Asthma and Air Pollution. Where are We?

Bénédicte Jacquemin¹ and Jordi Sunyer²

¹UMR-S 1168, VIMA: Ageing and chronic diseases. Epidemiological and public health approaches, INSERM, Villejuif, France; UMR-S 1168, Université Versailles Saint Quentin, France; Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; Universitat Pompeu Fabra (UPF), Barcelona, Spain; CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain; ²Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain; Universitat Pompeu Fabra (UPF), Barcelona, Spain; CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

ABSTRACT

Asthma incidence and prevalence have increased in the last decades, suggesting a role of environmental factors including air pollution. In this manuscript, we summarize the evidence of the role of air pollution on (i) asthma exacerbations, (ii) asthma incidence in children, and (iii) asthma incidence in adults, pointing out the most important publications in each of these three areas. There is solid evidence that air pollution causes asthma exacerbations, characterized by hospital admissions, emergency department or doctor’s visits, medication intake, or absenteeism. The evidence regarding the effect of long-term air pollution exposure on asthma onset is also quite robust. In children, many studies have associated air pollution or proximity to traffic with asthma incidence, and while there are some negative publications, the evidence for an association is appealing. In adults, several studies also point to a positive association between air pollution and asthma incidence. Furthermore, there is a lot of knowledge about the mechanisms of the different agents involved. Gases, that are oxidants, could be more associated with acute manifestations of the disease and particles, more related with chronic inflammation, could be more associated with incidence. Diesel particles have been associated with both exacerbations and incidence. However, research is still needed to better understand and identify the underlying mechanisms related to the specific pollutants and specific sources. More research is also needed to identify more susceptible groups such as males, non-smokers, or persons with another chronic condition such as atopy or obesity. (BRN Rev. 2015;1:78-91)

Corresponding author: Bénédicte Jacquemin, bj Jacquemin@creal.cat

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INTRODUCTION

Asthma incidence and prevalence have increased in the last decades, affecting between 5-10% of the population\(^1\). In 2010, asthma ranked as the 28th leading cause of disability adjusted life-years worldwide\(^2\). Asthma is a heterogeneous disease that appears more frequently in childhood, but can also appear in adulthood. Asthma is a particularly complex disease than can persist, remit, or show a variable disease activity over time\(^3,4\). Its increase in the last decades strongly suggests a role of environmental factors, which certainly play a role as acute triggers of attacks, but probably also as causative agents.

Research on environmental factors associated with asthma incidence or exacerbations is very extensive. In the 1980s, the first hypotheses explaining the incidence increase pointed to allergen exposure (or non-exposure), tobacco, and air pollution\(^5\). Outdoor air pollution is a complex and variable mixture of multiple pollutants. Transport, power generation, industrial activity, and biomass burning are the predominant anthropogenic sources. The mix of outdoor pollutants varies over space and time, reflecting the diversity of sources as well as the effect of atmospheric processes. Outdoor air pollution has evolved in the last decades. In Europe and North America, air pollution related to industrial effluents is better controlled, and episodes of severe air pollution related to industrial activity have mostly disappeared. Currently, the main source of air pollution in Europe and North America is vehicular traffic, and the air pollutants of major interest in urban areas are those related to traffic: nitrogen dioxide (\(\text{NO}_2\)) and particulate matter (\(\text{PM}\)), or ozone (\(\text{O}_3\)) which is a by-product of \(\text{NO}_2\).

With the decrease of air pollution levels in the 1980s, associated with a better control of industrial emissions and residential coal combustion, interest in air pollution research decreased as it was thought that air pollution levels were too low to be associated with health problems\(^6\). However, at the beginning of the 1990s, the Barcelona group found that air pollution levels below the air quality recommendations had an effect on respiratory health, namely on chronic obstructive pulmonary disease (COPD) exacerbations\(^7\). Also, studies in the USA, (“Six Cities” and ACS) showed that even at low concentrations, air pollution exposure was associated with an increase in respiratory and cardiovascular mortality\(^8,9\).

Since then it has not been possible to establish a threshold below which no adverse effects on health were found. Furthermore, it has been shown that air pollution exposure was not only associated with acute health effects, but also that long-term air pollution exposure was associated with chronic health effects.

