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REVIEW

Air pollution as noxious environmental factor in the development of cardiovascular disease

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ABSTRACT

A strong epidemiological association has been revealed between air pollution and the occurrence of cardiovascular disease (CVD). Deleterious consequences of such pollution, including myocardial infarction and coronary ischaemia, have occurred after both acute as well as chronic exposure to air pollution. The causal pathophysiological mechanisms through which these effects occur have not been identified but potential pathways include endothelial dysfunction and systemic reactions such as inflammation and oxidative stress. Because of increasing urbanisation and associated anthropogenic activities, air pollution is considered an important topic in public health and it remains challenging to translate these epidemiological observations into clinical consequences and guidelines. Nevertheless, for the high cardiovascular risk population, air pollution might have direct clinical relevance. In the future, more knowledge is required about the absolute risk of air pollution in specific high-risk populations and the pathophysiological mechanisms behind this relationship.

KEYWORDS

Air pollution, atherosclerosis, cardiovascular

INTRODUCTION

Cardiovascular disease remains the principle cause of morbidity and mortality in Western countries as well as in the developing world. In the Netherlands, cardiovascular disease causes more than 40,000 deaths each year.[1] In addition to well-established risk factors (such as dyslipidaemia and hypertension), exposure to air pollution has attracted a lot of attention in the media for its relationship with coronary ischaemia. A number of reports have noted associations between air pollution and the development of cardiovascular disease, pulmonary cancer and chronic obstructive pulmonary diseases.[2-4] In line with these observations, the World Health Organisation (WHO) estimated that each year approximately 800,000 people die prematurely which could be attributed to air pollution worldwide.[5] Air pollution is thought to predominantly exacerbate cardiopulmonary disease that causes death. Dutch national authorities estimate that 2300 to 3500 individuals a year will exhibit premature all-cause mortality due to fine particles. In case of long-term exposure, these effects are even more pronounced with a one-year life reduction for 18,000 individuals.[6] Against this background, various epidemiological studies have shown that increased levels of air pollution could augment cardiovascular morbidity and mortality due to ischaemic events, more frequent hospitalisations, worsening of heart failure and (ventricular) arrhythmias and that these effects occur both due to daily changes in air pollutant levels as well as due to lifetime exposure.[7]

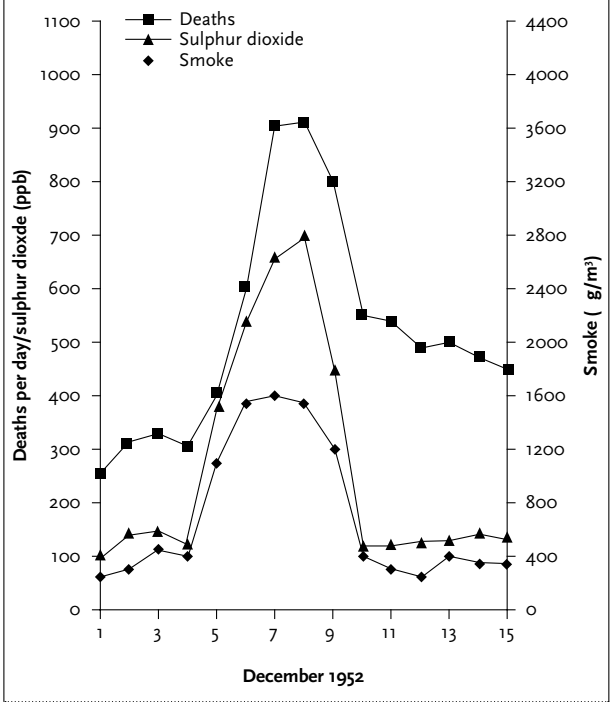
If air pollution has indeed become a relevant factor in the occurrence of cardiovascular disease, this should have worldwide consequences. Progressive dense urbanisation of distinctive regions is emerging globally with a concomitant increase in cardiovascular morbidity and mortality. This is also true for the urban regions on the African continent.[8] With this review, we aim to give an outline of current knowledge with regard to the relationship between air pollution and cardiovascular disease.

