Air pollution as an early determinant of COPD

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Early exposure to air pollution represents a potential determinant to develop COPD at an adult age, but methodological and conceptual improvements calling on interdisciplinary approaches are still needed to reach a stronger level of proof https://bit.ly/3xWwRwP

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Abstract

COPD is a progressive and debilitating disease often diagnosed after 50 years of age, but more recent evidence suggests that its onset could originate very early on in life. In this context, exposure to air pollution appears to be a potential contributor. Although the potential role of air pollution as an early determinant of COPD is emerging, knowledge gaps still remain, including an accurate qualification of air pollutants (number of pollutants quantified and exact composition) or the "one exposure–one disease" concept, which might limit the current understanding. To fill these gaps, improvements in the field are needed, such as the use of atmosphere simulation chambers able to realistically reproduce the complexity of air pollution, consideration of the exposome, as well as improving exchanges between paediatricians and adult lung specialists to take advantage of reciprocal expertise. This review should lead to a better understanding of the current knowledge on air pollution as an early determinant of COPD, as well as identify the existing knowledge gaps and opportunities to fill them. Hopefully, this will lead to better prevention strategies to scale down the development of COPD in future generations.

Introduction

COPD is a noncommunicable and heterogeneous disease that was reported to affect 251 million people in the world in 2016. COPD is currently the third leading cause of death in the world, accounting for 6% of all deaths globally [1]. COPD is a progressive and debilitating disease often diagnosed after 50 years of age, with patients potentially being asymptomatic for years before the initial diagnosis. As such, COPD has long been considered as an adult-only disease, resulting from exposure, at an adult age, to noxious agents, with cigarette smoking identified as the main risk factor for developing the disease. However, the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of COPD clearly indicates the occurrence of early life events as potentially important in the natural course of the disease: "COPD is a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particle or gases and influenced by host factors including abnormal lung development" [2]. Hence, air pollution could be considered as an early determinant of COPD given its effects on lung development. Indeed, air pollution is currently the third risk factor for early death worldwide [3] and it is acknowledged to be an important modulator of COPD morbidity and mortality. However, evidence for its causal role in adult-onset COPD remains insufficient to date [4], although a recent study by Shin *et al*. [5] might open new avenues in the field.

In this review, we will describe the current understanding of the potential role of air pollution as an early determinant of COPD, as well as the remaining gaps of knowledge and opportunities to fill them. Hopefully, this will lead to better prevention strategies to scale down the development of COPD in future generations.

COPD

COPD is actually an umbrella diagnosis. Indeed, the airflow obstruction that is characteristic of COPD patients results from a combination of small airway disease and emphysema (parenchymal destruction). The individual contribution of each of these phenotypes varies largely between patients, leading to a great heterogeneity in COPD phenotypes. Clinically, COPD is supposed to be considered in any patient presenting one of the following symptoms: dyspnoea, cough or sputum production [2]. The pathophysiological mechanisms underlying COPD are chronic inflammation, protease and anti-protease imbalance, oxidative stress, accelerated senescence, and autophagy [6].

Risk factors for developing COPD

Cigarette smoking and α1-antitrypsin (AAT) deficiency are, respectively, the most studied environmental and genetic risk factors for developing COPD, and more specifically emphysema as a key component of the disease. The first direct link between cigarette smoking and altered lung function was established in the late 1950s in the seminal study by Motley and Kuzman [7]. Notably, this study was designed to "establish an objective evidence as to whether or not a patient should stop smoking, particularly those presenting emphysema". It was shown that lung compliance decreased in all patients after smoking one cigarette and that arterial blood oxygen saturation and arterial oxygen tension decreased significantly in patients with severe or very severe emphysema only. The authors then concluded that "patients with severe emphysema would be better off if they stopped smoking". During the 1960s, a longitudinal study by Fletcher and Peto [8] established a landmark in the natural history of chronic airflow obstruction. Indeed, by measuring forced expiratory volume in 1 s (FEV_1) every 6 months for 8 years in 792 men (30–59 years) working in West London, the study emphasised the importance of smoking in causing airflow obstruction. Moreover, they determined for the first time that FEV_1 falls gradually over a lifetime and that smoking causes irreversible obstructive changes, with a rate of decline of FEV_1 that was much slower in ex-smokers than in continuing smokers. Interestingly, not all smokers in the study were susceptible to such changes and it is now understood that less than 50% of heavy smokers develop COPD during their lifetime [9], suggesting the involvement of risk factors other than cigarette smoking. Indeed, other environmental exposures, such as occupational exposures, are risk factors for developing COPD [10, 11]. It has been estimated, for example, that up to 19.2% of COPD cases among 10 000 adults aged 30–75 years are attributable to workplace exposures, such as farming, cleaning or industrial work [12, 13]. Importantly, particulate matter, various metals, solvents, fumes and gases present in air pollution are generated by industries and present at higher concentrations in workplaces. Moreover, indoor air pollution, such as that caused by biomass burning, is supposed to be a risk factor for developing COPD, at least among women in developing countries [13, 14].

