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The contribution of particulate matter to respiratory allergy: A review of current evidence

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Abstract

Background: Air pollution contributes to an estimated six million deaths per year. Epidemiological and experimental studies show an association between air pollutant exposure and respiratory allergy.

Objective: We aimed to write a narrative review of the epidemiology of air pollution-related respiratory-related allergic disorders (including asthma and allergic rhinitis) and the effects of air pollutants – with an emphasis on the particulate matter – on respiratory allergy-related health.

Methods: PubMed Medline was searched, and representative epidemiologic and controlled-exposure studies were selected by using terms for air pollutants, particulate matter, and respiratory allergy including asthma and allergic rhinitis.

Results: Epidemiological studies showed methodologic heterogeneity, including variability in study populations, geographical regions, types and sources of pollutants, methods for exposure estimation, approaches to controlling for confounding, and case definitions. This heterogeneity affected measures of association between studies. There is strong evidence to support an association between exposure to particulate matter and asthmatic exacerbations. Although data are inconclusive, several studies suggest exposure to particulate matter contributes to the development of asthma, allergic sensitization, and allergic rhinitis. Experimental studies, such as controlled-exposure studies, support a causal association between particulate matter and adverse health effects.

Conclusions: Particulate matter exposure can exacerbate pre-existing asthma and may contribute to developing asthma, allergic rhinitis, and aeroallergen sensitization. Short-term and long-term strategies are needed to reduce disease severity and prevent new-onset disease development. Additional research is needed to identify effective avoidance strategies and therapeutic approaches.

Key words: Air pollution, particulate matter, allergy, asthma, allergic rhinitis

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Abbreviations
- aOR. Adjusted odd ratio
- BAMSE, Barn Allergi Miljö Stockholm Epidemiologi
- BC, British Columbia
- CAPPS, Canadian Asthma Primary Prevention Study
- CHS, The Southern California Children's Health Study

Abbreviations (Continued)
- CHEER, Children's HEalth and Environmental Research
- CI, Confidence interval
- CO, Carbon monoxide
- COPD, Chronic obstructive pulmonary disease
- DEP, Diesel exhaust particles
- GINI, German Infant study on the influence of Nutrition Intervention
- GINIplus, German Infant study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy development
- HDM, House dust mites
- IgE: Immunoglobulin E
- ISAAC, The International Study of Asthma and Allergies in Childhood
- kAU/L: Kilo allergy unit per liter
- LISA, Influence of Life style factors on the development of the Immune System and Allergies in East and West Germany
- LISAplus, Influence of Life style factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics

Abbreviations (Continued)

- MAAS, Manchester Asthma and Allergy Study
- MeDALL, Framework of the European collaborative Mechanisms of the Development of Allergy
- NOx, Oxides of nitrogen
- O_3, Ozone
- OR. Odd ratio;
- PIAMA, Prevention and incidence of asthma and mite allergy
- PM, Particulate matter
- PM10, Inhalable particulate matter
- PM10-2.5, Coarse particulate matter
- PM2.5, Fine particulate matter
- PM0.1, Ultrafine particulate matter
- Vancouver, Vancouver birth cohort
- SO_2, Sulfur dioxide
- TMCHD, Taiwan Maternal and Child Health Database
- TRPA1, Transient receptor potential ankyrin-1
- VOCs, Volatile organic compounds

Introduction

Air pollution is the contamination of indoor or outdoor air by a range of substances that modify its natural characteristics.[1] Increasing air pollution is associated with rapid economic growth and industrialization.[2] Data from the Global Burden of Diseases 2015 study estimated that pollution contributes to nine million deaths per year, and air pollution – including ambient and indoor – was playing a role in at least six million deaths per year.[3]

Over the last several decades, the world has witnessed a concerning increase in the prevalence of allergic respiratory diseases.[4,5] Initially observed only in industrialized Europe and North America, more recently, many other countries with rapidly-growing economies (e.g., in Asia-Pacific, such as China) have experienced a similar rise in prevalence.[6] For example, previously low levels of allergy and asthma in Southeast Asia have escalated to match levels in Western countries. The causes are not fully understood but unlikely explained by genetic factors alone. Many epidemiological and experimental exposure studies suggest exposure to air pollutants is a driver.[7,8] Particulate matter (PM) with a median aerodynamic diameter ≤ 2.5 μm (PM2.5) has garnered particular interest among stakeholders concerned with the effects of air pollution on respiratory health at the population level because of its small size and high surface area to volume ratio.

