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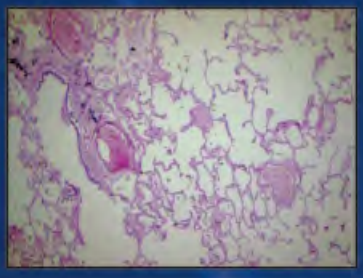

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Global Epidemiology of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is leading cause of morbidity and mortality all over the world. It poses a huge burden from healthcare costs on patients as well as on the healthcare infrastructure. Tobacco smoking remains the most important cause of COPD. The heavier the smoking, the more are the chances of COPD development. Among nonsmokers, indoor air pollution from smoke of biomass fuels and exposures to environmental tobacco smoke are the important risk factors. Chronic asthma and chronic bronchitis are also considered as risk factors for airway obstruction. COPD is progressive in course and leads to both respiratory and systemic disability. Prevention and management of COPD constitute a globally important healthcare agenda in the current century.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE DEFINITION

Chronic obstructive pulmonary disease (COPD) is recognized as an important cause of global burden from noncommunicable diseases (NCDs) and, therefore, included in the prioritized agenda for action for control of the NCD burden.[1] COPD is projected as a leading cause of death from disability and healthcare costs.[1,2] Furthermore, the magnitude of burden is almost similar in the developed and the developing countries of the world.[1-3] COPD characterized by "airflow limitation, which is not fully reversible", is now recognized "as a preventable and treatable disease with some significant extrapulmonary effect that may contribute to the severity in individual patients".[4] The disease definition, however, recognizes that the pulmonary component of airflow limitation is usually progressive.[4] Essentially speaking, COPD

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diagnosis, therefore, is based on the demonstration of airflow obstruction, though it covers a spectrum from that of chronic bronchitis characterized by bronchial wall inflammation and thickening to that of bullous emphysema, characterized by extensive alveolar wall destruction and bullae formation.

In a broader sense, patients with chronic cough and mucous hypersecretion, frequently labeled as chronic bronchitis, are also included under the umbrella of COPD. The earlier literature on the subject is repleted with the discussion on the differences between chronic bronchitis and emphysema.[5,6] It was indeed suggested in the past that "the term COPD had probably lost its usefulness," since the clinicians could only diagnose the condition as chronic bronchitis and emphysema.[5,6] Both chronic bronchitis and emphysema almost always coexist to a greater or a lesser degree. Therefore, the term COPD has found wider universal acceptance. It, however, remains enigmatic whether the patients with chronic bronchitis progress on to develop airflow obstruction and emphysema.

EPIDEMIOLOGICAL DIAGNOSIS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

It has been difficult to diagnose COPD in the epidemiological studies primarily, because of the lack of a uniformly accepted definition. Although most investigators agree with the need of demonstration of airway obstruction as an essential component of diagnosis, there exist marked variations attributable to the survey methods and statistical analyses.[4,7,8] Traditionally, the use of a standardized questionnaire has been the most commonly employed method to detect COPD (more precisely chronic bronchitis) in the population studies. A properly validated questionnaire provides a fair estimate of the disease prevalence. A questionnaire is an economical and easy method for field use. It has a few limitations when compared to the methodology using spirometry (with or without a bronchodilator) to document airflow obstruction. But spirometry on a large scale in the field studies is costly as well as difficult in technology and standardization.

Self-reporting of a doctor-diagnosed COPD or an equivalent condition has been also used for COPD surveys, but the method is known to provide the lowest estimates.[8] Self reported COPD can hardly be considered as relevant in most of the developing countries, such as in India, with overlap of terminology for COPD and asthma in local languages. Of the few studies, which are available on prevalence of COPD in India, none has employed the doctor-diagnosed COPD as the survey tool.[9]

GLOBAL CHRONIC OBSTRUCTIVE PULMONARY DISEASE PREVALENCE

There are a large number of studies available on the prevalence of COPD.[10-18] There exist marked variations in the prevalence estimates (Table 1). The pooled

Table 1: Prevalence Estimates of Chronic Obstructive Pulmonary Disease Reported from Different Countries

