What is the impact of outdoor pollution on children's asthma?

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Short title: Children's asthma and outdoor pollution

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Abstract

Outdoor pollution is a complex mix of more than 200 air contaminants. Among these pollutants, ozone, nitrogen dioxide and fine particles may generate bronchial inflammation and hyperreactivity. The hypothesis that pollution contributes to the development of asthma in children is based on epidemiological, clinical and experimental data. Many risk factors during the in utero and postnatal period have been identified in the aetiology of childhood asthma. During pregnancy, outdoor pollution was identified as a causal factor of respiratory disease in neonatal cohort studies. Several epidemiological studies also demonstrate that outdoor pollution is a trigger of asthma exacerbations. This review aims to highlight the current knowledge on outdoor pollution and asthma.

Keywords: Outdoor pollution; Ozone; Nitrogen Oxides; Particulate matters; Asthma; Children.

1. Outdoor pollution

1.1 What are we talking about?

Outdoor pollution is a complex mix of more than 200 air contaminants. There are two types of pollution: natural pollution and man-made or anthropogenic pollution. Natural pollution is produced from volcanoes, vegetable decomposition and pollinization. There are two groups of pollutants in the category of anthropogenic pollution: primary and secondary pollutants. The latter are produced from a chemical transformation of the former. These chemical reactions depend on temperature and therefore can be influenced by global climate warming. The indicators of primary pollutants are sulphur dioxide (SO_2), carbon monoxide (CO), sulphur monoxide (SO), lead (Pb), aromatic hydrocarbons and fine suspended particles. The indicators for secondary pollutants are nitrogen dioxide (NO_2) and ozone (O_3). They participate in the formation of other compounds such as nitrates (NO_3), sulphates (SO_3) and volatile organic compounds (VOCs). Ozone, NO_2 and fine particles are the main pollutants playing a role in asthma. Indeed, these pollutants are able to cause bronchial inflammation and bronchial hyperresponsiveness [1–6], both defining asthmatic disease.

1.2 What are the standards for assessing air pollution?

Since 1987, the World Health Organization (WHO) has established ambient air quality guidelines. They provided a scientific basis for protecting the health of populations from the effects of air pollution. In France, the term “ambient air quality standards” refers to French regulations, in particular Articles L221-1 and R.221-1 of the Environmental Code. It encompasses different types of regulatory values which are applied to different air contaminants and at different times. These standards have been used for the transposition of European directives (Table 1).

1.3 Ozone

Ozone (O_3) is formed from pollutants emitted by human activities and nature combined with solar activity. The main components are NOx and benzene, involving pollution-related engines. The production of O_3 is more elevated in summer than in winter. While the average O_3 concentration levels have not changed in summer over the past decade, the frequency of peak levels above the regulatory air quality standards for human health and vegetation protection has decreased. Currently, 13% of the pollution measuring stations, compared with 50% in the 2000s, show a failure to achieve the regulatory standards [7]. This trend is largely explained by a decrease in the emission of precursors of pollutants.

1.4 Nitrogen oxides

Nitrogen oxides (NO and NO_2) are mainly formed by combustion reactions. In France, vehicles account for 60%, and individual and collective heating systems for 20% of their production. The remaining 20% is related to the activities of power stations, cement plants, incinerators and the decomposition of nitrogen fertilizers after use. Diesel engines produce twice as much nitrogen oxides compared with gasoline engines. However, NO emissions, mainly from the transport sector, have decreased by 49% since the 2000s. During the same period, NO_2 concentrations in the air also decreased but to a lesser extent. With regard to these two pollutants, air quality standards for long-term human health protection were not achieved in 2017 for 9.5% of measuring stations, all located near road traffic [7].

Fine particles are defined according to their diameter: PM_{10} and $PM_{2.5}$, particles with a diameter less than or equal to 10 µm and 2.5 µm, respectively. The smaller the diameter, the higher the ability of the particles to be inhaled into the small airways. Intermediate-sized particles (10–2.5 µm) are mainly natural, while small-sized particles (less than 2.5 µm) are mainly of anthropogenic origin. In France, four main sectors share PM_{10} emissions: the residential and tertiary sector, of which mainly wood combustion, industry, farming activities, and transport. PM_{10} emissions decreased by 41% in all areas of activity during the period

2000–2017. The generation of $PM_{2.5}$ differs from that of PM10: residential and tertiary emissions predominate. There was a 48% reduction in $PM_{2.5}$ emissions during the same period. In 2017 there was even a decrease of 13 µg/m^3 and 11 µg/m^3 in the proximity of road traffic and in the urban zone, respectively [7].

In France, the levels of external pollutants decreased over the past decade. Nevertheless, peaks above the recommended thresholds for respiratory health occurred and were dependent on the seasons, on the urban areas or on road traffic.

