Environment and asthma in adults

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Available online: 3 September 2013

Summary

The present review addresses recent advances and especially challenging aspects regarding the role of environmental risk factors in adult-onset asthma, for which the causes are poorly established. In the first part of the review, we discuss aspects regarding some environmental risk factors for adult-onset asthma: air pollution, occupational exposures with a focus on an emerging risk represented by exposure to cleaning agents (both at home and in the workplace), and lifestyle and nutrition. The second part is focused on perspectives and challenges, regarding relevant topics on which research is needed to improve the understanding of the role of environmental factors in asthma. Aspects of exposure assessment, the complexity of multiple exposures, the interrelationships of the environment with behavioral characteristics and the importance of studying biological markers and gene–environment interactions to identify the role of the environment in asthma are discussed. We conclude that environmental and lifestyle exposures play an important role in asthma or related phenotypes. The changes in lifestyle and the environment in recent decades have modified the specific risk factors in asthma even for well-recognized risks such as occupational exposures. To better understand the role of the environment in asthma, the use of objective (quantitative measurement of exposures) or modern tools (bar code, GPS) and the development of multidisciplinary collaboration would be very promising. A better understanding of the complex interrelationships between socio-economic, nutritional, lifestyle and environmental conditions might help to study their joint and independent roles in asthma.

Asthma is a worldwide public health issue. This common chronic disease affects one out of twenty people in the world, i.e. 300 million people worldwide [1]. Since approximately 1980, the prevalence of asthma has doubled in westernized countries and may have reached a plateau in recent years in Europe [2,3]. The causes of this alarming change are unclear but cannot be
attributed only to changes in diagnosis and the reporting of symptoms over time. Most experts attribute the increase in asthma prevalence to changes in lifestyle, environmental (e.g. outdoor air pollution, occupational exposures, indoor pollution) and behavioral factors (e.g. diet), potentially in interaction with genetic factors [2,4–7]. Extensive research has been performed to identify changes in environmental determinants in recent decades [3]. Although the exact role of the environment in the development of asthma is largely unknown, strong evidence suggests that environmental factors play a key role in its induction or exacerbation [5,8,9]. Asthma is a heterogeneous disease, and categories such as childhood or adult-onset asthma are increasingly accepted as different phenotypes [10]. In addition, to better understand persistent asthma in adulthood, many experts have called for more research on different asthma phenotypes, including occupational asthma and asthma severity or control [10–12]. The role of environmental and behavioral factors might differ across these phenotypes.

In childhood, several environmental factors have been reported to be associated with asthma, including a protective effect of farming environment early in life or prenatally [13–15], a deleterious effect of exposure to second hand smoke, as well as a deleterious effect of exposure to air pollution [13,15–19]. The conclusions of a recent review on the induction of asthma and the environment [17] provide scientific support for public health efforts to limit in utero and postnatal exposure to tobacco smoke. Regarding air pollution, there is substantive evidence in children that proximity to traffic or traffic-related air pollution is associated with asthma exacerbations and incidence [20–22].

The present paper reviews recent advances regarding the role of environmental risk factors in adult-onset asthma, as its causes are poorly established [23]. In adults, it has been suggested that environmental risk factors play a smaller role in inducing new-onset asthma than host factors [24]. In the indoor environment, exposure to allergens such as dust mites, pets (especially cats and dogs), cockroaches, mice and fungi are important risk factors for the development and exacerbations of allergic asthma [8,9,15,19], and prevention and protective interventions have already been proposed [25,26]. The deleterious role of traffic-related air pollution on adult-onset asthma is less conclusive than in childhood-onset asthma [23]. Historically, the deleterious role of occupational exposure such as grain dust in asthma was described by Ramazzini (de morbis artificum diatriba, 1713) [27]. Asthma is now the main occupational respiratory disease and some preventive measures have already been taken for some of the occupational exposures evidenced in the last 40 years [5,28]. The role of nutrition and lifestyle has been studied recently [15,17,29]. In the first part of the review we discuss challenging aspects regarding some environmental risk factors for adult-onset asthma: air pollution, occupational exposures with a focus on an emerging risk represented by exposure to cleaning agents both at home and in the workplace, lifestyle and nutrition. Smoking, a major problem in respiratory diseases, is not included here, as it has been extensively reviewed previously [15,30]. The second part is focused on perspectives and challenges regarding relevant topics on which research is needed to improve the understanding of the role of environmental factors in asthma. Aspects of exposure assessment, the complexity of multiple exposures, the interrelationships between the environment and behavioral characteristics and the importance of studying biological markers and gene-environment interactions to identify the impact of the environment in asthma are reviewed.

**Outdoor air pollution**

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 exacerbations. Since then, many studies have assessed the association between air pollution and asthma phenotypes, going from time-series or panel studies,
that assess the short-term exposure to air pollution on acute manifestations of the disease [31–38], to cohort studies that assess longitudinally or cross-sectionally chronic exposure to air pollution on long-term manifestations of the disease [23,39,40] or on its incidence [23,41] and prevalence [42]. The air pollutants of major interest in the westernized world in urban areas are nowadays those related to traffic like nitrogen dioxide (NO2) and particulate matter (PM), or ozone (O3) which is a by-product of NO2. The effects of air pollution on asthma are biologically relevant as air pollution causes inflammation and oxidative stress, i.e. mechanisms that are involved in asthma exacerbation, asthma severity and probably in asthma development [43]. The acute effects of ambient air pollution on asthma are well established, leading to more severe morbidity and even mortality [44]. It is well known that short-term exposure to high concentrations of ambient air pollution contributes to exacerbations, emergency visits, increased medication intake and other acute manifestations occurring in asthma [31–38]. These associations have been mainly studied in the United States (USA) and in Europe, and mostly in adults. A recent review in the elderly showed a potentially more susceptible population, with an adverse effect of short-term exposure to air pollution on their respiratory health [45].