Severe AAT deficiency was the first documented genetic risk factor for COPD, with an incidental study in the early 1960s by Laurell and Eriksson [15]. The initial aim of this work was to better characterise a new type of dysproteinaemia, where very pronounced AAT deficiency was observed in five adult patients, all but one below 45 years old. The clinical observation of these patients determined that three of the five had widespread pulmonary lesions consistent with severe emphysema. Moreover, the sister of one of those three patients also had pronounced emphysema, leading the authors to suggest an inherited defect. They further confirmed this hypothesis by later conducting a family study of 14 family members [16]. Although AAT deficiency affects only a small number of COPD patients, it is now well accepted that this genetic condition considerably increases the risk of developing emphysema, bringing to the fore the importance of genetics into COPD susceptibility. Since then, and independently from ααt deficiency, several studies showed that the prevalence of abnormal lung function was higher among the relatives of patients with COPD [17]. In addition, twin studies also confirm that genetic variation can contribute to COPD development [18–21]. Several single-gene polymorphisms have also been suggested as being significantly involved in COPD pathogenesis, such as those implied in the oxidant–antioxidant system, inflammatory mediators or protease/antiprotease imbalance [22–26]. An important caveat regarding the current understanding of COPD genetics is that it does not allow to assess if these identified genes are directly responsible for COPD or are merely secondary markers of causal genes [23, 24].

Early origins of COPD

As mentioned earlier, it is important to note that until relatively recently and setting aside a genetic origin of the disease, COPD was mostly considered as an adult-onset disease mainly resulting from adult smoking and the accompanying accelerated decline of lung function. The first direct suggestion of paediatric origins of COPD was proposed by Burrows *et al.* [25], in a study where they compared, in the general population, 415 adults who had suffered childhood respiratory problems before the age of 16 years to 2211 adults who denied such history. From those subjects, they determined that the individuals presenting respiratory abnormalities in adulthood were often those who experienced childhood respiratory

problems. Moreover, subjects having a history of childhood respiratory disease and who smoked during adulthood presented a lower FEV_1 and % predicted forced expiratory flow after exhalation of 75% of the forced vital capacity ($V_{max25\%}$) compared with smokers without childhood respiratory disease. Although this study was not longitudinal and thus did not anticipate the occurrence of lung function trajectories, the authors suggested for the first time that "paediatric illnesses may be an important additional risk factor for adult cigarette smokers and that such childhood illnesses may account for a relatively large fraction of airway problems noted in adults who have never smoked cigarettes" [25]. Significantly, this study was published at the same time that FLETCHER and PETO [8] published their landmark study on the natural history of chronic airflow obstruction, introducing the concept of lung function trajectories. At that time, it was considered that lung function entering adulthood was similar in all adults and that its further decline was a question of smoking/not smoking combined with a particular susceptibility. Since then, much progress has been made and it is now established that the lung function entering adulthood is not the same for everyone and is highly dependent on events that occur at an earlier age, even in the pre-natal period.

Over the course of a lifetime, lung function trajectory can be schematically divided into three phases: lung growth, a plateau phase and a progressive decline. Lung growth starts *in utero* and reaches an optimal value at early adulthood, at around 20–25 years old [26–28]. At that time, lung function reaches a plateau that lasts a few years and then declines with normal aging. Importantly, the height of the lung function plateau varies among people. Accordingly, independently of the rate of lung function decline during adulthood, those with a limited maximum attainment in early adulthood are more likely to present abnormal lung function during late adulthood. Numerous studies have demonstrated that a limited lung function in infancy and/or childhood correlates with subsequent respiratory symptoms and/or diseases, making it highly important to secure the best quality of lung function as early as possible [29], particularly in the context of COPD. In the following, we will describe the different perinatal and early events that can influence the maximal lung function achieved in early adulthood, how they interplay and what is known about the resulting later susceptibility to COPD.