THE HISTORY OF AIR POLLUTION AND CARDIOVASCULAR DISEASE

The fact that air pollution could negatively affect human health is not just a current observation. In the past, various events have provided the first observations that air pollution

might have harmful effects on human health. The most well-known example is the impressive London fog episode in 1952 (*figure 1*). Between 5 and 9 December, an unusual dense fog covered the London area for four days. This was probably due to burning of large quantities of coal because of low temperatures combined with a diminished dispersing into the atmosphere of combustion products. Because of the subsequent high levels of atmospheric pollutants, about 4000 people died in the next two weeks as a consequence of both pulmonary and cardiovascular causes.[9] Similar events also occurred elsewhere. For example, in 1930, in the Meuse Valley in Belgium, one of the heaviest industrialised areas of that time, a period of severe fog led to a high prevalence of respiratory symptoms, retrosternal pain and early death among the population of the valley. A total of 60 deaths in the following three days were attributed to the fog and the subsequent marked rise in atmospheric pollutants.[10] These two different episodes became an important inspiration to execute additional studies into this phenomenon.

Figure 1. *The London fog 1952*



A four-day episode of severe fog led to increased levels of atmospheric pollutants and a subsequent rise in mortality during these days in London in 1952.
Source: http://www.ace.mmu.ac.uk/Resources/Fact_Sheets/Key_Stage_4/Air_Pollution/images/03a.jpg.

AIR POLLUTION AND CARDIOVASCULAR DISEASE

Exposure to air pollution has been associated with several adverse effects on human health including chronic obstructive pulmonary disease and pulmonary cancer. In the next paragraph we will focus on the cardiovascular effects of air pollution. Furthermore, we will limit our discussion to recently published studies on this topic with a special attention to the Western European region.

Short-term exposure

Several studies have shown a strong association between acute exposure to high levels of air pollution and the occurrence of acute coronary ischaemia. Within this perspective, short-term exposure refers to a few hours' exposure to high levels of air pollution, for instance a day with bad air quality day or a walk near a busy road.

Short-term exposure to various air pollutants could trigger the onset of ischaemic events. For instance, Peters *et al.* showed that exposure to high levels of $PM_{2.5}$ (particulate matter with diameter <2.5 μm) as well as a high traffic volume for only one or two hours could trigger the onset of a myocardial infarction.[11,12] In a study by Mills *et al.*, 20 male patients with a prior myocardial infarction were exposed to either dilute diesel exhaust (particulate matter 300 μg/m³) or filtered air in a controlled exposure chamber, while performing moderate exercise.[13] Heart rate increased equally during exercise in both groups. However, in the diesel-exposed group they documented significantly more ischaemic burden (defined as the depth multiplied by the duration of ST-segment depressions on 12-lead ECGs). The exposure in this study of 300 μg is not exceptional since concentrations of particulate matter can reach this level in heavy traffic, in occupational settings or in large cities. Within the Netherlands, the maximum peak levels of particulate matter that are measured by air quality stations are about 120 μg/m³. However, it is noteworthy that this peak level is a mean concentration over 24 hours. To translate this condition to that measured in the Mills' study one may assume that a one-hour exposure to 300 μg/m³ will increase your 24 hour accumulated exposure by only 12.5 μg/m³. Of importance, the day-to-day variation of particulate matter levels can vary between 10 and 15 μg/m³ on ordinary days. Thus, within this perspective, one hour exposure to 300 μg/m³ (Mills' study) is not excessively high, but apparently sufficient to induce coronary ischaemia.[13]

In addition to morbidity, short-term exposure is also associated with cardiovascular mortality. In the Air Pollution and Health: a European Approach 2 (APHEA2), a large European time-series study in 29 cities, the authors showed that each 10 μg/m³ increase of PM_{10} (particulate matter with diameter <10 μm) concentration was associated with an increase in non-accidental mortality of 0.68% (95% confidence interval [CI] 0.6 to 0.8%).[14] Differentiation in cause-specific mortality showed an increase of 0.76% (95% CI 0.47 to 1.05%) in cardiovascular deaths and 0.58% (95% CI 0.21 to 0.95%) in respiratory

deaths for each 10 μg/m³ increase in PM_{10} concentration.[15] In the Dutch region, PM_{10} levels are acknowledged to have a day-to-day and inter-regional variation of up to 20 μg/m³ and this increase in PM_{10} levels may indeed contribute to differences in morbidity and mortality rates.

