

Air pollution: from lung to heart

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Summary

Epidemiological, clinical, and experimental evidence correlates current levels of ambient air pollution with both respiratory and cardiovascular effects. Oxidative stress, inflammation, induction of a pro-coagulatory state and dysfunction of the autonomic nervous system appear to play a major role. Acute effects include changes in lung function, heart rate, blood pressure and inflammatory state, and clinical measures such as respiratory symptoms, thrombosis, myocardial infarction, arrhythmia, stroke, and death. In addition, there is an increase in the use of health care resources due to these effects. Long-term consequences of

accumulated exposure include adverse effects on lung growth, chronic bronchitis, lung cancer, and probably the development of asthma and atherosclerosis. These morbidities ultimately lead to shorter life expectancy. Host factors including genotype are important modifiers of the effects of air pollution. Further research will help identify susceptible subgroups and disentangle specific effects and mechanisms associated with various constituents and sources of air pollution.

Key words: particulate matter; ozone; environmental health

Introduction

Extreme air pollution events such as the historic London fog in 1952 made it clear that both the lung and the heart can be affected by high levels of ambient air pollution. A large body of epidemiological, clinical and toxicological data have accumulated indicating that cardiovascular and respiratory physiological processes and health are adversely affected by air pollutants despite the improved air quality since the 1950s [1]. In this review, we summarise the effects of acute and long-term exposure on both organ systems, emphasising the effects of long-term exposure on cardiovascular health. We refer primarily to other related

review articles and restrict references to single studies, to recently published studies or to those with a high impact. The distinction between acute and long-term effects is important both from a biologic and public health perspective. We define acute effects of air pollution as all those that occur within one or a few days of exposure, sub-acute effects as those that occur within several weeks, and long-term effects are the consequences of sub-clinical effects on chronic processes that ultimately lead to manifest morbidity and/or death. Effects of air pollution on reproductive health are not addressed herein.

Effects of acute air pollution exposure

A large number of studies have investigated whether daily changes in air quality are followed by acute changes in the health state of children and adults. Outcomes of various levels of severity have been investigated that range from sub-clinical functional changes to symptoms, impaired activities (eg school absences), doctors' or emergency room visits, hospitalisations and death [1, 2] (see table 1). Large multi-city projects such as the sem-

inal European APHEA project (Air Pollution and Health: A European Approach) or the U.S. counterpart NMMAPS (National Mortality and Morbidity Air Pollution Study) are particularly relevant [3, 4]. Small but significant increases in the daily total, respiratory, and/or cardiovascular morbidity and mortality have been observed in association with the fluctuations of daily pollution. As a rule of thumb, the acute increment of death per

Table 1

List of respiratory and cardiovascular physiologic, structural, and clinical outcomes reported to be associated with exposure to ambient air pollution (? means evidence is sparse).

Lung	Heart / vasculatur
Physiologic & structural changes	
Forced expiratory volume and flows	Heart rate (↑)
Inflammatory mediators (local and systemic)	Heart rate variability (↓)
Air way remodelling	Blood pressure
	Blood coagulation factors
	Vascular reactivity
	Inflammatory mediators
	Vessel structure
Acute clinical measures of effect	
Upper respiratory symptoms	Thrombosis
Lower respiratory symptoms	Myocardial infarction
Acute exacerbations of chronic bronchitis, asthma	Arrhythmia
Asthma medication use	Stroke
Death	Death
School / work absences	Use of health care resources due to all of the above
Use of health care resources due to all of the above	
Cumulative clinical effects	
Reduced lung growth	Reduced life expectancy
Reduced small airway function	(premature cardiovascular death)
Chronic bronchitis	? Atherosclerosis
Lung cancer	
Reduced life expectancy	
? Asthma onset	

10 µg/m³ increase in the daily levels of ambient particulate matter is approximately 0.5%, whereas inclusion of sub-acute effects leads to estimates three to four times larger. Particles have most often been used to characterise pollution, but gaseous pollutants almost certainly contribute to the risks. In fact, recent reviews have concluded that ambient ozone at levels usually observed during summer periods are associated with higher death rates, that are not explained by other pollutants or temperature [5].

Increases in daily levels of air pollution are also

correlated with higher hospital admissions and emergency room visits due to respiratory and cardiovascular events, including myocardial infarction, arrhythmias, and stroke [6]. Increased blood viscosity and blood pressure, decreased heart rate variability (HRV) and changes in the repolarisation patterns have all been shown to correlate with pollution. Moreover, discharges of implanted cardioverter-defibrillators (evidence of ventricular tachycardia and/or fibrillation) increase in an exposure-response manner with the daily level of ambient particulate matter [6].