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 owing to the advent of new methods to assess long-term exposure. The evidence of chronic effects of air pollution in asthma remains limited. The long-term effect of air pollution on new asthma onset has been mostly studied in children [20,22,46]. The evidence is less conclusive in adult-onset than in childhood asthma [21,41,46]. In adults, two recent reviews [23,41] suggested an association between long-term exposure to air pollution and asthma incidence, but the currently available studies on adult-onset asthma are not sufficient to allow conclusions to be drawn about the causal role of air pollution. However, several studies have shown a positive association between air pollution and asthma onset [47,48], and other studies have found that this association was modified according to genetic factors [49] (Table 1). Long-term exposure to O3 air pollution has been associated with new-adult onset asthma in different surveys [47,48,50–52]. Jacquemin et al. [52] showed an association between air pollution and asthma incidence among subjects free of asthma at least until late childhood. Long-term exposure to air pollution has also been associated with markers of asthma exacerbations but in larger time-frames [39,40,53]. In the French EGEA survey, long-term exposure was associated with total immunoglobulin E (IgE) [54], severity [39], and poorly controlled asthma [40]. Reported patterns of effect modification (e.g., by sex, atopy or smoking) were inconsistent. In most studies, markers of local traffic-related air pollution were used to characterize long-term exposure. However, the protocols, definitions of asthma, and exposure assignment used were rather heterogeneous. Disentangling the chronic and acute effects of air pollution is thus a challenge in modern air pollution epidemiology.

### Occupational exposures

Occupational exposure was recognized to cause asthma at the end of the 1970s [5,28,55,56]. Work-related asthma is now the most common occupational lung disease in industrial countries [57,58]. The number of established asthmagenic agents (specific dusts, gases or fumes known to induce asthma) identified in occupational asthma increased regularly from more than 150 at the end of the 1990s [55,59] to more than 400 known asthmagenses in 2012 [60]. The burden of occupational diseases is underestimated because of under-reporting, in part due to the lack of knowledge regarding specific occupational risks. Furthermore, the ‘healthy worker effect’, a source of selection bias in studies on work-related asthma, leads to masking or underestimation of associations [61]. The risk of asthma attributable to occupation has been estimated as approximately 15% [62]. Several studies have shown an increase in both the prevalence and incidence of occupational asthma over the past few decades [63,64]. Significant associations have been observed between occupational exposure to asthmagenses and more severe [65] or uncontrolled asthma [66]. Two physiopathology mechanisms have been proposed for occupational asthma:• immunological asthma (with a latency period) which is classified in two categories: IgE-dependent asthma (similar to allergic asthma not linked to work, mostly induced by high molecular weight agents) and non-IgE-dependent asthma (mostly induced by low molecular weight agents), and;• non-immunological asthma.

