physician; respiratory symptoms questionnaire | 8·9% (spirometry), 3·3% (physician), 2·7% (questionnaire) | .. | 30·1% (spirometry), 38·3% (physician), 30·9% (questionnaire) | .. | .. | Age, male sex, history of tuberculosis, wood smoke exposure (≥10 years), low educational attainment |
| Tan et al (2003)[27] | Asia-Pacific (12 countries‡) | .. | ≥30 | Validated estimation model for prevalence of COPD | 6·3%; range from 3·5% (Hong Kong and Singapore) to 6·7% Vietnam | .. | 39·7% (Thailand), 34·6% (Hong Kong), 34·4% (Singapore), 29·0% (Indonesia), 25·0% (Philippines), 23·0% (China), 22·0% (Australia), 21·0% (Malaysia), and Vietnam, 18·0% (Taiwan), 15·5% (Korea) 14·7% (Japan) | .. | .. | Old age, exposure to biomass fuel, female sex |
| Gunen et al (2008)[28] | Malatya, Turkey | 1160 | >18 | Respiratory symptoms questionnaire; postbronchodilator spirometry ($FEV_1$/FVC <0·70) | .. | .. | 27·5% | .. | .. | Exposure to biomass fuel |
| Kim et al (2005)[29] | Korea (nationwide) | 9243 | >18 | Postbronchodilator spirometry ($FEV_1$/FVC <0·70) | 7·8% | .. | 33·0% | 12·0% | 86·0% | Low socioeconomic status |
| Lindberg et al (2005)[30] | Norrbotten, Sweden | 666 | 20-69 | Spirometry: BTS (prebronchodilator $FEV_1$/FVC <0·70, $FEV_1$ <0·80), ERS (prebronchodilator $FEV_1$/FVC <0·88 for men and <0·89 for women), GOLD (postbronchodilator $FEV_1$/FVC <0·70), ATS (prebronchodilator $FEV_1$/FVC <0·75) | 7·6% (BTS), 14·0% (ERS), 14·1% (GOLD), 12·2% (ATS) | .. | 22·0% (BTS), 22·0% (ERS), 20·0% (GOLD), 33·0% (ATS) | .. | .. | Age, family history of obstructive lung disease |
| Fukuchi et al (2004)[31] | Japan | 2343 | ≥40 | Prebronchodilator spirometry ($FEV_1$/FVC <0·70) | 10·9% | .. | 25·0% | .. | .. | Old age, male sex |
| Cerveri et al (2001)[32] | Multinational (16 countries*; ECRHS) | 17 966 | 20-44 | British Medical Research Council respiratory questionnaire; prebroncho-dilator spirometry ($FEV_1$/FVC <0·70) | 3·3% | .. | 17·0% | 13·4% | 21·6% | Poor socioeconomic status, occupational exposure to vapours, gas, dust, or fumes |
| von Hertzen et al (2000)[33] | Finland (nationwide) | 7217 | ≥30 | Respiratory symptoms questionnaire; clinical examination; prebroncho-dilator spirometry ($FEV_1$/FVC <0·70) | 14·1% | .. | 20·2% | 8·8% | 50·9% | Not studied |

All studies were done in both men and women. $FEV_1$/FVC=ratio of forced expiratory volume in 1 s to forced vital capacity. ..=data not available or not studied. ERS=European Respiratory Society guidelines. BOLD=Burden of Obstructive Lung Disease criteria. ATS=American Thoracic Society guidelines. GOLD=Global initiative for chronic Obstructive Lung Disease guidelines. BTS=British Thoracic Society guidelines. *Australia, Belgium, Denmark, France, Germany, Iceland, Ireland, Italy, Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, UK, and USA. †Barranquilla, Bogota, Bucaramanga, Cali, and Medellin. ‡Australia, China, Hong Kong, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, Vietnam.