The effects of air pollution on asthma are biologically possible as air pollution causes inflammation and oxidative stress, i.e. mechanisms that are involved in asthma exacerbation, asthma severity, and probably in asthma development as well\(^10\). Particulate matter is categorized on the basis of its aerodynamic diameter and causes inflammation and oxidative stress in the lung at various levels, depending on the site of deposition when inhaled. Gases also interact with the lung at several levels (Fig. 1). In asthmatic volunteers, controlled exposures to sulphur dioxide (\(\text{SO}_2\)), \(\text{O}_3\), and \(\text{NO}_2\) at levels that are found in real-life situations induced bronchial hyperresponsiveness and inflammation and reduced the dose of aeroallergen needed to produce a given bronchial response.
The role of air pollutants in triggering asthma exacerbations in asthma patients has been established since many years. Several studies, although not all, support the role of air pollution or traffic proximity in the development of asthma in childhood. The role of air pollution in adult-onset asthma (i.e., asthma incidence) has been investigated in fewer studies and should not be extrapolated from studies in children because they are two distinct asthma phenotypes that have, at least partly, different clinical, biological, and genetic characteristics. Although we will not address it in this manuscript, it is important to note that there is also literature on the effects of air pollution on asthma-related traits or phenotypes, such as asthma control or severity, or atopy in asthmatics. Very briefly, it seems that air pollution could be associated with more severe attacks of asthma and a more severe asthma, and also with a poorer control of the disease. Regarding atopy, the literature is even less consistent and has mainly focused in children. For the moment, it is not possible to draw a firm conclusion about the effects on allergy, however some studies suggest that air pollution could be associated with atopy in children or higher levels of immunoglobulin E in subjects with asthma, but not in those without. Furthermore, a recent study showed that the effects of NO₂ on childhood asthma were modified by the presence of other allergic diseases, such as allergic rhinitis, eczema, or food allergy, suggesting a probable role for allergic sensitization in the pathogenesis of air pollution-related asthma.

In this manuscript, we will summarize the evidence for the role of air pollution on (i) asthma exacerbations, (ii) asthma incidence in

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**Figure 1.** Particulate matter and gases – interactions with respiratory tract. Particulate matter is categorized on the basis of its aerodynamic diameter, depending on site of deposition when inhaled. Gases cause lung damage at all the levels. NO₂: nitrogen dioxide; SO₂: sulphur dioxide.
children, and (iii) asthma incidence in adults, highlighting the most important publications in each of these three areas.

**ASTHMA EXACERBATIONS**

Air pollution epidemiology started in the 1970s by studying the short-term effects of air pollution on mortality and hospitalization and by focusing on respiratory causes, including those related to asthma. The effect of short-term exposure to air pollution on acute manifestations of the disease is usually assessed with time-series or panel studies. The markers of asthma exacerbations that were more frequently studied were hospitalizations or emergency visits due to asthma. In the 1980s, many studies showed an increase in hospital admissions due to asthma associated with \( \text{O}_3 \) and particles exposure in adults, children, and the elderly. Most of these studies were conducted in the USA\(^1\). They all described the health effects at concentrations below the North American air quality standards. One of the first studies in Europe showing an association between air pollution and asthma emergency visits was conducted in Barcelona. They showed that black smoke and \( \text{NO}_2 \) were associated with asthma visits, but they did not find associations with \( \text{SO}_2 \) and \( \text{O}_3 \).\(^2\) These results were confirmed in a study that included four European cities: Barcelona, Helsinki, London, and Paris within the framework of APHEA (Air Pollution and Health: A European Approach). They showed a significant increase in daily admissions for asthma in adults associated with \( \text{NO}_2 \) and non-significantly with black smoke. The association between asthma admissions and \( \text{O}_3 \) was heterogeneous among cities. In children, daily admissions increased significantly with \( \text{SO}_2 \) and non-significantly with black smoke and \( \text{NO}_2 \).\(^3\) Routine PM monitoring in Europe appeared after those for gases and a few years later, within the context of APHEA 2, it was confirmed that particle concentrations in eight European cities were positively associated with increased numbers of admissions for asthma in children and adults\(^4\). Since then, many studies have confirmed such associations for gases and particles for adults and children (e.g., the multicenter studies by Bell et al.\(^5\), Dominici et al.\(^6\), and Staffogia et al.\(^7\)). Selected articles are summarized in table 1. These results on emergency admissions as markers of exacerbations have been validated with other acute markers of the disease such as doctor’s or emergency departments’ visits\(^8-12\), medication intake\(^13-15\), or absenteeism\(^16\).

