

Air pollution and cardiovascular disease: the Paul Wood Lecture, British Cardiovascular Society 2021

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ABSTRACT

Air pollution is associated with up to 8.8 million excess deaths worldwide each year and is a major contributor to the global burden of disease. Cardiovascular conditions are the predominant cause for air pollution-related deaths and there is an urgent need to address the silent pandemic of air pollution on cardiovascular health. Air pollution exposure is associated with acute events like acute coronary syndrome and stroke, and with chronic conditions, such as atherosclerosis and heart failure. Several potential mechanisms have been proposed that link particle inhalation to cardiovascular disease including oxidative stress and inflammation, changes in autonomic balance and neuroendocrine regulation and the particle translocation into the circulation itself. This, in turn, can cause endothelial, vasomotor and fibrinolytic dysfunction and increased thrombogenicity and blood pressure which are implicated in the mediation of adverse cardiovascular events. Certain interventions can help mitigate these adverse effects. At an individual level, this includes the use of a facemask and indoor air purification systems. At an environmental level, interventions reducing the generation or release of combustion-derived pollutants are key and include public health policies to facilitate active transport, cleaner sources of energy and reductions in vehicular and fossil fuel emissions. In this review, we summarise the key pathways and mechanisms that draw together how air pollution can lead to adverse cardiovascular effects, as well as explore potential interventions to reduce the burden of air pollution-induced cardiovascular morbidity and mortality.

INTRODUCTION

Air pollution is a leading cause of mortality worldwide and is responsible for up to 8.8 million deaths globally (11.6% of all global deaths).¹ Historical examples of the dramatic health consequences of air pollution include the Great London Smog of 1952 (figure 1), which killed approximately 12 000 people.² This event altered how countries viewed and responded to air pollution. A number of legislative changes came into effect after this event including the United Kingdom Clean Air Act of 1956. Important interventions, such as the ban on coal sales in Dublin in 1990, have been shown to prevent over 8000 excess deaths.³ However, despite these new laws, air pollution and its associated mortality has continued to rise, with 90% of the world's population living in areas of air pollution above the limits recommended by WHO.⁴ Ambient (outdoor) air pollution has

been ranked as the sixth highest risk factor for disability-adjusted life-years and fifth for overall mortality.⁵ There are many professionals that are exposed to pollutants at work such as firefighters, road workers and farm labourers, and occupational air pollution exposure affects a substantial number of individuals worldwide. However, this is beyond the remit of this review and is not discussed further here.

Although respiratory effects of air pollution are well recognised, cardiovascular conditions are the predominant cause of mortality accounting for 40%–60% of premature air pollution-related deaths.⁵ In this short review, we discuss the key cardiovascular conditions associated with air pollution and the mechanisms by which particle inhalation can lead to cardiovascular effects.

WHAT IS AIR POLLUTION?

Ambient air pollution is a complex mixture of thousands of chemicals that encompass solid and liquid particles, hydrocarbons, metals and various gases, such as ozone, nitrogen oxides, volatile organic compounds and carbon monoxide. The composition varies according to the sources of pollution and the atmospheric conditions. The associations between air pollution and cardiovascular events tend to be most strongly associated with airborne particulate matter (PM).⁶ PM is categorised according to size and includes PM₁₀ (particles with a diameter of <10 µm), PM_{2.5} (<2.5 µm) and ultrafine PM_{0.1} (<100 nm) or 'nanoparticles'.

The mass of PM₁₀ and PM_{2.5} has generally fallen over the last 60 years in many European countries. However, over the same time period, there has been a steady increase in road traffic vehicles, the exhaust of which is rich in nanoparticles. Nanoparticles contribute little to the mass of PM, thus while the PM mass is falling in our environment, the same is not necessarily true of particle number and their surface area. Thus, combustion-derived nanoparticles generated by the present-day traffic are not adequately measured by the current stationary monitoring network that measures PM₁₀ and PM_{2.5}. Nanoparticles are believed to be particularly harmful due to their large reactive surface area with which they interact with cells and carry relatively large amounts of harmful chemicals. Because of their incredibly small size, they are also able to penetrate deep into the lung and from here, they can potentially gain access to the circulation and wider human body.



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Figure 1 The Great London Smog, 1952.

AIR POLLUTION AND ASSOCIATED CARDIOVASCULAR CONDITIONS

The adverse effects of air pollution on cardiovascular health have been established through several epidemiological and observational studies (examples given in [table 1](#)).

Coronary artery disease

Coronary artery disease is the number one cause of mortality and disability affecting 197.2 million individuals worldwide.⁷ Air pollution is now a well-recognised risk factor for coronary artery disease.

A systematic review and meta-analysis found that $PM_{2.5}$ along with nitrogen dioxide, sulfur dioxide and carbon monoxide were associated with an increased risk of myocardial infarction.⁸ The European Study of Cohorts for Air Pollution Effects showed a 13% relative increase in non-fatal acute coronary events for every $5 \mu\text{g}/\text{m}^3$ increase in long-term exposure to $PM_{2.5}$.⁹ A population-based prospective study in 4494 participants analysing the effect of residential traffic exposure and coronary atherosclerosis showed that long-term residential exposure was associated with coronary artery calcification.¹⁰ After adjusting for individual risk factors, halving the distance between a major road and residence was associated with a 7% increase in coronary artery calcification. Similarly, long-term residential exposure to $PM_{2.5}$ was associated with a 5.9% increase in carotid intima-media thickness.¹¹ These studies established the link between long-term air pollution and standard quantitative measures of atherosclerosis.