***Table:*** **Studies of chronic obstructive pulmonary disease (COPD) prevalence in never-smokers**

### Composition of smoke from biomass fuel smoke

Biomass is a biological substance derived from a plant or animal source (panel). The combustion efficiency of these fuels is very low, leading to high indoor concentrations of substances that are harmful to health. Domestic fuels can be viewed in an energy ladder, with increasing efficiency and cost, and decreasing pollution further up the ladder. Dried animal dung and scavenged twigs and grass, which are cheap, inefficient, and most polluting, are at the bottom of the ladder. Crop residues, wood, and charcoal are intermediate biomass fuel, and kerosene, coal, and bottled or piped gas are the most efficient combustible energy sources. Electricity is at the top of the energy ladder.[59] The smoke emitted from burning of biomass contains a large number of pollutants: particulate matter of less than 10 μm in aerodynamic diameter ($PM_{10}$), carbon monoxide, nitrogen dioxide, sulphur dioxide, formaldehyde, and polycyclic organic matter, including carcinogens (eg, benzpyrene).[60]

Dependent on the type of fuel, ventilation, and duration of combustion, burning of biomass fuel generates a mean concentration of 300–3000 μg/m³ $PM_{10}$ in 24 h, and concentrations of 30 000 μg/m³ can be reached during cooking periods.[39] WHO safety standards specify that ambient $PM_{10}$ concentration is 150 μg/m³ in 24 h. Some of the most polluted urban cities in the world have ambient $PM_{10}$ concentrations of less than 300–500 μg/m³. The US Environmental Protection Agency (EPA) issues a public alert at $PM_{10}$ concentrations of 350 μg/m³ and declares a public emergency at 500 μg/m³. In homes using biomass fuel, concentrations of carbon monoxide can be 2–50 parts per million (ppm) in 24 h, and 10–500 ppm during cooking.[61] By comparison, EPA safety standards specify that carbon monoxide concentration should be no more than 10 ppm in 8 h.

### Risk of COPD for babies and children

In developing countries, women are traditionally responsible for cooking, so the exposure is highest for them and their young children (figure 3), especially since infants are often carried on the mother's back. Typically, exposure to high concentrations of air pollutants lasts for 3–7 h per day for many years. Results from a Guatemalan study showed that babies born to mothers exposed to biomass smoke from open fires have birthweights 60–70 g lower than do those exposed to pollutants from chimney stoves, electricity, or gas.[61] By comparison, babies born to mothers exposed to environmental tobacco smoke have birthweight 30–40 g lower than the population mean.[61] Low birthweight is an independent risk factor for COPD that is associated with poor lung growth and lung function during childhood and adulthood.[62]

Indoor air pollution from burning wood, animal dung, and other biofuels is a major factor in acute lower-respiratory-tract infections, which are the most important cause of death for children in developing countries.[63] Such infections account for 20% of the estimated 12 million deaths in children younger than 5 years that occur every year, and about 10% of perinatal deaths.[64] Nearly all these deaths occur in developing countries, with the heaviest burdens in Asia (42%) and Africa (28%).[63] Children who survive these infections are likely to have unhealthy lungs that might predispose them to COPD in later life. Poor socioeconomic status and poor nutrition might also contribute to the risk of COPD.

***Panel:* Non-smoking risk factors associated with chronic obstructive pulmonary disease**

Indoor air pollution
- Smoke from biomass fuel: plant residues (wood, charcoal, crops, twigs, dried grass) animal residues (dung)
- Smoke from coal

Occupational exposures
- Crop farming: grain dust, organic dust, inorganic dust
- Animal farming: organic dust, ammonia, hydrogen sulphide
- Dust exposures: coal mining, hard-rock mining, tunnelling, concrete manufacturing, construction, brick manufacturing, gold mining, iron and steel founding
- Chemical exposures: plastic, textile, rubber industries, leather manufacturing, manufacturing of food products
- Pollutant exposure: transportation and trucking, automotive repair

Treated pulmonary tuberculosis

Lower-respiratory-tract infections during childhood

Chronic asthma

Outdoor air pollution
- Particulate matter (<10 μm or <2·5 μm diameter)
- Nitrogen dioxide
- Carbon monoxide