Recently, several studies have tried to identify the component or the source of pollution associated with asthma hospitalizations. Basagaña et al.\(^17\) found in Europe an increase in respiratory hospitalization with several PM constituents such as elemental carbon or nickel. Such elements come from different sources and some of them are highly correlated and therefore it was difficult to attribute effects to a particular constituent or to identify any source specifically. In the USA, adverse associations with pediatric asthma were observed with particles generated from diesel-fuelled vehicles and gasoline-fuelled vehicles\(^18\), while in another study they found that emergency visits for pediatric asthma were strongly associated with high exposures on days with multi-pollutant mixtures; but they could not identify any specific combinations that were more harmful than others\(^19\). However, a very important and interesting experimental real-life
Table 1. Key epidemiological papers regarding the short-term effects of air pollution on asthma exacerbations

<table>
<thead>
<tr>
<th>Reference</th>
<th>Brief description of the study</th>
<th>Key findings</th>
</tr>
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<tbody>
<tr>
<td>Sunyer et al. 21</td>
<td>Multi-city time series, 4 European cities. 1986-92. O₃, NO₂, SO₂</td>
<td>Daily admissions for asthma in adults increased with NO₂. In children, daily admissions increased with SO₂.</td>
</tr>
<tr>
<td>Atkinson et al. 22</td>
<td>Multi-city time series, 8 European cities. 1988-1997. PM₁₀, O₃, NO₂, SO₂, CO</td>
<td>PM is associated with increased admissions for respiratory diseases.</td>
</tr>
<tr>
<td>Bell et al. 24</td>
<td>Multi-site time-series models in 202 US counties. 1999-2005. PM₂.₅</td>
<td>PM₂.₅ was associated with respiratory admissions.</td>
</tr>
<tr>
<td>Stafoggia et al. 26</td>
<td>Multi-city time series, 8 European cities. 2001-2010. PM₁₀, PM₂.₅, PMcoarse</td>
<td>PM₂.₅ and PMcoarse were associated with respiratory hospitalizations.</td>
</tr>
</tbody>
</table>

CO: carbon monoxide; NO₂: nitrogen dioxide; O₃: ozone; SO₂: sulphur dioxide; PM: particulate matter; PM₁₀: particulate matter with an aerodynamic diameter ≤ 10 μm; PM₂.₅: particulate matter with an aerodynamic diameter ≤ 2.5 μm; PMcoarse: particulate matter with an aerodynamic diameter ≤ 10 μm and > than 2.5 μm.

Condition study (detailed in the discussion) showed that exposure demonstrated a causal nature in the functional exacerbation (forced expiratory volume in one second, FEV₁, decline in asthmatics) due to diesel particles 34.

The literature on asthma symptoms associated with long-term-exposure to air pollution is very extensive, suggesting also a chronic effect of air pollution in asthma expression in both children 35,36 and adults 37-39.

Asthma Incidence in Children

The research on the chronic long-term effects of exposure to air pollution in asthma is more recent than the research on its acute effects, mainly due to the development of new methods to assess long-term exposure to air pollution. The long-term effect of air pollution on new-onset asthma has been mostly studied in children 40 and is quite extensive. In children, proximity to traffic is associated with an increase in asthma prevalence and incidence 41-43, with substantial evidence for a causal asthmogenic role of the pollutants occurring in high concentrations along busy roads. The Southern California Children’s Health Study contributed with several analyses to the evidence that proximity to traffic or air pollution was associated with asthma 41,42,44. They also found that long-term exposure in early childhood was associated with impaired lung development, as we will detail later 45. These results were confirmed by several European studies 43,46. Within the Spanish INMA cohort (Childhood and Environment), it was observed that early-life exposure to ambient air pollution may increase the risk of upper and lower respiratory tract infections in infants 47. These results were confirmed within the context of ESCAPE including INMA and another six European cohorts 48. Selected articles are summarized in table 2.