Long-term exposure

Not only short-term exposure but also chronic exposure could effect the development of cardiovascular disease. Within this perspective, chronic exposure refers, for instance, to subjects who lived for months or years near heavy traffic roads or in areas with enduring high levels of air pollution such as large cities. A German study showed that a higher prevalence of clinically manifest CVD was present in those subjects who lived within 150 metres of a major road.[16] After adjusting for background air pollution and other conventional cardiovascular risk factors, the relative risk of future CVD was 1.85 (95% CI 1.21 to 2.84). In support of these epidemiological observations, people who live near a major road displayed more coronary artery calcifications: living within 50 metres, 51 to 100 metres and 101 to 200 metres was associated with odd ratios of 1.63 (95% CI 1.14 to 2.33), 1.34 (95% CI 1.00 to 1.79), and 1.08 (95% CI 0.85 to 1.39), respectively, for marked coronary artery calcification (defined as more than the 75th percentile for age and gender assessed by electron-beam computed tomography).[17] In addition to cardiovascular morbidity, long-term exposure to air pollution is also associated with cardiovascular mortality. A large Dutch cohort study showed that living near a major road (within 100 metres of a freeway or within 50 metres of a major urban road) was related to total mortality (relative risk 1.41, 95% CI 0.94 to 2.12) and an even more significant relationship was found with cardiopulmonary mortality (relative risk 1.95, 95% CI 1.09 to 3.52).[18] Noteworthy, positive associations between background concentrations of air pollution and mortality were less pronounced than those for traffic-related air pollution and mortality indicating that traffic per se might be an important source of the occurrence of harmful health effects.

AIR POLLUTION IN THE NETHERLANDS

Although air quality in general has improved significantly over the past few decades,[19] harmful effects on human health (with major manifestations for lung and cardiovascular disease) have also been reported under current air pollution levels. With the aim to reduce those negative health effects, several initiatives under the aegis of the European Union were launched to set limit levels for distinctive components from which air pollution is composed (*table 1*). Nevertheless, upper limits are frequently surpassed in almost all large European cities, including the Dutch.

Table 1. *Air quality limit values in the European region*

	Current		2015-2020	
	Daily	**Annual**	**Daily**	**Annual**
PM10	50 μg/m³*	40 μg/m³	50 μg/m³*	40 μg/m³
PM2.5	-	-	-	25 μg/m³

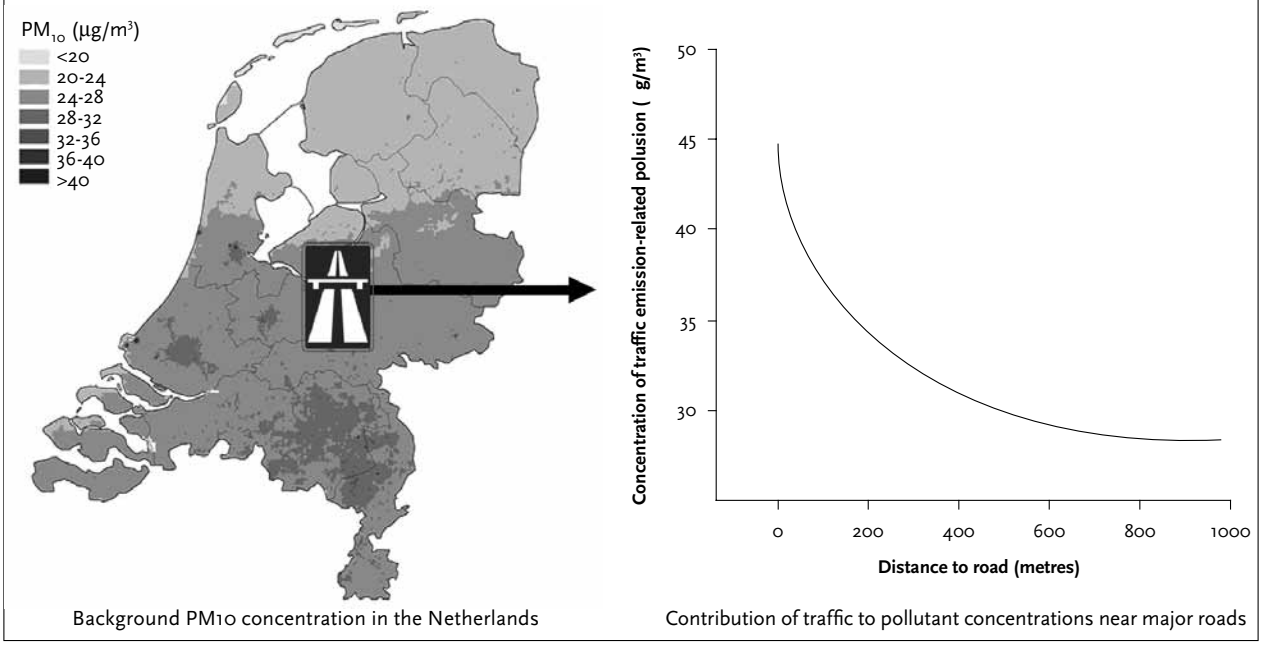
*Allowed to exceed on 35 days per year. Current and future daily and annual limit values as estimated by the European Union for particulate matter. Exceedence of daily limit value for PM10 is allowed on 35 days per year with an annual limit value of 40 μg/m³. In the current values there is no limit set for PM2.5.