Poor socioeconomic status

Low educational attainment

Poor nutrition

## Occupational exposures

Findings from early studies reported that exposure to toxic gases in the workplace,[65] grain dust in farms,[66] and dust and fumes in factories[67] was strongly associated with COPD. In 2003, results of a systematic epidemiological review into occupational factors associated with COPD by the American Thoracic Society showed that about 15% of COPD cases might be attributable to workplace exposure;[68] and a subsequent follow-up provided similar estimates.[69]

In a study of 1258 adults older than 40 years, Lamprecht and colleagues[70] reported that the risk of COPD (defined as postbronchodilator $FEV_1/FVC$ <0·70) attributable to farming was 7·7%, and about 30% of farmers had at least mild COPD. According to results from a Norwegian study, livestock farmers have a 40% (95% CI 10–70) higher risk of COPD than do crop farmers, which is strongly correlated with concentrations of ammonia,

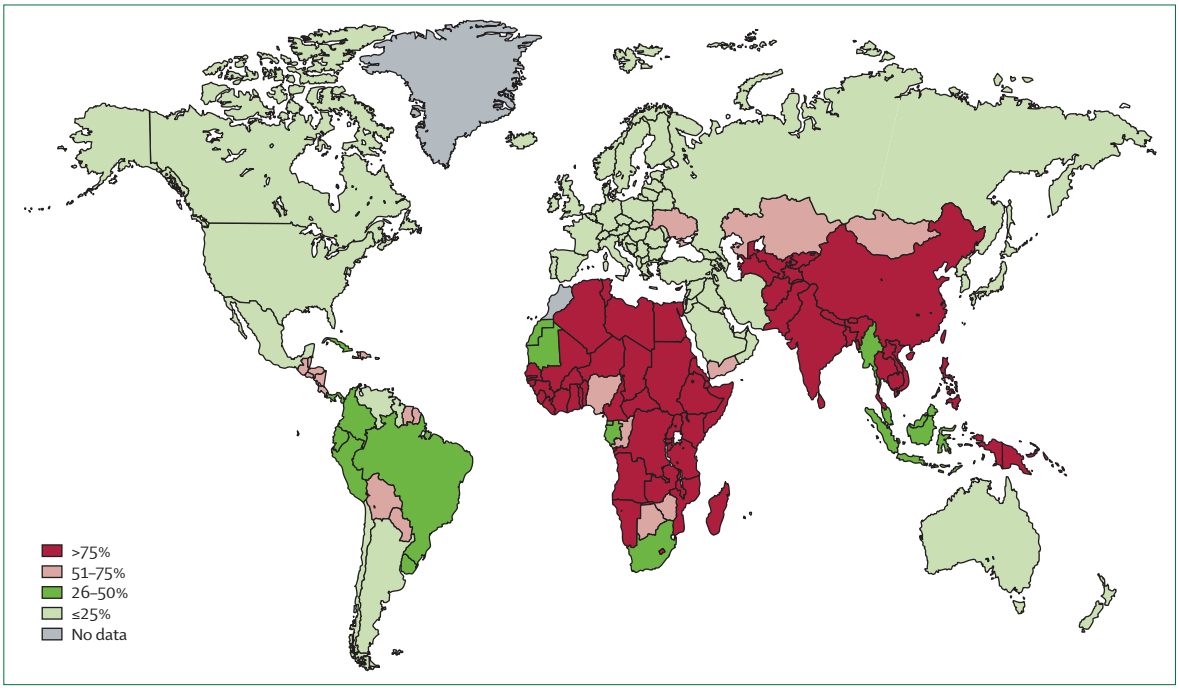


***Figure 2:*** **Proportion of households using biomass fuel for cooking worldwide**
Data sourced from WHO[35] (data from 2000 or latest available data).

hydrogen sulphide, and inorganic and organic dusts.[71] Furthermore, farmers rearing more than one type of livestock (eg, sheep, goats, and poultry) had a significantly greater risk of having COPD than did those rearing one type only. The association of COPD with farming has been predominantly recorded in atopic farmers (from positive skin prick tests to common aero-allergens), suggesting that atopic farmers might have increased susceptibility to COPD.

