Origins of chronic obstructive pulmonary disease 2

Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment

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Chronic obstructive pulmonary disease (COPD) was traditionally thought to be caused by tobacco smoking. However, recognition of the importance of non-smoking-related risk factors for COPD has increased over the past decade, with evidence on the burden, risk factors, and clinical presentations of COPD in never-smokers. About half of all COPD cases worldwide are due to non-tobacco-related risk factors, which vary by geographical region. These factors include air pollution, occupational exposures, poorly controlled asthma, environmental tobacco smoke, infectious diseases, and low socioeconomic status. Impaired lung growth during childhood, caused by a range of early-life exposures, is associated with an increased risk of COPD. Potential mechanisms for the pathogenesis of COPD in never-smokers include inflammation, oxidative stress, airway remodelling, and accelerated lung ageing. Compared with smokers who develop COPD, never-smokers with COPD have relatively mild chronic respiratory symptoms, little or no emphysema, milder airflow limitation, and fewer comorbidities; however, exacerbations can still be frequent. Further research—including epidemiological, translational, clinical, and implementation studies—is needed to address gaps in understanding and to advance potential solutions to reduce the burden of COPD in never-smokers.

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This is the second in a **Series** of three papers about the origins of chronic obstructive pulmonary disease

For the **Origins of chronic obstructive pulmonary disease Series** see www.thelancet.com/series/origins-of-COPD

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive lung disease characterised by respiratory symptoms associated with chronic airflow limitation that affects an estimated 300 million people globally. COPD is the third leading cause of death worldwide, with about 3·2 million people dying from COPD annually.[1] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition states that COPD is "usually caused by significant exposure to noxious particles or gases".[2] Although cigarette smoking has traditionally been considered the most frequent and important cause of COPD, causative factors other than cigarette smoking are increasingly recognised worldwide.[3,4] An understanding of the factors that contribute to the development of COPD in never-smokers, the mechanisms of disease pathogenesis, and the relationship between specific risk factors and the clinical features and course of disease will help to inform strategies for disease prevention and the development of therapeutic interventions to mitigate or treat the effects of COPD.

In this Series paper, we aim to provide an update on COPD in people who have never smoked. In a 2009 Review of COPD in non-smokers, published in *The Lancet*,[3] Salvi and Barnes systematically reviewed the available literature and reported that about 25–40% of all COPD globally is accounted for by factors other than tobacco smoking. Since then, more evidence has emerged of the growing burden of COPD in non-smokers. We review the current evidence base for the epidemiology, clinical characteristics, and prognosis of COPD in never-smokers. We provide a synthesis of the evidence for non-smoking-related risk factors for COPD, including potential mechanisms of action and approaches to risk modification that could help to reduce the burden of COPD, and outline directions for future research. The ultimate objective is to raise awareness of the health issue of COPD in people who have never smoked, and to translate evidence into clinical practice and policy, to optimise prevention and treatment of this devastating disease.

Key messages

- About half of all COPD cases worldwide are due to non-tobacco-related risk factors
- Countries with lower SDI tend to have a higher proportion of cases of COPD associated with non-tobacco-related risk factors than do countries with higher SDI
- Risk factors for COPD in never-smokers include exposure to household biomass smoke, outdoor air pollution, occupational exposures to dust and fumes, poorly controlled asthma, environmental tobacco smoke, history of pulmonary tuberculosis, recurrent respiratory tract infections, and low socioeconomic status; these non-tobacco-related factors disproportionately affect women
- Impaired lung growth during childhood, with lack of attainment of maximal lung size and low baseline lung function, is associated with an increased risk of COPD
- A range of biological mechanisms is involved in the development of COPD in never-smokers, with distinct cellular features and molecular pathways implicated for specific risk factors
- Never-smokers with COPD have milder chronic respiratory symptoms and airflow limitation than do smokers with COPD, but still have a poor prognosis with an increased risk of exacerbations; research is urgently needed to develop a strong evidence base for the management of COPD in never-smokers
- To improve outcomes in at-risk populations, effective strategies for education, public health intervention, and early detection are essential for prevention, diagnosis, and timely management of COPD in never-smokers

COPD=chronic obstructive pulmonary disease. SDI=sociodemographic index.

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For more on the **GOLD initiative** see https://goldcopd.org

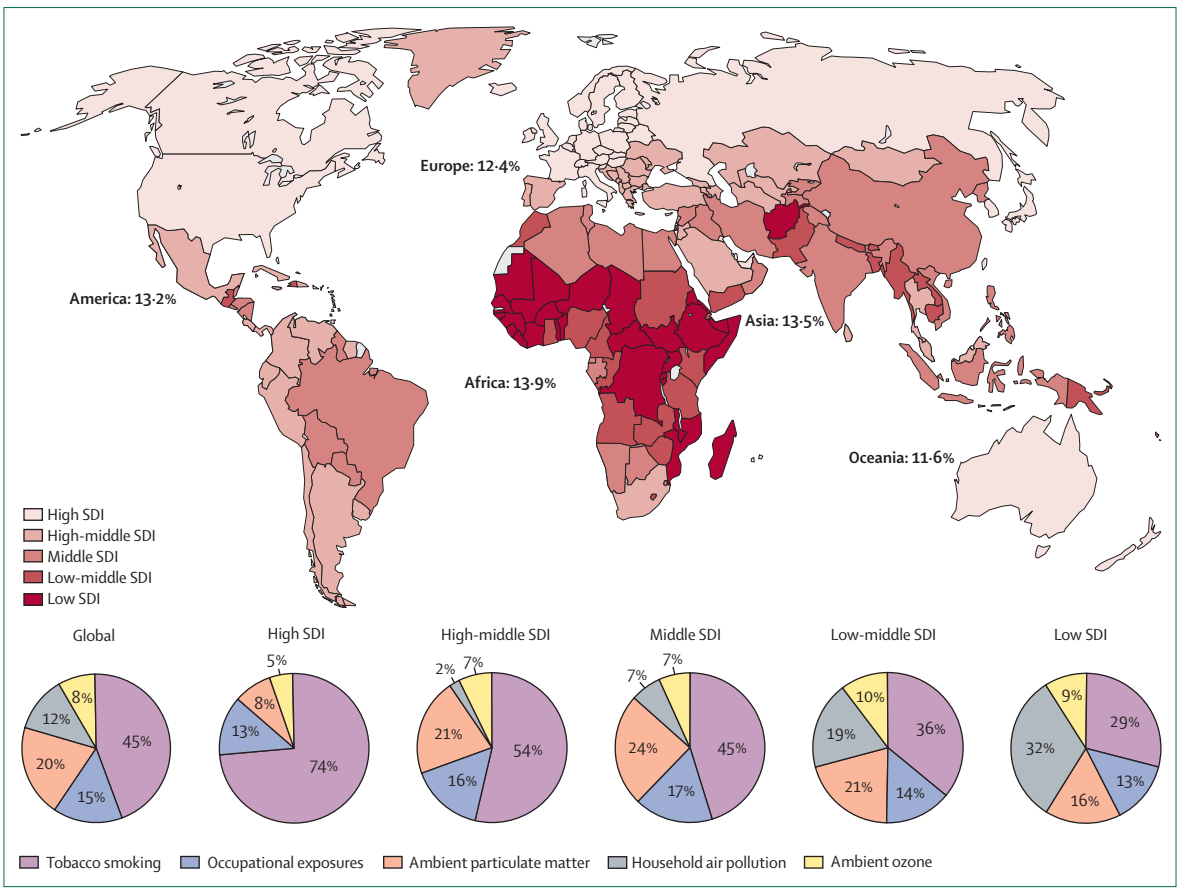

Figure: **Global risk factors associated with COPD according to SDI**
The global prevalence of COPD is estimated to be around 13·1%;[6] however, prevalence varies substantially within and between countries, and data for many geographical regions are scarce or absent. The map shows estimates of COPD prevalence for each continent (data from Blanco and colleagues[6]), with SDI highlighted for each country.[5] The pie charts show the (rounded) percentage of COPD-associated DALYs per 100 000 population attributable to different environmental risk factors globally and according to SDI, based on Global Burden of Disease Study 2019 data.[5] These data confirm the greater burden of COPD in never-smokers than in smokers in terms of DALYs worldwide, and show that the effect of non-smoking-related risk factors is stronger with decreasing SDI.[5] COPD=chronic obstructive pulmonary disease. DALYs=disability-adjusted life-years. SDI=sociodemographic index.