Biologic mechanisms

Causality is supported by an increasing, albeit fragmentary, body of research that addresses biologic mechanisms of the observed effects [6, 7]. Evidence is strongest for (interrelated) pathways of action – namely, oxidative stress and inflammation, induction of a pro-coagulatory state, dysfunction of the autonomic nervous system, and ischaemic responses in the myocardium [2, 6]. The observation of ambient particulate matter in the heart muscle cells and the brain may also suggest diffusion of particles which may lead to direct toxic effects. In fact, studies with artificial ultrafine particles had demonstrated direct penetration into the blood stream [2].

Oxidative stress and inflammation: High concentrations of oxidants and pro-oxidants contained in ambient air pollution, such as particulate components of various sizes and compositions (eg ultrafine PM, transition metals, reactive organic compounds), and gases such as ozone (O₃) or nitrogen oxides (NO, NO₂) promote oxidative stress and respiratory inflammatory responses [7]. Mediated through cytokines and chemokines, the pulmonary responses also lead to sub-clinical systemic

inflammation with alterations in the vascular system. Moreover, inflammation itself is a potent source of oxidant stress which leads to DNA damage.

Autonomic function: Activation of pulmonary neural reflexes due to interactions between pollutants and lung receptors may initiate changes in the autonomic function and partly explain the observed cardiovascular effects. Studies show a rather immediate decrease in heart rate variability (HRV) after exposure to ambient particles, and the decreased parasympathetic input may explain the increase in arrhythmias and cardiovascular mortality associated with ambient pollution [6].

A recent panel study conducted among elderly highlights the complexity of interrelated mechanisms [8]. As shown before, Schwartz et al. observed a decrease in HRV with increasing pollution. However, effects were absent in subjects treated with statins – lipid-lowering and anti-inflammatory medication. Moreover, HRV was affected only among genotypes with reduced abilities to balance oxidative stress, namely those with the GSTM-null polymorphism.

Long-term cumulative effects of air pollution

The question arises whether and to what extent acute sub-clinical effects of air pollution may contribute to the long-term development of respiratory and cardiovascular diseases. Cohort studies are essential to address chronic exposure effects. The largest one, the American Cancer Society Study (ACS), followed some 150,000 adults over more than 15 years [9]. Investigators reported strong associations of long-term levels of ambient air pollution with cardiovascular death [9]. More sophisticated individual residential assignment of pollutants using geostatistical techniques led to considerably larger estimates such as a 24% change in cardiovascular death for a 10 µg/m³ contrast in long-term residential outdoor PM_{2.5} [10].

However, these mortality studies raise the question as to whether air pollution only triggers events among those with underlying susceptibilities due to other causes (eg COPD, diabetes, hyperlipidaemia, smoking) or whether air pollution contributes in a *sustained, chronic manner* to the long-term pathophysiologic processes that ultimately lead to morbidity and mortality, independent of the level of pollution at the time of the event. The much larger associations between pollution and death observed in cohort studies as compared to acute effect studies are suggestive but do not prove such chronic effects [9]. More proximal outcomes, namely chronic functional or structural changes and the incidence of chronic diseases need to be investigated to clarify this issue.

Cross-community comparisons have usually failed to see a clear association between asthma incidence or prevalence and urban air pollution, despite the known causal role of pollution in triggering attacks among asthmatics. The California Children Health Study suggests that high oxidant pollution may contribute to the onset of asthma

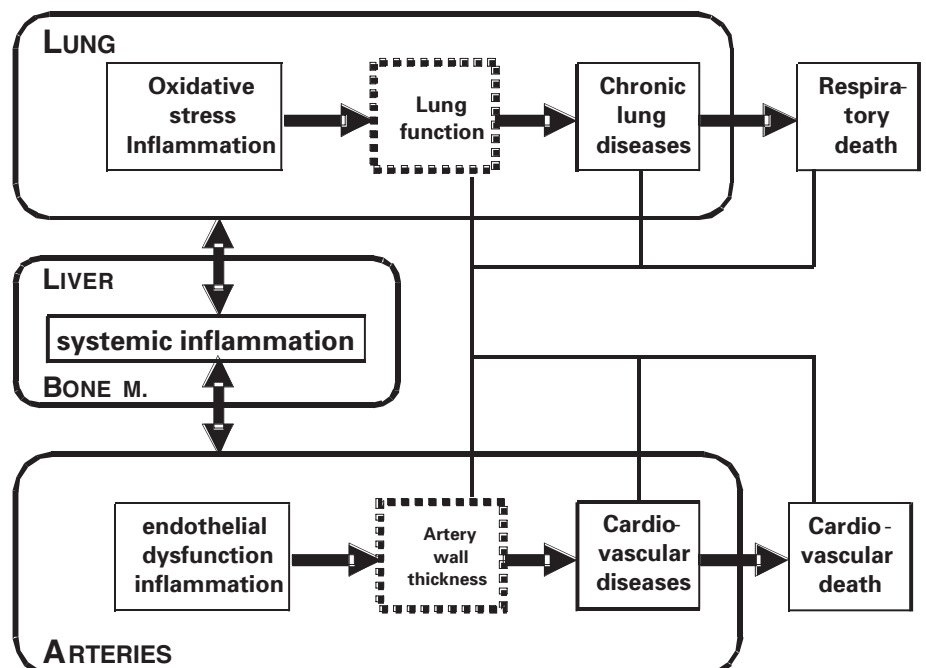
among children engaging in outdoor sports [11]. Recent studies observed higher asthma prevalence among children living along busy roads suggestive of a role of fresh exhaust pollutants in the development of asthma [12]. As shown by Gilliland et al. in a chamber study conducted with allergic patients, complex interactions of pollutants (diesel in this case), allergens, and genetic factors may be important in the genesis of this multifactorial complex disease [13].