2. Asthma

Asthma is the most common chronic disease in childhood and the prevalence of symptoms, of new cases of asthma and of health-care use worldwide has increased [8]. Data during the period 2004–2015 from the French health monitoring institute showed an increase of 3% and 2.7% per year in hospitalizations for asthma in boys and girls under 15 years of age, respectively [9]. Currently, the prevalence of asthma is 11%, 14.4% and 15.7% for children aged under 6, 6–11 years and 12 years or older, respectively [10]. Although asthma is a complex multifactorial disease characterized by bronchial inflammation [11, 12], airway inflammation may change in the course of life: It is mainly neutrophilic in preschool children, and eosinophilic in older children [13]. In addition, airway inflammation can be modified by early exposure to a respiratory harmful environment and is often associated with more severe disease [14]. Because early alteration of lung function has consequences on the respiratory health in adolescence and adulthood, it is necessary to account for all the risk factors related to the occurrence of bronchial inflammation [15–18]. Tobacco is a very well studied indoor pollutant. In utero maternal smoking modifies the epigenetic expression of the unborn individual, increasing their risk of becoming asthmatic during early childhood (OR=1.24) but also until adulthood (OR= 1.52). This risk is increased if maternal and paternal smoking

persist after birth [19–21]. It has been established that outdoor pollution caused wheezing exacerbations, and its impact on the initiation of asthma since in utero life is now considered.

3. Asthma and outdoor pollution.

Outdoor pollution is considered to be involved in this complex and multifactorial disease at different stages of life. However, it altered the in utero pulmonary development with an individual susceptibility according to genetic inheritance. It promotes allergy to aero-allergens and is a risk factor for exacerbations in children (Figure1). As there is an increase in asthma prevalence and at the same time a reduction in the exposure to major pollutants, it is not easy to evaluate and demonstrate the role of pollutants in asthma prevalence since the beginning of the twenty-first century. The role of pollutants was established in cohorts submitted during a short exposure to high levels of pollutants, showing clear exacerbations of asthma.

3.1 Outdoor pollution and lung development.

Exposure to outdoor pollutants in utero was studied in animal and in vitro models. Pre- and postnatal exposure to PM2.5 in mouse models altered the alveolar structure and elastic properties of the lungs, caused persistent bronchial hyperresponsiveness and increased the inflammatory response to oxidative stress [22, 23]. However, prenatal exposure alone does not alter lung function [22].

Neonatal cohort case–control studies reported an increased risk of developing paediatric asthma when newborns were exposed to traffic-related pollutants in utero: NO_2, O_3 and fine particulate matter [24–27]. The risk increased in proportion to the level of these pollutants. For example, an exposure of 10 $\mu g/m^3$ NO_2 during in utero life increased the risk of paediatric asthma 1.10-fold in a Canadian study [28]. However, these studies did not distinguish between immediate prenatal and postnatal exposure. Indeed, the measurement of air pollution

is relatively coarse, and the gestational age studied was an average age because the stage of in utero growth was not accurately determined. More recently, Hsu et al. [29] evaluated maternal exposure to $PM_{2.5}$ weekly during the entire pregnancy, and analysed this in utero exposure and the occurrence of asthma in the offspring. They adjusted their statistical model for potential confounding factors, including atopy, exposure to allergens, maternal asthma, household and socio-economic status. The study included 736 full-term newborns, and the authors reported that the increase in $PM_{2.5}$ concentrations during the period of 16–25 weeks of gestation was associated with the development of early childhood asthma [29]. This period of gestation corresponds to the end of the pseudoglandular stage and the canalicular period of pulmonary development, meaning the development of the respiratory tract, the airway epithelium and the differentiation of type I pneumocytes [30]. The epithelium started to secrete immune modulators such as interleukin (IL)-25 and IL-33, considered to be involved in the initiation of asthma. In the gender-stratified analyses, the association was limited to boys. A limitation of the study was that $PM_{2.5}$ concentrations inside buildings were not collected. As with the other cohort studies, the odds ratio was low (OR=1.2), but this risk added to other risks such as in utero tobacco exposure, family atopy or the occurrence of viral infections in early childhood.

In the Paris neonatal longitudinal cohort study, 3840 healthy, term newborns were recruited from five Parisian maternity hospitals between February 2003 and June 2006. Among these, 1080 who attended the 8- to 9-year-old medical examination successfully performed spirometry tests and had complete prenatal, early, and lifetime traffic-related air pollution (TRAP) exposure estimates [31]. Pre- and postnatal TRAP exposures were estimated based on daily NO_x measurements ($NO + NO_2$). This cohort study observed that lung function was impaired at age 8, regardless of whether (a) the mother was exposed to NO_x during the second trimester of pregnancy, (b) the infants underwent postnatal exposure and early viral

respiratory infection, or (c) there was early allergen sensitization [31]. This highlights the complex interaction of the known risk factors of asthma.