The latter is usually considered to be induced by a single exposure to a high level of irritants but the mechanism is unknown. There is increasing debate regarding whether exposures at a low-to-moderate level may induce such asthma as well [67]. Maestrelli et al. evaluated the contribution of host factors and workplace exposure to the risk of a poor outcome of occupational asthma [68]. They concluded that older age, high molecular weight agents, impaired lung function and longer duration of exposure at the time of diagnosis were associated with a worse outcome of occupational asthma. Regarding potential modifying factors, gender has been rarely studied whereas atopy and smoking at diagnosis did not seem to influence the outcome of occupational asthma, which was often poor after diagnosis. Occupational asthma has been prevented or reduced successfully limiting the use of agents that cause asthma such as enzyme in detergents and powdered latex gloves, or by replacing them [17]. Possibly owing to preventive measures, a decrease in work-related asthma associated to organic dusts, high molecular weight agents (latex), chemical products...
TABLE 1
Main results of studies assessing the association between air pollution and new adult-onset asthma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pollutant</th>
<th>Association for the general population</th>
<th>Main message</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDonnell et al. [50]</td>
<td>O3, PM10, SO2, NO2</td>
<td>Not applicable as only non-smokers</td>
<td>O3 8 hour average is associated with adult asthma incidence in males. No other pollutants (including NO2 or PM10) were associated with asthma incidence</td>
</tr>
<tr>
<td>1999 ASHMOG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modig et al. [51]</td>
<td>NO2 (modeled at home)</td>
<td>In subjects who lived &gt; 2 years at the present home OR for living close to high traffic flow: 2.4 [0.9-6.2] OR for an increase of 1 µg.m⁻³ of NO2: 1.1 [0.9-1.2]</td>
<td>Living close to high traffic was non-significantly associated with asthma incidence. NO2 was associated with adult asthma incidence only in subjects with a positive SPT</td>
</tr>
<tr>
<td>2006, Lulea, Sweden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modig et al. [48]</td>
<td>NO2 (modeled at home)</td>
<td>Asthma incidence (for a consistent age of onset) OR for NO2 per an increase of 10 µg.m⁻³: 1.5 [1.0-2.4] OR for distance to major road &lt;50m: 3.9 [1.9-7.8]</td>
<td>NO2 exposure and living close to a major road were associated with asthma onset and incidence in adults</td>
</tr>
<tr>
<td>2009 RHINE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacquemin et al. [52]</td>
<td>NO2 (modeled at home)</td>
<td>OR for NO2 per 10 µg.m⁻³: 1.4 [1.0-2.0] When only considering those reporting age of asthma onset between the 2 surveys: 1.7 [0.99-3.0]</td>
<td>NO2 was associated with asthma incidence in adults</td>
</tr>
<tr>
<td>2009 ECRHS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacquemin et al. [53]</td>
<td>See above</td>
<td>Ratio of mean score (RMS) per 10 µg.m⁻³ in subjects with a 0 score and no asthma at baseline: 1.3 [1.1-1.4]</td>
<td>NO2 is associated with the asthma score, which is an alternative to assess asthma incidence in adults. Association was stronger in never-ex smokers</td>
</tr>
<tr>
<td>2009 ECRHS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castro-Giner et al. [49]</td>
<td>See above</td>
<td>Association of NO2 per 10 µg.m⁻³ increase in this gene x air pollution interaction: NQO1 rs2917666 CC: 2.0 [1.2-3.7] NQO1 rs2917666 GC/GG: 1.3 [0.8-2.0]</td>
<td>A significant interaction was found between NQO1 rs2917666 and NO2 for new-onset asthma</td>
</tr>
<tr>
<td>2009 ECRHS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Künzli et al. [47]</td>
<td>Change in traffic related PM10 (modeled at home)</td>
<td>Not applicable as only tested in never-smokers In never-smokers: HR 1.3 [1.0-1.6] per 1 µg.m⁻³ of change in traffic PM10</td>
<td>Increase in traffic PM10 is associated with asthma incidence in adult non-smokers Residential proximity to busy roads was not associated with asthma</td>
</tr>
<tr>
<td>2009 SAPALDIA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table adapted from those of Jacquemin et al. [23].

ASHMOG: Adventist Health and Smog Study; APMoSPHERE: Air Pollution Modeling for Support to Policy on Health and Environmental Risk in Europe; COPD: chronic obstructive pulmonary disease; ECRHS: European Community Respiratory Health Survey; HR: hazard ratio; NO2: Nitrogen dioxide; OR: Odds ratio; O3: Ozone; PM: Particulate matter; PM10 i.e. particles smaller than 10 microns; RHINE: Respiratory Health in Northern Europe; SAPALDIA: Swiss Study on Air Pollution and Lung and Heart Diseases in Adults.

(such as isocyanates, aldehydes) other than cosmetics and cleaning products has been suggested in France [69,70].

Cleaning agents: an emerging public health issue, occupational and indoor exposures

Many people are regularly exposed to disinfectant or cleaning agents worldwide and there is growing evidence that healthcare workers and cleaners are commonly and highly exposed to these agents [71,72]. Evidence of an adverse effect of cleaning products or disinfectants in asthma mostly comes from studies on occupational risk factors, but a deleterious role of domestic cleaning exposure has also been observed [73] (table II). This exposure may represent an important public health issue, especially in women. In hospitals, some suspected carcinogenic agents like formaldehyde have been substituted by new substances that are potentially asthmagenic [72]. The application of guidelines to protect patients from healthcare-associated infections has resulted in an increased frequency of disinfection tasks [96] as well as increased use of disinfectant or cleaning sprays. Exposure to cleaning products is common both in the workplace and at home (exposure less controlled than at work [17], and...
TABLE II
Findings from epidemiological studies regarding the association between asthma and exposure to cleaning products

<table>
<thead>
<tr>
<th>Cross-sectional</th>
<th>Longitudinal (prospective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current asthma, adult onset asthma, new-onset asthma</td>
<td>Asthma symptoms/ exacerbations, severe asthma, poorly controlled asthma</td>
</tr>
<tr>
<td>Occupations only</td>
<td>5 studies [74–78] Increased asthma risk in healthcare workers (personal care workers, nurses…) and in cleaners</td>
</tr>
<tr>
<td>Occupational exposure to cleaning/disinfecting products overall</td>
<td>2 studies [59,82] Increased asthma risk in subjects exposed to industrial cleaning products</td>
</tr>
<tr>
<td>Occupational exposure to specific cleaning/disinfecting products or tasks</td>
<td>6 studies [84–89] Increased asthma risk in subjects exposed to bleach, ammonia, sprays, detergents, medical instrument cleaning, or decalifiers</td>
</tr>
<tr>
<td>Domestic use of cleaning sprays</td>
<td>1 study [94] Domestic use of cleaning sprays associated with current asthma, poorly controlled asthma, and IgE-dependent asthma</td>
</tr>
</tbody>
</table>