Air pollution exposure is associated with coronary artery disease and with acute coronary events. Peters *et al* conducted a case-crossover study to evaluate whether traffic exposure was linked to acute myocardial infarction. The odds ratio (OR) for exposure to traffic 1 hour before a myocardial infarction was 2.73 (95% CI 2.06 to 3.61) after adjustment for confounders such as exertion.¹²

Cerebrovascular disease

Cerebrovascular disease is one of the leading causes of death and long-term disability affecting 101.5 million people globally.⁷ Evidence suggests that air pollution increases the risk of stroke.

One of the earliest studies investigating the link between stroke and air pollution was a time-series study from South Korea which concluded that PM_{10} and gaseous pollutants, such as ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide, were major risk factors for mortality following acute stroke.¹³ More recently, the Northern Manhattan study, reported that residential proximity to a major roadway was associated with a 42%

higher relative risk of incident ischaemic stroke.¹⁴ In a systematic review and meta-analysis of 94 studies across 28 countries, we have reported a 1% absolute increase in the risk of admission to hospital due to stroke, and stroke-associated mortality for every $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ and PM_{10} (relative risk: 1.01 and 1.004, respectively).¹⁵ The Women's Health Initiative study of 65 893 postmenopausal women without previous cardiovascular disease reported a dramatic 35% increase in the relative risk of cerebrovascular events, and an 83% increase in the relative risk of death from cerebrovascular causes per $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$, after adjusting for known risk factors such as age, smoking status, body mass index, hypertension and diabetes mellitus.¹⁶ Furthermore, prestroke exposure to PM_1 and $PM_{2.5}$ is associated with an increased risk of recurrent stroke events (HR with 95% CI PM_1 : 1.05 (1.02 to 1.09); $PM_{2.5}$: 1.03 (1.00 to 1.06)).¹⁷

Heart failure

Heart failure represents the final shared pathway for many cardiac diseases. Current worldwide prevalence of heart failure is estimated at 64 million cases accounting for the loss of nearly 10 million disability-adjusted life-years.¹⁸

Increases in PM concentration are linked with heart failure hospitalisations and deaths. An English cohort study found associations between long-term exposure to PM and nitrogen dioxide with the development of heart failure.¹⁹ In a systematic review and meta-analysis of 35 studies, a short-term increase in gaseous and particulate pollutants was associated with adverse heart failure outcomes that included hospitalisation and death.²⁰ A $10 \mu\text{g}/\text{m}^3$ increase in the concentrations of $PM_{2.5}$ and PM_{10} was associated with 2.12% and 1.63% increase in the risk of heart failure hospitalisation or death respectively, and the strongest associations were seen on the day of exposure compared with 24–48 hours after exposure.²⁰ A more recent time-stratified case-crossover study of 105 541 patients hospitalised for chronic heart failure across 26 large Chinese cities reported that an inter-quartile range (IQR) increase in $PM_{2.5}$ and PM_{10} corresponded to a 1.2% and 1.3% absolute increase in hospitalisations due to heart failure, respectively.²¹

Other cardiovascular conditions

Other cardiovascular conditions linked to air pollution include arrhythmias and cardiac arrest. In an analysis of four observational studies, a $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ was associated with 0.89% increase in the risk of atrial fibrillation.²² Similarly, in a systematic review of eight studies, Teng *et al* reported a 2%–7% increase in the risk of out-of-hospital cardiac arrest with PM exposure.²³ However, there is currently no strong evidence linking ventricular arrhythmogenesis to air pollution.

FROM PARTICLE INHALATION TO THE CARDIOVASCULAR SYSTEM

There has been speculation regarding how air pollution and particle inhalation can lead to detrimental cardiovascular effects ([figure 2](#)) and various theories have been proposed. We here provide a brief overview of these theories.

Oxidative stress and inflammation

Acute and chronic lung inflammation are risk factors for cardiovascular disease. Common air pollutants like oxides of nitrogen, ozone and PM all share a common property of being pro-oxidant. Exposure to these pollutants can cause oxidative stress via a plethora of cellular mechanisms including uncoupling of

Table 1 Examples of studies investigating association of air pollution with different cardiovascular conditions