3.2 Outdoor pollution and asthma exacerbations.

The link between a short exposure to pollutants and exacerbation of asthma is clearly established. In the Ile de France area, exacerbation of asthma accounted for 3.7% of paediatric emergency visits, and the impact of pollution on these cases was studied from 2010 to 2015. Data on the levels of air pollutants (nitrogen dioxide, ozone, PM_{10} and $PM_{2.5}$), meteorological data, trends in RSV infections and pollen exposure were collected from the relevant institutional database. Only $PM_{2.5}$ was independently associated, in a non-linear manner, with asthma exacerbations. A concentration of 13.5 $\mu g/m^3$ $PM_{2.5}$ was associated with a 50% risk to trigger an asthma attack. The European ($25\mu g/m^3$/year) and WHO ($10\mu g/m^3$/year) $PM_{2.5}$ thresholds were applied in this model and associated with a respective 65% and 42% risk of triggering an asthma attack [32]. A study conducted with children aged 3–18 years from southeast France measured the levels of pollutants in the vicinity of the children's homes [33]. An increase in asthma visits to emergency units was associated with (a) a short exposure to PM_{10} but not to $PM_{2.5,}$ (b) boys, (c) young age, and (d) outdoor temperature. Conversely, wind speed, which moved the pollutants, was a protective factor. A previous study already reported a causal relationship between exposure to PM_{10} and hospitalization for respiratory diseases [34]. The link between pollutants generated by road traffic and asthma exacerbations has been reported worldwide. The Phase 3 ISAAC epidemiological study recruited more than 500,000 children and adolescents on five continents [35]. The analyses identified a dose effect of the road traffic pollutants on the occurrence of asthma symptoms (permanent asthma, current wheezing and severe asthma symptoms).

3.3 Allergy and outdoor pollution

The study by Pénard-Morand et al. [36] focused on the long-term exposure effect to outdoor pollution on asthma symptoms, occurrence of eczema and allergic rhinitis. Exposure to benzene, volatile organic compounds, SO_2, PM_{10}, NO and CO was assessed over 3 years. For children residing at the same address for at least 3 years, asthma, eczema, allergic rhinitis or pollen sensitization was significantly augmented in neighbourhoods where high levels of benzene, volatile organic compounds and PM_{10}.were measured. For the children living at the same address since birth, the risk of suffering from asthma increased with the exposure to benzene (OR: 1.3 [1.0–1.9]; p=0.04) and PM_{10} (OR: 1.4 [1.0–2.0]; p=0.05). The other link between air pollution and asthma is the facilitating role of aeroallergen awareness by the pollutants. They allow the allergens to be deposited in the respiratory tract via being borne by the fine particles, the epithelial permeability related to oxidative damage and the enhanced antigenicity of pollen components resulting from chemical modifications or a direct adjuvant effect (i.e. diesel particles) [11].

3.4 Lung function decline and outdoor pollution

In Canada, spirometry was performed on 182 children with asthma aged 9–14 years and repeated during the 3-month study. Bronchial obstruction of the large and distal airways was assessed by measuring FEV_1 and DEM_{25-75}, respectively. A drop in these bronchial flows was associated with increasing exposure to SO_2, NO_2 and $PM_{2.5}$ [37]. These results were reported with higher pollutant levels, however [38, 39].

4. Consequences of outdoor pollution on asthma treatment

Currently, practitioners should take into account outdoor pollution in their clinical practice, particularly for children with severe or uncontrolled asthma. Alerts on the occurrence of peaks of pollution have been implemented and are addressed to professionals or institutions caring for vulnerable populations, obviously including children. They are also freely available on-line for the general population. These alerts suggest avoiding unnecessary outdoor activities,

since exercise increases the ventilation per minute and therefore the total amount of inhaled pollutants. This exclusion of outdoor activities during the period of poor air quality can be explained to the parents and children, or caregivers, and added to the asthma action plan. Inhaled corticosteroid (ICS) therapy remains the best treatment to limit the occurrence of exacerbations. Thus, the daily air environment of the child plays a role in the decision regarding the duration of long-term ICS treatment. Moreover, peak pollution levels could be concomitant with exposure to seasonal aeroallergens, i.e. pollens or fungi [40, 41]. Owing to the potent interaction of asthma with allergens or smoking, the practitioner should attempt to eliminate them as far as possible. To advise the pregnant mother on the early exposure of her foetus and subsequently her newborn seems difficult. Nevertheless, the air environment combining passive smoking, indoor and outdoor pollution, and the known risk factors of asthma, such as family atopy and viral infections, should be identified early. This allows practitioners to provide explanations and advice on risk factors that may be modifiable.