Women remain more prone than men to this type of exposure [71,72,90,94]. Cleaning and disinfecting products contain numerous chemicals, which may be irritants (bleach, ammonia) or sensitizers (perfumes) and may cause asthma with partly unknown mechanisms. Mixing bleach with ammonia or acids (often used as decalifiers) may result in inhalation accident, a possible cause of acute irritant-induced asthma [97]. Bello et al. [96] classified the use of cleaning sprays, which has increased in recent decades [98], as high risk for inhalation exposure. The level of exposure may vary according to the chemical properties, the number of products applied, and other characteristics (ventilation, volume) [96]. Associations with asthma have been observed for specific exposures (table II) such as ammonia, bleach, decalifers, cleaning sprays and disinfectants (formaldehyde, glutaraldehyde). Regarding specific phenotypes, associations with asthma (current, adult-onset, exacerbations) have been observed in several cross-sectional studies. Subjects exposed to industrial cleaning products and nurses were at increased risk of new-onset asthma [81]. In two studies investigating the effect of domestic use of cleaning products, associations were observed between the use of cleaning sprays and asthma incidence [95] or poorly-controlled asthma [94]. Non IgE-dependent [80,83] and IgE-dependent [94] mechanisms have been suggested for exposure to cleaning products in the workplace and at home (in spray form), respectively. Few studies have investigated the specific asthma phenotypes associated with exposure to cleaning products and a better characterization of phenotypes may provide new insight regarding possible mechanisms [71]. Although it has received little attention, there is increasing evidence for the deleterious role in asthma of the use of cleaning products in spray forms, both at work and at home [91,94,95,99]. The risk of asthma attributable to domestic exposures to cleaning sprays might represent as much as 15% in adults [95]. Among adults, the deleterious role of
weekly use of cleaning products in spray form during household cleaning tasks has been shown for asthma [94,95] and cardiovascular disease (especially among subjects with obstructive lung disease) [100]. The same trend was observed between daily use of sprays at home and wheezing in children [101]. In addition, findings among young children [102,103] show that frequent use of household products by the mother during pregnancy is associated with persistent wheezing in children.

Lifestyle and nutrition

Changes in dietary habits (less fruits/vegetables, more ready to eat meals), the obesity epidemic, and the decrease in physical activity, have been suggested to play a role in the increase of asthma worldwide [15,17,29]. Regarding obesity, a large number of papers have been published on the topic over the last 10 years, showing that obesity precedes asthma [104], and that obesity-related asthma is a distinct asthma phenotype [10]. Despite a general consensus defining obesity as a risk factor for asthma, the precise mechanisms are still unknown.

A possible link between obesity and asthma is diet, as body composition is the result of both dietary behavior and physical activity. It has been hypothesized that the increase in asthma prevalence may be due to changing antioxidant intake, increasing dietary ratio of n-6:n-3 polyunsaturated fatty acids (PUFA), and vitamin D deficiency [29]. The main findings regarding the effect of foods, nutrients and dietary patterns on asthma have recently been summarized [29]. Overall, findings underscore the importance of conducting prospective studies and clinical trials to better understand the role of diet in the etiology of asthma. Besides the protective effect of diet, there is also a need to further study foods or nutrients with a potential deleterious effect.

Among adults, several observational studies have reported negative associations between asthma and a low dietary intake of vitamin E, vitamin C, carotenoids, selenium, polyphenols, fruits and vegetables and PUFA (Table III). The lack of longitudinal studies is striking in comparison with the large number of observational studies performed. To our knowledge, only four longitudinal studies have been performed to study the association between dietary intake and adult-onset asthma and three of them failed to report any association [106,112–114]. A recent study conducted in the USA among 4,162 participants aged 18-30 yr reported that intake of long-chain n-3 polyunsaturated fatty acids, which are abundant in fish, was inversely associated with the incidence of asthma over 20 years [114]. Several randomized control trials (RCTs) have been conducted, but they do not support the use of vitamin C, vitamin E, selenium or n-3 PUFA supplements to complement conventional therapy for asthma [105]. Vitamin D intake represents a combination of dietary intake of vitamin D (e.g. fortified milk) and vitamin D synthesized in the skin upon exposure to UVB radiation from sunlight, so most of the published studies focused on serum vitamin D level (25(OH)D). Few cross-sectional or case-control studies have been conducted regarding vitamin D, and they have reported conflicting findings [116,117]. However, a recent cross-sectional study among 6,857 adults from the NHANES study reported a positive association between low vitamin D levels with wheezing, history of asthma and asthma exacerbations [116]. To our knowledge, only one longitudinal study has been performed and reported no association between serum 25(OH)D and incident asthma [117]. Until now, no RCTs have been published, but there are several ongoing clinical trials [127]. Overall, the body of observational evidence is inherently weak because of the biases and limitations of the cross-sectional and case–control studies that predominate.

Most of the studies on diet and asthma have focused on the protective effects of diet through its antioxidants and/or anti-inflammatory properties. However, diet contains also numerous compounds exhibiting oxidant/nitrosative activity, such as cured meat. Although a strong positive association was reported between cured meat intakes with newly-diagnosed chronic obstructive pulmonary disease (COPD) [128,129] and COPD exacerbations [130], no association was reported between cured meat intake and adult-onset asthma [128,129]. Further studies are needed to identify foods and/or nutrients with a deleterious effect.