Study	Study design and follow-up duration (if applicable)	Participant number/number of studies included and study/participant characteristics	Major findings
Mustafic <i>et al</i> ⁸	Meta-analysis	34 studies	<ul style="list-style-type: none"> ▶ An increase in the concentration of all the main pollutants by 10 µg/m³ was significantly associated with an increased risk of MI (carbon monoxide: 1.048; 95% CI 1.026 to 1.070; nitrogen dioxide: 1.011; 95% CI 1.006 to 1.016; sulfur dioxide: 1.010; 95% CI 1.003 to 1.017; PM₁₀: 1.006; 95% CI 1.002 to 1.009 and PM_{2.5}: 1.025; 95% CI 1.015 to 1.036).
ESCAPE study, Cesaroni <i>et al</i> ⁹	<ul style="list-style-type: none"> ▶ Prospective cohort study and meta-analysis ▶ Median follow-up: 11.5 years 	100 166 participants with no baseline coronary artery disease, enrolled between 1997 and 2007	<ul style="list-style-type: none"> ▶ A 5 µg/m³ increase in PM_{2.5} was associated with 13% increased risk of coronary events (HR 1.13, 95% CI). ▶ A 10 µg/m³ increase in PM₁₀ was associated with 12% increase in coronary events (HR 1.12, 95% CI).
Hoffman <i>et al</i> ¹⁰	Population-based, prospective study	4494 participants (age 45–74 years) from Heinz Nixdorf Recall cohort study	<ul style="list-style-type: none"> ▶ Participants living within 50, 51–100 and 100–200 m of a major road had ORs (95% CI) of 1.63, 1.34 and 1.08, respectively for a high coronary artery calcification (assessed by CT), compared with participants living >200 m away from a major road. ▶ A reduction in the distance between the residence and a major road by half was associated with a 7.0% increase in coronary artery calcification.
Kunzli <i>et al</i> ¹¹	Cross-sectional study	798 participants, healthy men and women >40 years of age with biomarkers (elevated LDL cholesterol or homocysteine) that suggested increased risk of future cardiovascular disease	<ul style="list-style-type: none"> ▶ For a 10 µg/m³ increase in PM_{2.5}, the CIMT increased by 5.9% (95% CI 1% to 11%). ▶ The association of PM_{2.5} and CIMT was highest in women aged >60 years (15.7%, 95% CI 5.7% to 26.6%).
Peters <i>et al</i> ¹²	Case crossover study	691 participants. Participants had a confirmed MI and had survived for at least 24 hours post-MI	<ul style="list-style-type: none"> ▶ Exposure to traffic was associated with an increase by a factor of 2.60 to 3.94 in the risk of onset of MI within 1 hour (OR 2.92, 95% CI, p<0.001).
Hong <i>et al</i> ¹³	<ul style="list-style-type: none"> ▶ Time series study ▶ Duration of the study: 4 years 	Not applicable	<ul style="list-style-type: none"> ▶ An increase in PM₁₀ concentration was associated with an increase of 1.5% (95% CI 1.3% to 1.8%) in stroke mortality. ▶ Stroke mortality increased by 3.1% (95% CI 1.1% to 5.1%) for an increase in nitrogen dioxide, 2.9% (95% CI 0.8% to 5.0%) for an increase in sulfur dioxide and 4.1% (95% CI 1.1% to 7.2%) for an increase in carbon monoxide.
The Northern Manhattan (NOMAS) study, Kulick <i>et al</i> ¹⁴	<ul style="list-style-type: none"> ▶ Population-based cohort study ▶ Follow-up duration: 15 years 	3287 participants. Participants were over 40 years of age, with no history of clinical stroke	<ul style="list-style-type: none"> ▶ Participants living <100 m from a roadway had a 42% (95% CI 1.01 to 2.2) higher rate of ischaemic stroke versus those living >400 m away. ▶ This association was more pronounced among non-smokers (HR 1.54; 95% CI 1.05 to 2.26) and not evident among smokers (HR 0.69, 95% CI 0.23 to 2.06).
Shah <i>et al</i> ¹⁵	Systemic review and meta-analysis	94 studies with 6.2 million events across 28 countries	Admission to hospital for stroke or related mortality was associated with an increase in concentrations of PM _{2.5} (1.011 per 10 µg/m ³ , 95% CI 1.011 to 1.012) and PM ₁₀ (1.003 per 10 µg/m ³ , 95% CI 1.002 to 1.004).
Women's health initiative study, Miller <i>et al</i> ¹⁶	<ul style="list-style-type: none"> ▶ Population-based cohort study ▶ Median follow-up: 6 years 	65 893 postmenopausal women without previous cardiovascular disease	For each increase of 10 µg/m ³ in PM _{2.5} , there was a 35% increase in risk of cerebrovascular events and 83% increase in risk of death from cerebrovascular events.
Atkinson <i>et al</i> , 2013 ¹⁹	Retrospective cohort study	836 557 patients from a cohort study aged between 40 and 89 years	An interquartile change in PM ₁₀ and nitrogen dioxide (3.0 and 10.7 µg/m ³ , respectively) both produced an HR of 1.06 (95% CI 1.01 to 1.11) after adjusting for confounding factors.
Shah <i>et al</i> ²⁰	Systematic review and meta-analysis	35 studies	Heart failure hospitalisation or death was associated with increases in carbon monoxide (3.52% per 1 ppb, 95% CI 2.52 to 4.54), sulfur dioxide (2.36% per 10 ppb, 95% CI 1.35 to 3.38), nitrogen dioxide (1.70% per 10 ppb, 95% CI 1.25 to 2.16), PM _{2.5} (2.12% per 10 µg/m ³ , 95% CI 1.42% to 2.82%) and PM ₁₀ (1.63% per 10 µg/m ³ , 95% CI 1.20 to 2.07).
Liu <i>et al</i> ²¹	Time series study	105 501 heart failure hospitalisations from 26 large Chinese cities	An IQR increase in PM _{2.5} , PM ₁₀ , sulfur dioxide, nitrogen dioxide, carbon monoxide and ozone concentrations on the day corresponded to 1.2% (95% CI 0.5% to 1.8%), 1.3% (0.5% to 2.0%), 1.0% (0.2% to 1.7%), 1.6% (0.6% to 2.5%), 1.2% (0.5% to 1.9%) and 0.4% (0.9% to 1.7%).
Shao <i>et al</i> ²²	Meta-analysis	461 441 participants from 4 studies	There was a statistically significant association between atrial fibrillation development and all gaseous pollutant as well as PM _{2.5} (nitrogen dioxide: 1.19% (95% CI 0.70% to 1.67%), carbon monoxide: 0.60 (0.20 to 1.09), sulfur dioxide: 0.90 (0.60 to 1.28), ozone: 1.09 (0.20 to 1.86), PM _{2.5} : 0.89 (0.20 to 1.57)).

