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Ambient air pollution and the lungs: what do clinicians need to know?

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Educational aims

- To provide physicians with knowledge of the common ambient air pollutants and their adverse effects on human lungs.
- To emphasise the fact that neonates, children and adults with pre-existing lung diseases are a susceptible population that need to be protected from the harmful effects of ambient air pollution.
- To educate physicians about the role of oxidative stress in mediating the harmful effects of ambient air pollution, and the consequences that individuals with inherent defects in antioxidant defence genes may be more vulnerable to the harmful effects.
- To provide physicians with current knowledge on the available dietary and drug sources of antioxidants which have the potential to enhance lung defence mechanisms against the harmful effects of air pollution.
- To encourage physicians to act as advocates to help reduce the levels of ambient air pollutants and to conduct research that will not only identify susceptible individuals by conducting genetic studies, but will also help in developing interventions that will reduce the harmful effects of ambient air pollutants.

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Summary

Ozone, oxides of nitrogen, sulphur dioxide and particulate matter are the important ambient air pollutants associated with adverse health effects. A large number of ambient air pollutants have been isolated from the fetal cord blood indicating that babies are exposed to air pollutants even before they are born. Children and the elderly are most susceptible to the harmful effects of ambient air pollutants. High levels of ambient air pollutants are associated with increased incidence or worsening of asthma and increased risk of developing allergic diseases, respiratory symptoms and respiratory tract infections. Mortality rates also increase in individuals with pre-existing cardiorespiratory diseases. The underlying mechanism for the harmful effects is the generation of oxidative stress which induces a strong respiratory as well as systemic inflammatory response. Individuals with genetic defects in enzymes associated with antioxidant defences seem to be particularly vulnerable to the harmful effects of air pollutants. Supplementation with antioxidants such as *N*-acetyl cysteine and sulforaphene has shown some protective effects in preliminary studies. High doses of vitamin C and vitamin E have shown some benefit in genetically susceptible asthmatic children. Physicians should play an important role in advocating to governments for a reduction in ambient air pollutants using innovative strategies and stricter legislation. Clearly more research is required to better understand intervention strategies to reduce morbidity and mortality due to ambient air pollutants, but in the meantime, the least we can do is to supplement diets with rich sources of antioxidants.

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Each day, we humans require ~400 L of oxygen to keep ourselves fit and well. This huge requirement of oxygen can only be met by inhaling about 10,000 L of ambient air into the lungs, which in turn gets distributed *via* the extensive branching network of the airways into tiny alveolar sacs that comprise a surface area of ~100 m^2. Because such a large volume of ambient air comes directly in contact with the airway mucosa and the large surface area of the lung parenchyma everyday, the quality of air that we inhale determines the health of our lungs. Moreover, a significant amount of inhaled air pollutants enters into the systemic circulation *via* the lungs and then has the potential to affect other body organs. Rapidly growing urbanisation and industrialisation accompanied by increased amounts of fossil fuel burning has contributed significantly to deteriorating air quality standards in most modern cities. Approximately 50% of people (3 billion) in the world live in urban cities and towns and are exposed to increasing levels of ambient air pollutants. The remaining 50% of people live in homes that use biomass fuel for cooking and heating [1] , which generates very high levels of indoor air pollutants. Air pollution from both indoor and outdoor sources is a major contributor to deteriorating lung health in developed and developing countries alike. Air pollution is a major environmental risk to health and is estimated to cause ~2 million premature deaths worldwide per year. In this review, we discuss the impact of common ambient air pollutants on respiratory health and offer some potential measures that can be employed to help reduce these health impacts.

Which ambient air pollutants have a significant impact on respiratory health?

Ambient air pollutants arise from a wide variety of sources and are classified into primary and secondary categories. Primary air pollutants are emitted directly into the ambient air and include carbon monoxide (CO) and sulphur dioxide (SO_2). Secondary air pollutants are formed in the air as a result of chemical reactions with other pollutants and these include ozone (O_3) and nitrogen dioxide (NO_2). Some pollutants, such as particulate matter (PM) can have both primary and secondary components. All these pollutants have been shown to have significant impacts on human health. Table 1 lists the common sources of these pollutants, although most of them are emitted from motor vehicle exhausts and industrial sources. Among

Table 1 Common ambient air pollutants and their sources

Pollutant	Major sources
Primary air pollutants	
CO	Automobile exhausts Emissions from large industrial combustion sources such as electrical power plants
SO_2	Burning of fossil fuels (coal and oil) Smelting of mineral ores that contain sulphur Diesel exhaust Volcanic eruptions
Secondary air pollutants	
NO_2	Combustion processes such as heating Power generation Motor vehicle exhausts (petrol, diesel and compressed natural gas)
O_3	Formed by photochemical (sunlight) reactions in the presence of precursor pollutants such as nitric oxide, NO_2 and volatile organic compounds Burning of fire crackers
Primary and secondary air pollutants	
PM	Emitted from power stations, motor vehicle exhausts (especially diesel vehicles), road dust and other anthropogenic sources

all these pollutants, PM air pollution has received major attention since it has been shown to have a significant impact not only on the lungs, but also on the cardiovascular system.