5. Conclusion

Thus, outdoor air pollution plays a role in asthma exacerbations, asthma control and asthma initiation through various mechanisms. These negative effects vary according to the level and duration of pollutant(s) exposure, the genetic susceptibility of the host and the other risk factors for asthma.

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Table 1: Air quality according to European Community and to WHO standards

Pollutants	Concentration in µg/m^3		Exposure time	Alert threshold in µg/m^3 in France
	France (2010)	WHO (2005)		
PM_{10}	40	20	1 year	80/day
	50	50	24 h*	
$PM_{2.5}$	25	10	1 year	
		25	24 h	
Ozone	120	100	over 8 h	240 over 1 h
Nitrogen dioxide	40	40	1 year	400 over three consecutive hours
	200**	200	1 h	

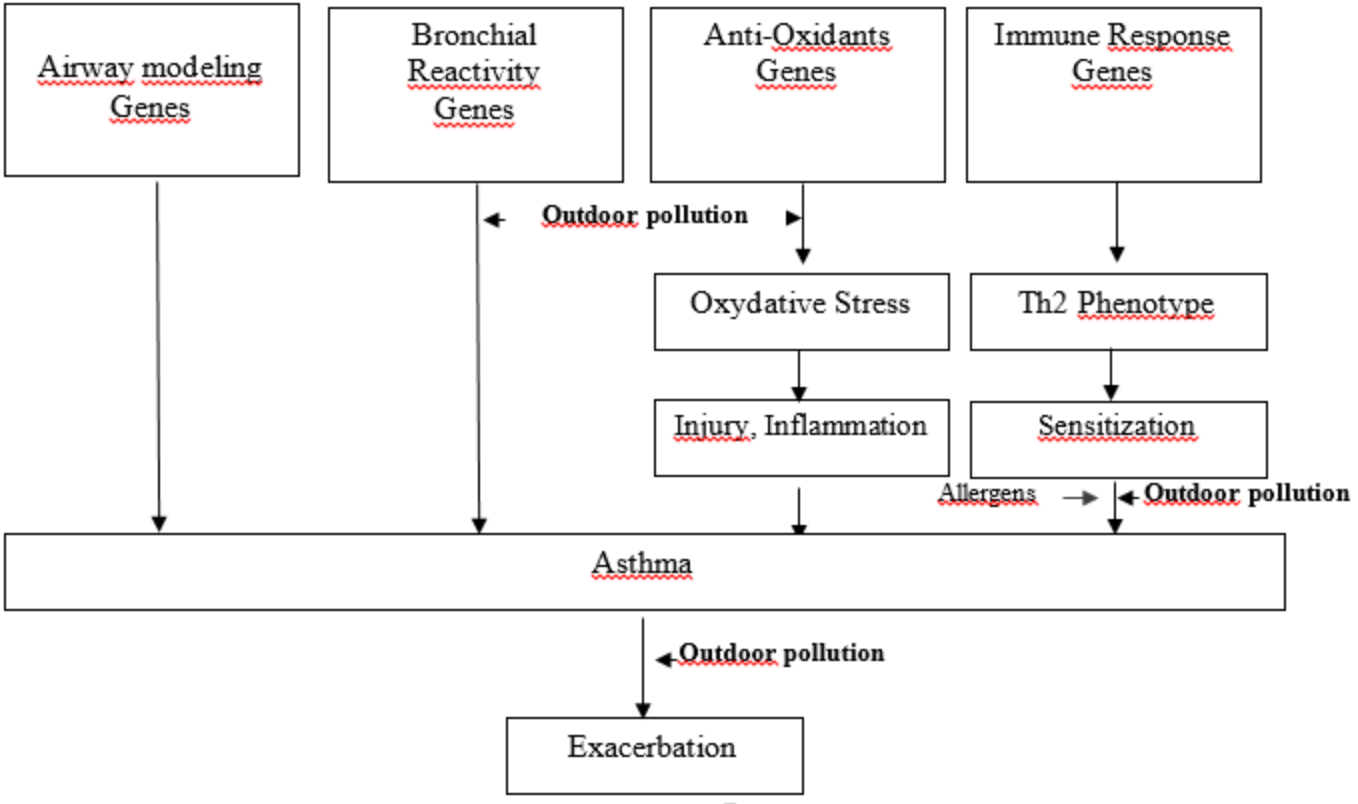
*: threshold not to be exceeded more than 35 times/year.

**: threshold not to be exceeded more than 18 h/year.

WHO: World Health Organization

Figure 1 : Role of air pollution in children's asthma (modified scheme by Guarnieri et al.[42])

Conflicts of interest: none


Airway modeling Genes
Bronchial Reactivity Genes
Anti-Oxidants Genes
Immune Response Genes
Outdoor pollution
Oxydative Stress
Th2 Phenotype
Injury, Inflammation
Sensitization
Allergens
Outdoor pollution
Asthma
Outdoor pollution
Exacerbation