Continued

Table 1 Continued

Study	Study design and follow-up duration (if applicable)	Participant number/number of studies included and study/participant characteristics	Major findings
Teng <i>et al</i> ²³	Meta-analysis	8 studies	<ul style="list-style-type: none"> ▶ An increase of out-of-hospital cardiac arrest risk ranged from 2.4% to 7% per interquartile increase in average PM exposure on the same day and up to 4 days prior to the event. ▶ The strongest risk OR of 3.8%–4.6% per 20 ppb ozone increase of the average level was within 2 hours prior to the event.

CIMT, carotid intima-media thickness; ESCAPE, European Study of Cohorts for Air Pollution Effects; MI, myocardial infarction.

nitric oxide synthetase (producing reactive nitrogen species), mitochondrial dysfunction and formation of reactive oxygen species.²⁴ Reactive oxygen and nitrogen species, in turn, act as site-specific and central mediators of inflammation, often amplifying the effects of each other. Prolonged exposure to air pollution leads to a chronic low-level inflammation in the lungs.²⁵ Furthermore, inflammatory and oxidative stress markers can be detected in the blood after air pollution exposure.²⁶ Systemic inflammatory mediators can, in turn, interact with the atherosclerotic process, leading to their progression, destabilisation or rupture of plaques and subsequent acute coronary or cerebrovascular syndromes.²⁷ Evidence from studies in mice suggests that upregulation of the pulmonary antioxidant barrier, due to overexpression of extracellular superoxide dismutase (an enzyme responsible for breaking down superoxide free radicals), may lessen the adverse systemic vascular effects of air pollution, suggesting that pulmonary oxidative stress may be critical in modulation of systemic responses to air pollution.²⁸

Changes in autonomic balance or neuroendocrine regulation

Adaptive stress responses are mediated via neuroendocrine sympathetic adrenal medullary and hypothalamic-pituitary-adrenal axes affecting the autonomic nervous system in all living organisms. Ying *et al* observed that exposure to concentrated ambient PM_{2.5} in mice is associated with an increase in

basal blood pressure and urinary norepinephrine excretion. This increase in basal blood pressure was attenuated by the centrally acting α_{2a} agonist guanfacine, suggesting a role of increased sympathetic tone in PM exposure-induced hypertension.²⁹ Another study demonstrated that diesel exhaust particles exacerbate the damage caused by myocardial ischemia in rats, an effect that can be prevented by pharmacological inhibition of the autonomic nervous system.³⁰

Similar effects have been seen in humans. Li *et al* found higher blood pressure and plasma concentrations of stress hormones, such as corticotrophin-releasing hormone and adrenocorticotrophic hormone, in healthy individuals exposed to higher PM_{2.5} concentrations.³¹ Across numerous studies, exposure to PM_{2.5} is associated with a reduction in heart rate variability and an increase in blood pressure, suggesting a reduction in parasympathetic activity and an increase in the sympathetic activity in response to air pollution.³² Indeed, Rankin *et al* observed that short-term acute exposure to diesel exhaust causes a rapid increase muscle sympathetic nerve activity in healthy volunteers. This provides further support for the hypothesis that sympathetic nervous system modulation underlies some of the cardiovascular effects of air pollution.³³