Particulate matter

PM can be both a primary and a secondary air pollutant. Particulates are emitted from a number of natural and anthropogenic sources, such as the combustion of fossil fuels. Particles having an aerodynamic diameter of <10 µm are called PM_{10} and those <2.5 µm are called $PM_{2.5}$. Particles <1 µm in diameter are called ultrafine particles or nanoparticles. Particles in these size ranges can easily enter into the distal portions of the lung and the systemic circulation. Moreover they act as vehicles transporting toxic chemicals into the human respiratory system [2]. The major sources of PM pollutants in the ambient air are motor vehicle exhausts (especially diesel exhausts), road dust and other anthropogenic sources.

Diesel exhaust particles

Diesel combustion engines are one of the major sources of PM_{10} and $PM_{2.5}$ in most urban cities (figure 1), largely because they emit up to 1,400 times more particles than petrol combustion engines [3]. Moreover, the number of diesel cars has increased markedly in most countries (up to 50% of car sales in Europe) over the past decade. This is because diesel engines are a lot more fuel efficient and are widely promoted as "green" because they emit lower amounts of greenhouse gases (CO and carbon dioxide (CO_2)), although this is significantly offset by the large amount of PM they produce. Diesel exhaust particles mainly comprise elemental carbon at the core, adsorbed onto which are polyaromatic hydrocarbons and transition metals such as nickel and vanadium. The mass median diameter of these particles is ~100 nm and therefore on a mass basis they have a much greater surface area and a greater ability to generate reactive oxygen species.

Fireworks

All fireworks contain carbon and sulphur, which are necessary for burning. In addition, different substances are added (arsenic, manganese, sodium oxalate, aluminium and iron dust powder, potassium perchlorate, strontium nitrate and barium nitrate) to give colour. The burning of fireworks releases a large amount of air pollutants, particularly SO_2, CO_2, CO and PM along with several metal salts for example aluminium,

Figure 1
Diesel vehicles are a major source of PM air pollution.

manganese and cadmium, which are associated with serious health hazards [4]. Large numbers of fireworks are burnt in many countries, especially during festive seasons, and the accompanying personal exposures can be very high (figure 2). The burning of fireworks during the Diwali festival in India has been shown to be associated with ambient levels of SO_2 peaking at 5.67 ppm [5]. These levels are 200 times above the safety limits set by the World Health Organization.

How does ambient air pollution affect respiratory health?

Antenatal effects of exposure to ambient air pollutants

The harmful effects of ambient air pollution begin even before the child is born. In a study conducted by the Environmental Working Group in collaboration with Commonweal in New York, NY, USA, researchers detected the presence of ≥200 different chemicals and ambient air

Figure 2
Burning of fireworks during festivals (e.g. *Diwali in India) is associated with high levels of ambient air pollutants, in particular SO_2.*