Years	Countries	Authors	Prevalence incidence	Comments
2003	Asia-Pacific region (12 countries)	Tan et al.[11]	6.3%	Estimation model based on the local prevalence of risk factors for COPD
	Australia		4.7%	
	China		6.5%	
	Japan		6.1%	
	Hong Kong		3.5%	
	Singapore		3.5%	
2011	China	Fang et al.[12]	5–13%	Review of prevalence studies
2008	Latin America—Sao Paulo, Brazil, Mexico City, Mexico, Montevideo, Uruguay, Santiago, Chile, Caracas, and Venezuela	Menezes et al.[13]	14.3% (GOLD stage II–IV 5.6%)	Post-bronchodilatory spirometry
2012	India			
	Different centers over different time periods	Jindal et al.[9]	M = 1.9–9.4% F = 1.2–4.9%	Review of 11 population studies
	INSEARCH (CB)	Jindal et al.[21]	3.5% M = 4.3% F = 2.7%	Multicentric questionnaire-based study at 12 centers
2006	Global estimates (28 different countries) • COPD • CB alone • Emphysema	Halbert et al.[8]	 7.6% 6.4% 1.8%	Systematic review and meta-analysis • 37 studies • 38 studies • 8 studies
2001	Industrialized countries	Anto et al.[15]	5–15%	Lung function impairment
	USA • White population		M = 4–6% F = 1–3%	FEV_1 <60 or 65% of predicted
	• Black population		M = 3.7% F = 6.7%	
	UK		M = 10% F = 11%	FEV_1 of 2 or more SD below predicted value
	Denmark, Norway, and Spain		3.7%, 4.5%, and 4.8%, respectively	CB
2007	European Union: young adults (12 countries) • COPD incidence • CB incidence rate ratio	deMarco et al.[23]	2.8 cases/1000/year 1.85	Longitudinal cohort study of 5,002 subjects (aged 20–44 years) from 1999 to 2002

COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease; FEV_1, forced expiratory volume in 1 second; CB, chronic bronchitis.

prevalence was reported as 7.6% in an elegant systematic review and meta-analysis of 37 studies from 28 different countries.[8] The burden of obstructive lung disease (BOLD) initiative provided pooled estimates of prevalence of global initiative for chronic obstructive lung disease (GOLD) stage II or higher COPD as 10.1% overall (11.8% for men and 8.5% for women).[10] COPD in 12 Asia-Pacific countries and regions is reported to vary from 3.5% in Hong Kong and Singapore to 6.7% in Vietnam with the combined prevalence of 6.3%.[11] In China, the prevalence is reported to vary between 5 and 13% in different provinces/cities.[12]

The PLATINO study on burden of COPD in Latin America that employed post-bronchodilator spirometry for diagnosis reported the prevalence estimate of 14.3% of airway obstruction; the proportion of subjects in states II–IV of the GOLD classification was 5.6%.[13] There are many other reports from different countries and/or regions, which report variable estimates of prevalence.[14-18]

Epidemiology of COPD in India has drawn interest of investigators for about half a century.[19] Most investigators have generally employed the questionnaire diagnosis of chronic bronchitis.[9] Nationwide estimates of chronic bronchitis are now available from 16 different centers though the results of the Indian study on epidemiology of asthma, respiratory symptoms, and chronic bronchitis (INSEARCH).[20,21] The pooled prevalence of chronic bronchitis in the INSEARCH study is reported as 3.5% overall (4.3% in men and 2.7% in women) amongst adults of over 35 years of age.[20,21]

Causes of Variations in Prevalence

There are several different factors, which can account for the variable estimates of prevalence of COPD in different regions, and sometimes in the same region at different periods of time, or in reports by different investigators (Table 2). The definition of COPD used for a particular report is an important consideration.[4,7] A large number of studies, particularly from the developing countries have employed the symptomatic definition of chronic bronchitis as a surrogate to represent COPD.[20-22] Prevalence of COPD with chronic bronchitis definition was 6.4%, while it was 8.9% with spirometric estimates in 101 prevalence estimates from 28 different countries.[8] Most investigators, however, rely on spirometry as an important criteria as per GOLD definition of COPD. The prevalence of airway obstruction is further dependent on the spirometry criteria recommended in the GOLD, American Thoracic Society (ATS), or the European Respiratory Society guidelines. It is the post-bronchodilator spirometry that is employed to define the airway obstruction.