Epidemiology of COPD in never-smokers

According to the Global Burden of Disease Study 2019,[5] which defined COPD according to spirometric criteria—post-bronchodilator FEV_1 to forced vital capacity (FEV_1/FVC) ratio of less than 0·7—the estimated contribution of tobacco smoking to COPD-associated disability-adjusted life-years per 100 000 population was 44·6% globally. This proportion varied markedly with sociodemographic index (SDI): in countries with a high SDI, smoking contributed to 73·9% of COPD, at high-middle SDI quintiles this figure was 53·7%, at middle SDI quintiles 45·2%, at low-middle SDI quintiles 36·1%, and at low SDI quintiles 28·8% (figure). The prevalence of COPD by continent has been estimated to be 12·4% in Europe, 13·9% in Africa, 13·2% in America, 13·5% in Asia, and 11·6% in Oceania;[6] these geographical distribution estimates include moderate prevalence in countries where smoking rates are low but non-tobacco exposures are high. Overall, as wealth decreases, non-tobacco-related risk factors for COPD become more important, highlighting the factors at play in the relationship between poverty and COPD in people who have never smoked. Common risk factors for COPD in never-smokers are listed in panel 1.

See **Online** for appendix 1

Large-scale studies, most of which used a spirometric definition of COPD, have reported that 22–51% of people with COPD have never smoked (defined as <100 cigarettes in a lifetime); conversely, estimates of the prevalence of COPD in never-smokers range from 4% to 16% (table 1; see appendix 1 for an expanded table showing associated risk factors in prevalence studies of COPD).[7–17] Estimates of COPD in never-smokers vary, depending on the population, the means of measurement, and the socio-cultural setting. In regions where spirometry is underused in clinical practice, reliance on self-reported diagnosis of COPD leads to a marked underestimation of COPD prevalence.[15,18] In a study of 30 874 participants from 44 sites worldwide, 26% of all participants reported having ever had a lung function test and 5% had received a diagnosis of COPD, whereas twice as many (10%) had a

post-bronchodilator FEV_1/FVC that was below the lower limit of normal (LLN).[8,19] A further limitation of epidemiological studies is the use of only one point in time for spirometry measurement to define COPD, rather than multiple spirometric measurements, made at several timepoints, which might make the diagnosis of COPD more robust.

The variability in COPD prevalence estimates in smokers and never-smokers is evident in many studies.[12,20,21] In Guangzhou, China, 7% of people in the Burden of Obstructive Lung Disease (BOLD) study had COPD according to spirometric classification (GOLD stage of at least 2; moderate severity).[22] However, the proportion of never-smokers with GOLD stage 2–4 COPD was surprisingly low (4·1% in men and 4·5% in women). Smoking rates in men have remained at more than 50% in most provinces in China, but in women, the combined effects of environmental exposures other than active smoking—passive smoking, indoor and outdoor air pollution, and occupational particulate exposures—are key contributors to COPD.[21,23] This sex difference in risk factors for COPD can also be seen in high-income countries (HICs). In the Rotterdam Study,[15] the proportion of female participants with COPD who were lifelong never-smokers was 27%, compared with 7% for male never-smokers. Among patients with incident COPD who had never smoked, the proportion of people exposed to passive smoking was 51% and the majority (77%) of these passive smokers were female.[15]

Obtaining accurate estimates of COPD prevalence is challenging, particularly given the use of different criteria to define COPD, and the marked variation in prevalence estimates in both smokers and never-smokers underlines this difficulty.[20] Factors such as low levels of clinical suspicion and testing,[8] rurality, low socioeconomic status, low education and health literacy levels, and variations in non-tobacco exposures—all of which might be associated with considerable underdiagnosis of COPD in never-smokers—add to the challenge of accurately quantifying COPD prevalence in never-smokers.[24,25] A compounding factor is that awareness of COPD is very low in underprivileged areas, as shown by a community survey in urban slums and rural areas around Pune city in India.[26]

In summary, the epidemiology of COPD in never-smokers is highly variable and depends on the socio-demographic features that characterise the region and the population studied. Environmental risk factors are the major determinants of risk of developing airflow limitation with features of COPD in never-smoking adults, even in high-income settings, and include passive smoking, occupational exposures to gases, dusts, and fumes, and a history of childhood asthma or tuberculosis (see below). The importance of non-smoking-related risk factors was highlighted in the BOLD study,[27] which showed that, after cigarette smoking, the next most influential risk factors included poor education levels, occupational exposure (working in a dusty job for ≥10 years), low body-mass index, and a history of tuberculosis, although relative risks (RRs) were highly variable across study sites.

Panel 1: **Risk factors for COPD in never-smokers**

- Air pollution
  - Indoor (eg, smoke from biomass fuel)
  - Outdoor (eg, particulate matter and NO_2)
- Asthma
- Occupational exposures
  - Coal dust
  - Livestock farming and agriculture
  - Biological dusts, mineral dusts, gases or fumes
- Infections
  - Tuberculosis
  - HIV
  - Recurrent childhood respiratory infections
- Low maximally attained lung growth (due to a range of factors)
- Low socioeconomic status (comprising a range of risk factors for impaired lung growth and COPD)
- Environmental tobacco smoke
- Dietary factors
- Older age
- Genetic factors

COPD=chronic obstructive pulmonary disease.

Clinical characteristics and prognosis of COPD in never-smokers

Several important differences exist between tobacco-related COPD and COPD that occurs in never-smokers (table 2).[13,28–30] In never-smokers with COPD, there is often a younger age of onset,[13] a relatively even sex distribution of disease (or female predominance), generally less sputum production,[7,13] less exertional breathlessness,[11] milder airflow obstruction, and normal diffusing capacity of the lung for carbon monoxide (DLCO).[7,13,28,30,31] There is also less severe emphysema,[13,28,30,31] but more small airways disease, especially in those with asthma,[32] on chest CT scans in never-smokers with COPD compared with those with smoking-related COPD. Chronic bronchitis (mucus hypersecretion) is more common with biomass smoke exposure than with cigarette smoking.[33] Respiratory exacerbations were equally prevalent in ever-smokers and never-smokers with COPD in the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study.[13] The rate of FEV_1 decline is significantly lower for patients exposed to biomass smoke than it is for tobacco smokers,[30,34] with the low FEV_1 often reflecting lower baseline values rather than accelerated decline.[35] The risk of lung cancer is increased in never-smokers with COPD compared with never-smokers without COPD, and is as high as that for ever-smokers without COPD.[36]

