



Effects of air pollutants on upper airway disease

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Purpose of review

We discuss the effects of air pollutants on upper airway disease; the topic has hitherto received little attention.

Recent findings

Several epidemiological studies have shown that air pollutants aggravate airway diseases including asthma, bronchitis, and chronic obstructive pulmonary disorder. Pollutants also have negative effects on other upper airway diseases such as allergic and nonallergic rhinitis, sinusitis, and otitis media. Traffic-related air pollutants (diesel exhaust particles and nitrogen dioxide and tobacco smoke) have been widely studied in this context. Increasing evidence suggests that particulate matter, photochemical pollutants, and ozone are associated with such conditions. Young children and the obese are more vulnerable. Work *in vivo* and *in vitro* has explored the relationships between pollutants and disease, and possible pathophysiological mechanisms. Reactive oxygen species, apoptosis, and inflammation are all in play.

Summary

Traffic-derived materials and tobacco smoke are major air pollutants that aggravate upper airway disease. Novel mechanisms of action have been suggested and risk factors have been defined. However, the data are conflicting, and controlled prospective studies are required.

Keywords

air pollutants, allergy, otitis media, rhinitis, sinusitis

INTRODUCTION

Air pollution adversely affects human health. The principal pollutants include particulate matter, ozone, and nitrogen dioxide (NO₂). Air pollutants constitute a toxic mixture of particles and gases emitted in large quantities from many different combustion sources, including vehicles and factories. Indoor pollutants include smoke from tobacco, cooking, and the burning of wood and other material in stoves and fireplaces; dust particles resuspended during cleaning; and outdoor particles that infiltrate the indoor environment [1].

Air pollutants are known risk factors for the development of asthma, bronchitis, pneumonia, and chronic obstructive pulmonary disease [2,3]. However, the effects of pollutants on upper airway disease have been minimally studied. Although upper airway disease *per se* is not associated with high mortality, the public health repercussions are severe because such disease is common, particularly in young children [4]. Air pollution is thought to be an important risk factor for the development of upper airway disease. Recently, several possible pathological mechanisms have been suggested, but the data are conflicting. A better understanding of the mechanisms of air pollution and their links

with upper airway disease will contribute to disease prevention. The present review describes air pollutants that contribute to upper airway disease, the diseases of concern, and the findings and limitations of prior studies.

RHINITIS (ALLERGIC AND NONALLERGIC) AND ENVIRONMENTAL AIR POLLUTANTS

There is conflicting evidence on whether traffic-associated air pollutants are risk factors for the development of allergic conditions [5]. Residence

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KEY POINTS

- Epidemiological studies have shown that air pollutants are risk factors for the development of both lower and upper airway disease. Such conditions include allergic and nonallergic rhinitis, sinusitis, and otitis media. However, the data are conflicting and better-designed studies are required.
- Work *in vivo* and *in vitro* has shown that air pollutants increase the risk of disease. Pollutants trigger the generation of reactive oxygen species, induce apoptosis, and increase inflammation and mucin production. However, these effects are evident at only very high pollutant concentrations and the long-term effects of exposure to pollutants have not been studied.
- Traffic-associated air pollutants and tobacco smoke have been widely studied, and they clearly exacerbate airway disease. Particulate matter, photochemical pollutants, and ozone have been investigated in this context. For the management of both upper and lower airway disease, which is a major public health concern, it is important to understand air pollution risk factors.

within 100 m of a road with a traffic intensity more than 10 cars/min (the 24 h mean) is associated with elevated frequencies of asthma and allergic rhinitis triggered by allergens, but not with diseases caused by factors other than allergens. Schoolchildren aged 6–14 years who are exposed to traffic-associated air pollutants are at increased risks of asthma, allergic rhinitis, allergic sensitization, and reduced lung function (as reflected by Forced expiratory volume in 1 second (FEV1), FEV1/forced vital capacity, and forced expiratory flow 25–75% values [6^{***}]). Relative humidity exhibits a strongly negative correlation with rhinitis symptoms ($r = -0.91$) whereas the monthly mean daily concentrations of inhalable particles and NO₂ are positively correlated with this condition ($r = 0.89$ and 0.88 , respectively) [7^{***}]). Sand dust is a major problem in East Asia; particulate matter of aerodynamic diameter less than 10 µm (PM10) is of particular concern. However, Kang *et al.* [8^{*}] found that PM10 concentrations less than 150 µg/m³ did not affect the allergic symptoms of allergic rhinitis patients, which were in fact more affected by total time spent outdoors.