In the literature on children, it is interesting to note that proximity to traffic, more than air pollution exposure per se, seems to be associated with asthma. For example, in the European ESCAPE study 49 including five cohorts, the authors did not find an association between modelled air pollution and childhood asthma.
Table 2. Key epidemiological papers regarding the long-term exposure of air pollution on asthma onset in children

<table>
<thead>
<tr>
<th>Reference</th>
<th>Brief description of the study</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jerrett et al.</td>
<td>217 children from the Southern California Children's Health Study, followed up from the age of 10 to 18. Home NO₂ monitors</td>
<td>NO₂ was associated with the onset of asthma</td>
</tr>
<tr>
<td>McConnell et al.</td>
<td>2,497 4-6 year old children from the Southern California Children's Health Study followed-up for 3 years. Central monitoring O₃, PM and NOₓ and traffic-related air pollution derived from dispersion models</td>
<td>Both proximity to traffic and NO₂ were associated with asthma onset</td>
</tr>
<tr>
<td>Gehring et al.</td>
<td>Birth cohort study with an 8-year follow-up. NO₂, PM₁₀, and soot estimated by land-use regression models</td>
<td>PM₁₀, NO₂ and soot were associated with incidence of asthma, prevalence of asthma, and prevalence of asthma symptoms</td>
</tr>
<tr>
<td>Gauderman et al.</td>
<td>208 children from the Children’s Health Study, followed up from the age of 10 to 18. Home NO₂ monitors and distance to freeways derived by geographic information systems</td>
<td>NO₂ and distance to freeways were associated with asthma incidence</td>
</tr>
<tr>
<td>Brauer et al.</td>
<td>4,000 children followed-up from birth to 4 years. NO₂ and PM₂.₅ estimated by land-use regression models</td>
<td>Traffic-related pollution was associated with doctor-diagnosed asthma</td>
</tr>
<tr>
<td>Möltner et al.</td>
<td>Five European cohorts. NO₂, NOₓ, PM₁₀, PM₁₀, black smoke derived from land use regression models</td>
<td>No significant association between air pollution exposure and childhood asthma prevalence</td>
</tr>
</tbody>
</table>

NO₂: nitrogen dioxide; NOₓ: nitrogen oxides; O₃: ozone; PM: particulate matter; PM₁₀: particulate matter with an aerodynamic diameter ≤ 10 μm; PM₂.₅: particulate matter with an aerodynamic diameter ≤ 2.₅ μm.

Asthma prevalence, but they did not test for proximity to traffic. While the evidence supporting the negative effect of air pollution on asthma incidence is still quite accepted, this issue raises the question of which air pollution element or source is the one causing negative health effects in children, and evidence is pointing to combustion/diesel exhaust.

Another issue we would like to discuss is that time of exposure could be particularly important regarding respiratory health in children. Morales et al.⁵⁰ found that prenatal exposure to residential traffic-related air pollution was associated with long-term lung function deficits at preschool age. These results are closely related to the growing and solid evidence in the literature associating prenatal exposure to air pollution with low birth weight⁵¹,⁵², as it is well known that birth weight has an impact on health at later ages, including respiratory health. Therefore, prenatal exposure to air pollution could play an important role in later asthma development.

**Asthma Incidence in Adults**

The evidence is less extensive in adult-onset than in childhood asthma⁴⁰. The earliest study to identify an association between long-term exposure to air pollution (i.e., O₃) and asthma incidence was a cohort of non-smoking Californian Seventh-Day Adventists assessing the long-term health effects of ambient air pollutants (AHSMOG). They found a positive association, but only for males⁵³. The study by Modig et al.⁵⁴ was the first to investigate the contribution of traffic-related pollution to adult-onset asthma, and suggested an association of traffic-related NO₂ with asthma incidence, but the study lacked statistical power. The Respiratory Health in Northern Europe study⁵⁵ and the European Community Respiratory
Health Survey\textsuperscript{56} also reported a positive association between NO\textsubscript{2} and asthma incidence. In the latter cohort, results were confirmed using asthma definition-based symptoms\textsuperscript{59}. The Swiss study on air pollution and health in adults found similar results, but using the traffic fraction of PM and only in never-smokers\textsuperscript{57}. A recent US study suggested an association of particulate matter with an aerodynamic diameter ≤ 2.5 \(\mu\)m (PM\textsubscript{2.5}) with incident asthma in women\textsuperscript{58}. Within the context of the European Study of Cohorts for Air Pollution Effects (ESCAPE) including six cohorts, the authors also found that asthma incidence was positively associated with NO\textsubscript{2} but lacked the power to find an association with PM\textsubscript{2.5}. Even if, compared to the child literature, evidence is less extensive, it strongly suggests that air pollution could also be associated with asthma incidence in adults. Selected articles are summarized in table 3.

### INTERPRETATION OF FINDINGS

Air pollution is associated with acute and chronic manifestations of asthma and very probably also associated with asthma onset in both children and adults (Table 4). However, some issues still need to be discussed and clarified so we will raise some of these in the following sections.