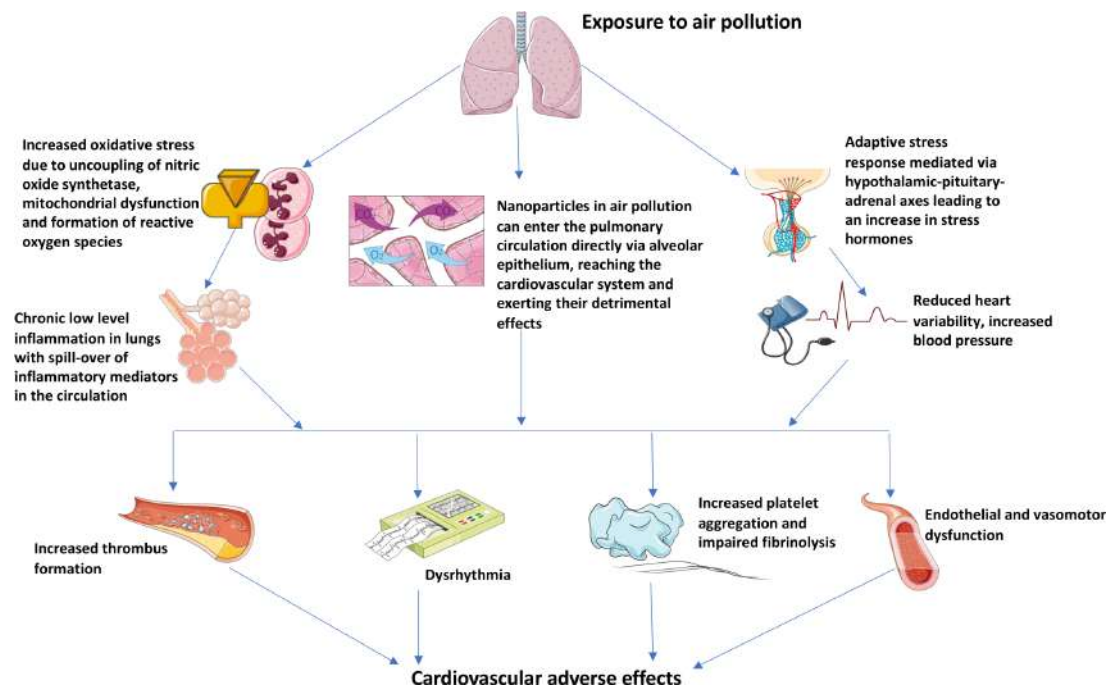


Figure 2 Mechanisms underlying cardiovascular adverse effects due to air pollution.

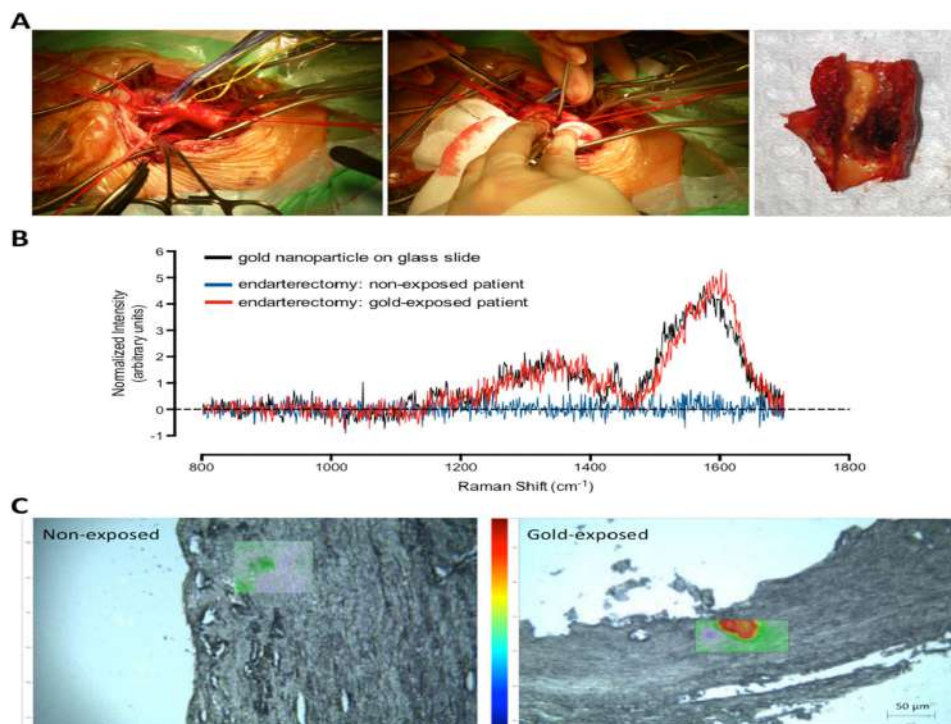


Figure 3 Gold nanoparticles exposure in patients undergoing carotid endarterectomy. (A) Isolation of atherosclerotic plaque from the carotid artery. (B) Overlaid representative Raman spectroscopy spectra: black=silver-stained endarterectomy sample from non-exposed patient, and red=silver-stained endarterectomy sample from gold-exposed patient. (C) Visualisation of gold in endarterectomy samples using heat map of Raman intensity. Highlighted box within tissue denotes scanned area, with blue-green colour representing baseline intensity (no gold) and red colour showing high Raman intensity (gold particulate).³⁶

Particle translocation hypothesis

The particle translocation hypothesis has been suggested as one of the biological mechanisms that link air pollution to cardiovascular disease. Nanoparticles in air pollution are small enough to cross the alveolar-capillary membrane to enter the circulation and to exert their adverse effects directly on the cardiovascular system. This hypothesis has been tested in both *ex vivo* and *in vivo* models.^{34 35} We have studied this in a mouse model of atherosclerosis using gold nanoparticles as a surrogate for diesel exhaust particles. Gold nanoparticles can be detected at very low concentrations and provides a means of allowing quantification of even very low levels of particle translocation. We demonstrated that after pulmonary instillation, gold nanoparticles could be detected in blood as well as the vasculature.³⁶ Moreover, nanoparticle deposition was greater in atherosclerotic arteries, suggesting a preferential accumulation at sites of vascular inflammation. Parallel studies were performed in human volunteers. First, 16 healthy volunteers inhaled gold nanoparticles for 2 hours followed by serial sampling of blood and urine. Gold was detected in blood and urine across the 24 hours after exposure. Levels were substantially higher following inhalation of 5 nm particles compared with 30 nm particles, demonstrating that smaller particles more readily translocated than larger particles.³⁶ We next undertook gold nanoparticle inhalation in patients with recent cerebrovascular accident, 24 hours before they underwent carotid endarterectomy.³⁶ Gold could be detected in the excised plaques confirming particle translocation into the circulation, and accumulation at sites of vascular injury and disease (figure 3). Translocation of inhaled nanoparticles into the systemic circulation and accumulation in inflamed tissues could be a direct mechanism linking environmental nanoparticles and cardiovascular disease, as well as the

growing number of associations observed between PM and other organs of the body.³⁷