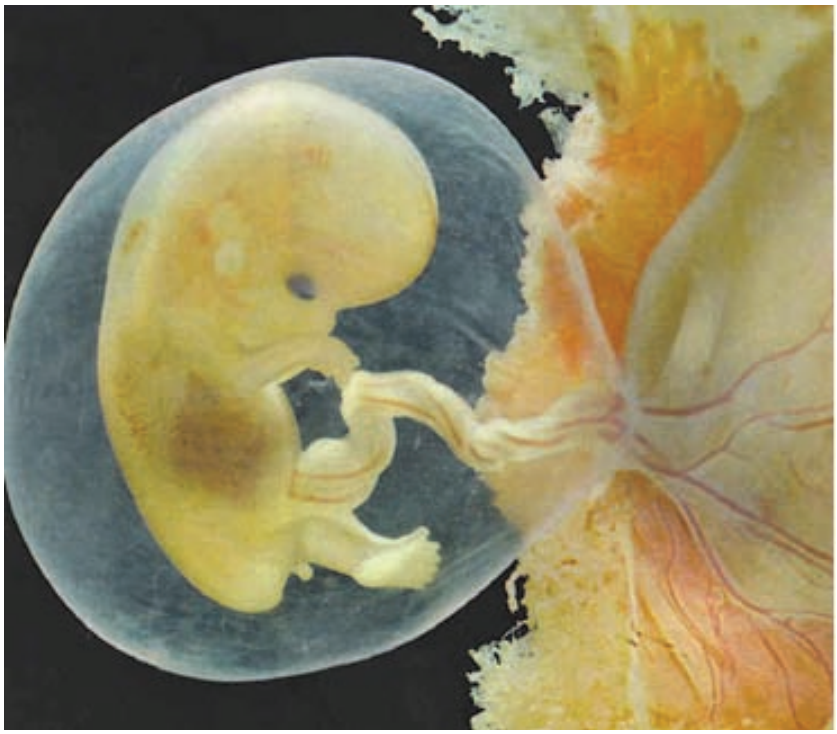

Figure 3
Ambient air pollutants inhaled by pregnant mothers reach the growing fetus via *the umbilical cord*.

pollutants in the umbilical cord blood of 10 randomly selected babies [6]. The sources of these pollutants included burning of coal, gasoline and garbage, indicating that ambient air pollutants can traverse the lungs of pregnant mothers, enter into the systemic circulation and reach the growing fetus *via* the umbilical cord. The placenta, does not seem to offer any protection against the passage of these harmful pollutants into the fetus (figure 3). These pollutants that enter into the fetal circulation may have a significant impact on growth and development by interfering with intracellular signalling pathways. Babies born to mothers exposed to high levels of ambient air pollutants have showed increased incidence of intrauterine growth retardation, low birth weight, pre-term birth and increased perinatal morbidity [7]. Increased prevalence of sudden infant death syndrome has also been found in association with increased levels of ambient air pollutants in time-series analysis [8]. A recent study from Japan has demonstrated that intrauterine exposure to high levels of traffic-related air pollutants and/or such exposure soon after birth increases the risk of developing allergic disorders in infants [9].

Neonatal effects

Postnatal lung growth is divided into the first 3 yrs of life where new alveoli are developed, and later childhood where lung growth occurs by expansion. The effect of very early environmental exposures may therefore be more damaging, or at least qualitatively different, to exposures in later childhood [10]. A study from 11 cities in Canada that investigated the association between daily ambient levels of O_3, CO, SO_2 and NO_2 and daily neonatal admissions for respiratory problems found a significant correlation. The strongest effects were observed for ambient NO_2 and O_3. A study from Krakow, Poland, reported that during the first year of their life, babies born to mothers exposed to high levels of PM air pollution during pregnancy had a 4.8-fold increased risk of cough, a 3.8-fold increased risk of wheeze without cold, and an 82% increased risk of a runny or stuffy nose as compared with babies born to mothers exposed to lower levels of air pollution [11]. Miller *et al.* [12] reported similar observations from New York, but also reported a higher prevalence of asthma in children by the age of 2 yrs in mothers who were exposed to high levels of polyaromatic hydrocarbons during gestation. The above studies suggest that early exposure to ambient air pollutants increases the prevalence of respiratory symptoms and the risk of developing asthma during early childhood.

Children are uniquely vulnerable

Children seem to be particularly susceptible to the harmful effects of ambient air pollution because their lungs are growing. Lung growth is guided by a complex and precisely timed sequence of chemical messages. Many ambient air pollutants are chemicals that have the potential to interfere with these signalling pathways. The number of alveoli increases from 24 million at birth to 267 million at 4 yrs old and eventually to 600 million at adulthood [13]. Compared with adults, children have poor defences against PM and gaseous air pollutants, have a differential ability to metabolise and detoxify environmental agents and have an airway epithelium that is more permeable to inhaled air pollutants [14]. Also, children have a greater level of physical activity than adults (an average physical activity duration of 124 *versus* 21 min per day) [15], hence the intake of air into the lungs is much greater than adults per day. Children spend more time outdoors than adults, particularly in the summer and in the late afternoon. Some of that time is spent in activities that increase ventilation rates. Greater intake of air means greater amounts of ambient air pollutants will enter into the lungs. During exercise, there is a 5-times greater deposition of particles into the lungs than during rest. Per bodyweight, the volume of air passing through the lungs of a resting infant or child is twice that

of a resting adult under the same conditions, and therefore twice as much (per bodyweight) of any chemical in the atmosphere could reach the lungs of an infant [16].