Given the growing burden of air pollution-related allergic respiratory disorders, clinicians need to be aware of the possible effects of this exposure on their patients. In this article, we discuss in detail the association between allergic respiratory disease and air pollution, with an emphasis on PM which the World Health Organization recognizes as the main air quality indicator.[9]

Air pollutants

Air pollutants are composed of a heterogeneous mixture of suspended gases, liquids, and solids, and they are classified according to their physicochemical properties (**Figure 1**). Sources of air pollution include combustion of man-made or naturally-occurring biomass or fossil fuels. Man-made sources include burning materials, industry, vehicular traffic, and

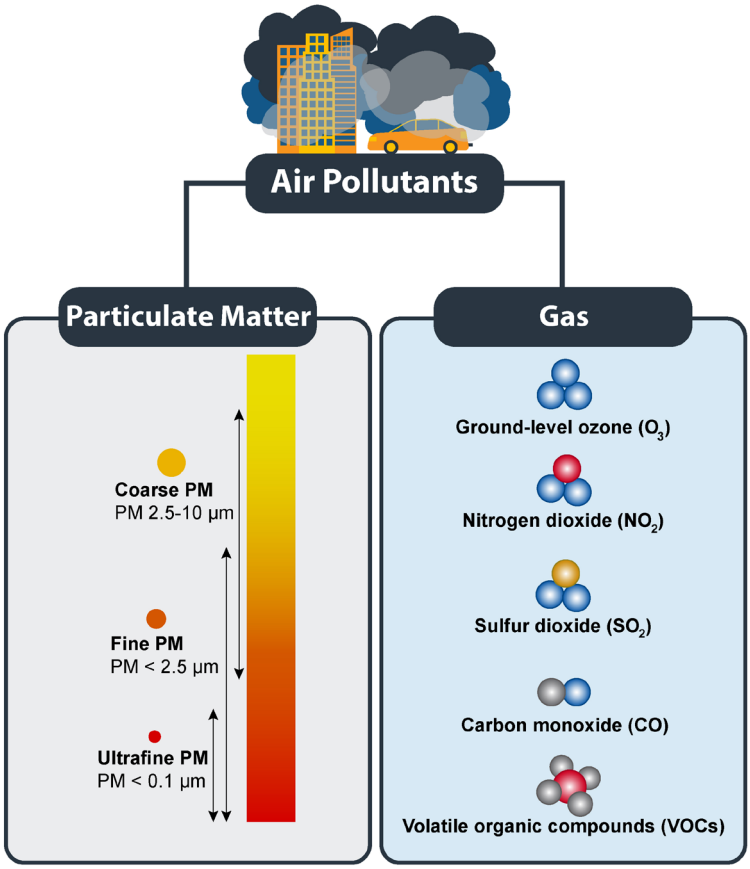

Figure 1. Classification of air pollutant according to some physical properties
Abbreviation: PM, particulate matter

environmental tobacco smoke. Naturally-occurring sources include volcanic ash, wildfires, various gases, and spontaneous secondary pollutants. Air pollutants may interact with airborne allergens. *In vitro* and animal studies have shown that combined exposure to air pollutants and allergens may have synergistic adverse effects on allergic respiratory conditions.

Particulate matter

The airborne PM is a mixture of liquid droplets and solid particles, such as dust, dirt, soot, or smoke. Airborne PM varies in size, composition, and origin and is often classified by median aerodynamic diameter, which dictates its various properties, including whether, where and how well it is deposited in the respiratory tree.

PM is composed of a mixture of organic and inorganic compounds along with various elements and ionic species (such as sulfate, nitrate, and ammonium ions). The ambient PM in any particular geographic location is affected by local mixtures of gaseous pollutants, topography, and seasonal weather and industry patterns. For example, PM may be influenced by seasonal changes in emission sources and atmospheric influences including wind speed, temperature, relative humidity, mixing height, and rainfall.[10] As expected, the composition of PM influences its adverse health effects. PM may be primary or secondary: primary PM is man-made or natural and released directly into the environment, while secondary PM is composed of airborne compounds (e.g. organic carbon and sulfates) that have undergone photochemical reactions in the atmosphere.[11]