Methodological difference also accounts for differences in variation of prevalence estimates. As stated earlier, the estimates are lowest when based on self reporting of a doctor-diagnosed COPD. The doctor-diagnosed COPD is more likely to reflect

Table 2: Reasons of Variations in Prevalence Estimates of Chronic Obstructive Pulmonary Disease

Methodological

- Definition of COPD employed for prevalence estimates
- Survey method
  - Questionnaire
  - Objective measurement: type of tests, technical variations, standardization, etc.
  - Doctor-diagnosed COPD
- Type of sample: sampling method
  - Size of sample
  - Selection of subjects

Population differences

- Demographic variations and differences in prevalence of risk-factors
- Urban–rural divide
- Socioeconomic heterogeneity

COPD, chronic obstructive pulmonary disease.

"clinically significant" disease, while the estimates with the use of spirometry are likely to be higher with inclusion of subjects with asymptomatic airway obstruction.

There are variations in COPD prevalence with demographic variables, e.g., age, sex, place of residence, and socioeconomic conditions. Place of residence (rural vs. urban) and socioeconomic conditions in particular are largely responsible for differences in prevalence between the developed and the developing countries.[10,13,20-22,24,25] Several environmental risk factors are likely to be more prevalent in the developing and underdeveloped countries. The healthcare and economic burden of COPD in the low income countries is higher, but the reported estimates of prevalence remain variable. Age and sex differences account for a large degree of heterogeneity in prevalence estimates of COPD across different cities and populations.[26] The cumulative prevalence increases with an increase in age—it is distinctly uncommon in the younger populations below 40 years of age. Male sex predominance is primarily attributable to a higher smoking prevalence. Women exposed to indoor air pollution from solid-fuel combustion are equally predisposed to develop chronic bronchitis and COPD.

RISK FACTORS

A large number of environmental and sociodemographic factors have been shown as important for development of COPD (Table 3). Of them, inhalational exposures constitute the most important group of causes.

Table 3: Risk Factors for Chronic Obstructive Pulmonary Disease

Demographic

- Age and sex
- Place of residence
- Socioeconomic grouping
- Occupation and income

Environmental exposures

- Tobacco smoking
- Environmental tobacco smoke exposure (passive smoking)
- Exposure to domestic fuel combustion
- Occupational exposures
- Ambient air pollution

Miscellaneous risk factors

- Genetic
- Chronic cough and asthma
- Respiratory infections

Inhalational Exposures

Tobacco smoking

There is an overwhelming evidence of relationship between tobacco smoking and COPD.[10,13,21,22,27] Tobacco smoke contains several thousands of gaseous or particulate irritants and chemicals, which damage the bronchial walls and alveolar septae causing inflammation, fibrosis, and destruction. Most of these reports show a dose-dependent relationship, i.e., the heavier the smoking, the more are the risks of COPD development. Smoking of different forms of tobacco is responsible for COPD. In India, for example, the risks for COPD in "bidi" and "hookah" smokers are even higher than in cigarette smokers.[20] Similarly, the "sheesha smoking" in the Middle East countries, such as Saudi Arabia is shown to be responsible for airway obstruction.[28]

The menace of tobacco-smoking and the burden of COPD along with tuberculosis (TB) and HIV infection have posed threat of epidemic proportions to the global healthcare infrastructure.[29] Tobacco and COPD behave like parallel epidemics—100 million deaths were caused by tobacco in the 20th century and up to 1 billion deaths are estimated from the tobacco use in the 21st century. COPD is rapidly becoming a global public health crisis.[30] COPD burden in India is equally enormous, although it is not yet fully appreciated in health plans.[21,31,32]

Indoor Air Pollution

The use of solid fuels (biomass like dried cattle dung, crop residue, wood stock, and coal) for combustion in the homes for cooking and heating produces a lot of visible and invisible smoke responsible for high levels of indoor pollution. Several of the risks of exposure to biomass fuel combustion are similar to those of tobacco smoking. Chronic bronchitis and COPD are, therefore, commonly seen in the exposed nonsmoker populations, especially the women.[21,33-35] Variation in levels of household air pollution also account for differences in prevalence of COPD in different global regions.[10,13,22] For example, in China, the COPD prevalence in rural women exposed to household pollution was 3 times higher than the urban women.[33] The prevalence is similarly high amongst nonsmoker women from several other developing and low-income countries.[22,33-38]