Recent analyses have identified harmful environments with regard to air pollution densities. In heavy traffic, occupational settings and in the world's largest cities, particulate matter levels up to 400 μg/m³ have been documented.[19] Due to dense urbanisation, larger areas in the Netherlands, Belgium, Germany and Italy will suffer from higher levels of air pollution than areas in other parts of Europe. In most regions in the Netherlands, limits of air quality raise frequently with PM_{10} (particulate matter with diameter <10 μm) peak levels above 100 μg/m³.[20]

Interesting in the dilemma of air pollution is the aspect of its crossing of national borders. For instance, in the Netherlands, 30% of all airborne fine particles find their origin in nature (e.g. sea salt, soil dust), whereas 20% consist of anthropogenic origin that is generated in our own region (e.g. industries, refineries, agriculture). The remaining 50% have a foreign anthropogenic origin.[21] Only intensive international collaboration could therefore result in significant improvements in air quality and, as a consequence, health.

Furthermore, air pollution concentrations and the contribution of different sources can differ between different seasons; in the Dutch region, elevated particulate matter concentrations have been found in the winter, probably due to an increased contribution from traffic. In contrary, higher sulphate levels have been measured in the summer, because sulphate originates from oxidation of SO_3 by a photochemical process. Also, most days with severe smog (O_3 >240 μg/m³) have been recorded on summer days with a temperature of more than 25°C.[22] These observations are of special interest because in areas with high urbanised regions (for instance in the Netherlands), the average level of ambient air particles (as part of background pollution) is equally spread with only small variations with regard to different isolines. As a consequence, air samples taken from sites near a high volume traffic road most accurately reflect the long-term exposure to air pollution for an individual in that area (*figure 2*).

Figure 2. *Background and traffic-related air pollution concentrations in the Netherlands*



Background PM10 concentration in the Netherlands

Contribution of traffic to pollutant concentrations near major roads

BIOLOGICAL EFFECTS OF AIR POLLUTION

In order to explain these long- and short-term epidemiological observations regarding the relationship between air pollution and cardiovascular morbidity and mortality, the pathophysiology has not been elucidated as of yet. Potential mechanisms include increased oxidative stress, systemic inflammation, endothelial dysfunction, pro-atherothrombosis, hypertension and autonomic dysfunction.[23-27] Despite these numerous mechanisms, one may assume a different mechanism for the harmful biological effects of acute versus chronic exposure. Short-term exposure especially exerts endothelium-mediated processes (such as impaired vasodilatation and more coronary vasoconstriction) and an increase of sympathicotonus.[26] In healthy volunteers, these effects persist until 24 hours after exposure.[28] In long-term conditions systemic responses (e.g. oxidative stress, hypertension, inflammation) are more dominant.

It is unknown whether systemic effects of air pollution could be explained by pulmonary inflammation or by translocation of specific air borne particles from the alveolar space into the circulation.[29] In case of the last option, airborne particles could be part of micellar structures (lipophilic compounds), while hydrophilic airborne compounds circulate in aqueous solution. Currently, we are evaluating whether lipophilic airborne structures could be carried by large lipoproteins, such as chylomicrons and VLDL, and whether these loaded lipid particles could be deposited in the vessel wall with subsequent generation of atherogenic cascades (Trojan horse hypothesis).[30]

WHAT ARE THE LESSONS FOR CLINICAL PRACTICE?

Despite the strong relationship between acute and chronic air pollution levels and the occurrence of cardiovascular morbidity and mortality,[31] a major question remains as to the extent to which air pollution can account for significant changes in clinical conditions.