For more on the **BOLD study** see https://www.boldstudy.org

For more on **air pollution** see https://www.who.int/health-topics/air-pollution/

For more on **occupational health** see https://www.who.int/health-topics/occupational-health

For more on the **CanCOLD study** see http://cancold.ca/cancold-study/

	Setting (study name)	Never-smokers (n)	Definition of COPD	Prevalence of COPD in never-smokers	Prevalence of never-smokers among people with COPD
Zhou et al (2009)[7]	China (CESCOPD)	12 471	Post-bronchodilator FEV_1/FVC <0·7	5%	39%
Lamprecht et al (2011)[8]	14 countries (BOLD)	4291	Post-bronchodilator FEV_1/FVC <0·7	12%	28%
Hagsted et al (2012)[9]	Sweden (OLIN)	770	Post-bronchodilator FEV_1/FVC <0·7	7%	20%
Perez-Padilla et al (2012)[10]	Five Latin American cities (PLATINO)	2278	Post-bronchodilator FEV_1/FVC <0·7	4%	26%
Thomsen et al (2013)[11]	Denmark (Copenhagen General Population Study)	26 005	FEV_1/FVC <LLN	6%	22%
Smith et al (2014)[12]	China Kadoorie Biobank	317 000	Pre-bronchodilator FEV_1/FVC <0·7 and <LLN	4% (females); 5% (males)	Not measured
Tan et al (2015)[13]	Canada (CanCOLD)	2295	Pre-bronchodilator FEV_1/FVC <0·7 and <LLN	6%	29%
Lee et al (2016)[14]	Korea (KNHANES IV and V)	8984	Post-bronchodilator FEV_1/FVC <0·7	7%	31%
Terzikhan et al (2016)[15]	The Netherlands (Rotterdam Study)	4997	Post-bronchodilator FEV_1/FVC <0·7	6%	27% (females); 7% (males)
Wang et al (2018)[16]	China (China Pulmonary Health study)	36 429	Post-bronchodilator FEV_1/FVC <0·7	6%	51%
Warkentin et al (2019)[17]	UK Biobank cohort	218 892	FEV_1/FVC <0·7 or FEV_1 <80% of Global Lung Initiative predicted FEV_1 reference value	16%	Not measured

Studies published since the 2009 *Lancet* Review of COPD in non-smokers.[3] BOLD=Burden of Obstructive Lung Disease. CanCOLD=Canadian Cohort of Obstructive Lung Disease. CESCOPD=Chinese Epidemiological Survey of COPD. COPD=chronic obstructive pulmonary disease. FVC=forced vital capacity. KNHANES=Korea National Health and Nutrition Examination Survey. LLN=lower limit of normal. OLIN=Obstructive Lung Disease in Northern Sweden. PLATINO=Latin American Project for the Investigation of Obstructive Lung Disease.

Table 1: **Large-scale studies of COPD prevalence in never-smokers**

	COPD in ever-smokers	COPD in never-smokers
Typical age of onset	>40 years	>30 years
Sex	More males than females affected	Males and females affected equally, or more females than males affected (especially in LMICs)
Symptoms	More cough and dyspnoea (relatively less sputum production)	More cough (relatively less dyspnoea and sputum production)
Respiratory exacerbations	Frequent (and potentially severe)	Frequent (and potentially severe)
Comorbidities	Prevalent	Generally less prevalent
Risk of lung cancer	High	High
Lung physiology	More severe airflow obstruction; greater increase in RV/TLC (hyperinflation); increase in airway resistance; less small airways obstruction; reduced DLCO	Milder airflow obstruction; increase in RV/TLC (hyperinflation); greater increase in airway resistance; more small airways obstruction; normal DLCO
FEV_1 decline	Can be rapid	Usually normal
Lung CT imaging	Less air trapping due to small airways obstruction; more emphysema	More air trapping due to small airways obstruction; less emphysema
Sputum inflammatory cells	Greater increase in neutrophils	Increase in neutrophils; relatively greater increase in eosinophils
Pharmacological responses	Long-acting bronchodilators favoured over inhaled corticosteroids in terms of safety and effectiveness, especially among those with predominant emphysema	Not known

COPD=chronic obstructive pulmonary disease. DLCO=diffusing capacity of the lung for carbon monoxide. RV=residual volume. TLC=total lung capacity.

Table 2: **Clinical characteristics of COPD in never-smokers compared with ever-smokers**[13,28–30]

Two representative case studies of COPD in never-smokers are provided in panel 2 and panel 3. Overall, never-smokers with COPD tend to have milder respiratory disease than do ever-smokers with COPD, with less associated cardiovascular comorbidity, although there is still substantial morbidity from hospital admissions for COPD and pneumonia.[11]

Multiple subphenotypes are likely to exist within the group of non-smokers with COPD. Understanding associations between specific risk factors and clinical characteristics might help to explain the heterogeneity of mechanisms leading to COPD (table 3).[37–52] Such an understanding should also contribute to the development of more targeted preventive and therapeutic approaches based on exposure to risk factors and differing COPD phenotypes.

Risk factors for COPD in never-smokers

As evidence pertaining to the epidemiology, clinical characteristics, and prognosis of COPD in never-smokers has emerged, so too have data on the various non-smoking-related risk factors for COPD. In some individuals with COPD, a single causal factor might drive the development and progression of disease. In others, a combination of risk factors might contribute to the disease process. For people with low socioeconomic status, for example, a distinct range of factors might contribute to an increased risk of COPD in different settings. There is now a pressing need to translate knowledge of risk factors and causal pathways for COPD into strategies for prevention and treatment that reflect the range of relevant factors in individuals at risk of disease or in those with established COPD.

Air pollution

Risk of COPD

According to the Global Burden of Disease Study 2019,[5] air pollution contributes to about 50% of the risk of COPD, and more so in low-income and middle-income countries (LMICs). Components of outdoor air pollution have been associated with risk of developing COPD.[53] Cross-sectional analysis of data from the UK Biobank (303 887 adults) showed an increased risk of COPD with high concentrations of ambient air pollution—particulate matter ($PM_{2·5}$, PM_{10}, and NO_2, as determined by land-use regression-based estimates—after controlling for confounding factors including cigarette smoking.[54] Residential ambient $PM_{2·5}$ contributed to 5·6% of COPD prevalence, compared with 12·1% for current or past cigarette smoking. Ambient air pollution concentrations were associated with chronic bronchitis in never-smokers in cohort studies in the USA ($PM_{2·5}$ and NO_2)[55] and the Netherlands (black carbon and NO_2).[56]

An important source of indoor air pollution in domestic settings is biomass fuel used for cooking and heating in enclosed spaces.[57] WHO estimates that, worldwide, 2·6 billion people are exposed to polluting energy sources from household cooking and heating, and that there are nearly 4 million deaths each year from exposure to household smoke emitted from solid fuels.[58] In women who cook at home using polluting biomass fuel, it has been estimated that 13 years of exposure at 2 h per day leads to lung function decline that is equivalent to 10 pack-years of cigarette smoking.[59]

A number of epidemiological studies have reported an increased risk of COPD with biomass smoke exposure. Exposure to coal and wood fuels for household cooking and heating increased the risk of incident COPD (adjusted hazard ratios [HRs] ranged from 1·06 to 1·21) in a prospective cohort of 475 827 adults in the China Kadoorie Biobank, particularly in women and never-smokers, and with longer duration of exposure.[60,61] In a study of 12 396 adults in 13 LMICs, people exposed to smoke from indoor biomass fuels had a greater risk of COPD (odds ratio [OR] 1·41, 95% CI 1·18–1·68) than did those without exposure, an effect that was stronger in women.[62] Furthermore, household air pollution was estimated to contribute to 13% of COPD prevalence in these LMICs, compared with 12% from cigarette smoking.[62] In a study of women in Mexico, COPD related to biomass smoke exposure tended to have an airway-predominant phenotype, with more gas trapping and less emphysema on chest CT than did cigarette smoke-related COPD.[63] Finally, a cross-sectional study in rural India of women who never smoked reported that 51% used solid biomass as fuel for cooking, which was associated with an increased risk of chronic bronchitis (OR 1·96, 95% CI 1·06–3·64) and airflow obstruction (5·55, 3·51–8·78).[64] By contrast, other studies have not shown an association of biomass smoke with COPD,[65–67] possibly due to the difficulty in identifying a true control group when much of the population has been exposed to biomass smoke for long periods of time.