Passive Smoking

Environmental tobacco smoke or side-stream smoke constitutes an important source of indoor air pollution in homes and offices with smokers. Exposure of nonsmokers to environmental tobacco smoke from smokers (passive or second-hand smoking) is another important risk factor for COPD, mostly in women.[21,39,40] Though small, the risk is more than amongst the nonsmoking, non-environmental tobacco smoke exposed populations. Environmental tobacco smoke exposure from others may also play an additive role to smoking as a risk factor in smokers. Passive smoking in mother during pregnancy has been shown to affect the lung development *in utero* and results in altered lung function in the baby.[41] This has been also speculated as a risk factor for development of chronic lung disease later in adulthood.

Outdoor Air Pollution

Outdoor (or ambient) air pollution commonly results from industrial and vehicular exhausts, forest fires, dust storms, and combustion of crop residue in the open fields. Vehicular emission in cities is shown to relate to lung function impairment.[42] The exact role of ambient pollution in the development of COPD is unclear but has been blamed as one of the risk factors.[43,44] In an earlier cross-sectional population study from Delhi, the prevalence of asthma, chronic bronchitis, and COPD was reported as similar in the 2 pollution zones, but the lung function of asymptomatic nonsmokers was consistently and significantly better among residents of lower-pollution zone.[45]

Occupational Exposures

Continued exposure to organic and inorganic dusts, chemical agents, and fumes among workers engaged in different occupations is an important but relatively

under-recognized cause, which accounts for about 15–20% of COPD overall and over 31% among never-smokers.[46-48] Several occupations which are associated with high COPD prevalence include manufacturing of plastics, textiles, rubber, leather products, food processing, etc. Exposure to organic dusts and toxic gases in farms and factories is similarly associated with COPD.

Occupational exhausts in heavy industry towns are frequently responsible for ambient air pollution, causing chronic respiratory diseases and COPD amongst general population. In India, the respiratory symptoms were distinctly more common in the population of an industrial city than those in the less industrial city.[49] Similarly, the prevalence of COPD defined by GOLD II criteria was seen in 10% in north-east England in a recent study. The respiratory symptoms were present in 55% of general population exposed to occupational air pollution.[50]

Asthma, Chronic Cough, and Chronic Bronchitis

The relationship between chronic cough, chronic asthma, and COPD has been discussed and debated for long times. The BOLD collaborative research group had recently analyzed data from 14 countries that participated in the international population-based BOLD study.[51] Never-smokers comprised 23.3% of those classified with GOLD stage II + COPD. Prior diagnosis of asthma was one of the factors identified with an increased risk of COPD among never-smokers.[51]

Asthma as one of the causes of COPD had been recognized for almost 50 years since when the "Dutch hypothesis" of allergic origin of chronic bronchitis was postulated.[52,53] It is quite likely that the chronic airway inflammation in asthma causes thickening and fibrosis of airways responsible for irreversible airflow obstruction (airway remodeling).[54] Asthma as a risk factor of COPD has been also suggested by the findings of a longitudinal study, which demonstrated lung changes in the poorly treated chronic asthma patients as similar to those seen in COPD.[55] In another study from Switzerland, never-smokers with COPD were more likely to be male and asthmatics.[56] Airway hyper-responsiveness and a family history of asthma were reported as important COPD determinants in a European cohort of young adults.[57] The ATS public policy statement on causal risk factors of COPD includes chronic asthma as "associated with irreversible loss of lung function"; however, it remains uncertain, if there exist important phenotypic differences.[44]

Chronic cough suggesting the diagnosis of chronic bronchitis as a cause of COPD has been similarly debated. Chronic cough/phlegm was found as risk factor independent of the smoking habit for COPD. There was a 3-fold increased risk on follow-up of the European cohort of young adults.[23] Similar observations were reported in the Japanese men.[58] The Japanese study reported the stage 0 disease diagnosed as per GOLD 2001 guidelines (suggesting chronic bronchitis alone)

as "relevant for the identification of subjects at risk of developing COPD".[58] In another European study, the chronic bronchitis phenotype of COPD was associated with worse respiratory symptoms and higher risks of acute exacerbations.[59]