Effects on schoolchildren

A number of epidemiological studies have reported associations between residential and school proximity to busy roads as a surrogate for high levels of ambient air pollution, and a variety of adverse respiratory health outcomes in children, including presence of respiratory symptoms and worsening of asthma exacerbations [17–23]. A growing number of studies also showed that children living in homes that are situated near roads with heavy truck traffic have an increased risk of new-onset asthma and asthma exacerbations accompanied by increased school absenteeism and asthma-related hospitalisations [18, 19]. A recent study from Cincinnati, OH, USA, revealed that children exposed to the highest tertile of traffic exhaust had a 45% increased risk of recurrent dry cough at night compared with children who were less exposed [20]. BRAUER *et al.* [21] reported positive associations between markers of traffic-related air pollution and respiratory health outcomes, including asthma onset, incidence of wheeze, ear-nose-throat infections and serious colds or flu in a large cohort of children 4 yrs of age, effects that were first noted at the age of 2 yrs [22]. More recently, a Dutch study has reported that ambient PM air pollution mainly arising from motor vehicular exhausts was significantly associated with increased incidence of asthma among schoolchildren [23]. In a study that investigated the association between the prevalence of wheeze and allergic symptoms and truck traffic density in 13 and 14 yr old school children from Munster, Germany, BEHRENS *et al.* [24] reported that compared with children who lived in 'never exposed to truck traffic areas', those children who lived in areas with rare, frequent and constant flow of truck traffic had a 29%, 58% and 57% increased prevalence of wheeze, respectively. Similarly, the prevalence of allergic rhinitis increased by 20%, 35% and 69%, respectively. The above studies suggest that children who live or study in areas of heavy traffic (figure 4), especially with a large number of diesel vehicles, have a significantly increased risk of developing asthma, allergic rhinitis and other respiratory symptoms. Children who have pre-existing asthma suffer worse symptoms when ambient air pollution levels are high.

Figure 4
Traffic congestion – a major cause of ambient air pollution in all major cities in world.

Effects on lung function and lung growth in children

In a prospective study of 10-yr-old children that started with 1,759 children and lasted for 8 yrs, GAUDERMAN *et al.* [25] found a significant association between lung function parameters (forced expiratory volume in 1 s) and ambient levels of NO_2, acid vapour, $PM_{2.5}$ and elemental carbon, even after controlling for known confounding factors. Children who lived in areas with relatively higher ambient PM air pollution had a significant decrease in FEV1 values compared with children who lived in areas with lower PM air pollution levels. These effects were similar in males and females and remained significant even among children with no history of asthma. The magnitude of these effects was similar to those observed due to effects of maternal smoking reported in earlier studies [26, 27]. Schoolchildren residing in the city of Leicester, UK, showed a significant decrement in lung function parameters that were associated with an increased number of carbon particles within the alveolar macrophages obtained by sputum induction [28], indicating that children exposed to higher levels of PM air pollution show significant decrements in lung function parameters. Current levels of ambient air pollutants, even those recorded in some of the relatively cleaner cities in the world have shown a significant adverse impact on lung growth in schoolchildren.

Effects on respiratory symptoms in adults

Adults exposed to high levels of ambient air pollution have shown increased prevalence of chronic

cough, phlegm and breathlessness [29]. KNOX *et al*. [30] have shown that the allergenicity of grass pollens increases by a factor of up to 50, as determined by the amount of allergen-specific immunoglobulin E in nasal lavage, when it is mixed with diesel exhaust particles. Moreover, diesel exhaust particles can also induce the formation of new allergen sensitisation when instilled into the nose. Diesel exhaust particles therefore not only enhance the development of new allergies, but also amplify existing allergic disorders. Epidemiological studies across the world have shown a consistent association between increased levels of particulate air pollution and mortality due to cardiovascular and respiratory disease especially among older people [31]. In Switzerland, increased average annual ambient concentrations of NO_2 and PM were found to be associated with increased adjusted 1-yr prevalence of chronic cough or chronic phlegm production and breathlessness among adult never-smokers [32]. The risk of pneumonia also increases when elderly subjects are exposed to high levels of PM air pollution [33]. High levels of ambient O_3 have been shown to trigger asthma attacks and reduce lung function in adults [34]. The harmful effects of ambient air pollutants, especially in adults, are not only restricted to the lungs, but also cause significant increases in cardiovascular disease [35, 36]. Traffic policemen and bus drivers who spend long hours on busy roads inhaling high levels of ambient air pollutants in India show a significant increase in lung oxidative stress and increased prevalence of cough, breathlessness and wheeze [37]. Ambient air, particularly in densely populated urban environments, contains a variety of known human carcinogens, including organic compounds such as benzol(a)pyrene and benzene, inorganic compounds containing elements such as arsenic and chromium and radionucleotides [38] that increase the likelihood of lung cancer. Trucking industry workers who have had regular exposure to vehicle exhaust from diesel and other types of vehicles on highways, city streets and loading docks have an escalated risk of lung cancer with increasing years of work [39].