MECHANISMS OF CARDIOVASCULAR DYSFUNCTION Endothelial, vasomotor and fibrinolytic dysfunction

Abnormal endothelial function plays an initiating and integral role across the pathophysiology of vascular disease. We have demonstrated that acute exposure to dilute diesel exhaust can impair vascular function in a manner similar to that observed in cigarette smokers.^{38 39} This vascular endothelial impairment lasts for >24 hours and appears to involve a reduced availability of nitric oxide that is indicative of oxidative stress.³⁸ This can have important downstream effects as evidenced by the greater ST-segment depression on the ECG in patients with ischaemic heart disease exercising in the presence of diesel exhaust emissions (figure 4).⁴⁰ This may also explain why patients with pre-existing stable coronary artery disease are more susceptible to the adverse effects of air pollution.⁴¹

Increased thrombogenicity

Thrombosis is one of the central pathophysiological processes involved in acute coronary and cerebrovascular events. Thrombus formation involves a delicate interplay between platelets, coagulation and fibrinolytic factors, and interaction between the vascular wall and endothelial cell-derived mediators. Exposure to air pollution can affect platelet activation, coagulation and fibrinolysis leading to a pro-coagulant and anti-fibrinolytic state.⁴² We observed that fibrinolytic responses are impaired in healthy individuals after a 1-hour exposure to dilute diesel exhaust emissions.⁴⁰ Rich *et al* observed an improvement in haemostatic factors like P-selectin and von Willebrand factor

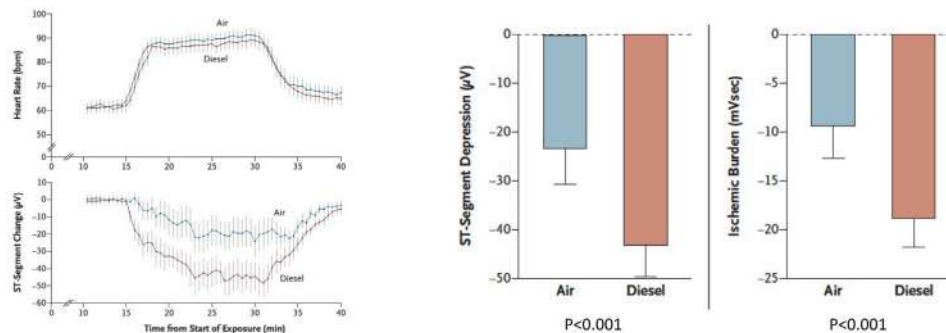


Figure 4 Myocardial ischemia during 15 min intervals of exercise-induced stress and exposure to diesel exhaust or filtered air in the 20 subjects. Panel A shows the average change in the heart rate and in the ST-segment in lead II. Panel B shows the maximum ST-segment depression during inhalation of diesel exhaust as compared with filtered air ($p=0.003$), and panel C shows the total ischaemic burden during inhalation of diesel exhaust as compared with filtered air ($p<0.001$); the values in panels B and C are averages of the values in leads II, V₂ and V₅. In all three panels, red indicates exposure to diesel exhaust, and blue exposure to filtered air. T bars denote SEs, and mVsec denotes millivolt seconds.⁴⁰

in healthy adults after air pollution measures were imposed in Beijing during the 2008 Olympic games.⁴³ Using a validated ex vivo model of deep arterial injury, we have demonstrated that inhalation of dilute diesel exhaust emissions activates platelets and increases the thrombogenicity of blood in healthy individuals.⁴⁴ Together with the effects on vascular function, these pathways represent plausible pathophysiological mechanisms to explain the association between air pollution and acute atherothrombotic events.

INTERVENTIONS TO REDUCE AIR POLLUTION EXPOSURE

The relationship between fine particulate pollution and cardiovascular mortality is supra-linear, being steeper at very low levels of exposure, and less so at higher levels. There is currently no apparent safe threshold of air pollution. In terms of cardiovascular mortality, the strongest associations are observed for coronary artery disease and stroke, although a similar exposure-response curve is proposed for many cardiovascular and non-cardiovascular causes of mortality.^{16, 45} It is unclear if the underlying biological mechanisms that lead to adverse cardiovascular effects differ according to the levels of air pollution exposure and this is an important research question to address. However, it is certain that relatively low-level exposure to air pollution substantially contributes to cardiovascular mortality and therefore it is crucial to tackle this issue.