Pre-term birth is one of the major factors influencing lung function later in life. It is estimated that approximatively 15 million babies are born prematurely each year, making prematurity the leading cause of death in children under the age of 5 years [30]. Prematurity refers to infants born before 37 weeks of pregnancy, with three subcategories: extremely pre-term (<28 weeks), very pre-term (28 to <32 weeks) and moderate to late pre-term (32 to <37 weeks) [31]. Pre-term birth can therefore occur at the end of the canalicular stage (when bronchioli appear and alveolar epithelium development starts) or saccular stage (when branching morphogenesis reaches an end, alveolar epithelial differentiation continues and surfactant production begins) [32, 33], while normal lung function is fully achieved at 36 weeks of gestation, *i.e.* at the end of the saccular/beginning of the alveolar stage of lung development [34]. As such, premature birth is highly important since it emerges in a critical window of rapid lung development, *i.e.* before the onset of lung alveolarisation. Numerous studies have shown that pre-term birth is associated with reduced lung function later on, such as low expiratory flow at 1 month of age, obstruction of small airways and low FEV_1 during childhood or early adulthood (reviewed in [29]). This is observed even in healthy premature infants. Importantly, premature infants born before 28 weeks gestational age remain at high risk of developing bronchopulmonary dysplasia (BPD), a chronic lung disease characterised by impaired lung and airway function, subsequent to the impairment of alveologenesis and paucity of microvasculature [35, 36]. BPD is more likely to occur in infants born extremely pre-term (below 1500g); indeed, more than 70% of infants born at 22–24 weeks of gestation are diagnosed with BPD [37]. Pre-term survivors with a history of BPD are consistently reported to have impaired airflow from childhood to adolescence [38]. This may continue until adulthood as survivors of moderate or severe BPD are found to have emphysema at a young adult age [39]. Intrauterine growth restriction (IUGR), characterised by insufficient and inappropriate fetal growth, is a known risk factor for pre-term birth. IUGR affects 5–10% of all pregnancies and is associated with decreased lung function trajectories [40]. Moreover, long-term follow-up studies have shown that a low birth weight is associated not only with a decreased lung function in adulthood, but also a reduced lung capacity and elasticity, resembling a COPD phenotype [40]. Altogether, these early life events might represent a particular susceptibility to develop COPD at adult age.

Another important contributor to early alterations of lung function is maternal cigarette smoking during pregnancy, which, incidentally, also constitutes a risk factor for pre-term birth. Over the last two decades, epidemiological studies have consistently reported an association between maternal smoking during pregnancy and respiratory disorders in offspring, with a higher risk of pre-term birth and low birth weight [41–43], as well as a higher risk of developing lung diseases such as BPD, asthma, pulmonary infectious disease and low respiratory illness [44–47]. Maternal smoking during pregnancy is also reported to be associated with a reduction of lung function in children at the age of 18 months, the effect being greater in

female children [48]. Experimental studies suggest that abnormal lung development and lung alveolarisation, associated with decreased lung volume and function, could be the mechanisms underlying these consequences of maternal exposure during gestation [49–52]. Studies that report a direct link between maternal smoking during pregnancy and COPD development remain sparse, mainly because birth studies in this context are unrealistic due to the necessary observation time. One study conducted in COPD patients by Beyer *et al.* [53] showed that those raised in households with smoking mothers had a lower FEV_1 than those raised without maternal second-hand smoke exposure. Paternal smoking during childhood, however, had no influence on the further lung function of COPD patients. Interestingly, maternal smoking during pregnancy is also associated with increased risk, for the children, for early tobacco experimentation [54–56], which is a known risk factor for developing COPD later in life.

Caesarean section (C-section) is now a very common surgery. Children born by C-section present decreased respiratory system compliance [57], significantly lower thoracic gas volume, stiffer lungs, higher total pulmonary resistance and lower tidal and minute volume compared with those born by vaginal delivery [58]. Epidemiological studies report that C-section is associated with an increased risk of neonatal respiratory distress syndrome [59], as well as a higher incidence of having asthma compared to babies delivered vaginally [60]. Moreover, a meta-analysis of 26 studies conducted by Bager *et al.* [61] shows that C-section delivery is highly associated with allergic rhinitis, asthma and hospitalisation for asthma. One of the hypotheses is that children born by C-section are more likely to have aberrant microbiomes, which consequently may alter immune system development and influence atopy. The development of asthma during childhood is particularly significant in the context of later COPD development, as children born with a reduced lung function are more likely to have asthma [62] and children with asthma often have impaired lung function, which might be persistent through adulthood [63]. This persistent decreased lung function may be the result of the lung's failure to reach the expected plateau phase at adulthood. Moreover, the lung function outcome in adulthood is highly determined by asthma severity during childhood and children with severe asthma have a 32 times higher risk of developing COPD as an adult compared with those who are nonasthmatic [64, 65]. Overall, individuals born by C-section are more likely to develop respiratory disorders together with an increased risk of reduced lung function, both of which may cause permanent impaired lung function and COPD at an adult age.