The home environment contains many sources of air pollutants, which are complex mixtures of agents; some are generated indoors and others infiltrate from the outdoors. Indoor pollutants vary in terms of concentration and hazard, geographic distribution, ethnicity of the residents, and their socioeconomic status [9,10].

Exposure of children (6–7 years of age) and adolescents (13–14 years of age) to indoor risk factors (including smoke), secondhand smoke, and mold aggravates preexisting allergic rhinitis and asthma [11^{*}].

In a systematic review of 97 studies on allergic rhinitis [12^{*}], the condition was not associated with active smoking in adults, but was associated with passive exposure to smoking. In both children and adolescents, it was associated with both, and exposure to secondhand smoke was associated with a modest increase in the risk of allergic disease. In another study [13], teenagers with perennial allergic rhinitis who were actively exposed to tobacco smoke exhibited increased eosinophil counts in the nasal mucosa, which may not have been associated with eosinophil apoptosis or the frequency/severity of nasal symptoms.

In Kang *et al.* [8^{*}], relationships were evident between a high level of exposure to photochemical or gaseous pollutants (ozone, carbon monoxide, NO₂, and sulfur dioxide) and both the risk and prevalence of symptomatic asthma, rhinitis, and atopic eczema. The authors analyzed 1340 children (men: women, 51.4:48.6) with a mean (SD) age of 6.84 (0.51) years. Ozone exposure was also associated with allergic rhinitis in children living in industrial areas, the rate of novel sensitization to outdoor allergens, and both current wheezing and allergic rhinitis. *De novo* ozone-mediated sensitization to outdoor allergens may explain the observed association [14]. In one study [15], 11 cycles of ozone exposure induced persistent rhinitis, squamous metaplasia, and epithelial hyperplasia in the anterior nasal airways of infant monkeys, resulting in a 39% increase in the numerical density of epithelial cells. It also induced a 65% increase in glutathione concentration in the nasal airway, indicating that exposure to ozone, early in life, triggers persistent epithelial changes in the nasal passages and potentially increases the susceptibility of children living in polluted environments to respiratory illness.

Although ozone is not considered an aeroallergen, exposure to this irritant has been reported to trigger or exacerbate preexisting allergic airway diseases including allergic rhinitis and asthma in both laboratory animals [16] and humans [17,18^{***}].

Inhalation of ozone (commonly present in photochemical smog) injures the airway and causes inflammation. Elevated ambient ozone concentrations have been epidemiologically associated with nasal airway activation of neutrophils and eosinophils. Ong *et al.* [18^{***}] found that acute exposure to ozone (over 1–2 days) caused nasal epithelial injury, resulting in cell death and neutrophilic rhinitis,

whereas repeated daily exposure to ozone (for 9 days) triggered eosinophilic rhinitis and lymphoid cell-dependent epithelial remodeling. This suggests that a novel pathogenic pathway of nasal eosinophilic inflammation may be in play in susceptible study participants living in polluted environments (e.g. in both atopic and nonatopic children of communities subjected to photochemical smog).

Epidemiological studies have shown that air pollution increases the prevalence of respiratory diseases in children. Significant increases in hospital admissions for asthma, allergic rhinitis, and upper and lower respiratory tract diseases have been observed. In a previous study [19], the adjusted odds ratios for exposure to PM_{2.5} (at increments of 10 µg/m³) were 1.15 and 1.21 for asthma and allergic rhinitis combined with asthma, respectively. PM₁₀ exposure significantly increased hospital admissions for all conditions studied, including asthma, allergic rhinitis, and upper and lower respiratory tract diseases.

The reported associations between traffic-related air pollution (TRAP) and allergic rhinitis have been inconsistent, possibly because of under-explored gene–environment interactions. In one study [20], a generally null effect of TRAP on allergic rhinitis and aeroallergen sensitization was not affected by particular variants of the GSTP1, Tumor necrosis factors (TNF), Toll-like receptor 2 (TLR), or TLR4 genes. Children carrying the minor rs1800629 TNF or rs1927911 TLR4 allele may be at a higher risk of allergic rhinitis.