Various interventions that reduce exposure to air pollution have been investigated as potential means to mitigate the adverse cardiovascular consequences of air pollution. In 15 healthy volunteers undertaking a 2-hour roadside walk in Beijing, we observed lower ambulatory blood pressures and greater heart rate variability when participants wore a facemask.⁴⁶ Using the same study design, the use of a facemask in patients with stable coronary artery disease was associated with lower self-reported symptoms, reduced maximal ST-segment depression, lower mean arterial blood pressure and increased heart rate variability.⁴⁷

Another potential air pollution intervention is the use of air purifiers to lower indoor particulates. In a study of college students in Shanghai, indoor air purification was associated with lower systolic and diastolic blood pressure, and lower plasma concentrations of several inflammatory and thrombogenic biomarkers.⁴⁸ Indoor air purification has also been associated with short-term reductions in stress hormones, such as cortisol, cortisone, epinephrine and norepinephrine.³¹

Given the importance of particulates in vehicle emissions, we have investigated whether exhaust ‘particle traps’ can attenuate the adverse cardiovascular effects of vehicle exhaust. In a cross-over controlled exposure study, filtration of particles from diesel exhaust emissions using a particle trap reduced ex vivo thrombus formation and improved vasomotor and fibrinolytic function when compared with unfiltered dilute diesel exhaust.⁴⁹

While the results of these interventional studies are promising, achieving population and global level impacts on morbidity and mortality will require substantial and coordinated legislative changes to reduce the sources of air pollution. Air quality and climate policies can provide mutual benefits. This is particularly the case in relation to efforts to decrease reliance on combustion of fossil fuels, which produce both greenhouse gases and pollutants that are linked to adverse health effects. A shift to clean renewable sources of energy, and the use of low or zero emission vehicles will be an important means of achieving the necessary reductions in air pollution levels. However, a greater shift towards active travel will have a bigger impact on pollution levels as well as simultaneously improving personal health through the health benefits of the exercise itself. A precedence for change has already been set by the marked reduction in the incidence of acute myocardial infarction and strokes following legislation to restrict tobacco smoking in public places.⁵⁰ A similar decisive and committed approach to reduce air pollution could also greatly reduce the burden of cardiovascular disease.

CONCLUSION

Air pollution has a staggering impact on global burden of morbidity and mortality, and is one of the leading modifiable risk factors for cardiovascular disease. Air pollution is a ‘silent’ pandemic deserving of an urgent and unwavering global effort to mitigate its effects. Stronger legislative measures to reduce air pollution and to encourage active travel will be rewarded with gains for both our environment and our health.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