Early determinants that can modify lung function trajectories, such as pre-term birth, maternal smoking during pregnancy, IUGR or paediatric respiratory disease, are now considered as being potentially linked to a particular susceptibility to develop COPD at an adult age. It is obvious that these determinants are intimately linked, highly interplaying with each other, while they cannot account for the totality of the origins of the development of the disease. Recently, the influence of air pollution on the development of COPD has been considered and we will develop this specific issue in the following section.

Air pollution as an early determinant of COPD

One of the first examples of scientific evidence that air pollution has deleterious effects on health was published after a peak pollution episode in the Meuse Valley in 1930 [66]. Such evidence has been extended with the description of the London smog episode of late 1951, when 4000 additional deaths were counted after 4 days of intense industrial air pollution, compared to the same period in the years before [67]. Numerous studies followed these two seminal papers and air pollution is now recognised as the main environmental risk factor for health. As such, it represents a major global public health issue; it is currently the fourth leading risk factor for mortality worldwide [3]. Globally, nine out of 10 people breathe polluted air and there are 7 million deaths annually due to air pollution [68–70]. Moreover, fine particulate matter (particulate matter (PM) equal or inferior to 2.5 µm in diameter ($PM_{2.5}$)), household air pollution and ozone (O_3) together contribute as much as 40% of deaths from COPD [3]. In the following, we will describe what is known about the acute/long-term effects of air pollution on healthy and compromised lungs, with a particular focus on COPD disease, and then discuss how air pollution could be considered as an early determinant of COPD.

The health effects of air pollution can be observed either after pollution peaks (acute effects) or because of long-term exposure to elevated levels of pollutants (chronic effects). In healthy adult subjects, numerous studies have shown that acute exposure to air pollution peaks is accompanied by a transient decrease in lung function with or without accompanying symptoms. The same is true for children, which could be of interest for the later development of COPD [3, 67, 71–73]. Using an interesting set-up, a recent study performed in healthy students (mean age 15.1 years) from an isolated island in Japan without major artificial sources of air pollutants showed that increases in black carbon and O_3 concentrations had acute effects on the pulmonary function of these students, with decreased FEV_1 or peak expiratory flow, respectively [72]. In the same way, studies have shown that exposure to elevated levels of carbon

monoxide (CO), nitrogen dioxide (NO_2) or PM equal or inferior to 10 µm (PM_{10}) increased the percentage of emergency department visits for acute exacerbations of COPD in Brazil and Italy [73, 74]. Smoke and wildfires also increased the risk of emergency visits in COPD patients [75, 76]. However, in a more integrated Korean COPD subgroup study of the "external" and "internal" factors associated with exacerbation of COPD, PM_{10} level was significantly associated with acute exacerbations of COPD in the univariate analysis but not in the multivariate analysis.

