



Air pollution, genetics, and allergy: an update

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Purpose of review

Air pollution has been increasingly associated with diverse adverse health outcomes, including airway diseases. Data suggest that gene–environment interactions are important in this context. However, evidence regarding causal effects of exposure and development of allergic conditions specifically remains immature. We review the developments of the past 18 months regarding air pollution, genetics and epigenetics, and allergy.

Recent findings

Conflicting evidence for air pollution as causative in the development of allergic disease persists. However, recent data support the associations between long-term exposure to traffic-related pollutants and newly developed sensitization in children. Studies from India and China demonstrate the global burden of health-related costs attributed to air pollutants and allergic diseases. The effect of exposure seems to be modified by coexposures of allergens as well as genetic variants, particularly those moderating response to oxidative stress. Potential links between exposures and epigenetic (DNA methylation) changes with consequences for disease development are also reinforced.

Summary

Data over the past 18 months support prior literature that air pollutants cause exacerbation, and possibly onset, of allergic disease. Regarding the onset of asthma specifically, the evidence of causality has grown significantly, but it remains difficult to separate allergic from nonallergic asthma. Effect of modification by genetic variants and epigenetic changes warrants further study.

Keywords

air pollution, allergy, epigenetics, genetics

INTRODUCTION

Air pollution has been associated with an increasing range of adverse health outcomes, particularly respiratory, as has been noted in several previous reviews (including some with an emphasis on the genetic influences within this dynamic) [1,2[¶]]. The principle air pollutants of concern are generally particulate matter (which is categorized as PM_{2.5} to describe particulate matter of 2.5 µm or less in terms of mean aerodynamic diameter or PM₁₀ to describe particulate matter of 10 µm or less in terms of mean aerodynamic diameter), ozone, or NO_x [oxides of nitrogen, including nitrogen dioxide (NO₂)]. Historically, nonspecific cardiorespiratory mortality has been perhaps the most prominent outcome associated with these exposures [3] – this is deserved and understandable from a global public health perspective, given the widespread nature of ambient air pollution, and the tremendous international burden of ischemic cardiac disease, lung cancer, chronic obstructive pulmonary disease (COPD), and asthma [4]. Somewhat more recently, a focus on the link between air pollutants and allergic phenomena has gained increased attention

based on the plausibility that irritant pollutants can facilitate the access of allergens to immune-mediating cellular pathways or otherwise synergize allergenic effects. Given the increasing prevalence [5] and socioeconomic burden [6] of allergic disease, this is inherently important and it also affords an opportunity to understand the biology of synergistic exposures [7]. With the acceleration of genomics' application within public health science has come an insight into how variants in certain genes can critically influence the relationship between air pollution and allergic outcomes [1,8[¶]]. Given the

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Curr Opin Allergy Clin Immunol 2012, 12:000–000

DOI:10.1097/ACI.0b013e328357cc55

KEY POINTS

- Both epidemiological and experimental data support the notion that exposure to air pollution may induce sensitization to common allergens.
- The global burden of air pollutants in relation to allergic rhinitis is reinforced in the recent studies.
- There appear to be important interactions between allergens and traffic-related air pollution in mediating asthma, though it remains difficult to separate allergic from nonallergic asthma.
- Few studies have adequately addressed whether air pollution may be linked to eczema and further studies are warranted.
- Gene–environment interactions and a link between exposure and epigenetic changes have been reported in several studies; the main challenge in future studies is to understand and interpret the observed interactions in terms of the underlying biology and pathophysiology.

rapid pace of development in this area, we decided to review the developments of the past 18 months and provide a focal discussion regarding air pollution, genetics, and allergy.

AIR POLLUTION AND SENSITIZATION

Earlier results from cross-sectional studies published some 10 years ago have shown positive associations between air pollution and elevated total IgE, or sensitization to airborne allergens in children [9]. It has also been observed that children exposed to environmental tobacco smoke may be particularly sensitive to traffic-related exposure [10]. Somewhat more recent findings from the Swedish birth cohort study Barn Allergi Milieu Stockholm Epidemiologi (BAMSE) indicate that exposure during the first years of life may be key for later development of allergic sensitization [11]. Data from the Dutch prevention and incidence of asthma and mite allergy (PIAMA) and the German Infant Nutritional Intervention Study (GINI) and Influences of Lifestyle-related Factors on the Immune System and the Development of Allergies in East and West Germany (LISA) studies have also shown positive associations between air pollution and sensitization to common allergens in preschool children [12,13]. However, a later follow-up from the PIAMA cohort showed no association between early life exposure and sensitization at 8 years of age [14].