Results from longitudinal studies have associated COPD with occupational exposures in coal miners, hard-rock miners, tunnel workers, and concrete manufacturers. In heavily exposed workers, the effect of dust exposure might be greater than that of smoking.[72] Construction workers exposed to fumes and mineral dust have a significantly higher risk of death due to COPD than do unexposed construction workers.[73] Persistent exposure to silica in construction, brick manufacturing, gold mining, and iron and steel foundries is strongly associated with COPD; average respirable dust concentration is 10 000 μg/m$^3$.[74]

In NHANES III,[12] Behrendt identified several occupations that were associated with high prevalence of COPD: plastic, textile, rubber, and leather manufacture; transportation and trucking; manufacture of food products; automotive repair; and some personal services (eg, beauty care).[75] The proportion of patients with COPD attributable to occupation was about 19% overall and 31% in never-smokers. Increased prevalence of COPD has also been reported in occupations associated with chronic exposure to diesel exhaust (eg, garages and mines) and other irritant gases and vapours.[76]

The population-attributable fraction for COPD associated with occupational exposure varies between 9% and 31%.[77] But the true population-attributable risk due to occupational exposures remains unclear, especially in developing countries, largely because the epidemiological definition of COPD has not been standardised and few studies have been done. Longitudinal epidemiological studies that use a standard epidemiological definition of COPD, well refined endpoints, and sophisticated designs need to be complemented by experimental studies to provide mechanistic explanations for findings from epidemiological studies.

## Pulmonary tuberculosis

Pulmonary tuberculosis is associated with chronic airflow obstruction, especially the COPD phenotype, at diagnosis,[78,79] during treatment,[80] and several years after treatment has ended.[81] Such infection is associated with airway fibrosis, and the immune response to mycobacteria can result in airway inflammation, which is characteristic of COPD. The degree of airflow obstruction is correlated with the extent of disease assessed by radiography, sputum production, and length of time after diagnosis or treatment completion.[82] Prevalence of airflow obstruction varies from 28%[81] to 68%[82] of patients with pulmonary tuberculosis. In a study of fully treated patients attending for routine follow-up, the proportion with airflow obstruction was 48%;[83] the proportion increased with duration since treatment completion, but age was not a confounding factor.

In a nationwide survey of 13 826 adults in South Africa, results suggested that the strongest predictor of COPD was history of pulmonary tuberculosis: odds ratio 4·9 (95% CI 2·6–9·2) for men and 6·6 (3·7–11·9) for women.[24] Furthermore, the risk of COPD was more strongly associated with tuberculosis than with tobacco smoking or exposure to smoke from biomass fuel. The study was limited by use of self-reported symptoms of a chronic productive cough to define COPD, but the findings suggest that pulmonary tuberculosis is an important risk factor. A subsequent study from five cities in Colombia,[26] which defined COPD by postbronchodilator spirometry ($FEV_1$/FVC <0·70), reinforced the strong association of COPD with history of pulmonary tuberculosis (2·9, 1·6–5·5), and the weaker association with tobacco smoking (2·6, 1·9–3·5).

In a large population-based study (sample size 5571) in five Latin American cities, the prevalence of COPD (defined by postbronchodilator $FEV_1$/FVC <0·70) was 30·7% for patients with a history of pulmonary tuberculosis compared with 13·9% for those without.[25] History of pulmonary tuberculosis increased the risk of COPD by 4·1 times for men and 1·7 times for women, after adjustment for age, sex, education, ethnic origin, smoking status, exposure to dust and smoke, and respiratory morbidity in childhood.