Besides foods and nutrients per se, studying dietary patterns might provide insight regarding the role of diet not only through biological mechanisms, but also through social aspects. Diet is an essential aspect of lifestyle, with specificities between countries and social groups due to cultural, social and environmental factors [14]. Investigating dietary patterns is a new approach in the nutritional epidemiology of chronic diseases to assess the effects of overall diet [131]. Results regarding dietary patterns in adulthood are conflicting. In cross-sectional studies, dietary patterns are usually associated with asthma [118–120,132], although these findings were not confirmed in longitudinal surveys [121,123–125]. Taken together, the data are still conflicting. All the published studies on respiratory diseases and diet are very heterogeneous regarding exposure assessment (food frequency questionnaires, 24-hour recall, biological markers), phenotype (asthma, wheezing), or study design (case-control, cross-sectional, longitudinal), and very few randomized clinical trials have been published.

Research needed to improve understanding of environmental factors

The complex relationships between various socio-economic, environmental and lifestyle conditions, genetic pathways and the clinical expression of asthma are illustrated in figure 1. The following section discussed exposure assessment and the
### Table III

**Main findings regarding the diet-asthma association in adults**

<table>
<thead>
<tr>
<th>Foods and nutrients</th>
<th>Cross-sectional or case/control study</th>
<th>Longitudinal study</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary intake of vitamin E</td>
<td>Between 5 and 10 studies [29,105] Overall, negative association between high vitamin E intake with asthma and asthma severity</td>
<td>1 study [106] Negative association between high dietary intake of vitamin E and the risk of asthma-onset over a 10-year period</td>
<td>1 study [107] (n = 72, 6-wks of intervention) No association between dietary supplementation with vitamin E and bronchial reactivity or asthma in adults with mild to moderate asthma</td>
</tr>
<tr>
<td>Dietary intake of vitamin C</td>
<td>Between 5 and 10 studies [29,105] Overall, negative association between high intake of vitamin C with asthma and asthma severity</td>
<td>1 study [106] No association between dietary intake of vitamin C and the risk of asthma-onset over a 10-year period</td>
<td>More than 10 studies [108] Overall, no effect of dietary vitamin C supplementation on asthma</td>
</tr>
<tr>
<td>Dietary intake of vitamin A</td>
<td>Between 5 and 10 studies [29,105] Overall, negative association between high intake of vitamin A with asthma and asthma severity</td>
<td>1 study [106] No association between dietary intake of vitamin A and the risk of asthma-onset over a 10-year period</td>
<td>No study</td>
</tr>
<tr>
<td>Dietary intake of selenium</td>
<td>More than 10 studies [29] Overall, association between dietary selenium intake and asthma</td>
<td>No study</td>
<td>2 studies [109,110] Association between selenium supplementation and an improve clinical evaluation, but no association with lung function (n = 24, 14-wks of intervention) [109] No association between selenium supplementation and lung function and asthma symptom scores in adults with asthma (n = 197, 24-wks of intervention) [110]</td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td>More than 10 studies [29] Overall, a beneficial effect of fruits and vegetables intakes on current asthma, asthma symptoms and asthma control</td>
<td>No study</td>
<td>1 study [111] (n = 137, 14-wks of intervention) Positive association between inducing a high intake of fruits and vegetables in adults with asthma on clinical asthma outcomes</td>
</tr>
<tr>
<td>Dietary intake of PUFA (n-3, n-6)</td>
<td>Between 5 and 10 studies Overall, negative association between omega-3 intake and asthma</td>
<td>4 studies [106,112–114] 3 studies: no association between omega-3 intake and adult-onset asthma [106,112,113] A recent study reported a significant negative association between omega-3 intake and adult-onset asthma [114]</td>
<td>Between 5 and 10 studies [115] Overall, inconclusive findings</td>
</tr>
<tr>
<td>Serum vitamin D levels</td>
<td>Between 5 and 10 studies [29] Overall, conflicting results. A recent study (6,857 adults, NHANES): positive association between low vitamin D levels and wheezing and asthma exacerbations [116]</td>
<td>1 study [117] No association serum 25(OH)D levels and incident asthma in adults</td>
<td>No study</td>
</tr>
<tr>
<td>Dietary patterns</td>
<td>5 studies [118–122] Overall, association between dietary patterns with asthma and asthma control</td>
<td>4 studies [121,123–125] Overall, no association between dietary patterns and adult-onset asthma</td>
<td>1 study [126] (n = 38, 12-wks of intervention) No association between inducing adherence to the Mediterranean diet, in adults with asthma, and asthma symptoms and asthma control</td>
</tr>
</tbody>
</table>

interrelationships between environmental and lifestyle factors for which research is needed to improve understanding of the role of environmental factors in asthma. The importance of studying genetic pathways, biological markers and gene-environment interactions to identify the role of the environment in asthma and public health issues is then addressed.

**Exposure assessment**

When assessing the effects of air pollution on asthma, larger studies with more consistent and precise definitions of phenotypes and exposure assessment for local traffic-related pollutants (e.g., ultrafine particles) are needed. The proximity model is the method mostly commonly used in epidemiological studies to assess air pollution concentrations, e.g. from the closest monitoring station or the proximity to a major road. In the last decade, several methods have been developed to better estimate long-term exposure to air pollution within each city and/or area. Some studies have combined personal or home measurements with any of the models described previously in order to improve the precision of the estimates. All these methods need geocoded addresses and GIS (Geographical Information System) software and expertise. They all have advantages and limitations but there is no consensus regarding a “gold standard”, and their development depends on the resources available [133]. Another aspect to be taken into account, when assessing long-term effects of air pollution, is the need for appropriate retrospective assessment of exposure, an issue especially relevant when assessing incidence. Further longitudinal studies with detailed information at baseline are warranted. Most epidemiological studies that evaluated the long-term effects of air pollution exposure on asthma assessed exposure to air pollution at home, without taking into account time spent in traffic or exposure to outdoor air pollution at work. Finally, another aspect to be taken into account when assessing the effects of air pollution on respiratory health is the air pollution compounds responsible for the effects as outdoor air pollution is a complex mixture of many compounds.