The epidemiological associations are supported by the experimental data indicating that diesel exhaust particles (DEPs) may induce IgE responses directly by acting on B-cells and enhance the

production of cytokines that favor the development of an allergy-prone immune response [15]. Animal model also have shown effects of diesel exhaust on allergic sensitization in mice [16,17], although exact mechanisms by which air pollution compounds may induce allergic sensitization are still not fully understood. Few studies have been able to convincingly show that exposure to air pollutants is associated with sensitization to single, specific allergens and the current understanding is that exposure is related to unspecific triggering of atopy-related immune responses not restricted to one particular allergen.

Publications over the past 18 months build on the prior literature summarized above

In 2011, Gruzieva *et al.* [18[¶]] from the BAMSE study reported the results from the 8-year follow-up and showed that traffic-related air pollution (TRAP) exposure (measured as individual annual PM₁₀ and NO_x average levels) did not seem to increase the overall risk of sensitization at 8 years of age. However, among nonatopic children (up to 4 years of age), the incidence of sensitization to food allergens up to 8 years of age was positively associated with high exposure [odds ratio (OR) 2.30; 95% confidence interval (CI) 1.10–4.82]. Also in this study, exposure during the first year appeared more important for disease development relative to exposure later in life. Positive associations between another air pollutant (ozone) and the rate of newly developed sensitization to outdoor allergen were also found in a Korean study on 1340 school children followed during a 2-year period [19[¶]].

Experimental studies have recently shed some light on whether exposure to gases (e.g. NO_x and NO₂) or particles (e.g. PM₁₀ and PM_{2.5}) have equal effect on the risk of developing sensitization to common allergens. In a Norwegian study on mice, intranasal exposure to ovalbumin (OVA) with or without DEPs present, immediately followed by exposure to NO₂ was induced and the production of allergen-specific IgE antibodies was then measured [20[¶]]. DEPs in combination with OVA stimulated the production of allergen-specific IgE antibodies, whereas NO₂ did not. Thus, based on this experimental study, traffic-related NO₂ seems to be of less importance than diesel particles for the development of atopy.

AIR POLLUTION AND ALLERGIC RHINITIS

It is well known that irritants such as particles or gaseous compounds may cause immediate upper and lower respiratory symptoms. Relatively few

studies have addressed the causal relationship between exposure to traffic-related air pollutants and allergic rhinitis (or hay fever), and conflicting results have been presented [9]. In young children, allergic rhinitis is rather uncommon [21] and data are naturally sparse for this age group. However, positive associations from large epidemiological studies have been observed in studies on school-age children conducted in different countries worldwide [14,22].

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Time series analyses performed in Beijing, China, 2009–2010 indicate that short-term exposure (sulfur dioxide primarily) may be an important trigger of adverse effects in adult patients with allergic rhinitis [23]. Studies in Korea also support associations between air pollution load in residential areas and prevalence of allergic rhinitis in children [24]. Limited conclusions of causality can be drawn from these ecological studies as information on individual exposure and disease onset is missing, but they underline the global burden of air pollutants in relation to common diseases such as allergic rhinitis. Recent data from Mumbai, India, a mega city with more than 12 million inhabitants, also demonstrate the burden of health-related costs attributed to air pollutants and allergic rhinitis and other airway diseases [25].

Reported proximity of residence to roads has been used in several studies as a proxy for exposure to heavy traffic. Using this method, rather strong associations between children exposed to heavy traffic and rhinitis or rhinoconjunctivitis (OR 3.39; 95% CI 1.24–9.27) was reported from Singapore on almost 3000 children [26[¶]]. Interestingly, there were no associations found for children sleeping in air-conditioned homes, suggesting that air-conditioning may modify the health effects of traffic among preschool children, possibly by reducing the indoor pollutant exposure from traffic.