Adults exposed to high levels of ambient air pollutants therefore have an increased risk of developing respiratory symptoms, asthma, chronic obstructive pulmonary disease, allergic rhinitis, lower respiratory tract infections and lung cancers. Elderly subjects with underlying respiratory or cardiovascular disease are more likely to die when pollution levels are high. Apart from their impact on the respiratory system, ambient air pollutants, and in particular, PM also increase the risk of cardiovascular diseases and cardiovascular mortality.

How do ambient air pollutants damage the lungs?

The harmful effects of ambient air pollutants are caused by the formation of reactive oxygen species, which in turn induce oxidative stress in the lungs inciting a powerful cellular and mediator inflammatory response that spills into the systemic circulation and causes harmful effects in other body organs [40]. We have earlier demonstrated that a single 1-h exposure to high levels of diesel exhaust, commonly encountered alongside roads with heavy diesel traffic, in healthy human volunteers under controlled conditions, increases airway mucosal numbers of neutrophils, T lymphocytes, B lymphocytes and mast cells, and is accompanied by increased levels of inflammatory mediators in the lungs (histamine, fibronectin, interleukin-8 and growth-related oncogene-α) and a systemic inflammatory response associated with increased levels of circulating neutrophils and platelets in the blood [41]. Ambient air pollutants therefore cause not only oxidative stress-induced airway inflammatory responses, but also cause systemic inflammatory responses by stimulating bone marrow cells to release inflammatory cells [42].

Genetic susceptibility

The harmful effects of ambient air pollutants, especially O_3, NO_2 and PM, are mediated by the generation of reactive oxygen species which interact with different cellular and structural cells in the airways to cause inflammatory responses. The human body offers resistance to these responses by mounting an antioxidant defence, which comprises glutathione, vitamin C, vitamin A, uric acid and CO. Among these, glutathione appears to be the most potent antioxidant that protects the lungs from harmful effects of air pollutants [43].

Mutations in the genes responsible for reduced glutathione synthesis have been shown to be associated with greater decrements in lung function after exposure to O_3 [44], greater allergic responses and reduced lung function after exposure to diesel exhaust particles. Importantly, the glutathione S-transferase Mu 1 (GSTM1) mutation that is associated with reduced glutathione production is seen in ~50% of the global population and varies from 25% to 75% across different countries. It seems likely that individuals with this mutation are genetically more susceptible

to the harmful effects of ambient air pollutants. Polymorphisms within the nicotinamide adenine dinucleotide phosphate (NADPH) quinine oxidoreductase-1 (NQO1) gene have also been shown to modify respiratory symptoms, lung function and risk of asthma in response to exposure to O_3 and diesel exhaust particles [25]. Animal studies have reported that polymorphisms in the tumour necrosis factor-α gene influence lung function in response to O_3 inhalation [45]. These studies indicate that susceptibility to the harmful effects of ambient air pollutants may be genetically determined.

What role can physicians play?

Help reduce the burden of ambient air pollution

Advocate for policy change

A study has estimated that if ambient air pollution levels were reduced to match levels in the cleanest community, then annual asthma-related emergency department visits and asthma hospitalisation rates would decrease from 22% to 6%, prevalence of bronchitis would decrease from 40% to 20% [46], asthma-related school absenteeism would reduce by two-thirds and new cases of asthma among the most active children living in polluted communities would decrease by 75% [47]. With the realisation that ambient levels of air pollutants in most cities and towns worldwide are associated with a significant impact on lung health, it is imperative to take appropriate steps to reduce the levels of key pollutants, such as PM, oxides of nitrogen, SO_2 and O_3. Physicians and healthcare providers should advocate and educate governmental officials and policy makers and make them realise that the health of people should be at the top of the list of competing priorities for policy making [48]. This can be achieved through good urban planning measures, innovative traffic management strategies [49], supporting technology advancements to use cleaner fuels and cleaner engines, and enforcing strict legislative norms for industrial emissions.

Physicians should also advocate for governments to set air quality standards to protect the health of their citizens. The government should routinely monitor important ambient air pollutants and the public should be informed when levels are above the safety limits, so that necessary preventive measures be advised to individuals who are susceptible to the harmful effects of air pollutants.

Reduce personal exposures

Despite the best intentions and efforts of most governments to reduce outdoor air pollution levels these are unlikely to reduce substantially in the near future. The only options at hand then are to reduce personal exposures and to decrease susceptibility. Patients with asthma and COPD need to be particularly educated to avoid high-level exposures and to avoid outdoor activities during periods of high pollution. They should be told to reduce outdoor activities when the air quality index is in the unhealthy range, increase peak flow checks during periods with poor air quality and exercise away from major roads [36]. Several recent studies [15] have shown that children attending schools located within 75m of highways have a higher prevalence of asthma than children attending schools located further away from high traffic areas, therefore when new schools are being designed the distance from busy motorways should be taken into consideration.