Miscellaneous Risk Factors

Respiratory Infections

Respiratory infections (viral and bacterial), including TB are reported as risk factors for COPD.[4,37] COPD in these conditions is attributed to airway inflammation, hyper-responsiveness, and exacerbations leading on to bronchial wall fibrosis, thickening, and impairment of lung function. TB has been particularly reported from the developing countries like India, South Africa, and Latin America.[4,13,16] The ATS statement lists TB with impaired lung function as an uncertain phenotype compared with COPD.[44]

Genetic Factors

The best evidence for genetic risk factors is available from the familial occurrence of COPD in siblings of smoking parents and in severe hereditary deficiency of α_1-antitrypsin.[60,61] Although a variety of genetic polymorphisms for COPD have been reported, there is no clear association which can be considered as important. Presently, it seems that the interaction of environment-gene factors determines the development of COPD.

Socioeconomic Factors

There is evidence to suggest a higher risk among people of lower socioeconomic groups. This may be possibly attributed to their crowded dwellings, exposures to polluted environments, poor nutrition, and increased occurrence of respiratory infections.[4] Similarly, malnutrition may be associated with development of emphysema. Such a role has not been clearly documented through epidemiological studies.

GLOBAL BURDEN OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD remains a leading cause of morbidity and mortality all over the world. It accounts for almost 5% of all deaths globally, and predicted to become the 3rd leading cause of deaths by the year 2030.[3] Incidentally, COPD is one NCD whose mortality rates are projected to continue to rise in both the developed and the developing countries.[3,62,63] Although the data on mortality from India are poor, it is estimated as the second biggest cause of death from NCDs in India.[3]

COPD is an important cause of loss of function and of progressive disability. COPD is now recognized to be complicated with the presence of several non-pulmonary systemic manifestations.[64,65] It is not only the breathlessness, which

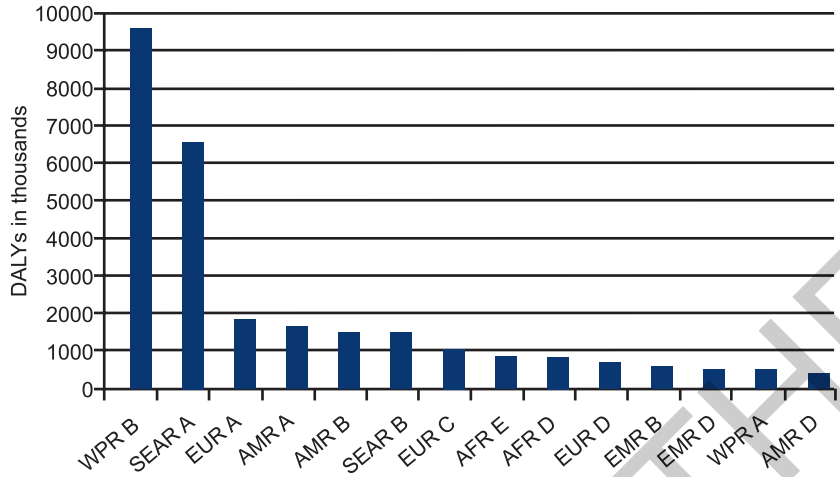
limits the patient's movements but also the associated weakness, muscle fatigue, emaciation, and loss of bony and muscle mass, which restrict the activities of daily living slowly confining the patient to the bed. There is also an increased incidence of cardiovascular events from ischemic coronary vascular disease and cardiac arrhythmias. Systemic manifestations, in particular the cardiovascular diseases, are also responsible for the high COPD mortality. A significant number accounting for almost a third of COPD deaths are attributable to acute cardiovascular episodes. Frequent exacerbations of COPD are also responsible for increased inflammation and systemic manifestations. They add to both the morbidity and mortality of COPD.