Mosquito coils are used by more than 2 billion people living mainly in tropical countries to prevent mosquito bites, and are often made from coconut husk mixed with pyrethrum, the insecticide that kills mosquitoes. These coils tend to be burnt for 6–7 h in the night, and when the bedroom doors and windows are shut, they produce enormous concentrations of indoor $PM_{2·5}$ (>2200 mcg/m³). Burning one mosquito coil has been estimated to produce an amount of $PM_{2·5}$ pollution equivalent to that of 100 cigarettes.[68] Because people exposed to mosquito coils have a numerically higher frequency of breathlessness, cough, and wheeze,[68] this seems to be an important risk factor for COPD and warrants further research.

***Panel 2:* Case study 1—COPD in a never-smoker with environmental tobacco smoke exposure during childhood**

The patient was a 57-year-old woman who worked as a primary school teacher in an urban setting in a high-income country. She presented with increasing exertional dyspnoea. She had noticed chest tightness and breathlessness while doing housework, when rushing or anxious, and when walking her dog up hills. She also reported an intermittent cough, usually non-productive except after viral respiratory infections, which had occurred two or three times a year over the previous 5 years. After these infections, her cough and chest tightness persisted, sometimes for 4–6 weeks. She very rarely noticed a wheeze. Her general practitioner had prescribed salbutamol, which gave relief, but she found herself using it every day.

There was no history of allergies, rhinosinusitis, hayfever, or eczema, and no family history of asthma. Her chest tightness could be triggered by sudden changes in air temperature, aerosol sprays, smoke, or strong smells. She was a lifelong never-smoker and had worked mainly as a teacher in a smoke-free workplace. In childhood, she had often had bouts of winter bronchitis, although she recovered well and had no apparent limitation when playing sport in her teens and early adult life. Her parents were both heavy smokers and she described substantial exposure to environmental tobacco smoke, indoors and outdoors, as a child and through her adolescent years.

On examination at rest, she was comfortable, with no peripheral signs of severe lung disease, no nasal obstruction, and no neck masses. Her chest was clear on auscultation. Oxygen saturation by finger oximetry was 98%. Spirometry on presentation showed that her FEV_1 was 1·35 L (52% predicted), which improved to 1·49 L (58% predicted) after 400 mcg salbutamol. Post-bronchodilator FEV_1/FVC was 0·54. Lung volumes showed gas trapping and hyperinflation (RV 3·45 L, 160% predicted; RV/TLC 142% predicted); DLCO and KCO were normal (98% and 97% predicted, respectively).

She commenced use of an inhaled corticosteroid–long-acting β_2-adrenoceptor agonist inhaler and gained symptomatic benefit but no significant change in FEV_1 or FEV_1/FVC. Tiotropium was added, again with symptomatic benefit, and—along with pulmonary rehabilitation—her exercise capacity also improved. She has had one to two courses of antibiotics and systemic steroids each year over the past 5 years, but has never required a hospital admission for an exacerbation. Her lung function has progressively declined and, 10 years since commencing treatment, her post-bronchodilator FEV_1 is 1·06 L (50% predicted) and FEV_1/FVC is 0·55. Her oxygen saturation remains normal at 97%.

COPD=chronic obstructive pulmonary disease. DLCO=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. KCO=carbon monoxide transfer factor. RV=residual volume. TLC=total lung capacity.

For the **UK Biobank** see https://www.ukbiobank.ac.uk/

For the **China Kadoorie Biobank** see https://www.ckbiobank.org/

Panel 3: **Case study 2—COPD in a never-smoker with exposure to smoke from biomass fuels used in indoor cooking**

The patient was a 38-year-old woman residing in a rural village about 60 km from the city of Pune in India, who was referred by her local general practitioner for cough with mucoid sputum, and shortness of breath at rest that worsened on exertion. These symptoms had been present for more than 6 months and she had been treated with antibiotics and cough syrups, with no significant relief. Neither she nor anybody in her family smoked tobacco and she had no known past or family history of asthma or pulmonary tuberculosis.

Although she was primarily a homemaker, she often worked in the fields and helped her husband with growing and harvesting crops and milking cows for local milk distribution. The crop residues and the dung of cows were important sources of fuel for cooking. She cooked food in an indoor kitchen with only one small window, no chimney, and no exhaust fan. She often used dried animal dung or crop residues to light the fire, along with locally available dried twigs and wood. She cooked on a traditional stove made of mud. The smoke from the burning of biomass fuels would remain in the kitchen for a long time. She said that the smoke helped to keep mosquitoes away. She had started helping her mother to cook when she was 15 years old using the same traditional stove and biomass fuels. Since getting married, she had spent a substantial portion of each day cooking food for her family.

On examination, her oxygen saturation was 97%, respiratory assessment showed a few scattered wheezes, and cardiovascular and other systems were normal. Spirometry showed that her post-bronchodilator FEV_1/FVC was 0·65 and FEV_1 was 68% predicted. Bronchodilator reversibility was 8% and 110 mL. Impulse oscillometry showed a raised R5 value of 140% predicted and raised R5–R20 values of 155% predicted. DLCO was 82% predicted. High-resolution chest CT showed air trapping on expiration, suggestive of small airways obstruction.

She was treated with inhaled tiotropium and formoterol, and her symptoms improved over 6 weeks. She was strongly encouraged to stop using biomass fuels for cooking and was introduced to a government scheme that promotes and provides liquefied petroleum gas as a cleaner fuel for cooking. She and her family were encouraged to educate the local community about the harmful effects of burning biomass fuel for cooking in poorly ventilated kitchens.

COPD=chronic obstructive pulmonary disease. DLCO=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. R5=total airway resistance at 5 Hz. R5–R20=peripheral airway resistance (ie, difference between resistance at 5 Hz and 20 Hz).