More than 2 billion people are infected with *Mycobacterium tuberculosis* and about 9·2 million new cases of tuberculosis are detected every year. 80% of the people infected live in only 22 countries,[84] with an especially high burden in Asian, African, and Latin American countries. Therefore, the cumulative burden of COPD associated with pulmonary tuberculosis is likely to be much greater than previously believed, especially in developing countries. Whether this phenotype of COPD behaves similarly to COPD from smoking, and what the appropriate pharmacotherapy should be are as yet unknown.

## Chronic asthma

In 1961, Orie and colleagues[85] postulated that asthma and COPD share a common background, and differentiation into each disease can be modulated by environmental and host factors. Although this hypothesis is unresolved,[86] chronic airway inflammation and airflow obstruction in individuals with asthma and increased airway hyperresponsiveness might cause lung remodelling from thickening and fibrosis of the airway walls.[87] This remodelling could result in irreversible and progressive airflow obstruction and development of COPD. Poorly treated chronic persistent asthma or severe asthma can cause changes in the lungs that are similar to those resulting from smoking.[88] In patients with severe asthma, the pattern of airway inflammation is similar to that in COPD, with increased neutrophils, interleukin 8, proteases, and oxidative stress, and reduced responsiveness to corticosteroids.[86] These similar features might indicate common mechanisms between COPD and asthma that are related to the intrinsic determinants of disease severity.

Chest Research Foundation, Pune, India

*Figure 3:* **Use of biomass fuel for cooking in an Indian village**

In a 5-year longitudinal study with 10 952 participants, Ulrik and Lange[89] showed that patients with a new asthma diagnosis had lower initial values of lung function and greater rate of $FEV_1$ decline than did those without asthma. 15-year follow-up of these patients showed that those with self-reported asthma still had an increased rate of $FEV_1$ decline,[90] indicating that asthma might be associated with reduced baseline $FEV_1$ and increased rate of decline in pulmonary function, which are characteristic of COPD. However, many patients with asthma retain normal or near normal lung function throughout life, and only a subset of patients seem to show the pattern of progressive decline in lung function.

According to findings from a US-based study that followed-up 3099 patients for 20 years, those with active asthma were 10 times more likely to develop symptoms of chronic bronchitis and 17 times more likely to be diagnosed with emphysema than those without asthma, even after adjustment for confounding factors.[88] Asthma was the strongest risk factor for subsequent COPD, more than even tobacco smoking (hazard ratio 12·5 *vs* 2·9, attributable risk 18·5% *vs* 6·7%). Primary care clinicians have reported patients with acute bronchitis that changes into chronic asthma and later into severe COPD.[91]

In a retrospective analysis of more than 300 patients with obstructive airways diseases from a rural population in India, findings showed that more than 75% of patients with poorly treated asthma who had received oral bronchodilator drugs alone for a long period had symptoms characteristic of COPD.[92] Therefore, poor treatment of chronic and severe asthma worldwide, especially in developing countries, might substantially contribute to the burden of COPD. Control of asthma with corticosteroid treatment might prevent irreversible airflow obstruction.[93]

## Outdoor air pollution

The contribution of outdoor air pollution to COPD was investigated in 1958 in UK postmen—the prevalence of COPD was higher in those working in more polluted areas than in those working in areas with less pollution, and the association was independent of smoking.[8] Results of a later study showed reduced lung function in postmen who worked in more polluted cities than in those who worked in less polluted areas.[94] These findings have been reinforced by studies in the general population in the UK[95] and USA,[96] and in people living close to roads with heavy motor vehicular traffic.[97,98] Over the past two decades, air pollution in most cities has decreased substantially in developed countries, but increased in developing countries (eg, in Asia, South America, and Africa), largely because of growing industry and traffic congestion. Raised concentrations of both gaseous and particulate matter components of urban ambient air are associated with increasing respiratory morbidity and cardiovascular mortality, and possibly COPD.[99] The association between high concentrations of outdoor air pollutants and COPD exacerbations and worsening of pre-existing COPD is supported by strong evidence,[100] but the evidence to support an association with new cases of COPD is not yet available; large, multinational, prospective epidemiological studies are needed to address this important issue.