The morbidity of COPD, assessed from the presence of symptom burden is even more than that with cancer.[66] Although the symptom-burden is similar, patients with COPD suffer more, because of their longer life span than that of patients with cancers. The COPD burden in terms of morbidity by estimates of loss of disability-adjusted life years (DALYs) was reported as 1.68 years of living with disability per 1,000 population.[67] This represented 1.8% of morbidity burden from all causes. The burden was greater in men (1.93%) than in women (1.42%). DALYs for COPD account for the total period of years lost, because of the premature mortality and years lived with disability adjusted for the severity of disability. COPD is projected to rise to become the 5th leading cause of loss of DALYs worldwide in the year 2020.[68] Globally, the Western-Pacific region (with low child and adult mortality) had the highest magnitude of lost DALYs from COPD (Figure 1).[67]

COPD poses a huge economic burden on patient's family as well as the healthcare infrastructure.[62] The fiscal burden results from direct costs related to disease management and indirect economic losses suffered from loss of wages and other incomes due to disability and premature mortality. In the European Union, the total direct costs of respiratory diseases are about 6% of the total healthcare budget, of which COPD accounts for 56% of respiratory disease costs.[69] In the United States, an earlier United States government health-insurance program reported the annual per capita costs for patients with COPD as 2.5 times the expenditures for people with COPD in individuals of over 65 years of age.[70] In India, the limited data show that a COPD patient spends about one-third of his income on his disease management. The direct costs in 2006 amounted to over 25.2 thousand crores and estimated to rise to 48.3 thousand crore in 2016.[71]

SECULAR TRENDS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

There are limited data on temporal trends in the morbidity and mortality from COPD. Changes in mortality from COPD among adults were studied in the United States in 2 national cohorts, recruited during 1971–1975 and 1988–1994,



AFR, Africa; AMR, America; EMR, Eastern Mediterranean; EUR, Europe; SEAR, South East Asian Region; WPR, Western Pacific Region. A, very low child and adult mortality; B, low child and adult mortality; C, low child mortality and high adult mortality; D, high child and adult mortality; E, high child mortality and very high adult mortality.

Figure 1: Estimated chronic obstructive pulmonary disease disability-adjusted life years by WHO region 2002. *Data from* Lopez AD, Shibuya A, Roa C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J.* 2006;27:397-412, *with permission.*

of National Health and Nutrition Examination Survey (NHANES) I and III, respectively.[72] The COPD mortality in NHANES III had declined by 15.8% for those with moderate or severe disease; the secular decline benefited COPD patients less than those with normal lung function.[73] Longitudinal trends from the developing countries in the Asia-Pacific regions and Latin America, which are now emerging in a limited manner, largely point to the issues of underdiagnosis and healthcare burden from COPD.[73,74]

CONCLUSION

COPD has emerged as an important global threat to the health-care infrastructure, particularly of the developing countries. The world-wide variations in the prevalence are attributable partly to the methodology employed in a particular study, but largely to the differences in the presence of risk factors of tobacco smoking, environmental tobacco smoke exposure, and solid-fuel combustion. Occupational air pollution and chronic airway inflammation of poorly-controlled asthma are also recognized as important risk factors. Fortunately, most of the risk factors of COPD are avoidable, therefore, stressing the importance of public health measures for disease occurrence as well as prevention.

Editor's Comment

There are wide variations in the prevalence of COPD across countries. The global prevalence of physiologically defined chronic obstructive pulmonary disease (GOLD stage 2 or more) in adults aged ≥40 years is approximately 9–10%. This variation in the estimated prevalence is due to the method of diagnosis and classification of COPD. The INSEARCH that included a total of 85,105 men and 84,470 women from 12 urban and 11 rural areas reported the overall prevalence of chronic bronchitis in adults ≥35 years as 3.49% (ranging 1.1% in Mumbai to 10% in Trivandrum). This study also highlights the wide variations in the prevalence of COPD in India, pointing towards the need for indepth study to understand the issues involved in the causation of COPD. Genome-wide association study has identified important loci that are associated with COPD susceptibility. Tobacco smoking is the most important cause of COPD. Exposure to smoke from biomass solid fuel combustion is also related to the development of COPD. This is of particular importance to India and other countries where biomass fuel is commonly used for cooking and heating purposes.

Vannan K Vijayan

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