Assessment methods to evaluate occupational exposure and especially cleaning products need improvement in order to strengthen the evidence regarding the potential role of specific chemicals. Currently, assessment of exposure to specific cleaning products both in the workplace and at home is generally based on self-reporting, which may generate a differential misclassification bias [72,134]. Some studies have evaluated occupational exposures through job exposure matrices but few have used case-by-case expertise [72,84]. Research is underway in a broader perspective to assess the microbiome [135] and the exposome [136]. Available data on the exposome may be of great interest to evaluate environmental exposure and to study associations with asthma [69]. More objective exposure assessment methods that are applicable to large populations, such as task-exposure matrices or the use of quantitative measurements, need to be developed to improve exposure assessment.

Home environments might be major sources of aero-contaminants and it has been suggested that VOC (Volatile Organic Compounds) should be measured at home to better evaluate domestic exposure to cleaning products and potentially to cosmetics, which were recently suggested as a potential risk factor for asthma and allergic diseases [69,137–139]. In recent surveys, home visits using bar codes of various products were performed and may provide objective tools to validate or improve questionnaires used in epidemiological surveys [140,141]. It would be important to collect more precise information regarding specific products used at home, the type of presentation (cream, liquid or spray; aerosol with or without gases) and the way they are used including ventilation in the house, which can influence exposure [96].

In conclusion, more work and expertise are needed to assess potential environmental determinants in asthma.
Interrelationship between environmental and behavior factors

Exposures to the various environmental and behavioral risk factors for asthma vary over time, are interrelated and may be influenced by the time-varying clinical expression of the disease (figure 2). The healthy worker effect illustrates such an interrelationship between one asthma risk factor (i.e. occupational exposures) and the disease, with opposing effects of occupational exposure on asthma, and of asthma on job choice [61,142]. Other behavioral changes influenced by the disease may impact the level of physical activity [143], avoidance of polluted places, or domestic habits (e.g., the use of cleaning sprays) [94]. Such interplay between risk factors and the disease may create complex situations of time-varying confounding [144,145]. Prospective studies with precise assessment of asthma history as well as several lifetime risk factors are needed to disentangle these complex phenomena. Beyond the availability and quality of the data, several analytic approaches have recently been developed for causal inference in epidemiology [146]. For instance, graphical approaches, such as directed acyclic graphs, allow synthetic representations of putative causal relationships and are useful for identifying possible sources of confounding [147]. Marginal structural models have been developed to address the challenging issue of time-varying confounding [144]. These methods are of particular interest to better characterize the effect of environmental and behavioral risk factors for asthma.

Besides nutrition per se, the interrelationships between nutritional factors (diet, obesity, physical activity) are important challenges for epidemiological researchers. They are interlinked, i.e. body composition is the result of dietary behavior and physical activity, and each of them has been suggested to play a role in asthma. Addressing the diet-asthma association therefore means accounting for these interrelations. As recently underlined, substantial shortcomings have been observed in the handling of confounding and effect modification in the diet-asthma association [148]. Further work is warranted to find a stronger scientific basis to support nutritional recommendations that lower the risk of asthma. Until now, the method used to control for confounding in the diet-asthma association was to investigate the possible effect of each risk factor adjusted for all the other risk factors, leading to the issue of over-adjustment [143]. Very few studies have investigated the joint roles of nutritional factors as determinants of asthma. Recent approaches to causal inference offer a framework [149] that may help addressing these issues. The role of socio-economic factors in asthma has been scarcely discussed in reviews on the environment [15]. Socio-economic status (SES) is linked to air pollution, occupation, nutrition and lifestyle factors. In most studies, SES is often evaluated only in terms of educational level or job category estimates [150–152]. Therefore, SES was not taken into account when studying associations between occupational exposures and asthma. Regarding domestic exposures, household help which is strongly related to SES, has not been taken into account until now. Diet, an important aspect of lifestyle, is also linked to social factors [14].

Recent studies suggested that low SES plays a role in both childhood- and adult-onset asthma [15]. However, the association between SES and asthma prevalence and incidence in adults is not well understood and is a matter of debate [150,153–157]. Although sparsely studied, lower SES seems to be associated with more symptomatic/severe asthma [156,158–160] or poorly controlled asthma [161]. Poor adherence to inhaled corticosteroids seems associated with lower income and lower educational level [162–164]. SES is difficult to define in epidemiology and various indicators are required in health research [165]. Various deprivation indices are available as a proxy of SES [165–168] but they have been scarcely used to study the association with asthma [158,159,169]. Additional work is warranted on methodological aspects such as the accuracy and consistency of these indices and to evaluate

**Figure 2**

Complex time-related relationships between socio-economic, environmental conditions and respiratory diseases
SES through both individual and geographical indices and its relation with asthma phenotypes. In a recent study, Roberts et al. discussed the role of air pollution and social deprivation status, a proxy of SES, on severe exacerbations of asthma \[159\]. They observed a stronger association between social deprivation and asthma exacerbation than for air pollution for which the association did not remain significant after adjustment for SES. In addition, as subjects with asthma are more susceptible to the adverse effects of air pollution and possibly more bothered by air pollution \[170\], asthmatics who may afford to choose may move to less polluted areas. This would result in the selection of healthier people living in more polluted sites, comparable to the selection patterns observed in occupational settings. Whether the socioeconomic patterning of air pollution contributes to the socioeconomic pattern of asthma is not established. The current lack of consensus may reflect a great geographical variability in the direction and magnitude of these associations. It would be helpful to characterize whether environmental injustice regarding air pollution exists and whether it contributes to a differential distribution of asthma outcomes. As recently underlined \[15,159\], further analyses are warranted to clarify the role of SES in the associations between environment and asthma.