Reduce susceptibility to the harmful effects of air pollutants

Antioxidant supplementation

The harmful effects of ambient air pollutants become pronounced when the antioxidant defence mechanism becomes weak. Supplementation with antioxidants may therefore strengthen defence mechanisms and reduce the harmful effects of air pollution. Animal studies have demonstrated that diesel exhaust particle-induced airway eosinophilic inflammation and goblet cell hyperplasia can be attenuated by supplementation with *N*-acetyl cysteine (NAC), an antioxidant that increases the level of glutathione in the lungs [50]. More recently we reported that supplementing bus drivers who are chronically exposed to high levels of vehicular air pollutants in India with 1,200 mg NAC per day significantly reduced lung oxidative stress and improved lung function parameters [43]. Preliminary evidence suggests that dietary supplementation with sulforaphene, a potent inducer of antioxidant enzymes, reduces inflammatory responses, especially in those exposed to diesel exhaust particles [51] and therefore offers promise as an air pollution chemoprotective agent [52]. Sulforaphene is produced naturally by cruciferous vegetables (vegetable that have cross-shaped petals) including Brussels sprouts, turnips, cabbage, broccoli and cauliflower (figure 5).

Supplementation with vitamin C and vitamin A, especially in high doses, has shown some

Figure 5
Cruciferous vegetables are a rich source of antioxidants.

beneficial effects on small airway function in asthmatics exposed to O_3 who inherently synthesise low levels of glutathione. The results of animal studies suggest that supplementation with vitamin C and vitamin E modulates the pulmonary response to exposure to photo-oxidants, such as O_3 or NO_2, and that vitamin C, uric acid and glutathione located in the respiratory tract lining fluid are consumed on exposure to O_3 and NO_2 [25, 50, [53]]. However, more evidence is required before we can recommend regular use of antioxidant supplements. In the mean time it seems prudent to at least encourage vulnerable individuals to eat vegetables and fruits that are rich in antioxidants. Individuals who are most likely to benefit from regular antioxidant supplementation are those who have genetic defects in enzymes that are associated with reduced antioxidant production (*e.g.* GSTM1 null, glutathione S-transferase pi gene and NQO1). There is an urgent research need to develop a knowledge base of personalised interventions that can enhance anti-oxidant defences in genetically susceptible groups to reduce adverse effects of air pollution.

Educational questions

1. Which of the following statements is false?
a) The harmful effects of air pollution start even before birth.
b) Diesel exhaust particles increase the allergenicity by 50 times.
c) Ozone is a primary air pollutant.
d) The harmful effect of air pollution is mediated by the generation of reactive oxygen species.

2. Which of the following mechanisms make children more susceptible to the harmful effects of air pollution?
a) Poor lung defences.
b) Greater level of physical activity.
c) Airway epithelium more permeable as compared with adults.
d) Only a) and c).
e) All of the above.

3. The following are environmental risk factors for childhood asthma, except
a) Passive smoking.
b) Carbon monoxide.
c) Residence within 70 m from main road.
d) Maternal exposure to high levels of air pollutants during pregnancy.
e) PM pollution.

4. Which of the following form part of the different mechanisms through which air pollutants cause damage to the lungs?
a) Genetic mutations.
b) Reactive oxygen species formation.
c) Oxidative stress.
d) Local and systemic inflammatory response.
e) All of the above.

5. Which of the following dietary supplements/drugs would you advise your patients to take to reduce the risk of lung oxidative stress?
a) Broccoli.
b) Vitamin B complex.
c) *N*-acetyl cysteine.
d) Vitamin C.
e) a), c) and d).
f) All of the above.