Mechanisms

A non-exhaustive list of potential mechanisms of action identified in translational studies of air pollution and other risk factors for COPD in never-smokers is provided in table 3. Exposure to components of ambient air pollution is associated with increased activation of proinflammatory and oxidative stress pathways in the lungs.[53] Exposure of human bronchial epithelial cells cultured at an air–liquid interface to diesel and biodiesel emissions leads to increased expression of interleukin-8 (IL-8), antioxidants, and cytochrome P450 1A1 (CYP1A1), and suppressed expression of superoxide dismutase (SOD1).[37,38]

Smoke from household air pollution activates different inflammatory pathways in the lungs from those activated by exposure to cigarette smoke.[69] In mouse models, exposure to particulate matter of biomass fuel collected from enclosed kitchens of rural communities in India caused acute neutrophilic infiltration in the lungs, with cow dung particulate matter causing more inflammation than wood smoke particulate matter.[70] Subacute exposure was associated with eosinophilic inflammation, antibody responses that were specific to the type of particulate matter, and destruction of alveoli, which was worse with wood smoke particulate matter.[70]

Human cellular models show a distinct response to household air pollution. Acute exposure of primary human small airway epithelial cells to smoke from animal dung at an air–liquid interface produced proinflammatory cytokine responses—elevated IL-8 and granulocyte-macrophage colony-stimulating factor (GM-CSF)—through activation of activator protein 1 (AP-1) and arylhydrocarbon receptor pathways.[39] Exposure to wood smoke particulate matter of alveolar macrophages from healthy individuals living in Malawi who were exposed naturally to household air pollution and of monocyte-derived macrophages from healthy volunteers in the UK led to similar inflammatory cytokine responses.[71]

Biomass exposure also impairs innate immune responses and might elicit autoimmune responses. Exposure of monocyte-derived macrophages to wood smoke particulate matter was associated with reduced macrophage phagocytosis of heat-killed *Streptococcus pneumoniae*, providing a link between exposure to household air pollution, impaired innate immunity, and respiratory infections.[71] A study in India found that the load of potentially pathogenic bacteria in sputum was significantly higher in individuals with COPD related to biomass smoke exposure than in controls (smokers, never-smokers, and individuals exposed to biomass smoke without COPD), and was associated with defective phagocytosis of heat-killed bacteria by monocyte-derived macrophages.[72] Furthermore, never-smokers with wood smoke-induced COPD had higher levels of anti-cyclic citrullinated peptide (CCP) antibodies, even without clinical evidence of rheumatoid arthritis (anti-CCP antibody is a hallmark of the condition), than did smokers with COPD, indicative of an autoimmune component.[73]

Risk modification

In some countries where outdoor air pollution is a major problem, such as those in many parts of Asia, safe air quality targets have been set and pollution reduced to safe levels through stringent management of traffic and vehicular emissions, as well as monitoring of industrial pollution. Scaling up and sustaining these interventions, and introducing simple and affordable technologies to reduce exposures, requires integrated engagement across sectors (health, industry, transport, government) and strong political support and investment. Despite some successes, exposure to outdoor air pollution remains a substantial threat to health worldwide and

For more on **national air quality standards** see https://www.who.int/tools/air-quality-standards

	Biomass smoke[37-39]	Asthma[40-42]	Occupational exposures[43]	Tuberculosis[44,45]	HIV[46-48]	Environmental tobacco smoke[49]	Impaired lung growth[50-52]
Pathways or pathology	Airway remodelling; oxidative stress; inflammation	Airway remodelling; bronchoconstriction; epithelial-to-mesenchymal transition	Inflammation	Tracheobronchial stenosis; small airway obstruction; bronchiolitis obliterans; matrix degradation	Altered immunity; respiratory infection; apoptosis; lung ageing	Inflammation; oxidative stress; epigenetics	Pathways and pathological features associated with various risk factors: maternal smoking; childhood respiratory infections and asthma; suboptimal nutrition; genetic factors
Cells, tissues, or structures involved	Bronchial epithelium; neutrophils; lymphocytes	Bronchial epithelium; smooth muscle; fibroblasts; goblet cells	Bronchial epithelium; monocytes; macrophages	Monocytes	Bronchial epithelium; $CD8^+$ lymphocytes; $CD4^+$ lymphocyte count	Bronchial epithelium; neutrophils; macrophages	Small airways and alveoli
Mediators	Cytokines; chemokines; MMP9, MMP12	Cytokines; TGF-β	Cytokines; adhesion molecules; pattern recognition receptors	Integrin αVβ3; MMP1, MMP10	MMP12; soluble CD14; reduced E-cadherin expression	Cytokines; p38 MAPK	Molecular and cellular responses to various in-utero and childhood exposures

A non-exhaustive list of potential mechanisms of action for risk factors for COPD in never-smokers identified in translational studies from the past 10 years. COPD=chronic obstructive pulmonary disease. MAPK=mitogen-activated protein kinase. MMP=matrix metalloproteinase. TGF-β=transforming growth factor-β.

Table 3: **Examples of putative mechanisms implicated in COPD in never-smokers**

must be addressed, particularly in settings where there are prolonged periods of exposure at concentrations above recommended national and international air quality targets.

Spirometry is an important tool for diagnosing COPD arising from chronic exposure to biomass smoke from cooking and heating in households, particularly in LMICs.[74] More targeted use of spirometry in LMICs could facilitate early diagnosis and increased awareness of risks to lung health, which in turn might enable a reduction in exposures to the affected individual and healthy family members and provision of early therapeutic intervention. Preventive public health and governmental measures are needed to reduce reliance on solid fuels for household use and mitigate risks of exposure. Many such initiatives are already underway, including interventions to reduce biomass smoke exposure by introducing flued stoves, to improve ventilation, and to provide alternative cooking stoves and non-biomass fuels,[57] but increased funding is needed for more widespread implementation.

Although the past decade has seen progress in understanding of the mechanisms by which exposure to air pollution might lead to increased risk of COPD, in the future, it might be possible to target these mechanisms of action to influence the development and course of COPD, ideally using personalised treatment approaches. However, the implementation of preventive measures will be key to reducing the burden of COPD and should be viewed as a priority for public health and research on a local, national, and international scale. Addressing the threats of outdoor and indoor air pollution from a range of sources will require strong public health policy combined with implementation targets and investment in education, public infrastructure, occupational health and safety regulations, and effective, practical strategies for implementation in diverse settings.

Asthma

Risk of COPD

The 2022 GOLD Strategy report highlights that asthma "may be a risk factor for the development of chronic airflow limitation and COPD",[2] acknowledging that adults with asthma could have a 12-times increased risk of acquiring COPD over time compared with those without asthma, after adjusting for smoking.

High levels of COPD in never-smokers were seen in the third National Health and Nutrition Examination Survey (NHANES III).[24] Among people with COPD, of the 24·9% of those with mild-to-moderate COPD who had never smoked, the majority were female (82·5%). A similarly high proportion of non-smokers has been found among people with COPD in population studies in Norway (30·8%)[75] and Italy (33·0%).[76] In HICs, asthma is the most common risk factor for COPD in never-smokers,[77] but other risk factors such as occupational and ambient exposures to dust and fumes should be considered, especially in low-income settings. Even in LMICs that have large rural populations with high levels of biomass exposure—such as India, South Africa, and China—asthma is likely to contribute to COPD risk, albeit in the absence of clinical diagnoses. Similar prevalence rates of asthma in non-smoking-related COPD of 25–30% have been reported in the USA, Europe, and China.[3,24,25]

In the CanCOLD study of 5176 adults aged 40 years or above,[13] the prevalence of COPD (FEV_1/FVC <LLN) in never-smokers was 6·4%, and this group comprised 27% of all participants with COPD. In never-smokers with COPD of all severities, common independent associations were older age and a history of asthma. A history of asthma was the most consistent independently associated risk factor for COPD regardless of smoking status.