Disentangling the chronic and acute effects of air pollution is a challenge in air pollution epidemiology. In the case of asthma, as shown

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**Table 3. Key epidemiological papers regarding the long-term exposure of air pollution on asthma onset in adults**

<table>
<thead>
<tr>
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<th>Brief description of the study</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonnell et al.\textsuperscript{53}</td>
<td>Cohort of 3,091 nonsmoker adults (age, 27-87) in US, followed up for 15 years. PM\textsubscript{10}, SO\textsubscript{2}, NO\textsubscript{2}, SO\textsubscript{2}, O\textsubscript{3}, and O\textsubscript{3} 8-hour average from the closest fixed monitoring stations</td>
<td>O\textsubscript{3} 8-hour average was associated with adult asthma incidence in males</td>
</tr>
<tr>
<td>Modig et al.\textsuperscript{54}</td>
<td>203 cases and 203 controls in Sweden, aged from 20 to 60. Home NO\textsubscript{2} monitors and proximity to traffic</td>
<td>Living close to high traffic was non-significantly associated with asthma incidence NO\textsubscript{2} was associated with adult asthma incidence only in subjects with a positive SPT</td>
</tr>
<tr>
<td>Modig et al.\textsuperscript{55}</td>
<td>Cohort in Sweden, including 3,824 adults (age, 15-45), followed-up for 9 years. NO\textsubscript{2} dispersion models and proximity to traffic</td>
<td>NO\textsubscript{2} exposure and living close to a major road were associated with asthma onset and incidence in adults</td>
</tr>
<tr>
<td>Jacquemin et al.\textsuperscript{56}</td>
<td>Prospective cohort, in European 17 cities (ECRHS), including 4,185 adults (age, 20-40) followed up for 10 years. NO\textsubscript{2} dispersion models</td>
<td>NO\textsubscript{2} was associated with asthma incidence in adults</td>
</tr>
<tr>
<td>Kunzli et al.\textsuperscript{57}</td>
<td>Prospective cohort in 8 Swiss areas, including 2,725 adults (age, 18-60), followed up for 10 years, traffic-related PM\textsubscript{10} dispersion model</td>
<td>Traffic PM\textsubscript{10} is associated with asthma incidence in adult nonsmokers</td>
</tr>
<tr>
<td>Young et al.\textsuperscript{58}</td>
<td>US cohort including 50,884 women followed up for 5 years PM\textsubscript{2.5} and NO\textsubscript{2} Kriging models</td>
<td>PM\textsubscript{2.5} and NO\textsubscript{2} were associated with asthma incidence</td>
</tr>
<tr>
<td>Jacquemin et al.\textsuperscript{59}</td>
<td>6 European cohorts of adults followed up for around 10 years. NO\textsubscript{2}, NO\textsubscript{x}, PM\textsubscript{2.5}, PM\textsubscript{10}, black smoke derived from land-use regression models</td>
<td>NO\textsubscript{2} was borderline significant associated with asthma incidence</td>
</tr>
</tbody>
</table>

NO\textsubscript{2}: nitrogen dioxide; O\textsubscript{3}: ozone; SO\textsubscript{2}: sulphur dioxide; PM: particulate matter; PM\textsubscript{10}: particulate matter with an aerodynamic diameter ≤ 10 \(\mu\)m; PM\textsubscript{2.5}: particulate matter with an aerodynamic diameter ≤ 2.5 \(\mu\)m.
previously, it appears that air pollution could be associated with both aspects, namely worsening of the pre-existent disease but also causing the disease. However, the underlying mechanisms through which air pollution could be associated with these two facets of the disease are still unclear, though it is likely that in both cases the effects are mediated by oxidative stress and inflammation\textsuperscript{60-63}. But mechanisms could be specific per pollutant. As alluded to above, evidence points towards combustion and diesel particle exposure as being responsible for asthma development in children. In child studies, it has been suggested that the mechanisms linked to asthma incidence include allergic sensitization, and diesel exhaust may act as an adjuvant affecting the immune response to environmental allergens, and air pollutant particles may act as carriers of microbes and allergens\textsuperscript{64,65}.