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REFERENCES

- Lelieveld J, Pozzer A, Pöschl U, *et al.* Loss of life expectancy from air pollution compared to other risk factors: a worldwide perspective. *Cardiovasc Res* 2020;116:1910–7.
- LOGAN WPD. Mortality in the London fog incident, 1952. *Lancet* 1953;1:336–8.
- Clancy L, Goodman P, Sinclair H, *et al.* Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet* 2002;360:1210–4.
- WHO statistics. Available: <https://www.who.int/news/item/27-09-2016-who-releases-country-estimates-on-air-pollution-exposure-and-health-impact>
- Cohen AJ, Brauer M, Burnett R, *et al.* Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017;389:1907–18.
- Brook RD, Rajagopalan S, Pope CA, *et al.* Particulate matter air pollution and cardiovascular disease. *Circulation* 2010;121:2331–78.
- 2021 AHA statistical update. Available: https://professional.heart.org/-/media/phd-files-2/science-news/2/2021-heart-and-stroke-stat-update/2021_stat_update_factsheet_global_burden_of_disease.pdf?la=en
- Mustafić H, Jabre P, Caussin C, *et al.* Main air pollutants and myocardial infarction. *JAMA* 2012;307:713.
- Cesaroni G, Forastiere F, Stafoggia M, *et al.* Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the escape project. *BMJ* 2014;348:f7412.
- Hoffmann B, Moebus S, Möhlenkamp S, *et al.* Residential exposure to traffic is associated with coronary atherosclerosis. *Circulation* 2007;116:489–96.
- Künzli N, Jerrett M, Mack WJ, *et al.* Ambient air pollution and atherosclerosis in Los Angeles. *Environ Health Perspect* 2005;113:201–6.
- Peters A, von Klot S, Heier M, *et al.* Exposure to traffic and the onset of myocardial infarction. *N Engl J Med* 2004;351:1721–30.
- Hong Y-C, Lee J-T, Kim H, *et al.* Effects of air pollutants on acute stroke mortality. *Environ Health Perspect* 2002;110:187–91.
- Kulick ER, Wellenius GA, Boehme AK, *et al.* Residential proximity to major Roadways and risk of incident ischemic stroke in NOMAS (the Northern Manhattan study). *Stroke* 2018;49:835–41.
- Shah ASV, Lee KK, McAllister DA, *et al.* Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ* 2015;350:h1295.
- Miller KA, Siscovick DS, Sheppard L, *et al.* Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007;356:447–58.
- Chen G, Wang A, Li S, *et al.* Long-term exposure to air pollution and survival after ischemic stroke. *Stroke* 2019;50:563–70.
- Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. *AME Med J* 2020;5:15.
- Atkinson RW, Carey IM, Kent AJ, *et al.* Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. *Epidemiology* 2013;24:44–53.
- Shah ASV, Langrish JP, Nair H, *et al.* Global association of air pollution and heart failure: a systematic review and meta-analysis. *Lancet* 2013;382:1039–48.
- Liu H, Tian Y, Song J, *et al.* Effect of ambient air pollution on hospitalization for heart failure in 26 of China's largest cities. *Am J Cardiol* 2018;121:628–33.
- Shao Q, Liu T, Korantzopoulos P, *et al.* Association between air pollution and development of atrial fibrillation: a meta-analysis of observational studies. *Heart Lung* 2016;45:557–62.
- Teng T-HK, Williams TA, Bremner A, *et al.* A systematic review of air pollution and incidence of out-of-hospital cardiac arrest. *J Epidemiol Community Health* 2014;68:37–43.
- Miller MR. Oxidative stress and the cardiovascular effects of air pollution. *Free Radic Biol Med* 2020;151:69–87.
- Gomes EC, Florida-James G. Lung Inflammation, Oxidative Stress and Air Pollution. In: *Lung inflammation*. InTech, 2014.
- Panasevich S, Leander K, Rosenlund M, *et al.* Associations of long- and short-term air pollution exposure with markers of inflammation and coagulation in a population sample. *Occup Environ Med* 2009;66:747–53.
- Stocker R, Keaney JF. Role of oxidative modifications in atherosclerosis. *Physiol Rev* 2004;84:1381–478.
- Haberzettl P, Conklin DJ, Abplanalp WT, *et al.* Inhalation of fine particulate matter impairs endothelial progenitor cell function via pulmonary oxidative stress. *Arterioscler Thromb Vasc Biol* 2018;38:131–42.
- Ying Z, Xu X, Bai Y, *et al.* Long-term exposure to concentrated ambient PM_{2.5} increases mouse blood pressure through abnormal activation of the sympathetic nervous system: a role for hypothalamic inflammation. *Environ Health Perspect* 2014;122:79–86.
- Robertson S, Thomson AL, Carter R, *et al.* Pulmonary diesel particulate increases susceptibility to myocardial ischemia/reperfusion injury via activation of sensory TRPV1 and β 1 adrenoceptors. *Part Fibre Toxicol* 2014;11:12.
- Li H, Cai J, Chen R, *et al.* Particulate matter exposure and stress hormone levels. *Circulation* 2017;136:618–27.
- Lee D-H, Kim S-H, Kang S-H, *et al.* Personal exposure to fine particulate air pollutants impacts blood pressure and heart rate variability. *Sci Rep* 2020;10:16538.
- Rankin GD, Kabéle M, Brown R, *et al.* Acute exposure to diesel exhaust increases muscle sympathetic nerve activity in humans. *J Am Heart Assoc* 2021;10:e018448.
- Kreyling WG, Hirn S, Möller W, *et al.* Air-blood barrier translocation of tracheally instilled gold nanoparticles inversely depends on particle size. *ACS Nano* 2014;8:222–33.
- Kreyling WG, Semmler-Behnke M, Seitz J, *et al.* Size dependence of the translocation of inhaled iridium and carbon nanoparticle aggregates from the lung of rats to the blood and secondary target organs. *Inhal Toxicol* 2009;21 Suppl 1:55–60.
- Miller MR, Raftis JB, Langrish JP, *et al.* Inhaled nanoparticles accumulate at sites of vascular disease. *ACS Nano* 2017;11:4542–52.
- Miller MR, Newby DE. Air pollution and cardiovascular disease: car sick. *Cardiovasc Res* 2020;116:279–94.
- Mills NL, Törnqvist H, Robinson SD, *et al.* Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. *Circulation* 2005;112:3930–6.
- Newby DE, McLeod AL, Uren NG, *et al.* Impaired coronary tissue plasminogen activator release is associated with coronary atherosclerosis and cigarette smoking. *Circulation* 2001;103:1936–41.
- Mills NL, Törnqvist H, Gonzalez MC, *et al.* Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *N Engl J Med* 2007;357:1075–82.
- Brook RD, Franklin B, Cascio W, *et al.* Air pollution and cardiovascular disease. *Circulation* 2004;109:2655–71.
- Robertson S, Miller MR. Ambient air pollution and thrombosis. *Part Fibre Toxicol* 2018;15:1.
- Rich DQ, Kipen HM, Huang W, *et al.* Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. *JAMA* 2012;307:2068–78.
- Lucking AJ, Lundback M, Mills NL, *et al.* Diesel exhaust inhalation increases thrombus formation in man. *Eur Heart J* 2008;29:3043–51.
- Apte JS, Marshall JD, Cohen AJ, *et al.* Addressing global mortality from ambient PM_{2.5}. *Environ Sci Technol* 2015;49:8057–66.
- Langrish JP, Mills NL, Chan JK, *et al.* Beneficial cardiovascular effects of reducing exposure to particulate air pollution with a simple facemask. *Part Fibre Toxicol* 2009;6:8.
- Langrish JP, Li X, Wang S, *et al.* Reducing personal exposure to particulate air pollution improves cardiovascular health in patients with coronary heart disease. *Environ Health Perspect* 2012;120:367–72.
- Chen R, Zhao A, Chen H, *et al.* Cardiopulmonary benefits of reducing indoor particles of outdoor origin. *J Am Coll Cardiol* 2015;65:2279–87.
- Lucking AJ, Lundbäck M, Barath SL, *et al.* Particle traps prevent adverse vascular and prothrombotic effects of diesel engine exhaust inhalation in men. *Circulation* 2011;123:1721–8.
- Pell JP, Haw S, Cobbe S, *et al.* Smoke-free legislation and hospitalizations for acute coronary syndrome. *N Engl J Med* 2008;359:482–91.