Women are more likely than men to have chronic airflow limitation related to asthma.[19] Lower education levels and, in non-smoking women, passive smoking[13]

and cardiovascular risk factors[78] have been identified as risk factors for mild COPD, whereas a history of hospital admission in childhood for respiratory illness (which could be a surrogate marker of childhood asthma)[13,79] and, in women, exposure to passive smoke and biomass fuel for heating are important risk factors for moderate-to-severe COPD.[13]

It is important to note that the asthma–COPD overlap phenotype might differ from spirometrically defined COPD in never-smokers, and might be due to airway remodelling as a consequence of asthma.[80,81] In several studies of asthma–COPD overlap, smoking has been reported as a more frequent feature than it is in asthma alone.[82,83] Among people with COPD, nearly 25% report a history of asthma and, conversely, having asthma increases the probability that a smoker will develop COPD.[84,85] Although this relationship has not been shown for non-tobacco-related COPD, it is plausible that having a history of asthma also increases the chance of developing COPD in biomass-exposed individuals. To understand the contribution of long-standing asthma and asthma pathophysiology to COPD, studies that exclude smokers are needed. The lack of agreement on a definition of asthma–COPD overlap has made assessment of its prevalence challenging, which strongly depends on how the condition is defined and the choice of denominator population. In many studies, asthma–COPD overlap is described as comprising a cluster of features associated with asthma and several features usually associated with COPD, and in some surveys the prevalence of asthma–COPD overlap in never-smokers is as high as 44%, whereas in others it is zero.[86,87]

In the Wellington Respiratory Survey of 3500 participants randomly selected from the electoral register, among those with COPD, the most commonly associated risk factor was asthma (53 of 96 participants [55·2%]).[88] However, this proportion was determined by spirometric diagnosis of COPD alone (ie, post-bronchodilator FEV_1/FVC <0·7), and might therefore represent the subset of patients with asthma who had poorly reversible airflow limitation.[89,90] Among the 96 participants with COPD, 61 (63·5%) were current or former tobacco smokers, again showing that about 36% had obstructive spirometry consistent with COPD, but were never-smokers. If spirometric criteria alone are used, as was the case in many epidemiological studies before the publication of the 2017 GOLD Strategy report,[91] people meeting the criteria should be described as having chronic airflow limitation rather than COPD. For the purposes of this discussion, spirometric features of airflow limitation alone do not equate to a diagnosis of COPD: a clinical diagnosis is based on an exposure history and clinical features, accompanied by diagnostic spirometry.[2] Where asthma prevalence is high, chronic airflow limitation could be due equally to airway remodelling in long-standing asthma[85] as to the many environmental factors that increase the risk of COPD in never-smokers. However, a cohort study in a randomly selected sample of the Danish general population found that the majority of never-smokers with chronic airflow limitation did not appear to have undiagnosed asthma, but instead had other risk factors implicated.[92]

In a population-based cross-sectional study using data from questionnaires and spirometry obtained during the fourth and fifth Korea National Health and Nutrition Examination Survey (KNHANES IV and V; n=15 063),[14] the prevalence of COPD in never-smokers was 7·1%. Age greater than 65 years, low body-mass index, and male sex conferred an increased risk for COPD (ORs >2·0) in never-smokers. Risk for COPD in never-smokers was also significantly higher in those with self-reported asthma (OR 2·72, 95% CI 2·05–3·60) and self-reported tuberculosis (4·73, 3·63–6·17) than in those without these conditions.

Mechanisms

Histological features of airway remodelling in asthma that might be present in people with COPD due to or associated with asthma include thickening of the basement membrane of the bronchial epithelium, increased airway smooth muscle mass, an increase in mucus-producing cells, subepithelial fibrosis, and neovascularisation.[93] The exact mechanisms that underlie airway remodelling are still uncertain,[94] but are likely to include chronic airway inflammation, as well as bronchoconstriction independent of inflammation, as shown by comparisons of allergen-induced and methacholine-induced bronchoconstriction through upregulation of transforming growth factor-β (TGF-β) and epithelial-to-mesenchymal transition in patients with asthma that led to persistent airflow obstruction (table 3).[40]

In the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) study,[41] gene expression signatures of airway samples from patients with severe asthma implicated an altered response to inhaled steroids, enhanced eosinophilic airway inflammation, an increase in $CD4^+$ T cells and IL-13, and reduced interferon-α (IFN-α) in persistent airflow limitation. Increased expression of connective tissue growth factor has been observed in airway smooth muscle, correlating with increased basement membrane thickness in bronchial biopsies.[42] The airway microbiome differs between inflammatory airway phenotypes in asthma,[95] which could influence airway remodelling, and thus chronic airflow limitation.

Risk modification

There are no studies that specifically address the treatment of COPD according to cause in never-smokers, but identification of specific inflammatory pathways associated with different risk factors might enable targeted treatment and facilitate the development of new therapeutic approaches for COPD associated with asthma. Although many studies are now examining

outcomes in different phenotypes of COPD, very few specifically address outcomes in COPD phenotypes related to asthma or to other factors such as exposure to biomass smoke or occupational hazards. Asthma-related COPD could fall into categories such as poorly reversible airways disease, fixed airways disease, or asthma–COPD overlap syndrome, but definition of this overlap syndrome has been challenging and there are few published studies specifically addressing optimal therapy.[96] At present, early diagnosis of asthma and appropriate pharmacotherapy with good adherence to treatment is key to the prevention of COPD associated with asthma.

Occupational exposures

Risk of COPD

Occupational exposure to vapours, gases, dusts, and fumes is a major risk factor for COPD in never-smokers.[8,97–99] Major occupational groups at risk include people working in farming, agriculture, industrial manufacturing and processing, mining, and in jobs with concentrated exposure to diesel exhaust fumes from machinery and vehicles, those working in the information industry and administrative support,[100] and sculptors, gardeners, and warehouse workers.[101] The population-attributable fraction for COPD from occupational exposure has been reported as 48% in a Danish cohort,[99] 53% in Swedish construction workers,[102] and 56% in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA).[103] In the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study,[104] severity of airflow obstruction was increased with longer duration of exposure (>15 years) and higher number of inhaled vapours, gases, dusts, or fumes. Occupational airborne exposure in never-smokers has been linked to increased severity of COPD (GOLD severity ≥2, OR 4·5, 95% CI 1·7–11·9)[98] and increased risk of mortality from COPD (RR 2·1, 95% CI 1·2–3·8).[102]

Mechanisms

Exposure to organic dust—eg, from crop and animal farming—is a common risk factor for COPD and might activate inflammatory pathways.[8,99] In-vitro studies have shown that exposure of A549 alveolar, BEAS-2B bronchial epithelial, and THP-1 monocytic cell lines to poultry dust extract leads to increased expression of proinflammatory cytokines, chemokines, adhesion molecules, and pattern recognition receptors involved in innate immunity, which further amplify the inflammatory response (table 3).[43] There is a need for further studies of mechanisms that induce COPD for other occupational exposures.

Risk modification

Primary preventive measures should be implemented and maintained at workplaces, and regulated by public health authorities, to minimise exposure of workers to known inhaled vapours, gases, dusts, or fumes. More detailed, prospective epidemiological and toxicology studies are needed to confirm the specific chemicals and agents that drive occupational risk for COPD, to formulate strategies for mitigating exposure.

Tuberculosis

Risk of COPD

A history of pulmonary tuberculosis is associated with an increased risk of COPD, with ORs ranging from 2·6 to 5·8.[10,97,105] Patients with treated tuberculosis can have obstructive or restrictive defects on spirometry,[106] and lower diffusing capacity and inspiratory capacity than patients with COPD without a history of tuberculosis.[107] The risk of COPD is higher with multidrug-resistant tuberculosis than with drug-susceptible tuberculosis,[108] reflecting reduced responsiveness to treatment and greater lung tissue damage in multidrug-resistant tuberculosis. Tuberculosis has been identified as a risk factor for COPD in several single-country[14] or multi-national studies;[27] this association highlights the fact that the risk factors for COPD in never-smokers vary depending on the geographical region, and that strategies to reduce the risk of COPD need to reflect the prevailing risk factors.