DEP disrupts tight junctions via a process involving the actions of reactive oxygen species, increasing the permeability of nasal epithelial cells. This may promote allergen delivery into subepithelial tissues, in turn contributing to the exacerbation of immediate allergic responses [21[■]].

RHINOSINUSITIS AND AIR POLLUTANTS

In terms of duration, acute rhinosinusitis is defined as rhinosinusitis that persists for less than 12 weeks whereas chronic rhinosinusitis is of longer duration. The cause of the condition remains unknown. As rhinosinusitis is heterogeneous in nature, various treatment regimens have been developed [22]. Sundaresan *et al.* [23] observed that many studies lacked data on environmental and occupational risk factors. As the levels of classical pollutants including sulfur dioxide, nitrogen oxides, and dust have significantly declined in recent decades, these pollutants may no longer be problematic. However, in a large, well designed cross-sectional study, Bhattacharyya [24] found that air quality was associated with the prevalence of rhinosinusitis. As air quality

improved, the incidence of rhinosinusitis fell. Wolf [25] reported positive correlations between the numbers of chronic rhinosinusitis patients and air pollution in Germany. Several studies have explored the effects of tobacco smoke on chronic rhinosinusitis patients. One recent review claimed that tobacco smoke (derived from either active smoking or passive exposure) contributed to the development of chronic rhinosinusitis [26]. However, there is no evidence that tobacco smoke is the initial trigger of the disorder [22].

The development of rhinosinusitis is also influenced by occupational environment. A recent study [27] showed that chronic rhinosinusitis is more prevalent in those occupationally exposed to gases, fumes, dust, or smoke; current smoking doubled the risk of chronic rhinosinusitis. Hox *et al.* [28] suggested that work-related exposure to low-molecular weight compounds (<5 kDa) rather than high-molecular weight compounds (>5 kDa) increased the requirement for revision endoscopic sinus surgery.

OTITIS MEDIA AND AIR POLLUTANTS

Smoking is a well known risk factor for the development of otitis media. Passive exposure to smoking causes otitis media in children [29,30]. TRAPs were recently shown to increase the risk of otitis media [31[■]]. In 10 European birth cohorts, the NO₂ level was significantly associated with otitis media development (odds ratio = 1.09; 95% confidence interval: 1.02, 1.16/10 µg NO₂/m³). In another study [32], air pollution increased the number of emergency department visits by young children with otitis media. In that study, both carbon monoxide and NO₂ levels were positively associated with the incidence of otitis media after adjustment for ambient temperature and relative humidity. The strongest associations were evident in the warmer months in both girls alone and in all patients, in terms of exposure to carbon monoxide and NO₂, and in boys alone in terms of exposure to carbon monoxide. In another study [33], an average increase of 10 µg/m³ in the NO₂ level during pregnancy was associated with increases in the frequency of infections in the lower respiratory tract and ear.

In experimental works [34–36], diesel exhaust particles, urban particulates, and acrolein all had cytotoxic effects on cell lines of the middle ear and in in-vivo animal models. *In vivo*, particulate matter induces a characteristic inflammatory response accompanied by changes in the expression levels of genes involved in inflammation and mucin production [37]. *In vitro*, particulate matter stimulates apoptosis, the expression of inflammatory cytokines

(TNF- α , cytochrome c oxidase subunit II), and transcription of a gene encoding mucin (Muc5AC) [38]. Furthermore, bacterial pathogens enhance inflammatory pathway activity [38].

CONCLUSION

Several recent studies have found associations between exposure to air pollutants and upper airway disease. Air pollutants such as diesel exhaust particles, smoke, and particulate matter have various effects in the context of such disease. However, the epidemiological data are inconsistent. Well designed and well controlled epidemiological studies are rare. More work is needed on emerging risk factors such as indoor air pollutants and particulate matter. In addition, the long-term effects of, and associations between, upper and lower respiratory tract infections require attention. Several experimental studies have suggested reasonable mechanisms of interaction. However, no animal model that facilitates essential mechanistic studies has yet been developed. In addition, the effects of low concentrations of pollutants have been but poorly evaluated.

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Conflicts of interest

There are no conflicts of interest.

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