References

1. Salvi S, Barnes P. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009; 374: 733–743.
2. Zhiqiang Q, Siegmann K, Keller A, *et al*. Nanoparticle air pollution in major cities and its origin. *Atmospheric Environment* 2000; 34: 443–451.
3. Britain's biggest and best car buyer's guide. *What car?* 1999; June: 37-41.
4. Ravindra K, Mor S, Kaushik CP. Short-term variation in air quality associated with firework events: A case study. *J Environ Monit* 2003; 5: 260–264.
5. Salvi S, Kokje K, Hake S, *et al*. Fireworks during Diwali festival have a significant impact on respiratory health: a study from India. *Eur Respir J* 2007*;* 20: Suppl. 30, 486s.
6. Environmental Working Group. Body Burden – The pollution in newborns. A benchmark investigation of industrial chemicals, pollutants and pesticides in umbilical cord blood. www.ewg.org/reports/bodyburden2/execsumm.php Date last accessed: January 5, 2010. Date published: July 14, 2005.
7. Wang L, Pinkerton KE. Air pollutant effects on fetal and early postnatal development. *Birth Defects Res C Embryo Today* 2007; 8: 144–154.
8. Dales R, Burnett RT, Smith-Doiron M, *et al*. Air pollution and sudden infant death syndrome. *Pediatrics* 2004*;* 113: e628–e631.
9. Miyake Y, Tanaka K, Fujiwara H *et al*. Residential proximity to main roads during pregnancy and the risk of allergic disorders in Japanese infants: the Osaka maternal and child health study. *Pediatr Allergy Immunol* 2010; Epub ahead of print. PMID: 19788536. DOI: 1399-3038.2009.00951.
10. Grigg J. Particulate matter exposure in children relevance to chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2000; 6: 564–569.
11. Jedrychowski W, Galas A, Pac A, *et al*. Prenatal ambient air exposure to polycyclic aromatic hydrocarbons and the occurrence of respiratory symptoms over the first year of life. *Eur J Epidemiol* 2005; 20: 775–782.
12. Miller RL, Garfinkel R, Horton M, *et al*. Polycyclic aromatic hydrocarbons, environmental tobacco smoke, and respiratory symptoms in an inner-city birth cohort. *Chest* 2004; 126: 1071–1078.
13. Trasande L, Thurston GD. The role of air pollution in asthma and other pediatric morbidities. *J Allergy Clin Immunol* 2005; 115: 689–699.
14. Schwartz J. Air pollution and children's health. *Pediatrics* 2004; 113: 1037–1043.
15. Salvi S. Health effects of ambient air pollution in children. *Paediatr Respir Rev* 2007; 8: 275–280.
16. Moya J, Bearer C, Etzel R. Children's behavior and physiology and how it affects exposure to environmental contaminants. *Pediatrics* 2004; 113: 996–1006.
17. Wjst M, Reitmeir P, Dold S, *et al*. Road traffic and adverse effects on respiratory health in children. Road traffic and adverse effects on respiratory health in children. *BMJ* 1993; 307: 596–600.
18. Behrens T, Taeger D, Maziak W, *et al*. Self-reported traffic density and atopic disease in children. Results of the ISAAC Phase III survey in Muenster, Germany. *Pediatr Allergy Immunol* 2004; 15: 331–339.
19. Gilliland FD. Outdoor air pollution, genetic susceptibility, and asthma management: opportunities for intervention to reduce the burden of asthma. *Pediatrics* 2009; 123; S168-S173
20. Sucharew H, Ryan P, Bernstein D, *et al*. Exposure to traffic exhaust and night cough during early childhood: the CCAAPS birth cohort. *Pediatr Allergy Immunol* 2010. Epub ahead of print. PMID: 19824943.
21. Brauer M, Hoek G, Smit HA, *et al*. Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur Respir J* 2007; 29: 879–888.
22. Brauer M, Hoek G, Van Vliet P, *et al*. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am J Respir Crit Care Med* 2002; 166: 1092– 1098.
23. Gehring U, Wijga AH, Brauer M, *et al*. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Respir Crit Care Med* 2009. Epub ahead of print. PMID: 19965811. DOI: 200906-08580C.
24. Behrens T, Taeger D, Maziak W, *et al*. Self-reported traffic density and atopic disease in children. Results of the ISAAC Phase III survey in Muenster, Germany. *Pediatr Allergy Immunol* 2004; 15: 331–339.
25. Gauderman WJ, Avol E, Gilliland F, *et al*. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004; 351: 1057–1067.
26. Tager IB, Weiss ST, Munoz A, *et al*. Longitudinal study of the effects of maternal smoking on pulmonary function in children. *N Engl J Med* 1983; 309: 699–703.
27. Wang X, Wypij D, Gold DR, *et al*. A longitudinal study of the effects of parental smoking on pulmonary function in children 6-18 years. *Am J Respir Crit Care Med* 1994; 149: 1420–1425.
28. Kulkarni N, Pierse N, Rushton L, *et al*. Carbon in airway macrophages and lung function in children. *N Engl J Med* 2006; 355: 21–30.
29. Zemp E, Elsasser S, Schindler C, *et al*. Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). The SAPALDIA Team. *Am J Respir Crit Care Med*. 1999; 159: 1257–1266.
30. Knox RB, Suphioglu C, Taylor P, *et al*. Major grass pollen allergen Lol p 1binds to diesel exhaust particles: implications for asthma and air pollution. *Clin Exp Allergy* 1997; 27: 246–251.
31. Seaton A, Godden D, MacNee W, *et al*. Particulate air pollution and acute health effects. *Lancet* 2004; 345: 176–178.
32. Zemp E, Elsasser S, Schindler C, *et al*. Long-term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). *Am J Respir Crit Care Med* 1999; 159: 1257–1266.
33. Schwartz J. Air pollution and daily mortality in Birmingham, Alabama. *Am J Epidemiol* 1993; 137: 1136–1147.
34. Stieb DM, Burnett RT, Beveridge RC, *et al*. Association between ozone and asthma emergency department visits in Saint John, New Brunswick, Canada. *Environ Health Perspect* 1996; 104: 1354–1360.
35. Mills NL, Tornqvist H, Robinson SD, *et al*. Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation* 2005; 112: 3930–3936.
36. Lucking AJ, Lundback M, Mills NL, *et al*. Diesel exhaust inhalation increases thrombus formation in man. *Eur Heart J* 2008; 29: 3043–3051.
37. Das P, Brashier B, Valsa S, *et al*. Bus drivers show higher levels of exhaled carbon monoxide, a marker of lung oxidative stress. *Eur Respir J* 2007*;* 20: Suppl. 30, 474s.
38. Beelen R, Hoek G, Brandt PA, *et al*. Long-term exposure to traffic-related air pollution and lung cancer risk. *Epidemiology* 2008, 19: 702–710.
39. Garshick E, Laden F, Hart JE, *et al*. Lung cancer and vehicle exhaust in trucking industry workers. *Environ Health*