One of the main challenges for studies addressing the health impact of air pollution is the assessment of exposure. Similar to the need to define the phenotypes and biologic features of study participants, exposure to ambient air pollution has to be assessed at an individual level. Numerous studies on the effects of air pollution are based on studies characterizing urban background pollution and/or the daily changes of key markers of this mixture. More recent approaches substantially improved the assessment of local contrasts occurring particularly in those pollutants and constituents that heavily depend on proximity to sources, such as traffic-related primary pollutants\textsuperscript{66}. However, personal assessment of exposures, integrating the various spaces people spent time and commute in, has so far been restricted to small-scale studies. All methods have advantages and limitations, but there is no consensus on a “gold standard” –which also depends on the study design– and their development depends on the resources available\textsuperscript{66}. A general challenge of exposure assessment, in particular in studies on the long-term effects of air pollution, is the scaling-up to large populations. Novel remote sensing, satellite-based tools combined with local measurements and land-use information may become highly attractive to define air quality retrospectively and prospectively in space and time (Fig. 2 and 3)\textsuperscript{67}. The combination of the pollution space with individually collected information on time-activity patterns, using personal mobile micro technology, will further improve the assessment of exposure on various time scales and for specific sources. The improvement of air pollution exposure assessment in a fine geographical scale on large populations, taking into account time-activity patterns, will allow us to better characterize and understand air pollution effects on asthma.

Air pollution is a mixture of multiple pollutants, some of them being highly correlated to each other either in time or space, if not both, making it difficult to identify the causal pollutants. It is interesting to note that American

\begin{table}
\centering
\caption{Summary of the air pollutant effects on asthma}
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Pollutant} & \textbf{Acute effects} & \textbf{Chronic effects} & \\
& & & \\
& & Children & Adults \\
\hline
Particulate matter & ++ & ++ & – \\
Nitrogen dioxide & +++ & ++ & ++ \\
Ozone & +++ & NA & NA \\
Traffic proximity & NA & ++ & – \\
\hline
\end{tabular}
\end{table}

- not sufficient evidence; + some studies find associations; ++ most studies find consistent results; +++ almost all studies find consistent results; NA: not available.
Figure 2. Map of nitrogen dioxide concentrations in 2005. Nitrogen dioxide (NO₂) LUR models for Western Europe (years: 2005-2007) based on > 1,500 EuroAirenet monitoring sites covering background, industrial, and traffic environments. Predictor variables include land use characteristics, population density, and length of major and minor roads in zones from 0.1 to 10 km, altitude, and distance to sea. The models were improved using satellite-based data (reprinted with permission from Vienneau et al.87. Copyright 2013 American Chemical Society).
Figure 3. Map of particulate matter with an aerodynamic diameter ≤10 μm concentrations in 2010. Nitrogen dioxide LUR models for Western Europe (years: 2005-2007) based on > 1,500 EuroAirnet monitoring sites covering background, industrial, and traffic environments. Predictor variables include land use characteristics, population density, and length of major and minor roads in zones from 0.1 to 10 km, altitude, and distance to sea. The models were improved using satellite-based data (reprinted with permission from Vienneau et al.67. Copyright 2013 American Chemical Society).

PM$_{10}$: particulate matter with an aerodynamic diameter ≤10 μm.
studies tend to find more negative effects of air pollution on asthma with PM or proximity to traffic and European studies with gases, namely NO$_2$. This could be due in part to the fact that particles have been measured routinely for more time in American cities, thus having more perspective for PM. Also, NO$_2$ is a marker of traffic and particularly of ultrafine particles. While in relation to mortality NO$_2$ is generally seen as a marker of traffic exposure, being an oxidant in relation to asthma attacks, it could play a causal role as a trigger. Another explanation could be that particle composition differs from one place to another. In fact, the notion of a “culprit pollutant” may be inherently flawed as pollutants contained in the mixture may act synergistically or even antagonistically. Characterizing exposure to “clustered” and source-specific pollutants at the personal level may have major advantages. To the extent that health effects depend on the nature and toxicity of pollutants, markers of such features of the mixture may be particularly appealing to address mechanisms and susceptibility factors.

