exposure to risk factors.

Other types of tobacco (e.g., pipe, cigar, water pipe)[72-74] and marijuana[75] are also risk factors for COPD. Passive exposure to cigarette smoke, also known as environmental tobacco smoke (ETS) and second-hand smoking, may also contribute to respiratory symptoms and COPD,[76] especially after long-term exposure.[77] Smoking during pregnancy poses a risk for the fetus, by altering lung growth and development *in utero*, and possibly priming the immune system by inducing specific epigenetic changes.[78] This is a good example of the GETomics approach discussed above. The fetus exposed to 'passive smoking' is likely to respond differently to a second GxE hit later in life.[7]

Biomass exposure

Tobacco smoking has been recognized as a major risk factor associated with COPD for over five decades, but this was largely because most research was conducted in high income countries. As more studies from LMICs were conducted,[19] it became apparent that non-smoking risk factors were more important in these parts of the world. Whilst tobacco smoking remains the leading risk factor for COPD in high income countries, accounting for over 70% of the cases, in LMICs tobacco smoking contributes to around 30% to 40% of the total burden.[9] Because the LMICs together contribute to over 85% of the total burden of COPD globally, non-smoking risk factors now contribute to over 50% of the global burden of COPD.[9]

Wood, animal dung, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to very high levels of household air pollution.[79] Household air pollution exposure is associated with an increased risk of developing COPD in LMICs[80] although the extent to which household air pollution versus other poverty-related exposures explain the association is unclear.[81-84] Almost three billion people worldwide use biomass and coal as their main source of energy for cooking, heating, and other household needs, so the population at risk worldwide is very large.[85,86] There is limited research about household air pollution related COPD or the interventions that could reduce the risk of developing it.[87] Based on a systematic review, the use of gas for heating and cooking reduced the risk of COPD and other respiratory diseases and may be considered as a transitional fuel option in areas where clean fuel (electricity) is not readily available.[88]

Many of the environmental exposures in LMICs are currently unregulated and, in combination with poverty and poor nutrition, amplify the risk of airway and lung parenchymal damage. Advocacy efforts to minimize exposure to risk factors must continue, based on robust evidence from epidemiological, translational, clinical and implementation research.[9] There are no randomized controlled trials (RCTs) that have addressed the appropriate pharmacotherapy of non-smoking COPD. There is therefore an urgent need to conduct robust RCTs to better understand the most effective treatment that can be offered to non-smoking COPD. Phenotypic differences between smoking and non-smoking COPD have been reported in only a few studies. In brief, compared to COPD in smokers, non-smoking COPD is more common in females, in younger age groups, exhibits similar (or milder) respiratory symptoms and quality of life, a lesser rate of decline in lung function over time, lower neutrophils and a trend towards higher eosinophil numbers in the airway sputum, similar spirometric indices, greater small airways obstruction (respiratory oscillometry and radiology), less emphysema and a similar defect in macrophage phagocytosis of pathogenic bacteria.[89-91] Potential molecular mechanisms for non-smoking COPD include inflammation, oxidative stress, airway remodeling and lung aging.[9] There is evidence from the SPIROMICS cohort study that the association of indoor PM2.5 with annual FEV1 decline differed by smoking status. Among people with, or at risk of, COPD former smokers living in high PM2.5 homes had rates of lung function decline similar to current smokers, whereas in low PM2.5 homes lung function decline was similar to never smokers.[92] A small RCT has shown that in-home use of portable particulate air cleaners may help to improve outcomes such as moderate exacerbation risk and breathlessness, with people who spend more time indoors more likely to benefit.[93] However, there are still several knowledge gaps that exist. Research is urgently needed to fill these gaps, as COPD related to biomass exposure, tobacco smoking or various other causes (see below) might exhibit different clinical features and trajectories, and benefit from different approaches to both