**Biological and genetic aspects**

Adaptive responses to protect the lung against environmental toxic insults are activated through metabolic pathways in response to environmental exposures and may result in modification of:
- the regulation or the expression of proteins, or;
- metabolisms leading to the scavenging or the production of reactive metabolites.

These modified proteins and reactive metabolites are intermediate biological phenotypes throughout the causal chain between environmental factors and diseases, and are of great interest for investigating the internal exposome \[136\] and understanding the disease etiology. Biological phenotypes are classified as indicators of exposure to environmental factors or of internal dose, of biologically effective dose, of early biological effect, of damage, of disease or of susceptibility \[171\]. Biological markers can be measured in several fluids, and collected with minimal constraints on the participant, and in a standardized way in epidemiological studies \[172\]. In recent decades, the desire to measure biological phenotypes closest to the organ studied, e.g., the lungs for respiratory diseases, has seen the development of research on the condensate of exhaled air, whose collection is completely non-invasive and can be performed in many subjects, unlike bronchoalveolar lavage or induced sputum. This fluid is therefore of great potential value for respiratory epidemiology in order to study the biological mechanisms involved in asthma.

Among the several physiological processes that may be investigated in asthma, the response to oxidative/nitrosative stress is of major interest. The amount of biological evidence for a role of oxidative/nitrosative stress in asthma is increasing \[173\]. Studies in humans and animals have shown that:
- many pro-inflammatory mediators generate the production of reactive oxygen (ROS) and nitrogen (RNS) species;
- the nitric oxide (NO) released in the activated stage of the disease in the presence of environmental oxidative stress, may amplify the deleterious and harmful effects in the airways \[174\];
- eosinophils and neutrophils, which are inflammatory cells, also participate in the formation of ROS and RNS in asthmatic subjects.

Tobacco smoke \[175\], air pollution and occupational exposures, which all play a role in asthma, are environmental factors related to oxidative/nitrosative stress. Cigarette smoke is a highly complex mixture of over 4,700 chemical compounds and one puff of cigarette smoke contains millions of oxidants and high concentrations of NO \[176\]. Regarding air pollution, the most studied air pollutants are O\(_3\), NO\(_2\), and PM. O\(_3\) is the component of photochemical oxidants and ‘summer smog’. NO\(_2\) is a free radical that has the potential to deplete tissue antioxidant defenses and, as a result, cause injury and inflammation. PM are deposited selectively throughout the respiratory tract at locations determined primarily by their size. The chronic effects of air pollution and its associated biological mechanisms are not well known, but the mechanisms of action most widely proposed are through oxidative stress and inflammation \[44,177\]. Numerous sources of evidence show that inhaled particles have adverse consequences for the lungs and other organs \[178\]. These effects mainly involve production of an inflammatory response, exacerbation of existing airway disease (e.g. hyperreactivity) or impairment of pulmonary defense mechanisms. Inhaled PM may increase the production of antigen-specific immunoglobulins, alter airway reactivity to antigens or affect the ability of the lungs to handle bacteria, suggesting that exposure may result in enhanced susceptibility to microbial infection. O\(_3\) acts as a powerful oxidizing agent that can cause adverse effects on human health, e.g. inflammation and irritation of the respiratory tract, increase in lung susceptibility to toxins and microorganisms as well as premature deaths. As for air pollutants, the mechanism of asthma induced by irritants is unknown but could be related to oxidative/nitrosative stress \[179,180\]. Among the cleaning agents, chlorine is a highly reactive gas and it seems likely that airway damage is induced via oxidative injury. Chlorine can combine with ROS to form a variety of highly reactive compounds that may lead to oxidation of epithelial proteins \[179\]. Interaction of chlorine with oxides of nitrogen may also occur, causing the chlorination and nitration of various amino acid residues, particularly tyrosine. Overall, studying
biological phenotypes related to oxidative/nitrosative stress in environmental and occupational asthma is of great interest to better understand the underlying mechanisms [181]. Studying genes by environment interactions (GxE) may help to identify the place of the environment in asthma [182]. A recent review on asthma GxE revealed the paucity of studies on the theme and illustrated the challenges from the recent literature, which has convincingly demonstrated few interactions till now [182]. It discussed the need to define new strategies beyond the single candidate gene approach and the fully agnostic pangenomic interaction study approach. Large epidemiogenetic studies conducted on genes involved in the response to oxidative/nitrosative stress and their interaction with environmental exposures in asthma are lacking [183,184]. Regarding a candidate gene approach, on a gene evidenced by GWAS, we showed that the increased risk of asthma conferred by 17q21 genetic variants [185] was restricted to early-onset asthma and that the risk was further increased by early-life exposure to environmental tobacco smoke [186], providing new insight into early-onset asthma. Studies have focused more on children than on adults and mostly on air pollution and smoking [49,187–191]. A few studies have been conducted on the concept of candidate interactions [192]. Interactions between fewer than 20 different genes and ambient air pollution or smoking on asthma, lung function growth and respiratory-related school absences have been investigated independently in children [49,187–191]. In adults, the effects of four genes on the association of traffic-related air pollution and adult asthma have been evaluated [47]. A pathway-based approach where several genes are selected for analysis based on biological knowledge can represent a good strategy for detecting relevant associations with biological and disease-related phenotypes as well as GxE interactions. To our knowledge, only one study has focused on gene by smoking interaction on asthma in adults considering genes involved in the same pathway [193]. By appropriately integrating the information on biological processes shared by genes, the canonical pathways to which they belong, and the knowledge of the environmental factor into the gene selection, the ability to identify the joint effects and interactions of environmental and genetic factors will be improved and will contribute to a better understanding of the etiology of complex diseases. None of the genetic studies to date has incorporated measurements of biological phenotypes involved in the response to oxidative/nitrosative stress. Understanding the mechanisms through which genes and the environment interact represents one of the major challenges for pulmonary researchers [9,182,194,195]. Furthermore, to clarify the role of inflammation and oxidative/nitrosative stress, evaluated by biological markers, in the associations between exposures and asthma, it would be useful to use causal inference approaches for mediation analyses [196–198]. These methods allow direct and indirect impact of exposures to be evaluated in settings where standard approaches might be biased, e.g. in the event of an interaction between the effect of the exposures and the intermediate phenotype (here, biological markers) on the outcome [197,199].