The incidence of chronic bronchitis has been investigated in a Californian cohort study only, [14] whereas the Swiss cross-sectional findings of higher prevalence of bronchitis in communities with higher pollution cannot unambiguously distinguish acute from chronic effects [15]. Lung cancer is an established long-term consequence of ambient air pollution and exposure to traffic emissions may be of particular importance [16].

One of the most intriguing findings at the interface of chronic respiratory and cardiovascular diseases originates from investigations of associations between forced expiratory lung function (LF) and long-term exposure to ambient air pollution. Reduced lung capacity (FVC, FEV₁) is a well established marker of both respiratory and cardiovascular health. In fact, prospective studies show not only a very strong association between FEV₁ and respiratory death but also with the concomitant risks of hospitalisation and death due to cardiovascular causes. Thus, the finding in the 8-year follow-up of Southern Californian children showing lung growth being affected by ambient urban air pollution is very relevant [17]. Those growing up in the most polluted towns were left with substantial deficits at age 18. The cross-sectional results of the SAPALDIA study (age 18 to 65) with lower levels of LF in more polluted towns indicate

Figure 1

Model of the interrelated pulmonary, systemic, and vascular chronic inflammatory responses to air pollution. Lung function and artery wall thickness are examples of markers of the continuous chronic process from health to disease. (Thin lines denote correlations established in epidemiological studies).



that the functional deficit remains into adulthood. We observed significant associations between lifetime ambient ozone and pulmonary function among college students but studies on chronic effects of ozone are not consistent [18].

The repeated acute inflammatory insults observed in experimental and epidemiological studies may contribute to the long-term development and course of chronic diseases. The reduction in LF involves various mechanisms but systemic factors including systemic inflammation are likely to play a role as all major non-pulmonary inflammatory diseases – such as diabetes, metabolic syndrome, atherosclerosis, rheumatoid arthritis or bowel diseases – are associated with reduced LF [2]. We suggest the model shown in figure 1 to link acute effects with chronic pulmonary and cardiovascular ailments. The model puts local and systemic inflammation into the centre but other mechanisms may be relevant as well (eg direct toxic effects on DNA that lead to cell death). There is ample experimental and/or epidemiological evidence for all the links indicated with arrows and lines. Pulmonary inflammation sustains sub-clinical systemic inflammation, which plays a pivotal role in atherosclerosis as the primary underlying mechanism of cardiovascular morbidity and mortality. All outcomes shown in the model are known to be associated with smoking. Ambient air pollution may act on these same pathways, and breath-

ing urban air may be considered a continuous and non-voluntary type of “low grade” smoking with qualitatively similar long-term effects on chronic respiratory and cardiovascular diseases.

The link between air pollution-induced inflammation and atherogenesis has been investigated experimentally in rabbits [19]. Four-week exposure to ambient PM resulted in dose-dependent alveolar and systemic inflammatory responses and the progression of atherosclerosis in the coronary arteries and the aorta. The atherogenic effects were associated with the extent of PM phagocytosed by alveolar macrophages in the lung and coupled with an enhanced release of bone marrow monocytes. These precursors of macrophages play an important role in atherogenic inflammatory responses. So far, only one study investigated the association between ambient pollution and atherosclerosis in humans [20]. The study used baseline data from two clinical trials conducted in the Los Angeles area. Carotid intima-media thickness (CIMT), an established marker of atherosclerosis, was the primary outcome. Novel spatial models of ambient fine particle surfaces allowed the assignment of pollution concentrations to each participant's home. For a contrast of $10 \mu\text{g}/\text{m}^3$ in ambient PM_{2.5}, CIMT was approximately 4–5% thicker. These results open new avenues in the investigation of the link between air pollution, lung function and atherosclerosis (figure 1).