Chronic exposure to air pollution is associated with an exaggerated decline of lung function that is particularly marked during the first years of life, including during the intrauterine period [77]. Indeed, in children, deleterious effects on lung growth and lung function have been reported after exposure to high levels of air pollution [78, 79]. Moreover, recent studies suggest that exposure to pollution during the intrauterine period may have deleterious consequences on fetal growth and development (decreased birth weight, increased risk for pre-term birth, *etc.* [80]). A very recent study showed that higher exposure to $PM_{2.5}$ in the first 16 weeks of pregnancy was associated with a significantly lower birth weight among other smaller fetal growth measures [81]. These observations may have a particular resonance in the context of the early origins of COPD. In the city of Guangzhou, China, a study comparing two highly polluted areas over 5 years showed that higher levels of air pollution (PM_{10}, NO_2 and sulphur dioxide (SO_2)) was associated with a significant reduction in lung growth, particularly for boys [82]. It is also interesting to note that China and India, nations with high levels of air pollution, alone contribute to half of the world's COPD cases [83]. In a seminal prospective study that followed children from 10 to 18 years of age in 12 cities in California, GAUDERMAN *et al.* [84] found a reduction in the total growth of FEV_1 that was associated with $PM_{2.5}$, NO_2, acid vapour and carbon particles. In communities exposed to the highest level of pollutants, the proportion of 18-year-old subjects having an FEV_1 of less than 80% of the predicted value was 4.9 times higher (a prevalence of 7.9%) than in communities with the lowest levels. Biomass burning can also represent a big contributor to air pollution, particularly in low- and middle-income countries (LMICs). According to a World Health Organization (WHO) estimation, about 3 billion people worldwide are exposed to biomass fuel and most of them live in LMICs [85], where the main risk factor for developing COPD is indoor biomass fuel exposure. Biomass fuel exposure is the leading risk factor of COPD among women in south, southeast and east Asia, and the Oceania super regions. Indeed, more than 90% of COPD deaths occur in LMICs and 75% of them are women [86]. In these countries, women are used to cooking with biomass fuel in poorly ventilated environments with their children. This could have dramatic consequences on the development of COPD later on in life and could identify biomass fuel exposure as an early determinant of COPD. Burning of biomass fuel can generate huge amounts of pollutants such as PM, CO, nitrogen oxides (NO_x), benzene and polycyclic aromatic hydrocarbons [87]. As an example, during cooking, the concentration of PM_{10} is reported to be up to 30 000 $\mu g \cdot m^{-3}$, whereas the WHO-recommended 24-h mean PM_{10} concentration is only 50 $\mu g \cdot m^{-3}$ [88]. Being repetitively exposed to these pollutants can have a substantial impact on the lung function of women and their children. Studies showed that women exposed to biomass fuel have a significantly low FEV_1/forced vital capacity ratio, together with a higher prevalence of cough, phlegm, wheeze and breathlessness, compared with those not exposed to biomass fuel [89–91]. The incidence of women exposed to biomass fuel smoke developing COPD is about 2.4 times higher than those exposed to liquefied petroleum gas [92]. Children exposed *in utero* to biomass fuel have significantly low birth weight and have lower respiratory infections [93]. Women exposed to air pollution during pregnancy are more likely to have children born pre-term and with low birth weight [94]. Altogether, these observations strongly suggest that early exposure to air pollution may lead to several events that act as susceptibility factors to develop COPD as an adult, thus making air pollution a potential early determinant of COPD (figure 1).

Several mechanisms could underlie the suggested role of air pollution as an early determinant of COPD. As stated earlier, the pathophysiological mechanisms underlying COPD are mainly chronic inflammation, protease and anti-protease imbalance, oxidative stress, accelerated senescence, and autophagy [6]. Many of these mechanisms have been described for air pollution and could therefore account for its adverse effects on (lung) health. First, the induction of an inflammatory response, which is an important driver of airway and lung parenchyma remodelling in COPD patients, has been described after exposure to air pollution; for example, increased plasma levels of pro-inflammatory cytokines such as interleukin (IL)-6, tumour necrosis factor-α and IL-1β in children and adults exposed to air pollution. Interestingly, these cytokines are also detected in bronchoalveolar lavage, serum or sputum from COPD patients, and are associated with pre-term birth [95–98]. Secondly, oxidative stress, which significantly contributes to the amplification and perpetuation of COPD inflammatory response, has been suggested to be the main mediator of air pollution toxicity [99, 100]. As an example, markers of oxidative stress such as 8-hydroxy-2-deoxyguanosine and 8-isoprostane are highly expressed in the exhaled breath condensate of COPD patients, as well as in

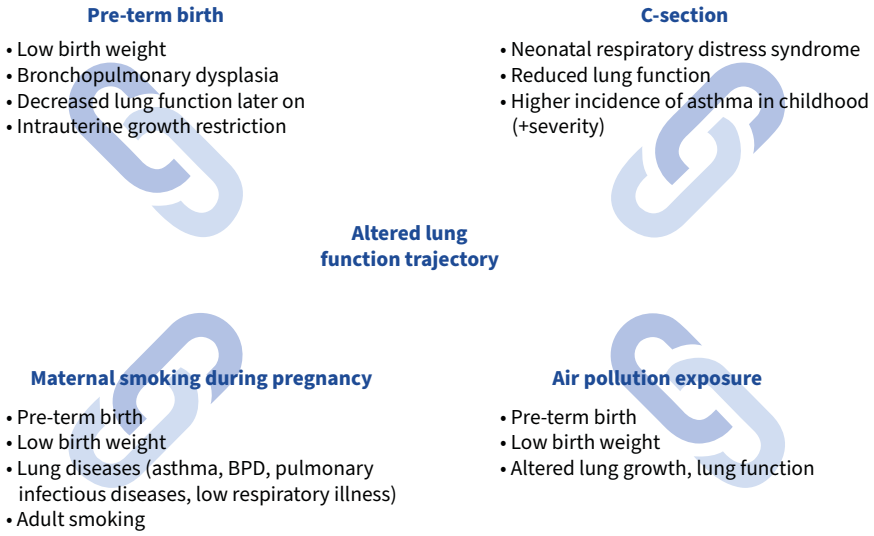

FIGURE 1 Early determinants of altered lung function trajectories and associated risk. BPD: bronchopulmonary dysplasia.