Urbanization and economic growth in many countries in Asia have increased industrial activities and motor vehicle emissions and as a result, caused air pollution to skyrocket.[6,12] In Southeast Asia, seasonal haze from biomass burning has drawn international attention for its adverse effects on regional air quality and human health. The haze contains large quantities of airborne PM which can be carried great distances by prevailing winds and cause similar problems in other countries, including Indonesia, Malaysia, Brunei, Thailand, Singapore, and the Philippines.[13]

Particulate matter and allergic respiratory diseases

PM likely induces lung injury via multiple mechanisms, including ciliary dysfunction, epithelial cells damage, inflammation, and oxidative stress.[14] The adverse health effects of PM10 and PM2.5 are the best established, but data are accumulating on the detrimental effects of ultrafine particles (UFPs) and nanoparticles.[15] Over the past two decades, epidemiologic studies have estimated the association of PM with new-onset and exacerbation of allergic respiratory diseases. Although the Asia-Pacific region has developing countries with many large cities with high concentrations of ambient air pollutants, less epidemiologic data has been generated from this region compared to North America or Europe.

Clearly, PM may induce exacerbations in allergic respiratory diseases; however, there is less clarity around whether PM can cause these diseases to occur de novo. Differing case definitions, geographic region of study, air pollutants understudy, and methods used to estimate exposure dose and health effects make it difficult to compare results across studies.

Infants and young children are particularly susceptible to the adverse health effects of air pollution because of their immature immune and respiratory systems, they spend more time outdoors than people in other age groups, and they breathe more air per unit of body weight compared with adults.[16-18] An association between PM exposure and new-onset allergic respiratory disease would be expected in these age groups. Therefore, a birth cohort study is considered the best available study design to investigate early childhood air pollutant exposure and the development of asthma and allergic disease.[19] Such studies have been conducted globally but predominantly in North American and Europe. We summarize the available birth cohort studies addressing the association between particulate matter exposure and respiratory allergy in **Table 1-2**.

Table 1. Birth cohort studies addressing the association between particulate matter exposure and asthma incidence/prevalence*

Name of original cohort/database	Author (Year of publication)	Year of study start	Country	Exposure period	Pollutant	Outcome
BAMSE	Gruzieva (2013) [60]	1994/1996	Sweden	First year of life	PM10	Increase asthma incidence at age 12 years **(aOR: 2.39; 95%CI 1.18-4.86, Exposure per 2 μg/m³ increase in PM10)**
CAPPS	Carlsten (2011) [59]	1995	Canada	Birth addresses	PM2.5	Increased asthma incidence **(OR: 3.1; 95%CI: 1.3-7.4)** and BHR at the age of 7 (in high-risk children¶)
GINI/LISA	Morgenstern (2008) [23]	1995/1999	Germany	Birth and current addresses	PM2.5	No association with prevalence of asthma until age 6 years
GINI/LISAplus	Gehring (2013) [93]	1995/1999	Germany	Birth and current addresses	PM2.5	No association with prevalence of asthma until age 10–11 years
MAAS	Molter (2015) [94]	1995/1997	Great Britain	First year of life	PM10	No association with prevalence of either asthma or wheeze until the age of 11

Table 1. (Continued)

Name of original cohort/database	Author (Year of publication)	Year of study start	Country	Exposure period	Pollutant	Outcome
PIAMA	Gehring (2010, 2015) [24,95]	1996/1997	Netherlands	Birth addresses	PM2.5	Increased asthma incidence **(aOR: 1.28; 95%CI: 1.10-1.49)** during the first 8 years of life At age 12 years, lifetime risks of asthma remained heightened.
Data from QICDSS	Tetreault (2016) [96]	1996/2011	Canada	Birth addresses	PM2.5	Increased asthma incidence **(HR: 1.31; 95%CI: 1.28-1.33)**
BC	Clark (2010) [58]	1999/2000	Canada	Prenatal + First year of life	PM10	Increased incidence of asthma up to 3-4 years of age. **(aOR: 1.09; 95%CI: 1.05-1.13 in utero exposure, aOR: 1.07; 95%CI: 1.03-1.12 in first-year exposure, per 1 μg/m^3 increase in PM10)**
Data from British Columbia Ministry of Health	Sbihi (2016) [97]	1999/2002	Canada	Prenatal	PM10	Increased asthma incidence in pre-school children **(aOR: 1.12; 95%CI: 1.05-1.19)**, not in school-age children
CHS	McConnell (2010) [98]	2002/2003	USA	Current exposure	PM2.5, PM10	No association with asthma incidence during 3 years of follow-up
ACCESS	Hsu (2015) [99]	2002/2009	USA	Prenatal	PM2.5	Increased asthma incidence by the age of 6 years in boys
TMCHD	Jung CR (2019) [100]	2004/2011	Taiwan	Prenatal + First year of life	PM2.5	Increased asthma incidence **(HR of asthma increased steeply at PM2.5 exposure > 93 mg/m^3)** during pregnancy, remained significant with postnatal exposure to 26-72 mg/m^3
CHEER	Song-I Yang (2018) [101]	2005/2006	Korea	Prenatal + First year of life	PM10	Increase asthma incidence **(aOR: 2.056; 95% CI: 1.240-3.409)** in school-aged children