Mechanisms

The mechanisms of development of COPD with tuberculosis are likely to involve endobronchial and lung tissue destruction from mycobacterial infection. Pathological features include tracheobronchial stenosis, small airway obstruction, bronchiectasis, bronchiolitis obliterans, and emphysema (table 3).[44] Innate immune responses activate tissue destruction through extracellular matrix degradation, with upregulation of integrin αVβ3 leading to adhesion of monocytes to the extracellular matrix and increased secretion of matrix metalloproteinases (MMPs).[45]

Risk modification

Patients with tuberculosis-associated COPD tend to be younger than patients with smoking-related COPD owing to the younger onset of exposure and infection with tuberculosis. Avoidance of delays in the initiation of treatment for tuberculosis, especially in younger people with developing lungs, might reduce the risk of COPD in the future. Given the large burden of tuberculosis in LMICs—especially in India, southeast Asia, and Africa—clinical and public health programmes should continue to aim to prevent tuberculosis transmission, promote early detection, and provide curative treatment to prevent pulmonary complications including COPD. Contact tracing is a key intervention to reduce tuberculosis transmission and therefore a crucial part of strategies to reduce tuberculosis-associated COPD. Research with a focus on the development of vaccines for tuberculosis, new strategies for diagnosis, and improved public health

systems for management will help to reduce the burden of tuberculosis and associated COPD.

HIV infection

Risk of COPD

People living with HIV have an increased risk of developing COPD. In a systematic review of 30 studies (151686 participants), COPD was more common in people living with HIV than in those who were HIV-negative (OR 1·14, 95% CI 1·05–1·25).[109] In a case-control study from Cameroon, which has a low prevalence of smoking, HIV was associated with COPD (FEV_1/FVC <LLN) with an OR of 2·8 (95% CI 1·2–6·7).[110] Predictors of COPD in people living with HIV infection included a history of pulmonary tuberculosis, chronic respiratory symptoms, and lower body-mass index. In a trial of antiretroviral treatment, the prevalence of COPD (FEV_1/FVC <LLN) was 6·8% in people living with HIV who had a CD4 cell count of more than 500 cells/μL before treatment, of whom 48% were never-smokers.[111] Never-smokers with HIV infection have a higher prevalence of emphysema and airway disease on chest CT than do never-smokers without HIV infection.[112]

Mechanisms

The link between HIV and COPD might arise from altered immune, inflammatory, and other mechanisms (table 3).[46] Lower CD4 cell counts have been associated with higher COPD and emphysema prevalence in patients with HIV.[113,114] Furthermore, lower CD4/CD8 ratios[115] and high levels of soluble CD14[114] have been associated with more severe emphysema. In cultures of bronchial epithelial cells at an air–liquid interface, exposure to HIV reduced expression of adhesion molecules (E-cadherin), increased permeability of the cell monolayer, and activated inflammation through extracellular signal-regulated kinase (ERK) phosphorylation.[47] Sputum of patients with HIV who were colonised with *Pneumocystis jirovecii* had increased levels of MMP12 and more severe airflow obstruction.[48]

Risk modification

Public health interventions should continue to prevent transmission and enhance control of HIV to minimise the risk of COPD.[46] COPD should be considered in people living with HIV who have respiratory symptoms, in whom spirometry should be undertaken for early detection and optimum management of COPD. As well as providing support for people living with HIV to avoid cigarette smoking, reducing detectable HIV viral load with antiretroviral therapy could ameliorate mechanisms leading to the development of COPD.

Impaired lung growth and early-life exposures

Risk of COPD

Impaired lung growth and lack of attainment of maximal lung size are recognised as factors that contribute to COPD.[116] In an analysis of three large cohorts, among the participants who were never-smokers and who developed COPD, 74% had low baseline lung function (percentage of predicted FEV_1 <80%) and non-rapid decline in FEV_1.[117] Thus, not all COPD in never-smokers is due to accelerated decline in lung function; instead, low baseline FEV_1 in early adulthood is an important risk factor for subsequent COPD that reflects multiple early-life exposures to risk factors such as biomass smoke or asthma, in addition to poor nutrition, parental smoking, and recurrent respiratory tract infections during childhood.[50,51] Preterm birth, which can lead to bronchopulmonary dysplasia and post-prematurity lung disease in infants and children, has also been associated with airflow obstruction and COPD in later life.[118]

Role of early-life exposures

A number of factors might contribute to impaired lung growth in childhood and early adulthood, including repeated respiratory infections, socioeconomic and dietary factors, and exposure to environmental tobacco smoke (second-hand smoke or passive smoking; table 3). In many communities affected by noxious and infective exposures, children aged 5 years and younger already have established respiratory symptoms of wet cough and wheeze, and have frequent respiratory infections that could have a lasting impact on lung function.[119] Interactions between factors associated with impaired lung growth—such as an increased risk of recurrent infections due to crowded living spaces and poor nutrition—are likely to have an important role in low-income settings.[119]

In 1781 never-smokers from the MESA cohort,[52] environmental tobacco smoke exposure in childhood was associated with a greater degree of early emphysema and overall percentage emphysema measured on cardiac CT scans that were used to screen for cardiovascular disease. Heavy maternal smoking (>20 cigarettes per day) during childhood increased the risk of airflow obstruction in middle-aged adults (OR 2·7, 95% CI 1·3–5·7).[120] In a study of 910 never-smokers in China, environmental tobacco smoke exposure was associated with increased mortality due to COPD (RR 2·3, 95% CI 1·1–5·0), as well as coronary artery disease, stroke, lung cancer, and all causes.[121] A genome-wide study using three Dutch and Swiss cohorts reported a number of interactions between environmental tobacco smoke exposure and single-nucleotide polymorphisms linked to pathways involving apoptosis, p38 mitogen-activated protein kinase (MAPK) activation, and tumour necrosis factor (TNF), indicating the potential contribution of genetic factors to lung injury responses leading to COPD in people who have never smoked.[49] Michael Cho and colleagues provide an overview of genetic risk for COPD in the first paper in this Series;[122] Rosa Faner and colleagues consider the role of gene–environment interactions and their association with lung function trajectories across the lifespan in the third paper.[119]

Risk modification

In addition to strategies for risk modification discussed in the previous sections—and the important goal of reducing environmental tobacco smoke exposure—identification of factors that can lead to low maximally attained lung function by the end of childhood could help with targeting of measures to prevent or reduce impairment of lung growth, which predisposes to COPD. For example, COPD risk could be modified through measures to reduce the chance of preterm birth, optimise management of respiratory disease such as asthma in childhood, reduce the risk and effect of repeated respiratory infections, and ensure adequate diet and healthy living conditions. Such strategies to reduce early-life exposures to risk factors for impaired lung growth and COPD will be key to improving lifelong lung health. Screening for low baseline lung function and early COPD during young adulthood (<40 years), especially in those with associated symptoms, could allow preventive measures to slow the progression of disease in at-risk individuals and enable appropriate pharmacotherapy to be offered to those with COPD.[50,123,124]