children exposed to air pollutants [101]. Moreover, in COPD, the imbalance between proteases and anti-proteases is the major reason for extracellular matrix degradation. Such imbalance has been described both in subjects and in experimental models after exposure to air pollution [102]. Furthermore, in a birth cohort of 641 newborns, placental shortening of telomere length, a marker of senescence, was observed in the newborns of mothers exposed to higher levels of $PM_{2.5}$ [103]. In addition, early pregnancy exposure to PM_{10} was associated with placental DNA methylation [104]. Remarkably, DNA methylation in COPD patients is highly associated with disease progression and severity, and cellular senescence is a well-known driver of COPD pathophysiology [105]. Finally, autophagy, which is deregulated in COPD patients, is reported to play a protective role in response to air pollution exposure [106]. Interestingly, a study by Li *et al.* [107] recently found that the disruption of placental autophagy flux was highly associated with IUGR.

Knowledge gaps

Our review brings together the multidisciplinary expertise of a paediatrician, an adult lung specialist, biologists specialised in lung pathophysiology in response to environmental exposures, as well as that, of note, of a specialist in atmospheric physico-chemistry. This is an important asset of this review as, although not systematic, it allows us to propose an innovative comprehensive discourse on the biological effects of air pollution. A physico-chemistry background is mostly missing in the current literature on the subject.

As discussed, exposure to air pollution appears to be a plausible contributor to the early origins of COPD. However, further evidence needs to be accumulated; for example, by setting up birth cohorts with lifelong follow-up, as COPD disease is only declared during (late) adulthood. Such research, as well as being difficult to implement, should moreover be accompanied by some knowledge gap-filling regarding air pollution characterisation and data measurement.

The European Environment Agency defines air pollution as "The presence of contaminant or pollutant substances in the air at a concentration that interferes with human health or welfare, or produces other harmful environmental effects" [108]. Pollutants come from both natural and anthropogenic sources and exist as gaseous or solid phases (aerosols). Over the last decades, atmospheric chemists have made considerable progress in understanding the origin of atmospheric pollution and its physico-chemical processes. In particular, they have identified that downstream of the pollution directly emitted into the atmosphere (known as primary pollution), a more hidden type of pollution develops, known as secondary pollution. This type of pollution is the result of multiple chemical reactions that take place in the atmospheric environment. As an illustration, the ozone peaks that some regions experience every summer originate from such processes, as well as the majority of fine (and impacting) particle episodes.

Secondary pollution has two characteristics making its removal a scientific and societal challenge. 1) It is much more diffuse and therefore much more difficult to regulate than primary pollution. Indeed, and

contrary to what was achieved in Europe in the 1970s and 1980s with the implementation of source reduction technologies (filtration of industrial emissions, revision of processes, desulphurisation of fuels, *etc*.), the source of secondary pollution is poorly defined geographically. 2) It is also extremely complex in its mechanisms: thousands of different chemical compounds are emitted into the urban atmosphere, which are then transformed according to multiple and variable processes depending on atmospheric and meteorological conditions, creating thousands of secondary species with their own physical, chemical and toxicological properties.

However, despite such complex problems, the very important progress made recently in the description of air pollution must be welcomed [109, 110]. Examples of pollutants present in the gaseous phase include O_3, sulphur oxides, CO, NO_x and volatile organic compounds (VOCs). Regarding the solid phase, it consists of gross PM (PM_{10}), fine PM ($PM_{2.5}$) and ultrafine PM ($PM_{0.1}$). It is remarkable that all the aforementioned pollutants only represent a tiny part of the air pollution mixture, as at any space and time, countless types of pollutants with significant chemical diversity coexist. These reactions are highly modulated over time, as the transformation time of different types of pollutants varies from a second to several minutes. Another knowledge gap regarding the characterisation of air pollution components is the lack of PM qualification beyond their size category. Indeed, the elemental composition of PM is currently missing from epidemiological studies. Given the various sources of PM, which are determined by their chemical content, it is critical to obtain this essential information.