***Not include meta-analysis, and retrospective cohort studies**

Abbreviations:

- aOR. Adjusted odd ratio;
- ¶ High risk was defined as having first-degree relative with asthma or two first-degree relatives with other IgE-mediated allergic disease
- ACCESS, Asthma Coalition on Community, Environment and Social Stress
- BAMSE, Barn Allergi Miljö Stockholm Epidemiologi
- BC, British Columbia
- CAPPS, Canadian Asthma Primary Prevention Study
- CHS, The Southern California Children's Health Study
- CHEER, Children's HEalth and Environmental Research

Abbreviations (Continued):

- GINIplus, German Infant study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy development
- LISAplus, Influence of Life style factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics
- MAAS, Manchester Asthma and Allergy Study
- MeDALL, Framework of the European collaborative Mechanisms of the Development of Allergy
- PIAMA, Prevention and Incidence of Asthma and Mite Allergy
- TMCHD, Taiwan Maternal and Child Health Database

Table 2. Birth cohort studies addressing the association between particulate matter exposure and allergic rhinitis/hay fever incidence/prevalence

Name of original cohort/database	Author (Year of publication)	Year of study start	Country	Exposure period	Pollutant	Outcome
Four European birth cohort (BAMSE, GINIplus, LISAplus, PIAMA)	Gehring (2015) [102]	1994/1999	Europe	Birth and current addresses	PM2.5, PM10	No association with allergic rhinitis incidence and prevalence from age 4 years to 14–16 years
GINI & LISA	Morgenstern (2008) [23]	1995/1999	Germany	Birth and current addresses	PM2.5	No association with allergic rhinitis incidence

Abbreviations:

- BAMSE, Barn Allergi Miljö Stockholm Epidemiologi
- GINI, German Infant study on the influence of Nutrition Intervention
- GINIplus, German Infant study on the influence of Nutrition Intervention plus environmental and genetic influences on allergy development
- LISA, Influence of Life style factors on the development of the Immune System and Allergies in East and West Germany

Abbreviations (Continued):

- LISAplus, Influence of Life style factors on the development of the Immune System and Allergies in East and West Germany plus the influence of traffic emissions and genetics
- PIAMA, Prevention and Incidence of Asthma and Mite Allergy

Particulate matter and aeroallergen sensitization

Allergic sensitization is generally defined as the development of IgE specific to one allergen and is a major risk factor for new-onset allergic respiratory disease.[20,21] The prevalence of aeroallergen sensitization pattern varies by region and country and results from studies aimed at assessing the association between PM and allergic sensitization are conflicting.[22-24]

Likewise, findings among birth cohort-based meta-analyses have been inconsistent. Bowatte, et al. reported a significant association between early childhood PM2.5 exposure and sensitization to outdoor aeroallergens but not indoor aeroallergens.[25] A meta-analysis of 5 European birth cohorts showed no clear association between either PM2.5 or PM10 exposure and allergic sensitization in children aged up to 10 years;[26] however, there was no adjustment for indoor aeroallergens and food allergens. In one study, investigators noted an association between PM2.5 exposure and sensitization to food allergens and outdoor aeroallergens, most commonly pollen.[25] Among food items, the clearest risk factor was peanut allergens which are known to interact with pollens, including birch.[27]