Four relevant open questions

Who is susceptible?

The tobacco disease epidemics have made it very clear that susceptibility to health effects related to airborne toxicant vary considerably among individuals. This paradigm is likely to hold for ambient air pollution as well. Studies suggest acute effects of air pollutants to be stronger among the elderly and subjects with preexisting diseases such as diabetes, asthma, chronic bronchitis, diagnosed cardiovascular diseases or a history of myocardial infarction, and, possibly, also among the obese. Of interest are interactions with genetic factors, in particular polymorphisms of genes that regulate the response to oxidative stress and inflammation [7]. The same polymorphisms that modify the effect of air pollution on HRV mentioned above [8] determine the atherogenic potential of smoking [21], and amplify the effect of in utero smoking on the occurrence of asthma and wheezing in offspring [22]. It remains to be shown whether all conditions that sustain sub-clinical systemic inflammation such as diabetes, metabolic syndrome, hypercholesteraemia, rheumatoid arthritis, or bowel diseases were to amplify effects of air pollution.

What pollutants and sources are most relevant?

The health consequences are unlikely to be the consequence of one or a few single pollutants but, more likely, are the result of the complex mixture of primary and secondary interacting constituents that lead to the observed effects through common (eg oxidant stress) and/or distinct (direct toxicity) pathways. Experimental studies are unable to mimic fully the ambient mixture, whereas epidemiological studies have limited capabilities to disentangle effects of specific constituents or sources of pollutants. Thus the question cannot be answered with any certainty [12]. A causal role of particles and of ozone can be inferred from many studies, whereas NO₂ may amplify effects of other pollutants or allergens [23]. The characterisation of exposure to traffic emissions has been improved considerably in recent studies; and it becomes increasingly apparent that living within 0–100 meters to the emissions from busy roads may impose a health threat [12, 24].

Is the magnitude of the reported risks relevant?

It is clear that current levels of air pollution lead to increases in adverse health effects (table 1)

of only a few percent or less across the typical ranges of ambient exposure observed in developed countries. This may mislead clinicians to consider air pollution an irrelevant issue. However, the size of the risk gradient is only one determinant of public health relevance. The number of people affected is the other key factor in the equation. Given no evidence for safe "thresholds of no effect" all people living in environments with ambient pollution above natural background are, in theory, exposed to some finite increased risk, conditional on susceptibility factors noted above. As a consequence, estimates of the public health burden of ambient air pollution are substantial. A tri-national European study attributed some 6% of all deaths and ~2% of hospital admissions to ambient air pollution [25], and studies not available at that time indicate that these rough estimates may have been conservative [10, 24].

Small shifts in the population mean of physiological markers such as blood pressure, lung function, or intima-media thickness (CIMT) ultimately translate into substantial changes in the number of people with clinically relevant conditions [26]. It has been estimated that a 10% increase in CIMT increases the risk for future myocardial infarction or stroke by approximately 15% [27].

Do reductions of ambient pollution concentrations reduce risk?

As a public health conclusion from the above, stringent clean air quality policies are required on both the national and international level to curb air pollution as a primary preventive strategy. An increasing body of "intervention-type" studies confirms that improvements in air quality, in fact, do lead to health benefits in the population. The 1991 coal ban in Dublin was followed by an immediate decline in pollution and a sustained ~10% decrease in cardiovascular mortality, corresponding to ~240–250 fewer cardiovascular deaths per year

[28]. Even subtle improvements in air quality as observed in Switzerland over the past 10 years led to reductions in respiratory symptoms among children [29], and preliminary findings of the SAPAL-DIA study suggest these air quality changes correlate with reduced age-related lung function decline rates in adults [30]. Lung growth of children moving into cleaner areas during the Children's Health Study follow-up also improved whereas those moving into more polluted communities experienced reduced growth rates [31]. A recent experiment has shown that a non-specific intervention such as a particle filter on a diesel engine, combined with the use of low sulphur diesel fuel can reduce drastically, if not eliminate, a myriad of pollutants and toxic reactions observed in the lungs of mice after exposure to diesel exhaust [32].

In summary, evidence is increasing that ambient air pollutants affect the autonomic nervous system and contribute to oxidative stress and systemic inflammation leading to cardio-respiratory effects [2]. This supports a causal interpretation of observations made in many epidemiological studies. Future research will need to clarify the life-time course of these effects, the relevance of cumulative exposure, as well as identify the most susceptible time periods and populations, and the pathophysiologic link between lung and cardiovascular ailments. Last but not least, pollution needs to be reduced, and air quality and health need to be monitored to be aware of trends and consequences.

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