Regarding data measurement, the spatial coverage of air quality measurement stations should be extended, as it currently highly depends on population density, which is not satisfactory. Moreover, only a few out of the thousands of pollutants receive attention in epidemiological or experimental studies, *i.e*. O_3, SO_2, NO_x, PM_{10}, and, more recently, $PM_{2.5}$ and VOCs. A very important missing member of this list of the particulate phase of air pollution is $PM_{0.1}$, which is increasingly described as playing a significant role in the health effects of PM [111–113]. This deserves a large deployment of $PM_{0.1}$ measuring stations, of which there are too few currently and only dedicated to research goals. Ultimately, this could lead to the extension of the list of regulated pollutants to this class of PM.

Finally, the reality of atmospheric pollution should be better considered not only in epidemiological studies but also in experimental ones, beyond the endless discussions on the relevance of pre-clinical models or *in vitro* approaches. Indeed, most studies only focus on a few (regulated) pollutants and, very importantly, each pollutant is considered individually, thus completely ignoring the complex nature of atmospheres, with their typical evolution in type, space and nature. In real life, however, each pollutant insults the lung in combination with other (numerous) pollutants, thus raising questions about the relevance of studies considering only one pollutant individually.

Opportunities

Two major opportunities could be considered in order to improve our understanding of the role of air pollution as a potential early determinant of COPD: the use of atmospheric chambers and the development of research related to the exposome.

Atmospheric simulation chambers are the most advanced tools used for elucidating the processes that occur in the atmosphere. They lay the foundations for air quality and climate models and help to interpret field measurements. Due to the complexity of the atmosphere, it is basically impossible to produce a "synthetic" atmosphere by mixing pure compounds, since 1) there are hundreds of them at very low mixing ratios, 2) many species are not stable or commercially available, and 3) their respective concentrations change over time and space. Until now, most experimental toxicological studies have been based on the study of one pollutant. A disruptive approach consists of reproducing multiphasic chemical processes in the laboratory to continuously produce environments representative of urban atmospheres and be able to study the impact of air pollution in the multi-pollutant synergy and multiphasic dimensions [114]. Such an innovative approach, adapted to *in vivo* and *in vitro* studies, is illustrated in figure 2. Some toxicologists and epidemiologists, who seek to determine the biological mechanisms that point to the molecules responsible for health impacts, are now turning to this type of experimental study because they are confronted with the complexity of the atmospheric environment [68].

In their seminal paper on the natural history of chronic airflow obstruction, Fletcher and Peto [8] stated that "The large social class gradient of mortality, which was … present long before there was any social class gradient in smoking, suggests that there must be causes related to style of living that have not yet been identified". This concept has been further extended to life-course environmental exposures, including lifestyle factors, from the pre-natal period onwards and the so-called exposome [115]. Interestingly, if the