## Socioeconomic status

Poor socioeconomic status is a risk factor independently associated with COPD, and is likely to be indicative of other factors such as intrauterine growth retardation, poor nutrition (low intake of antioxidants) and housing conditions, childhood respiratory-tract infections, and exposure to tobacco smoke, biomass smoke and other indoor air pollutants, and occupational risks. These factors might collectively contribute to the risk of COPD. Socioeconomic status has been shown to have a significant correlation with lung function, even after adjustment for smoking status, occupational exposures, and ethnic origin.[101] The magnitude of the effect of socioeconomic status, though variable, is about 300 mL $FEV_1$ in men and more than 200 mL $FEV_1$ in women. Therefore, socioeconomic status should be treated as an important risk factor for COPD.[102]

## Population-attributable risk factors

Non-smoking causes of COPD were conventionally estimated to contribute to a small proportion—10–15%—of cases in developed countries, but results of later studies suggest that the true contribution is much higher. Findings from the Swedish OLIN[103] and US NHANES III[104] studies reported that the population-attributable risk of COPD from smoking was 45% and 44%, respectively, indicating that more than half of COPD cases were due to non-smoking causes. In the BOLD study[105] of the prevalence of COPD in 12 countries (Australia, Austria, Canada, China, Germany, Iceland, Norway, Philippines, Poland, South Africa, Turkey, USA), Buist and colleagues reported a very high prevalence of COPD in never-smokers.

Up to half of COPD cases are due to non-smoking causes; most important risk factors are exposure to biomass smoke, occupational exposures to dust and fumes, history of pulmonary tuberculosis, history of chronic asthma, outdoor air pollution, and poor socioeconomic status. The relative burden of each of these risk factors will vary between countries, with history of chronic asthma less important than other factors in developing countries. Community-based studies of population-attributable non-smoking risk factors have been done in developed countries, but the relative risk associated with such factors in developing countries has yet to be established.

## Does COPD in never-smokers have a different phenotype?

Very few studies have investigated the non-smoking phenotype of COPD or made comparisons with the smoking phenotype. Ramírez-Venegas and colleagues[106] reported that Mexican women who had COPD and had been exposed to smoke from biomass fuel, had similar clinical characteristics, quality of life, and mortality to those with COPD due to tobacco smoking. However, Shavelle and co-workers[107] showed that in US patients with COPD the reduction in life expectancy was less for those who had never smoked than for those with COPD due to smoking. By comparison, Moran-Mendoza and collagues[108] reported that women with COPD due to exposure to biomass smoke had more lung fibrosis, greater pigment deposition, and thicker pulmonary artery intimas than did those with COPD due to tobacco smoking, who had greater emphysema and epithelial damage. Clearly further research is needed to elucidate phenotypes of COPD.

## Future directions

Little research has been done into the interaction of risk factors for COPD. The burden of COPD is increasing, especially in developing countries, because of increased cigarette smoking and passive smoke exposure, and also exposure to non-smoking risk factors. Several questions need to be addressed. What is the true burden of non-smoking COPD in different countries? Does non-smoking COPD have the same prognosis, the same radiographic and physiological features, and manifest with the same comorbidities as COPD induced by smoking? What is the airway cellular and mediator profile of COPD in never-smokers, and is it different from that in COPD induced by smoking? Should patients with non-smoking COPD receive the same treatment as those with COPD induced by smoking? Almost all large trials of pharmacotherapy for COPD have excluded patients who have no history of tobacco smoking. We need to use the answers to these questions to adapt health policy measures and reduce the burden of non-smoking COPD.

**Contributors**

The initial draft of the report was written by SSS and modified by PJB.

**Conflicts of interest**

PJB has received research funding and been a member of scientific advisory boards for AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Novartis, Pfizer, Teva, and Union Chimique Belge, some of which are marketing and developing treatments for COPD. SSS declares that he has no conflicts of interest.

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