Public health perspectives
Besides smoking which is an established major public health concern for which actions should be reinforced [200], the search to implement efficient public health actions are warranted in several domains. Even if the effects of air pollution are regarded by some as minimal, they have a big impact on public health as air pollution is ubiquitous and a non-avoidable risk factor in urban areas [201]. Furthermore, it has been shown that reducing air pollution levels and pollutants has beneficial effects on asthma on the short and long term [202–204]. In California, policies based on epidemiological evidence have been developed in order to minimize traffic around pre-existing schools and to set a critical minimum distance between schools and major traffic road for building new schools (www.oehha.ca.gov). It would be of great interest to investigate these effects in standardized ways [23]. Among adults, it is now established that occupational exposure to cleaning products is related to both asthma onset and exacerbations of pre-existing asthma [73]. Several questions remain regarding the specific cleaning products involved and their mechanisms so further research focused in these aspects is needed. However, the level of evidence is sufficient to justify public health actions, and potential prevention measures should be investigated. Regarding the role of domestic cleaning products in spray form for cleaning tasks, a deleterious role was suggested in asthma activity and incidence [94,95]. Among children, the deleterious role of the use of cleaning products at home, potentially in spray form, has been suggested in relation to respiratory symptoms [101–103]. Further analyses are warranted to clarify the role of domestic exposure to cleaning products in asthma especially in children by combining measurement of the home environment in addition to specific questionnaires on home cleaning tasks and products with the use of biological markers. Existing evidence is sufficient in this area to advocate public health actions and preventive measures should be investigated to limit the use of toxic cleaning products at home especially in spray form.

Few studies are available regarding the role of maternal occupational exposures during pregnancy on allergic respiratory diseases or asthma in children [205–208], and there is little consensus. Maternal exposures to deleterious factors during pregnancy such as indoor or outdoor pollution, occupational exposures and diet might alter the immune system of offspring [15,205,209]. At home, the frequent use of cleaning products by the mother during pregnancy was found to be associated with persistent wheezing in children [102,103]. Birth cohort
prospective surveys would be a unique opportunity to evaluate the impact of maternal workplace exposures on asthma in children [210]. Further studies are warranted among birth cohorts on the role of maternal exposures during pregnancy to domestic exposures to cleaning agents, occupational exposures to asthmogens, air pollution, diet, and respiratory health in childhood. From the public health perspective, it is particularly relevant to consider lifecourse exposure.

**Conclusion**

Environmental and lifestyle exposures may play an important role in asthma or related phenotypes. The lung is a key organ in relation with the environment as it is an open door to the environment. The changes in lifestyle and environment during recent decades have modified the specific risk factors in asthma even for long-standing recognized risks such as occupational exposures such as latex gloves, although preventive measures have been taken in this regard. To better understand the role of the environment in asthma, multidisciplinary collaborations are needed involving epidemiologists, industrial hygienists, social scientists, health geographers, biologists and geneticists. Evaluation of environmental exposures by the use of objective tools, modern technology such as bar codes, GPS and mobile phones and quantitative measurement of exposures would be of great interest. Information on the exposure may be useful to evaluate environmental exposure and to study the associations with asthma. A better understanding of the complex interrelationships between socio-economic, nutritional, lifestyle and environmental conditions might help to study their joint and independent roles in asthma.

**Disclosure of interest:** the authors declare that they have no conflicts of interest concerning this article.

**Funding:** French Agency of health safety, environment and work. ANSES-PNR-EST 2012-2-166 (SESAP). The French National Research Agency: ANR-2010-PS03-003 (AEGO).

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