Socioeconomic status

Risk of COPD

Lower socioeconomic status influences risk of COPD. In the 2007 China Chronic Disease Risk Factor Surveillance (CCDRFS) survey,[125] low educational attainment and lower household income were associated with higher risk of self-reported, physician-diagnosed COPD, including in the subgroup of never-smokers (OR for lower educational level 1·8, 95% CI 1·4–2·2, n=752; OR for lower household income 1·3, 1·1–1·6, n=680). Lower socioeconomic status was associated with higher risk of COPD in KNHANES IV, from 2007 to 2009.[97] Rural residence was associated with COPD (OR 1·3, 95% CI 1·1–1·6) among never-smokers in the USA.[126]

Related factors and risk modification

Factors that might explain the effect of lower socioeconomic status on COPD risk include exposure to biomass smoke, malnutrition, occupational exposures, poorer living conditions, reduced access to screening and health care, and less awareness of risks to lung health.[125] Exposures in early life could affect lung development and baseline lung function in early adulthood. Besides aiming to improve standards of living and reduce air pollution and occupational exposures, a goal of future studies should be to determine the most critical period in the lifecycle (eg, during lung development in childhood) in which factors associated with lower socioeconomic status confer the greatest risk for COPD. Raising awareness among those at risk would be beneficial to promote preventive measures.

Conclusions and future directions

For decades, airflow limitation that met spirometric criteria for COPD but was not caused by tobacco smoking was regarded as a rarity. If not associated with long-standing asthma, airflow limitation was considered to be due to occult exposures to dusts, fumes, and gases, often unknown to the individual and difficult to quantify, especially if there were multiple sources. The evidence discussed in this Series paper suggests that this view needs to be reconsidered, and that tobacco is just one of many risk factors for COPD.[127]

Removal of at-risk individuals from the suspected risk factor is the most important step to prevent the development of COPD if there is an ongoing source of exposure such as occupational fumes or biomass smoke. In the absence of research into optimal therapy for COPD in never-smokers, conventional approaches to COPD management based on the GOLD strategy[2] are advocated. Research is urgently needed to fill these gaps, as biomass-related COPD and other causes of COPD in never-smokers have clinical features and trajectories that differ from those of tobacco-related COPD, and might benefit from different approaches to both pharmacological and non-pharmacological management. Similarly, COPD associated with specific risk factors with distinct mechanisms of action, such as occupational or early-life exposures, might require different treatment approaches. The Chronic Airway Diseases Early Stratification (CADSET) research collaboration[128] will focus on the way in which trajectories of lung function through life affect the clinical presentation of chronic airways diseases, including COPD; through studies of the determinants and implications of lung function trajectories, the aim is to identify distinct biological mechanisms, endotypes, and associated biomarkers, which could help in the development of targeted strategies for the treatment and prevention of COPD.

For more on the **CADSET collaboration** see https://cadset.org/

Most importantly, many of the environmental exposures associated with an increased risk of COPD are particularly prevalent and currently unregulated in LMICs, where poverty is an underlying cause of increased risk for COPD in never-smokers. Women and children are highly exposed to biomass fuels and fumes through indoor cooking and heating, as well as through smoke and fumes in occupational settings, and increasingly bear the brunt of non-tobacco-related COPD. For many at-risk individuals, a common feature is likely to be exposure to a combination of several risk factors, such as overcrowding and poor nutrition (both indicators of low socioeconomic status), indoor burning of mosquito coils and incense (an example of early-life exposure to pollution), and recurrent respiratory tract infections, even in HICs.[129] In high-income settings, women who have never smoked also seem to be more likely than men who have never smoked to develop COPD.[15,27] As the global population increases and these exposures remain widespread, so the global prevalence of COPD is predicted to rise.[130,131] Ongoing studies (appendix 2, p 1) will shed further light on current trends in COPD in never-smokers and help to address unanswered questions (appendix 2, p 2).

See **Online** for appendix 2

Search strategy and selection criteria

We searched the Ovid version of MEDLINE using a combination of MeSH search terms and free-text terms to create a core search strategy for the topics "nonsmoker*" and "COPD" for papers published in English from Aug 1, 2009, to Sept 1, 2021 (using the Entry Date field for the MeSH searches and the Date Created field for the free-text search). Several aspects of this core topic were then searched with the terms "epidemiology", "risk factors", "occupational exposure", "air pollution", "tuberculosis", "asthma", "respiratory tract infections", "HIV", and "biomarkers". References were supplemented by additional key papers identified by the authors. The final list of cited articles was selected on the basis of their relevance to the aims of this Series paper.

It often falls to committed health professionals to raise awareness, lobby governments, and engage in policy setting and review to achieve policy and programme change. In LMICs, clinicians must become local champions for change, and advocate simple, affordable approaches that can be widely implemented. However, some of these initiatives will not be successful without political support, education, improved infrastructure, reliable services, and community engagement.

Education is key for all stakeholders—people at risk, health-care professionals, government, industry, and others—to understand the risks and the associations between exposure and illness. Women could be a key target for education as they spend more time with children and are often engaged in domestic activities with them. Further research to elucidate the relationship between early-life nutrition and increased risk of infection (and development of airflow limitation) in the context of noxious and infective exposures is also needed, as these exposures might interact.[129] Appropriate nutrition, reduced crowding, and even modest family planning practices can minimise the risk of poor nutrition and recurrent infections in children, and should be at the heart of efforts to improve lung health.

Early detection of COPD can play a part in reducing the risk of developing more severe COPD. Identifying COPD early can provide an opportunity for intervention through appropriate treatment and, crucially, by minimising ongoing exposure and driving research to define effective treatment strategies. This is especially relevant to countries with a high burden of tuberculosis, where prompt diagnosis enables minimisation of transmission risk, ongoing lung damage, and risk of developing tuberculosis-associated COPD. Public health authorities and clinicians also need strategies to overcome barriers to detection of COPD in never-smokers, such as low levels of clinical suspicion and testing, rurality, low socioeconomic status, low education and health literacy levels, and variations within or between countries in non-tobacco exposures, which presents a challenge for targeting screening efforts.

COPD in never-smokers remains an important challenge for clinicians, researchers, public health authorities, and communities worldwide. Advocacy efforts to minimise or prevent exposure to risk factors must continue, based on robust evidence from epidemiological, translational, clinical, and implementation research. Moreover, early diagnosis should be promoted and research efforts prioritised to identify optimal management strategies, tailored to the underlying causes and mechanisms of disease where possible, for never-smokers affected by COPD.

Contributors

All authors contributed equally to the concept, literature review, writing, and revisions of the manuscript.

Declaration of interests

IAY is a co-chair (unpaid) of the COPD-X Guidelines Committee of Lung Foundation Australia. CRJ reports receiving a grant to undertake an investigator-initiated clinical trial paid to her institution from GSK; consultancy fees from Novartis and AstraZeneca; honoraria for the development of educational materials from Boehringer Ingelheim, Novartis, and AstraZeneca; speaker's fees from Boehringer Ingelheim, Novartis, AstraZeneca, Cipla, and GSK; payment for expert testimony from Novartis and Chiesi; travel reimbursement from GSK, AstraZeneca, and Novartis; payment for advisory board membership and attendance at meetings from GSK, AstraZeneca, and Novartis; payment for attendance at meetings as a member of the National Dust Diseases Taskforce; and is chair (unpaid) of the board of Lung Foundation Australia and director (unpaid) of the Asbestos Diseases Research Institute. SSS is a member (unpaid) of the Board of Directors of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

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