We would like to draw attention to the literature about air pollution and lung function, which is a phenotype closely related to asthma. Numerous epidemiologic studies have shown decrements in pulmonary function that were associated with short-term air pollution exposure under real exposure conditions$^{68}$. In 2007, Mc Creenor et al.$^{34}$ conducted a very interesting experimental real-life exposure study, including 60 adults with asthma. Each participant walked for two hours in a very busy London street (Oxford Street) and, at a separate time, in a London park (Hyde Park). They found larger reductions in the FEV$_1$ and forced vital capacity (FVC) after walking in the street compared with walking in the park. The changes were greater in subjects with moderate asthma compared with those with mild asthma. These lung function test abnormalities were accompanied by increases in biomarkers of lung inflammation. These results contributed to confirm and better understand the acute effects of air pollution on the lung in asthmatics. Furthermore, long-term exposure to air pollution has also been associated with lung function growth$^{45}$, levels$^{69}$, and decline$^{70,71}$. The study by Gauderman et al.$^{45}$ was particularly important as it was one of the first to show prospectively in a large cohort that local exposure to traffic had adverse effects on children’s lung development, which could cause an impaired lung function in later life. All these features are implicated in both asthma aetiology and severity and very likely share mechanisms with asthma.

Another issue that we would like to discuss is whether it has been possible to identify susceptibility factors in the association between air pollution and asthma, in particular related to sex, atopy, or smoking. Actually, these factors have not systematically been addressed and the results are inconsistent. For example, as we have seen, many studies have found that air pollution was associated with atopy and/or asthma, but most of them lacked the power to address the question if air pollution was more associated with atopic asthma or non-atopic asthma, and those that looked for such interactions reported inconsistent associations. While results concerning sex differences are also inconsistent, some but not all seemed to find a higher association in males. It is interesting to note that in a prospective European meta-analysis including six cohorts, sex did not modify the associations between NO$_2$ and asthma incidence$^{59}$. Furthermore, all
cohorts showed positive associations between air pollution and asthma incidence in adults, except the Etude Epidémiologique auprès de femmes de la MGEN (Mutuelle Générale de l’Education Nationale) (E3N) cohort that only includes older women, mostly teachers. However, conversely, results from a nationwide US cohort suggest that air pollution exposure increases the risk of developing asthma in adult women. Regarding smoking, air pollution may be plausibly more asthmogenic in non-smokers, and several studies found greater associations between air pollution and asthma in non-smokers, but there is not sufficient evidence to draw a conclusion. Another interesting question is whether genes, mainly the ones involved in oxidative-nitrosative stress or inflammation pathways, may modulate the associations between air pollution and asthma. A recent review concluded that there is some evidence for an association between polymorphisms in inflammatory and immune-response genes and adverse respiratory outcomes from exposure to air pollution. However, the authors warned that more research is needed to confirm and quantify the strength of the interactions and to understand the mechanisms behind them.

To conclude the discussion, we would like to highlight several studies that have shown that efforts to reduce exposure are associated with lung function or asthma improvement. In a Swiss prospective cohort, decreasing exposure to airborne particulates appeared to attenuate the decline in lung function related to exposure to particulate matter with an aerodynamic diameter ≤ 10 μm (PM₁₀). In another Swiss study, it was observed that the reduction of PM exposures improved respiratory health in children. More recently, Adar et al. found that national and local diesel policies have reduced air pollutant concentrations exposures in the USA, so such decrease in exposure was associated with improved fractional exhaled NO₂/FEV₁ and FVC growth, and absenteeism, principally in children with asthma. And Gauderman et al. as part of the Children’s Health Study, found that long-term improvements in air quality were associated with statistically and clinically significant positive effects on lung-function growth in children. Whether all these improvements will actually result in fewer cases of asthma in the future still needs to be studied, but these results are promising.

**CONCLUSION**

There is growing and solid evidence that air pollution causes asthma exacerbations. The evidence regarding the effect of air pollution exposure on asthma onset is also quite robust, mainly in children but also in adults. Furthermore, there is a lot of knowledge about the mechanisms of the different pollutants involved. Gases that are oxidants could be more associated with acute manifestations of the disease, and particles that are more related with chronic inflammation could be more related to incidence. Diesel particles have been associated with both exacerbations and incidence. However, research is still needed to better understand and identify the underlying mechanisms related to the specific pollutants and specific sources. More research is also needed to identify more susceptible groups such as males, non-smokers, or persons with other chronic conditions, such as atopy or obesity. To achieve such goals, well-characterized and phenotyped large cohorts with detailed exposure assessment are necessary.
In the light of these results that show that air pollution exposure, and principally traffic-related air pollution exposure, has a major impact on respiratory health, the pulmonologists, as they did against the tobacco industry, should act as lobbyists and put pressure on local and European authorities in order to promote policies to better control emissions and therefore improve the respiratory health of the population.

CONFLICT OF INTEREST

All authors declare no relevant conflict of interest.

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