The biological plausibility of the etiologic association between PM and allergic sensitization is supported by experimental evidence indicating PM could enhance immunologic responses to allergens and induce inflammatory reactions in the airways. In a controlled-exposure study of atopic and non-atopic persons, nasal challenge with 0.3 mg of diesel exhaust particles (DEP) increased IgE production in nasal mucosa at 4 days without effects on the other immunoglobulin isoforms.[28] Compared with ragweed allergens alone, intranasal challenge with a combination of DEP and ragweed allergens induced markedly higher ragweed-specific IgE.[29] A similar effect was also observed in lower respiratory tract. Over a 3-week period, repeated intratracheal challenge with a combination of house dust mites (HDM) and DEP induced a greater increase in HDM-specific IgE compared to challenge with HDM alone.[30] The synergistic effect of DEP and aeroallergens is believed to be a key promoter of allergen-induced allergic respiratory disease. A series of controlled-exposure studies showed DEP affects multiple cell types, thus able to influence several important steps of the allergic cascade.[31] Other air pollutants including ozone, nitrogen dioxide, and sulfur dioxide also have allergen enhancing effects.[12]

Air pollutants may enhance aeroallergen sensitization through multiple mechanisms including the following: carrying aeroallergens into the airways, inducing epithelial permeability by promoting oxidative stress and inflammation, increasing the antigenicity of allergens via chemical modification, and by acting as an immunologic adjuvant.[32,33]

Although experimental studies suggest a causal association between PM exposure and outdoor aeroallergen sensitization, results from birth cohort studies have been inconsistent. In some studies, exposures below a putative sensitization threshold could mask the suggested association.[22,24] Likewise, inadequate duration of exposure and heterogeneity in the susceptibility of hosts could also influence outcomes.

To date, questions around the effects of long-term exposure to PM on allergic sensitization in Asian populations remain unanswered. Several issues, including whether higher concentrations of ambient air pollutants significantly enter the indoor environment by ventilation or infiltration (thus, increasing the likelihood of allergic sensitization to indoor aeroallergens), need further investigation.

Particulate matter and the development of allergic rhinitis

Allergic rhinitis (AR) is a disease characterized by IgE-mediated inflammation of the nasal mucosa occurring when a person is exposed to an aeroallergen. The prevalence of AR has markedly increased in many countries,[34] including many in the Asia-Pacific region.[35,36] Human and animal studies reveal short-term exposure to PM may increase symptoms of AR, but the role of PM in the development of AR is not well understood.[32,37,38]

Studies from North America and Europe suggested the prevalence of allergic diseases may be reaching a plateau,[39,40] whereas developing countries in Asia-Pacific with strong economic growth have experienced a dramatic increase over the last few years.[41] Urbanization is a known risk factor for respiratory allergies in children and young adults and is believed to be largely responsible for the uptick in prevalence in the Asia-Pacific.[42-45]

The relationship between the development of AR and PM exposure is inconsistent. Comparing results across studies is made difficult by their differing study designs, study populations, case definitions, methods to estimate pollutant exposure, and other regional differences. In one meta-analysis of birth cohorts, there was no increased risk for AR from exposure to PM2.5 [OR: 1.02 per 2 μg/m^3 increase in PM2.5 (95% CI: 0.72–1.43)].[46] In contrast, in another pooled meta-analysis of six birth cohorts, investigators observed an association between PM2.5 exposure at birth and AR diagnosis at the age of 7-8 years [OR: 1.37 per 5 μg/m^3 increase in PM2.5 (95%CI: 1.01-1.86)].[47] In a subgroup (of children who did not move their house during their first 8 years of life) from a birth cohort of 3863 Dutch children, researchers found an association between PM2.5 exposure and AR.[24]

To date, published data from Asian birth cohorts on long-term PM exposure and the development of AR is scarce. Authors have published prospective, non-birth cohorts, some of which were cross-sectional and/or retrospective, and these have extensive methodological heterogeneity.[48-53] A meta-analysis of Asian studies from 2000-2018 demonstrated an association between the prevalence of AR and PM exposure.[54] Although PM can enhance immunologic responses to allergens and induce inflammatory reactions in human nasal mucosa[28,29,31] and animal models confirm the same,[37] epidemiologic and experimental studies have not confirmed that PM induces the development of AR.