Nowadays, the estimated risk of cardiovascular disease for patients without previous CVD is based upon the presence of conventional risk factors including sex, age, smoking and systolic blood pressure.[32] In the near future, we should define to what extent air pollution adds to this individual cardiovascular risk profile and its ranking among the more conventional risk factors. From actual knowledge, it is plausible that a high exposure to air pollution might have an exaggerated effect on the development of complicated cardiovascular disease in those patients in whom one or more conventional risk factors are present or in those with previous CVD. Whether air pollution potentiates residual cardiovascular risk or has a positive interaction with conventional risk factors is not thoroughly elucidated yet.

Several clinical and epidemiological observations showed that the effects of air pollution might be more pronounced in patients with coronary artery disease, congestive heart failure or respiratory disease.[13,33] For instance, a recent observation in 12,865 North-American patients after a previous cardiac catheterisation showed that an increase of 10 µg $PM_{2.5}$ per cubic metre was associated with a 4.5% (CI 1.1 to 8.0) increased risk on acute ischaemic coronary

events.[34] Interestingly in their analysis was the fact that the most significant associations were found for that $PM_{2.5}$ exposure on concurrent and previous day, indicating a per acute effect of ambient fine particulate pollution on the presentation of ischaemic heart disease in patients with existing coronary heart disease. That study and a supportive one[11] convincingly show that a 10 to 25 $\mu g/m^3$ increase in $PM_{2.5}$ particles could be defined as a high-risk environment for patients after a (recent) coronary event or those with an increased cardiovascular risk profile. Indeed, the time subjects spent in their cars, on public transportation, or on their motorcycles or their bicycles was consistently linked with an increased myocardial infarction risk (onset of myocardial infarction one hour later) in patients who are susceptible for coronary heart disease.[12] In line with these observations, we recommend avoidance of environmental conditions in which an increase of 10 to 25 µm in $PM_{2.5}$ per cubic metre can be expected by regional weather forecasts for especially those patients after a (recent) ischaemic coronary event or those with an increased cardiovascular risk profile.

Discouraging these patients to travel outside in case of significant levels of air pollution or spending time in urban regions with a high dense fine particulate matter level in certain seasons (for instance the Athens region during summer time) will have several consequences for the clinical physicians and their advice for healthcare-related organisations. More initiatives concerning education should be developed for practising physicians to make them more aware of these associations, so they can advise their patients in creating the optimal living conditions. Complementary efforts should be expected from local and national governments with realisation of estate projects and measurements for appropriate inner house air quality. To support these last remarks, a Swedish study recently revealed these hazardous situations; increased levels of PM_{10} in a preceding two-hour exposure period gives rise to more ventricular arrhythmias in patients carrying an ICD.[35] Indeed, Berglind and colleagues have just published the results from a European multicentre study which showed that increased ambient air pollution was related with increased daily mortality in survivors from a myocardial infarction.[31] Of subsequent interest is whether patients with a specific profile (prone to develop ventricular arrhythmias for instance, first weeks after MI or in the presence of unstable angina), presence of certain weather conditions, living in the proximity of a road or being female with an age >60 years should be advised to change environment for a stay in a health resort for a certain period of time. Comparable beneficial effects on cardiovascular health have previously been attained in other conditions linked to air pollution; partners who stopped smoking reduced cardiovascular morbidity and mortality in passive (second hand) smokers, urban regions at the African continent had higher numbers for cardiovascular disease compared with their rural regions and living in a natural (green) environment decreased all-cause mortality, including from cardiovascular causes.[36] Finally, a recent analysis based on the correlation between reductions in particulate air pollution over the past few decades and increased life expectance in 217 counties in 51 metropolitan areas in the United States showed that a decrease of $PM_{2.5}$ of 10 $\mu g/m^3$ is associated with an increase in life expectancy of 0.61 (±0.20) year representing 15% of the overall increase in life expectancy in the study areas. These results were constant after adjustment for changes in socioeconomic, demographic, and smoking patterns over the same period.[37] Similar reductions in life expectancy have been estimated for the Netherlands[38] and these findings underline the importance of air pollution on human health.

CONCLUSION

Air pollution is an ecological and social dilemma in the Western world. In earlier times, several social movements, backed up by medical doctors, realised a change in environmental factors with, subsequently, a dramatic reduction in infectious disease. Currently, similar actions are required with regard to air pollution.

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