AIR POLLUTION AND ALLERGIC ASTHMA

Recent years has provided new evidence that particulate matter is associated with incident asthma, both in children and adults. The PIAMA study, a prospective cohort from the Netherlands, used a multi-pollutant model including NO₂, soot, and PM_{2.5} to demonstrate that PM_{2.5} levels were independently associated with significant increases in incidence and prevalence of asthma, as well as asthma symptoms [14]. Similarly, the Children's Health Study found an association between new-onset asthma and levels of

TRAP exposure [27]. Furthermore, PIAMA and a British Columbian birth cohort have associated in-utero and early life exposure to PM_{2.5}, black carbon, and soot with incidence of asthma, wheeze, and atopy to common allergens later in life [12,28]. A Swedish case-control study suggested that living close to roads with high traffic volumes increases incident asthma in people 20–60 years of age [29], and this was corroborated in a study assessing a broader age range (18–80 years of age) [30]. The Swiss Cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) study showed that PM₁₀ was significantly associated with adult-onset asthma in never smokers (hazard ratio of 1.30 for each µg/m³ increase in PM₁₀ over the study period of 11 years) [31]. However, few of these studies had the resolution to specify whether the asthma was allergic or nonallergic.

Publications over the past 18 months build on the prior literature summarized above

The above findings were supported by the examination of a novel birth cohort at high risk for allergic disease, and thus enriched in those thought to be susceptible to insults such as TRAP [32]. However, this study did not look specifically at allergic versus non-allergic asthma. Exposure to 'stop-and-go' traffic in the first year of life was associated with infant wheezing in a study from Cincinnati [33]. Here again, how closely 'wheezing' was aligned with an allergic phenotype is unclear, but interestingly the authors noted that endotoxin levels were protective against wheeze, suggesting an immunological interface to these effects. Interestingly, Cakmak *et al.* [34[¶]] reinforced the evidence that air pollution augments the effects of aeroallergens in mediating allergic exacerbation of asthma. This is important as it suggests that current understanding of dose-response relationships, in terms of traffic-related air pollutants and respiratory disease, may underestimate effects if not appreciation effects of coexposures such as allergens. Another helpful contribution was the work, by Dong *et al.* [35], regarding sex modification of air pollution effects on respiratory symptoms; in addition to providing support for the suggestion that susceptibility to allergy may enhance vulnerability to ambient air pollutant exposure, these authors showed that this may be particularly true among women. In contrast, others found either distinct seasonal attributions to either allergen or air pollution [36], or an apparent lack of interaction between air pollutants and allergens [37].

AIR POLLUTION AND ECZEMA

Given the association between air pollution and the allergic outcomes previously discussed, it was

natural to look at eczema as well. However, in a birth cohort of approximately 4000 children, TRAP was not associated with incident eczema [12]. Similarly, TRAP was not associated with eczema in a study of almost 4000 children followed from birth to 8 years of life [14]. Also in terms of prevalence, airborne particulate matter was unassociated with eczema [38]. In contrast, at least one reflection of TRAP, nitrogen dioxide, was associated with eczema in a birth cohort of 3860 children followed to 6 years of life [13].

We did not find any peer-reviewed literature from the past 18 months regarding novel findings that connect air pollution with eczema. One wonders whether this reflects a series of unpublished 'negative' findings. If so, there may be the potential for investigation of gene–environment interactions to provide insight given the growing evidence that innate immunity may mediate response to air pollution and that variants of genes related to innate immunity, such as *NOD1*, may confer some risk for both airway and skin disorders [39].

GENE-BY-AIR POLLUTION INTERACTIONS AND EPIGENETICS

Although there is a widespread knowledge that asthma and allergy results from multiple factors including gene–environment interactions, the vast majority of all studies on allergic diseases have not taken such interactions into consideration. Particularly challenging therein is how to model interactions and how to take high-order interactions (interaction between several factors) into consideration. Secondly, assessment of interactions demands large datasets and statistical power frequently poses a limitation.

Nonetheless, studying the effects of various air pollutants on respiratory health, in relation to an individual's genetic setup, is attractive given the emerging evidence across epidemiological and experimental research. Evidence from gene-expression analyses suggests that children may be particularly susceptible to adverse effects of exposure [40], which underlines the potential for new policies designed to protect such vulnerable populations.

Genes involved in the antioxidative system (e.g. *glutathione S-transferase [GST] M1* and *P1*), the inflammatory response (e.g. *TNF*), and innate immunity (e.g. *TLR2* and *TLR4*) have been the particular focus of studies of asthma and allergic diseases [2[•]]. The antioxidative system, highlighted by the GST enzymes, is a complex network involving a number of important enzymes and proteins. The GSTP1 enzyme, of particular interest in relation to the respiratory system, provides a substantial

fraction of the total GST activity in the lung [41] and may interact with other enzymes like 1-cysteine peroxiredoxin [42]. GSTP1 enzymatic activity has been shown to differ between isoenzymes with isoleucine or valine at position 105; Val105 enzymes having, for example, a higher catalytic capacity for polycyclic aromatic hydrocarbons (representing several different environmental pollutants), but on the other hand a lower conjugation capacity for benzene compounds [43]. Linking gene–environment interactions from epidemiological studies with functional, experimental studies is of crucial importance in order to fully understand and interpret the observed interaction in terms of the underlying biology and pathophysiology.