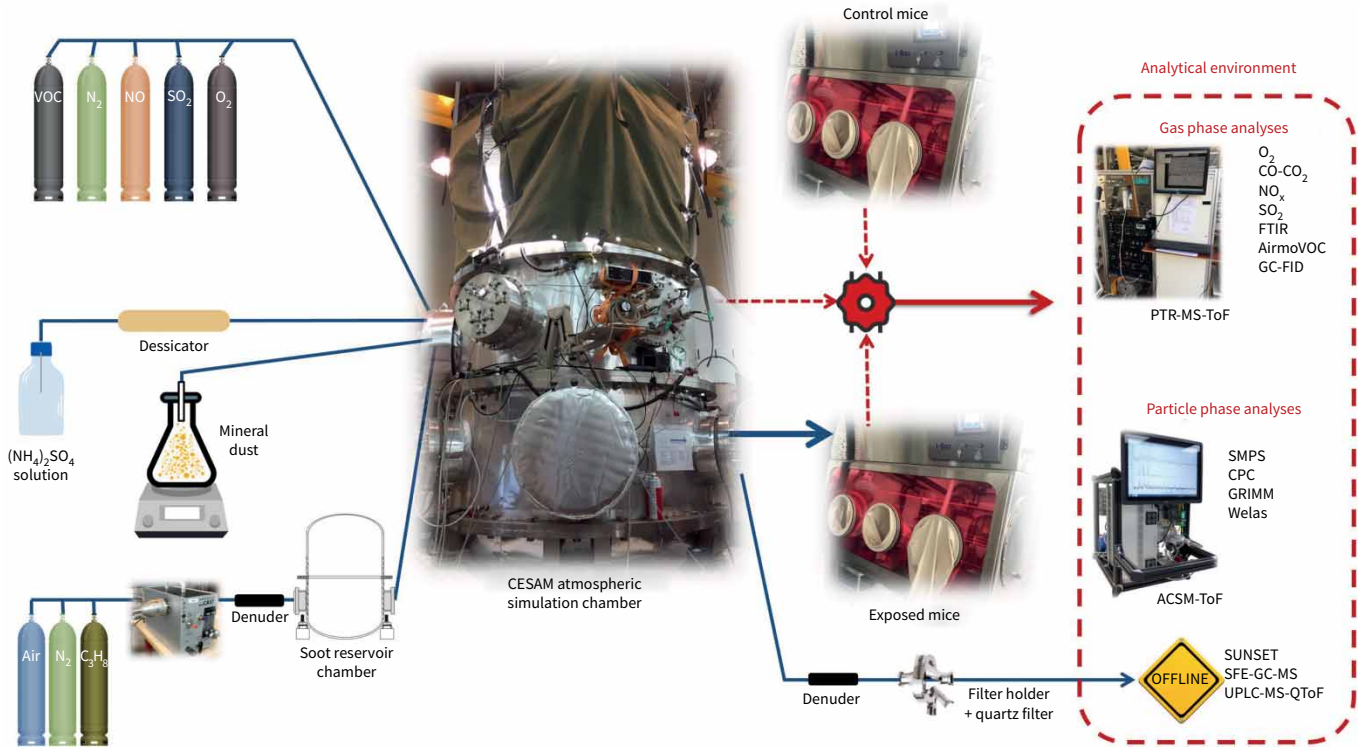

FIGURE 2 A schematic view of the atmospheric simulation, starting to the left with a continuous introduction of air and precursors in the atmospheric simulation chamber, then under the irradiation of Xe lamps at the top of the chamber the chemistry takes place, leading after a few hours to a secondary atmosphere "feeding" the exposure device where the exposed pre-clinical models are positioned, while the reference pre-clinical samples are exposed to a reference atmosphere (air filtered from pollutants). Analytical instruments allow to qualify/quantify the pollutants present in the simulated atmosphere, both online and offline (PolluRisk platform, France). ACSM-ToF: time-of-flight aerosol chemical speciation monitor; CESAM: multiphase atmospheric experimental simulation chamber; CPC: condensation particle counter; FTIR: Fourier-transform infrared spectroscopy; GC-FID: gas chromatography–flame ionisation detection; PTR-MS-ToF: proton transfer reaction time of flight mass spectrometry; SFE-GC-MS: supercritical fluid extraction with gas chromatography–mass spectrometry; SMPS: scanning mobility particle sizer; UPLC-MS-QToF: ultra-performance liquid chromatography quadrupole time of flight mass spectrometry; VOC: volatile organic compound.

Strengths

Clinical expertise of adult lung specialists
Clinical expertise of paediatrician lung specialists
Scientific expertise of atmosphere physico-chemists

Opportunities

Atmospheric simulation chambers
Exposome research

Weaknesses

Awareness about secondary pollutants
Qualification of PM beyond their size
$PM_{0.1}$ measuring stations
Spatial coverage of air quality measurement stations
Extend measurements beyond regulated pollutants

Threats

Lack of discussions between adult and paediatrician lung specialists
Complexity of air pollution
Need for interdisciplinarity

FIGURE 3 SWOT (strengths, weaknesses, opportunities and threats) analysis of the current knowledge of air pollution as an early determinant of COPD. PM: particulate matter; $PM_{0.1}$: PM equal or inferior to 0.1 µm in diameter.

word “exposome” is only recent, the concept is much older, as Hippocrates in *Airs, Waters and Places* mentioned that “Whoever wishes to investigate medicine properly, should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces … Then the winds, the hot and the cold … We must also consider the qualities of the waters, … and the mode in which the inhabitants live, and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labour, and not given to excess in eating and drinking”. Air pollution is obviously a major component of the exposome, but it must be considered together with other environmental exposures (chemical, physical, psycho-social and behavioural), to understand the exact interplay between all these factors. This could be particularly important in the context of COPD, as COPD patients are characterised by a high phenotypic variability of yet-unknown origin. Indeed, exposome studies could help understand the ins and outs of this variability, particularly considering the early origin of COPD (figure 3).

Conclusion

A large body of evidence in the available literature strongly suggests that air pollution can be considered as an early determinant of COPD. However, there is still a long way to go before we can know all the ins and outs of this interaction, and both methodological and conceptual improvements are needed to reach a stronger level of proof on that matter.

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