Particulate matter and the development of asthma

Asthma is a chronic airway disease characterized by airway inflammation, reversible airflow obstruction, and bronchial hyperresponsiveness. More than 300 million people suffer from asthma which results in approximately 250,000 deaths annually worldwide.[55] The cause of asthma is believed to be a complex combination of multiple genetic and environmental factors leading to heterogeneous phenotypes. Although many epidemiologic studies have demonstrated a higher prevalence of asthma in many different regions of the world, the exact

reasons remain unclear.[56,57]

Some evidence suggests PM contributes to asthma development, but findings are inconsistent. In most cohorts, the main source of air pollution was traffic-related (TRAP).[24,58-60] A meta-analysis of birth cohort studies from North American and Europe showed increased longitudinal childhood exposure to PM2.5 was significantly associated with the incidence of asthma [OR 1.14 per 2 μg/m^3 (95%CI 1.0-1.3)],[25] whereas another recent meta-analysis of birth cohort revealed no significant association.[61] In another meta-analysis of cohort studies, long-term exposure to PM2.5 was associated with asthma incidence and wheezing; however, the analysis included both children and adults and did not separately consider the potentially important different effects related to exposure to TRAP in children.[62]

There is great heterogeneity across Asian studies. Although there were a few prospective birth cohort studies from Asia, many ongoing studies had been conducting to address this issue. A recent prospective birth cohort study that included 184,604 children from Taiwan demonstrated that increased exposure to PM2.5 during the prenatal (gestational weeks 6-22 weeks) or postnatal period (9-46 weeks post-partum) was associated with increased asthma incidence. Interestingly, the risk of asthma sharply increased when PM2.5 exposure was greater than 93 μg/m^3 during pregnancy.[63]

Results from studies aimed at estimating the association between residential proximity to major roads and asthma prevalence have been inconsistent. The evidence is more consistent for the association between asthma prevalence and residence on roads carrying large amounts of truck traffic.[33] A case-control study in the United Kingdom of 6,147 children living within 150 meters of the main road showed the risk of wheeze increased with increasing proximity [OR: 1.18 per 30 meters in primary school children (95%CI: 1.00-1.16) and OR: 1.16 per 30 meters in secondary school children (95%CI: 1.02-1.32)]. Most of the increased risk was localized to within 90 meters from the roadside.[64] However, results from Japan did not support an association between roadside exposure and asthma prevalence.[65]

Molecular mechanisms and gene-environment interactions have been hypothesized to explain how air pollution could contribute to the development of asthma. It is likely that a host of genetic factors and PM and aeroallergen exposures could play a role in the pathogenesis of asthma.[33] We summarize these interactions in **Figure 2**.

Evidence, including from meta-analyses and mechanistic studies, shows ambient PM might play a role in causing asthma in susceptible individuals. Living near busy roads may increase the risk of asthma. A growing body of evidence suggests that exposure to TRAP accounts for many cases of asthma,