Epigenetic mechanisms such as DNA methylations may constitute a link between genetic and environmental factors, as several environmental factors have proved to influence methylation patterns (recently reviewed [2[•],44[•]]). Epigenetic analyses within the respiratory field have so far mostly been targeted to specific candidate genes such as *FOXP3* (involved in regulation of T-cell functions) [45].

Publications over the past 18 months build on the prior literature summarized above

The oxidative stress response is also orchestrated by the redox-sensitive transcription factor, NFE2L2 (also known as Nrf2) and its negative regulator protein KEAP1. Using a case-only approach, evidence for interaction between variants in *NFE2L2* and polluted residential area with respect to asthma was suggested [46]. Breton *et al.* [47^{••}] set out to determine whether sequence variation in genes in the glutathione synthesis pathway alters the susceptibility to air pollution effects on lung function; glutathione metabolism pathway genes *GSS*, *GSR*, *GCLM*, and *GCLC* were genotyped in 2100 children followed prospectively with lung function measurements. Variation in *GSS* was found to be associated with differences in susceptibility to adverse effects of pollutants on lung function growth. Further studies are warranted to evaluate whether these genes may mediate the pathophysiology specific to incident allergic disease.

Only recently, large-scale global methylation analyses have been published for COPD [48^{••}], but studies are yet to be presented for asthma and allergic diseases. A 'semi-global' methylation study (807 genes covered; Illumina GoldenGate Methylation Cancer panel I) on childhood wheeze in two Spanish cohorts (122 and 236 children) found associations with hypomethylation of *ALOX12* involved in arachidonic acid metabolism [49]. As discussed by

the authors and an editorial [50], sample size, temporal issues, tissue specificity, and relevance of genetic polymorphisms remain challenging areas for future epigenetic studies.

Studies on intermediate phenotypes, such as inflammatory markers in blood, sputum, or exhaled breath, can give valuable insights about pathological mechanisms. Two recent epigenetic studies used fractional concentration of exhaled nitric oxide (FeNO) [51] and markers of coagulation, inflammation, and endothelial function [52[■]], respectively, as outcomes for association analyses between air pollution exposure, methylation pattern, and outcome. Salam *et al.* demonstrated that short-term exposure (7-day average) PM_{2.5} exposure was associated with lower iNOS methylation and interaction between NOS2 promoter variants, iNOS methylation level, and PM_{2.5} exposure on FeNO levels was also detected. Evidence of effect of modification was also noted by Bind *et al.* [52[■]], where air pollution (e.g. particle number, black carbon, and NO₂) altered fibrinogen and other inflammatory markers more strongly among individuals having higher methylation status in specific genes (e.g. TLR2).

The suggested link between environmental exposures and DNA methylation changes with potential consequences for disease development was also reinforced by the recent findings from a study of long-term particulate exposure in a cohort of older men [53[■]]. Here again, allergic diseases were not specifically studied, but the results suggest that a further such study is warranted.

CONCLUSION

Conflicting evidence for air pollution as causative in the development of allergic disease persists. However, data over the past 18 months support prior literature that air pollutants cause exacerbation, and possibly onset, of allergic disease. Regarding the onset of asthma specifically, the evidence of causality has grown significantly, but it remains difficult to separate allergic from nonallergic asthma; dissecting the difference therein, though challenging, should be a focus of future work given the potential consequences on preventive and therapeutic strategies. The effect of exposure seems to be modified by coexposures of allergens as well as genetic variants, particularly those moderating response to oxidative stress. Potential links between exposures and epigenetic (DNA methylation) changes with consequences for disease development are also reinforced but need further study; several such initiatives worldwide are ongoing and the results are expected in the near future. A promising practical application of this emerging knowledge is application to policy-making,

wherein protection of the most vulnerable may be a priority.

Acknowledgements

The authors would like to thank Professor Göran Pershagen for reviewing this manuscript. Funding: This work was supported by the Institute of Environmental Medicine, Karolinska Institutet, the Swedish Heart and Lung Foundation and the Swedish Foundation for Strategic Research.

Conflicts of interest

There are no conflicts of interest.

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