Answers

1. c)
2. e)
3. b)
4. e)
5. e)

Perspect 2008; 116: 1327–1332.
40. Kelly FJ. Oxidative stress and its role in air pollution and adverse health effects. *Occup Environ Med* 2003; 60: 612–616.
41. Salvi S, Blomberg A, Rudell B, *et al*. Acute inflammatory responses in the airways and peripheral blood after short-term exposure to diesel exhaust in healthy human volunteers. *Am J Respir Crit Care Med* 1999; 159: 702–709.
42. Mukae H, Vincent R, Quinlan K, *et al*. The effect of repeated exposure to particulate air pollution (PM10) on the bone marrow. *Am J Respir Crit Care Med*. 2001; 163: 201–209.
43. Kelly F.J. Gluthathione: in defence of the lung. *Food Chem Toxicol* 1999; 37: 963–966.
44. Romieu I, Castro-Giner F, Kunzli N, *et al*. Air pollution, oxidative stress and dietary supplementation: a review. *Eur Respir J* 2008; 31: 179–197.
45. Yang IA, Holz O, Jorres A, *et al*. Association of tumor necrosis factor-alpha polymorphisms and ozone-induced change in lung function. *Am J Respir Crit Care Med* 2005; 171: 171–176.
46. McConnell R, Berhane K, Gilliland F, *et al*. Air pollution and bronchitic symptoms in Southern California children with asthma. *Environ Health Perspect* 1999; 107: 757–760.
47. McConnell R, Berhane K, Gilliland F, *et al*. Asthma in exercising children exposed to ozone: a cohort study. *Lancet*. 2002; 359: 386–391.
48. Gilliland FD. Outdoor air pollution, genetic susceptibility, and asthma management: opportunities for intervention to reduce the burden of asthma. *Pediatrics* 2009; 123: Suppl. 3, S168–S173.
49. MacNeil SJ, Goddard F, Pitman R, *et al*. Childhood peak flow and the Oxford Transport Strategy. Thorax 2009; 64: 651–656.
50. McLellan LI, Lewis AD, Hall DJ, *et al*. Uptake and distribution of *N*-acetylcysteine in mice: tissue-specific effects on glutathione concentrations. *Carcinogenesis* 1995; 16: 2099–2106.
51. Wan J, Diaz D. Antioxidant enzyme induction: a new protective approach against the adverse effects of diesel exhaust particles. *Inhal Toxicol* 2007; 19: 177–182.
52. Ritz S, Wan J, D Diaz-Sanchez D. Sulforaphane-stimulated phase II enzyme induction inhibits cytokine production by airway epithelial cells stimulated with diesel extract. *Am J Physiol Lung Cell Mol Physiol* 2007; 292: L33–L39.
53. Allen S, Britton J, Leonardi-Bee J. Association between antioxidant vitamins and asthma outcome measures: systematic review and meta-analysis. *Thorax* 2009; 64: 610–619.