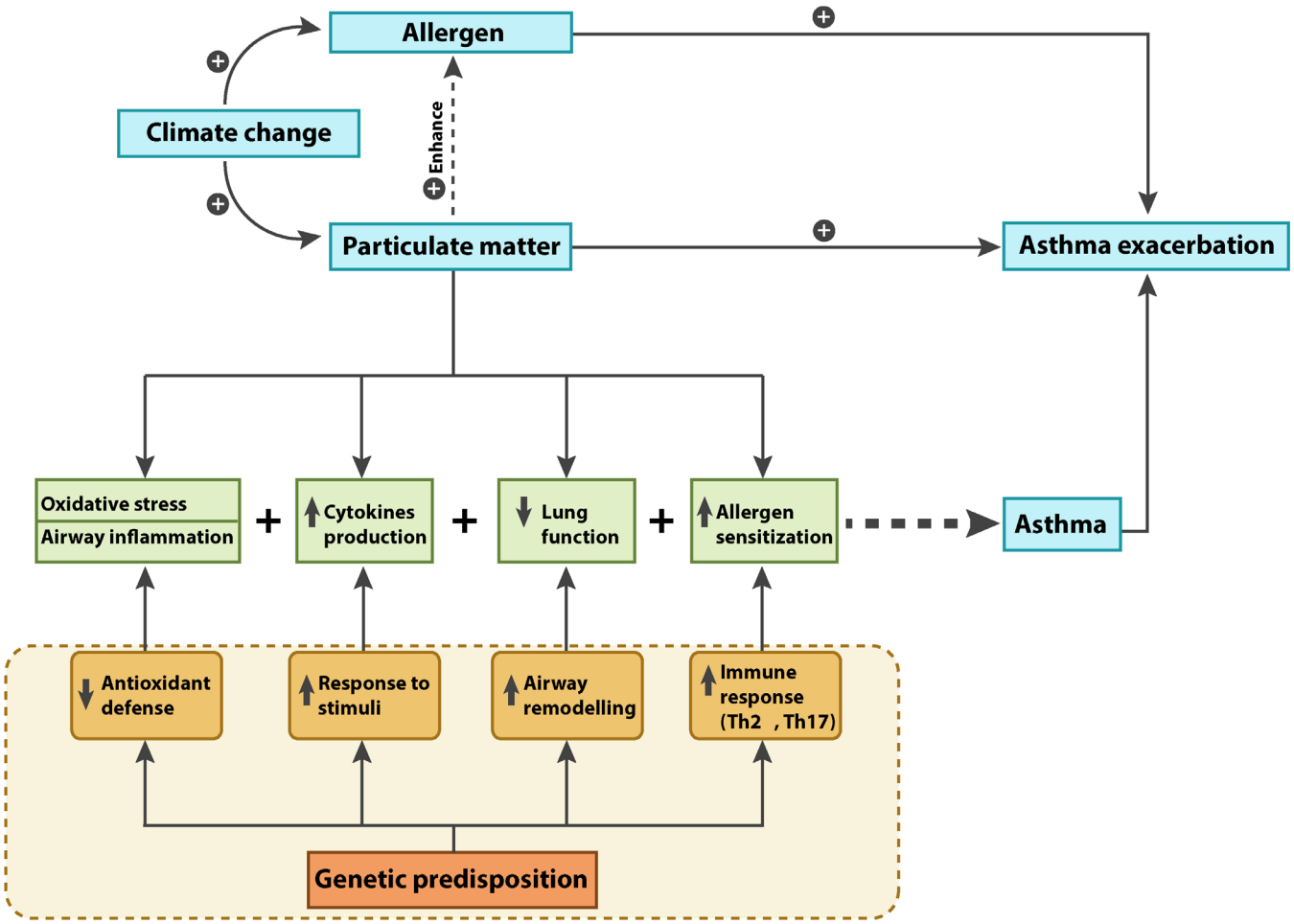

Figure 2. Model showing the possible interactions between genetics, particulate matter exposure, and aeroallergen exposure in asthma pathogenesis

although given the complex pathogenesis of asthma, other mechanisms are probably involved. More long-term, well-designed prospective cohort studies may provide conclusive evidence.

Particulate matter and asthmatic exacerbation

It is universally accepted that air pollution exposure is associated with exacerbations of asthma.[33] In 2015, 5-10 million emergency room visits globally could be attributable to PM2.5. Anthropogenic emissions were responsible for 73% of PM2.5.[66] Whether short-term, peak exposure to PM (e.g. in 1 hour) versus a longer average exposure (e.g. over a few days) is more strongly associated with asthmatic exacerbation remains unclear. Some evidence has shown peak exposure is more important than average longer-term exposure.[67] The existence of a lag period between exposure to PM and asthmatic exacerbation needs to be explored.[7]

Short-term exposure to ambient PM2.5 and PM2.5-10 in asthmatic children and adults has been associated with asthmatic symptoms in prospective cohort studies.[68,69] Long-term exposure to PM is also associated with uncontrolled asthma and decrements in lung function in both children and adults.[70,71] A meta-analysis of time-series studies showed short-term exposure to PM10 and PM2.5 increased the risk of asthma-related emergency room visits and hospitalizations.[7]

A meta-analysis focusing on the data from Asia found that short-term exposure to air pollution was associated with increased risk of hospital utilization for asthma and chronic obstructive pulmonary disease (COPD) in the whole population.[72] The association between PM and asthma exacerbations has also been supported by many experimental studies. In mouse models, exposure to PM resulted in allergic inflammation with Th2 and Th17 differentiation.[73,74] DEP exposure could exacerbate allergic asthma and airway inflammation, which is partly dependent on IL-17A.[30] In human challenge studies, the instillation of 100 μg of PM2.5 suspension into the lungs of healthy volunteers could also cause mild airway inflammation in healthy volunteers.[75]

Studies have demonstrated inflammation and oxidative stress in the human lower respiratory tract after exposure to PM. DEP can stimulate respiratory reflexes by activation of afferent, airway, chemo-sensitive C-fibers. Interactions between DEP and these afferents are mediated through an oxidative stress pathway that activates the transient receptor potential ankyrin-1 (TRPA1) ion channel.[76] Personal monitoring and implementation of an early action plan may reduce the frequency or severity of exacerbations due to PM.

Particulate matter and its pathophysiologic effects in the respiratory system

After inhalation, PM2.5 deposits in the deep airway and alveoli where it can cause structural damage and impair regular respiratory function. Published data has shown the association between PM2.5 exposure and effects on various respiratory diseases, such as asthma, COPD, and lung cancer.[33]

PM2.5 exposure has effects on the human respiratory system, including altering the immune response, inducing oxidative stress, and producing inflammation.[77] Alteration of immune response results from inducing transcription factors for stimulating cytokines that induce up-regulation of cell apoptosis, increase reactive oxygen species (ROS), and interrupt mitochondrial function.[78,79] PM2.5 exposure induces oxidative stress by increasing ROS and modifying cellular permeability. These ROS then further activate the inflammatory response and contribute to epithelial barrier dysfunction.[80] PM2.5 exposure also reduces transcription of antioxidant enzymes, intensifying the oxidant-antioxidant imbalance.[81,82] PM2.5 accumulation on airway epithelium can trigger the inflammatory signaling cascade, thereby inducing systemic immunological responses and inflammation.[83,84]

In addition, PM2.5 exposure may cause NK-cell dysfunction, and these cells are needed for eradicating *Staphylococcus aureus* infection.[85] This may contribute to the association between increases in ambient air pollution exposure and increasing pulmonary bacterial infection rates.

The contribution of outdoor particulate matter to indoor air quality

Most urban residents spend more than 80% of daily life indoors.[86] Therefore, the majority exposure to any airborne substance should occur there. Because ambient PM penetrates from comes indoors through ventilation systems and building leaks, researchers have focused on the relationship between indoor and ambient PM concentrations in various settings.[87] The indoor PM2.5 concentrations correlate with ambient PM2.5 concentrations in many studies.[87-89]

The relationship between indoor exposure to PM2.5 and asthma symptoms is similar to outdoor exposure. High indoor levels of PM2.5 were associated with acute respiratory symptoms and lung function impairment.[90] Similar results were observed in a Peruvian study involving 1441 adolescents aged 13-15 years; this study showed that living in a peri-urban setting, where indoor PM concentrations were elevated, was associated with asthma, atopy, and airway inflammation.[44]

PM reduction can improve health conditions in asthmatic subjects. A randomized controlled study showed that reducing indoor PM concentrations by using air cleaners was associated with a significant increase in symptom-free days in children with asthma.[91]

Indoor dwellers are still at risk from the adverse health effects of PM2.5. Efforts should focus on reducing ambient and indoor PM2.5. Currently, the contributions of air pollutant exposure within indoor environments, such as homes, schools, work offices, and enclosed modes of transportation, are understudied. New technologies might allow for assessment of exposure in these locations.[92]

Conclusion

Air pollution is a major problem with adverse health effects. A large and growing body of evidence supports the causal association between PM exposure and exacerbations of allergic respiratory disease, while an increasing body of evidence suggests long-term exposure to PM could contribute to the development of the allergic respiratory disease. We have concluded the causal association according to the cumulative of evidence in **Table 3**. Additional, well-designed studies are needed, especially from the Asia-Pacific region where the concentrations of ambient air pollution are much higher and

Table 3. The contribution of particulate matter to respiratory allergies according to recent evidence

Respiratory allergies	Epidemiological studies results	Birth cohort studies results	Conclusion from meta-analysis	Experimental studies	Conclusion of causal association*
Aeroallergen sensitization	Inconsistent	Inconsistent	- Inconsistent[25,26] - Significant association with outdoor aeroallergen, but not indoor aeroallergen (birth cohort)[25] - No significant association[26]	Supportive[28-31]	Possible
Asthma incidence/prevalence	Inconsistent	Inconsistent	- Inconsistent - Positive association (birth cohort)[25] - No significant association (birth cohort)[61]	Supportive[30,33]	Probable
Allergic rhinitis incidence/prevalence	Inconsistent	Inconsistent	No significant association (birth cohort)[25]	Supportive[28,29,31,37]	Possible
Asthmatic exacerbation	High degree of consistency from time-series and case-crossover studies	-	Increase risk (time-series and case-crossover)[103,104]	Supportive[30,73-75]	High

*The conclusions are based on the combination of both epidemiological research and experimental studies.

rising as urbanization increases in the region. For these populations, the development and implementation of governmental policies to improve air quality would not only improve the quality of life for individual citizens, but it would also reduce the threat of a looming allergic respiratory disease epidemic.

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